Industria y Comercio

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Delegatura de propiedad Industrial

División de Nuevas Creaciones

PCT

SOLICITUD

PATENTE DE INVENCIÓN

21 **EXPEDIENTE No.** 04-56363

54 **TÍTULO** COMPUESTOS DE SUCCINIMIDA HETEROCICLICOS FUSIONADOS Y ANALOGOS DE LOS MISMOS MODULADORES DE LA FUNCIÓN DEL RECEPTOR DE LA HORMONA NUCLEAR

51 **CLASIFICACIÓN INTERNACIONAL** A61K 31/40

71 **SOLICITANTE** BRISTOL-MYERS SQUIBB COMPANY

DOMICILIO PRINCETON, NEW JERSEY, ESTADOS UNIDOS DE AMERI

74 **APODERADO** RAMIRO CASTRO DUQUE

22 **BOGOTÁ, D. C.,** 16/06/2004

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(FORMA P 10)

PETITORIO

AS: 94.181

Industria y Comercio
SUPERINTENDENCIA

SUPERINDUSTRIA Y COMERCIO
Radicacion : 04056353 [illegible] Folios: 1528
Fecha (AMD): 2004-06-16 17:29:13
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 8020 DIVISION DE NUEVAS CONCESIONES

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: **BRISTOL – MYERS SQUIBB COMPANY** Dirección: P.O. Box 4000, Route 206 and provinceline Road, Princeton, NJ 08543-4000, Estados Unidos de América Nacionalidad o Domicilio: Estados Unidos Lugar de Constitución: Estados Unidos Teléfono: Fax: E-mail	**IDENTIFICACION** C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Cual_____ Número _____
3 **REPRESENTANTE O APODERADO**	Nombre: RAMIRO CASTRO DUQUE Dirección: Cra. 7 No. 16-56 Piso 9 Teléfono: 380-2200 Fax: 380-2700 E-mail:	**IDENTIFICACION** C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual_____ Número 170.322 TP 1003
4 **INVENTOR (ES) (72)**	Nombre: EN HOJA ANEXA Dirección: Nacionalidad o Domicilio: Estados Unidos de América (Respectivamente)	

5 PCT (86)
Solicitud Internacional No. PCT/US02/40598 Fecha 18-12-2002
Publicación Internacional No. WO 03/062241 A1 Fecha 31-07-2003

6 Título (54): COMPUESTOS DE SUCCINIMIDA HETEROCICLICOS FUSIONADOS Y ANALOGOS DE LOS MISMOS, MODULADORES DE LA FUNCIÓN DEL RECEPTOR DE LA HORMONA NUCLEAR

7 Clasificación Internacional (51) A61K31/40

8 Prioridad	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
SI ☒ NO ☐	US	19-12-2001	10/025,116

9 Comprobante de pago No. 04-39-538 **Fecha** 16-06-2004

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

2020-F08 (01-11-15)

2

10 ANEXOS

- [x] Comprobante de pago de la tasa de presentación de la solicitud. $422.000
- [ ] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [x] Poderes, si fuere el caso. Protocolo No. 19358
- [ ] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones
- [x] Copia de la solicitud Internacional. (Resumen, descripción, reivindicaciones, dibujos)
- [x] Traducción de la solicitud Internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- [x] Copia del examen preliminar efectuado por la IPEA.
- [x] Traducción 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 12x12.
- [ ] De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- [x] Otros - Tarjeta de Propietarios

11 FIGURA CARACTERÍSTICA:

12 Solicito la concesión de la patente.

NOMBRE: RAMIRO CASTRO DUQUE

FIRMA:

C.C. 170.322 de Bogotá T.P. 1003 del C.S.J.

Instrucciones para la presentación de los anexos, ver reverso de esta página.

Drigard & Castro
Abogados

Apartado 3692

Cra. 7 16-56
Bogotá - Colombia S.A.

Tel. Conm. 3802200
Tel./Fax: (57.1) 2827976
(57.1) 3802700

E.Mail:bricas@brigardycastro.com.co

AS: 94.181
PCT/US01/40598
BRISTOL-MYERS SQUIBB COMPANY

1. Mark E. Salvati
   9 Tracey Drive,
   Lawrenceville, NJ 08648,
   Estados Unidos de América

2. James Aaron Balog
   17 Terrell Road,
   Lambertville, NJ 08530
   Estados Unidos de América

3. Dacia A. Pickering
   507 Drexel Avenue,
   Lawrenceville, NJ 08648
   Estados Unidos de América

4. Soren Giese
   523 Windmere Way,
   New Hope, PA 18938
   Estados Unidos de América

5. Aberra Fura
   15 Cresthill Road,
   Lawrenceville, NJ 08648,
   Estados Unidos de América

6. Wenying Li
   6221 Town Place,
   Middletown, CT 06457,
   Estados Unidos de América

7. Ramesh N. Patel
   572 Cabot Hill Road,
   Bridgewater, NJ 08807
   Estados Unidos de América

8. Ronald L. Hanson
   54 Whitewood Drive,
   Morris Plains, NJ 07950
   Estados Unidos de América

9. Toomas Mitt
   1312 Aspen Drive,
   Plainsboro, NJ 08536
   Estados Unidos de América

10. Jacques Y. Roberge
    478 Ewing Street,
    Princeton, NJ 08540
    Estados Unidos de América

11. James R. Corte
    11 Abelia Court,
    Lawrenceville, NJ 08648
    Estados Unidos de América

12. Steven H. Spergel
    1807 Jericho Drive,
    Warrington, PA 18976
    Estados Unidos de América

13. Richard A. Rampulla
    5 Fairfax Court,
    Flemington, NJ 08822
    Estados Unidos de América

14. Raj N. Misra
    12 Eaton Place,
    Hopewell, NJ 08525
    Estados Unidos de América

15. Hai-Yun Xiao
    173 Jonathan Dayton Court,
    Princeton, NJ 08540
    Estados Unidos de América

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SUPERINDUSTRIA Y COMERCIO Folios: 1500
Radicacion : 04053353 03000000
Fecha (AAAA): 2004-05-16 17:29:12
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 04 - 39,538
FECHA : MAYO 17 DE 2004

C O N S I G N A C I O N

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
BRIGARD & CASTRO LTDA	CONSIGNACION	BANCO POPULAR	050-00110-6	21740989	17/05/2004	22,697,000.00

C O N C E P T O

CANT.	RENTISTICO	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._____

This page is not part of

the document!

US2002040598 / 2003-062241

1/6

Date: Jul 31, 2003

Recipient: IB

Address: ;Bureau international de l'OMPI;34, chemin des Colombettes;;;Geneve 20 1211;;CH

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
31 July 2003 (31.07.2003)

PCT

(10) International Publication Number
WO 03/062241 A1

(51) International Patent Classification[7]: C07D 491/00, A61K 31/40

(21) International Application Number: PCT/US02/40598

(22) International Filing Date: 18 December 2002 (18.12.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
10/025,116 19 December 2001 (19.12.2001) US

(71) Applicant *(for all designated States except US)*: BRISTOLS-MYERS SQUIBB COMPANY [US/US]; P.O. Box 4000, Route 206 and Provinceline Road, Princeton, NJ 08543-4000 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: SALVATI, Mark, E. [US/US]; 9 Tracey Drive, Lawrenceville, NJ 08648 (US). BALOG, James, Aaron [US/US]; 17 Terrell Road, Lambertville, NJ 08530 (US). PICKERING, Darcia, A. [GB/US]; 507 Drexel Avenue, Lawrenceville, NJ 08648 (US). GIESE, Soren [DE/US]; 523 Windmere Way, New Hope, PA 18938 (US). FURA, Aberra [ET/US]; 15 Cresthill Road, Lawrenceville, NJ 08648 (US). LI, Wenying [CN/US]; 6221 Town Place, Middletown, CT 06457 (US). PATEL, Ramesh, N. [US/US]; 572 Cabot Hill Road, Bridgewater, NJ 08807 (US). HANSON, Ronald, L. [US/US]; 54 Whitewood Drive, Morris Plains, NJ 07950 (US). MITT, Thomas [US/US]; 1312 Aspen Drive, Plainsboro, NJ 08536 (US). ROBERGE, Jacques [CA/US]; 57 Southern Way, Princeton, NJ 08540 (US). CORTE, James, R. [US/US]; 11 Abelia Court, Lawrenceville, NJ 08648 (US). SPERGEL, Steven, H. [US/US]; 1807 Jericho Drive, Warrington, PA 18966 (US). RAMPULLA, Richard, A. [US/US]; 5 Fairfax Court, Flemington, NJ 08822 (US). MISRA, Raj [US/US]; 12 Eaton Place, Hopewell, NJ 08525 (US). XIAO, Hai-Yun [CN/US]; 173 Jonathan Dayton Court, Princeton, NJ 08540 (US).

(74) Agents: PEIST, Kenneth et al.; Bristol-Myers Squibb Company, P.O. Box 4000, Princeton, NJ 08543-4000 (US).

(81) Designated States *(national)*: AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, 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, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

(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, SI, SK, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

Published:
-- *with international search report*
— *before the expiration of the time limit for amending the claims and to be republished in the event of receipt of amendments*

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 03/062241 A1

(54) Title: FUSED HETEROCYCLIC SUCCINIMIDECOMPOUNDS AND ANALOGS THEREOF, MODULATORS OF NUCLEAR HORMONE RECEPTOR FUNCTION

(57) Abstract: Fused cyclic compounds method of using such compounds in the treatment of nuclear hormone receptor-associated conditions such as cancer and immune disorders, and pharmaceutical compositions containing such compounds.

Fused Heterocyclic Succinimide Compounds and Analogs Thereof, Modulators of Nuclear Hormone Receptor Function

This application claims priority from and is a continuation-in-part of U.S. Application Serial No. 10/025,116 filed Decmber 19, 2001 and from U.S. Application Serial No. 60/233,519, filed September 19, 2000, from U.S. Application Serial No. 60/284,730, filed April 18, 2001, and from U.S. Application Serial No. 60/284,438, filed April 18, 2001, which provisional applications are incorporated herein by reference in their entirety, and further claims priority from and is a continuation-in-part of U.S. Application Serial No. 09/885,381, filed June 20, 2001, and U.S. Application Serial No. 09/885,827, filed June 20, 2001, which applications are incorporated herein by reference in their entirety.

Field of the Invention

The present invention relates to fused cyclic compounds, to methods of using such compounds in the treatment of nuclear hormone receptor-associated conditions such as cancer, and to pharmaceutical compositions containing such compounds.

Background of the Invention

Nuclear hormone receptors (NHR's) constitute a large super-family of ligand-dependent and sequence-specific transcription factors. Members of this family influence transcription either directly, through specific binding to the promoter target genes (Evans, in *Science* 240: 889-895 (1988)), or indirectly, via protein-protein interactions with other transcription factors (Jonat et al., *Cell* 62: 1189-1204 (1990), Schuele et al., *Cell* 62: 1217-1226 (1990), and Yang-Yen et al., *Cell* 62: 1205-1215 (1990)). The nuclear hormone receptor super-family (also known in the art as the "steroid/thyroid hormone receptor super-family") includes receptors for a variety of hydrophobic ligands, including cortisol, aldosterone, estrogen, progesterone, testosterone, vitamine D3, thyroid hormone and retinoic acid (Evans, 1988, supra). In addition to these conventional nuclear hormone receptors, the super-family contains a number of proteins that have no known ligands, termed orphan nuclear

hormone receptors (Mangelsdorf et al., *Cell* 83: 835-839 (1995), O'Malley et al., *Mol. Endocrinol.* 10: 1293 (1996), Enmark et al., *Mol. Endocrinol.* 10, 1293-1307 (1996) and Giguere, *Endocrin. Rev.* 20, 689-725 (1999)). The conventional nuclear hormone receptors are generally transactivators in the presence of ligand, and can either be active repressors or transcriptionally inert in the absence of ligand. Some of the orphan receptors behave as if they are transcriptionally inert in the absence of ligand. Others, however, behave as either constitutive activators or repressors. These orphan nuclear hormone receptors are either under the control of ubiquitous ligands that have not been identified, or do not need to bind ligand to exert these activities.

In common with other transcription factors, the nuclear hormone receptors have a modular structure, being comprised of three distinct domains: an N-terminal domain of variable size containing a transcriptional activation function AF-1, a highly conserved DNA binding domain and a moderately conserved ligand-binding domain. The ligand-binding domain is not only responsible for binding the specific ligand but also contains a transcriptional activation function called AF-2 and a dimerisation domain (Wurtz et al., *Nature Struc. Biol.* 3, 87-94 (1996), Parker et al., *Nature Struc. Biol.* 3, 113-115 (1996) and Kumar et al., *Steroids* 64, 310-319 (1999)). Although the overall protein sequence of these receptors can vary significantly, all share both a common structural arrangement indicative of divergence from an ancestral archetype, and substantial homology (especially, sequence identity) at the ligand-binding domain.

The steroid binding nuclear hormone receptors (SB-NHR's) comprise a sub-family of nuclear hormone receptors. These receptors are related in that they share a stronger sequence homology to one another, particularly in the ligand binding domain (LBD), than to the other members of the NHR super-family (Evans, 1988, supra) and they all utilize steroid based ligands. Some examples of this sub-family of NHR's are the androgen receptor (AR), the estrogen receptor (ER), the progesterone receptor (PR), the glucocorticoid receptor (GR), the mineralocorticoid receptor (MR), the aldosterone receptor (ALDR) and the steroid and xenobiotic receptor (SXR) (Evans *et al.*, WO 99/35246). Based on the strong sequence homology in the LBD, several orphan receptors may also be members of the SB-NHR sub-family.

Consistent with the high sequence homology found in the LBD for each of the SB-NHR's, the natural ligands for each is derived from a common steroid core. Examples of some of the steroid based ligands utilized by members of the SB-NHR's include cortisol, aldosterone, estrogen, progesterone, testosterone and dihydrotestosterone. Specificity of a particular steroid based ligand for one SB-NHR versus another is obtained by differential substitution about the steroid core. High affinity binding to a particular SB-NHR, coupled with high level specificity for that particular SB-NHR, can be achieved with only minor structural changes about the steroid core (e.g., Waller et al., *Toxicol. Appl. Pharmacol.* 137, 219-227 (1996) and Mekenyan et al., *Environ. Sci. Technol.* 31, 3702-3711 (1997), binding affinity for progesterone towards the androgen receptor as compared to testosterone).

Numerous synthetically derived steroidal and non-steroidal agonists and antagonists have been described for the members of the SB-NHR family. Many of these agonist and antagonist ligands are used clinically in man to treat a variety of medical conditions. RU486 is an example of a synthetic agonist of the PR, which is utilized as a birth control agent (Vegeto et al., *Cell* 69: 703-713 (1992)), and Flutamide is an example of an antagonist of the AR, which is utilized for the treatment of prostate cancer (Neri et al, *Endo.* 91, 427-437 (1972)). Tamoxifen is an example of a tissues specific modulator of the ER function, that is used in the treatment of breast cancer (Smigel, *J. Natl. Cancer Inst.* 90, 647-648 (1998)). Tamoxifen can function as an antagonist of the ER in breast tissue while acting as an agonist of the ER in bone (Grese et al., *Proc. Natl. Acad. Sci. USA* 94, 14105-14110 (1997)). Because of the tissue selective effects seen for Tamoxifen, this agent and agents like it are referred to as "partial-agonist" or partial-antagonist". In addition to synthetically derived non-endogenous ligands, non-endogenous ligands for NHR's can be obtained from food sources (Regal et al., *Proc. Soc. Exp. Biol. Med.* 223, 372-378 (2000) and Hempstock et al., *J. Med. Food* 2, 267-269 (1999)). The flavanoid phytoestrogens are an example of an unnatural ligand for SB-NHR's that are readily obtained from a food source such as soy (Quella et al., *J. Clin. Oncol.* 18, 1068-1074 (2000) and Banz et al., *J. Med. Food* 2, 271-273 (1999)). The ability to modulate the transcriptional activity of individual NHR by the addition of a small molecule ligand,

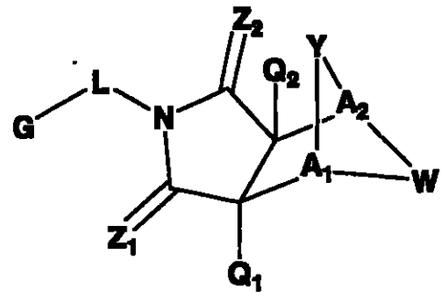
makes them ideal targets for the development of pharmaceutical agents for a variety of disease states.

As mentioned above, non-natural ligands can be synthetically engineered to serve as modulators of the function of NHR's. In the case of SB-NHR's, engineering of an unnatural ligand can include the identification of a core structure which mimics the natural steroid core system. This can be achieved by random screening against several SB-NHR's or through directed approaches using the available crystal structures of a variety of NHR ligand binding domains (Bourguet et al., *Nature* 375, 377-382 (1995), Brzozowski, et al., *Nature* 389, 753-758 (1997), Shiau et al., *Cell* 95, 927-937 (1998) and Tanenbaum et al., *Proc. Natl. Acad. Sci. USA* 95, 5998-6003 (1998)). Differential substitution about such a steroid mimic core can provide agents with selectivity for one receptor versus another. In addition, such modifications can be employed to obtain agents with agonist or antagonist activity for a particular SB-NHR. Differential substitution about the steroid mimic core can result in the formation of a series of high affinity agonists and antagonists with specificity for, for example, ER versus PR versus AR versus GR versus MR. Such an approach of differential substitution has been reported, for example, for quinoline based modulators of steroid NHR in *J. Med. Chem.*, 41, 623 (1999); WO 9749709; US 5696133; US 5696130; US 5696127; US 5693647; US 5693646; US 5688810; US 5688808 and WO 9619458, all incorporated herein by reference.

The compounds of the present invention comprise a core which serves as a steroid mimic, and are useful as modulators of the function of steroid binding nuclear hormone receptors, as well as other NHR as described following.

Summary of the Invention

The present invention provides fused cyclic compounds of the following formula I and salts thereof, which compounds are especially useful as modulators of nuclear hormone receptor function:



(I)

As used in formula I, and throughout the specification, the symbols have the following meanings unless otherwise indicated, and are, for each occurrence, independently selected:

G is an aryl or heterocyclo (e.g., heteroaryl) group, where said group is mono- or polycyclic, and which is optionally substituted at one or more positions, preferably with hydrogen, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, halo, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, aryl or substituted aryl, heterocyclo or substituted heterocyclo, arylalkyl or substituted arylalkyl, heterocycloalkyl or substituted heterocycloalkyl, CN, $R^1OC{=}O$, $R^1C{=}O$, $R^1C{=}S$, $R^1HNC{=}O$, $R^1R^2NC{=}O$, $HOCR^3R^{3'}$, nitro, R^1OCH_2, R^1O, NH_2, NR^4R^5, SR^1, $S{=}OR^1$, SO_2R^1, SO_2OR^1, $SO_2NR^1R^{1'}$, $(R^1O)(R^{1'}O)P{=}O$, oxo, $(R^1)(R^{1'})P{=}O$, or $(R^{1'})(NHR^1)P{=}O$;

Z_1 is O, S, NH, or NR^6;

Z_2 is O, S, NH, or NR^6;

A_1 is CR^7 or N;

A_2 is CR^7 or N;

Y is J-J'-J" where J is $(CR^7R^{7'})n$ and n = 0-3, J' is a bond or O, S, S=O, SO_2, NH, NR^7, C=O, OC=O, $NR^1C{=}O$, $CR^7R^{7'}$, $C{=}CR^8R^{8'}$, $R^2P{=}O$, $R^2P{=}S$, $R^2OP{=}O$, $R^2NHP{=}O$, $OP{=}OOR^2$, $OP{=}ONHR^2$, $OP{=}OR^2$, OSO_2, $C{=}NR^7$, NHNH, $NHNR^6$, NR^6NH, N=N, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo or aryl or substituted aryl, and J" is $(CR^7R^{7'})n$ and n = 0-3, where Y is not a bond (i.e., if

J' is a bond, then in at least one of J or J'' (each defined as $(CR^7R^{7'})n$), n is not zero);

W is $CR^7R^{7'}$—$CR^7R^{7'}$, CR^8=$CR^{8'}$, $CR^7R^{7'}$—C=O, C=O—C=O, $CR^7R^{7'}$—C=CH_2, C=CH_2—C=CH_2, $CR^7R^{7'}$—C=NR^1, C=NR^1—C=NR^1, NR^9—$CR^7R^{7'}$, N=CR^8, N=N, NR^9—$NR^{9'}$, S—$CR^7R^{7'}$, SO—$CR^7R^{7'}$, SO_2—$CR^7R^{7'}$, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, or aryl or substituted aryl, wherein when W is not NR^9—$CR^7R^{7'}$, N=CR^8, N=N, NR^9—$NR^{9'}$, S—$CR^7R^{7'}$, SO—$CR^7R^{7'}$, SO_2—$CR^7R^{7'}$, or heterocyclo or substituted heterocyclo, then J' must be O, S, S=O, SO_2, NH, NR^7, OC=O, NR^1C=O, OP=OOR^2, OP=ONHR^2, OSO_2, NHNH, $NHNR^6$, NR^6NH, or N=N; or

when W is $CR^7R^{7'}$—$CR^7R^{7'}$, the R^7 and $R^{7'}$ substituents in each occurrence may be taken together to form a substituted or unsubstituted carbocyclic or substituted or unsubstituted heterocyclic ring system which can be formed by any combination of R^7 and $R^{7'}$ attached to the same carbon atom;

Q_1 is H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocycloalkyl or substituted heterocycloalkyl, arylalkyl or substituted arylalkyl, alkynyl or substituted alkynyl, aryl or substituted aryl, heterocyclo (e.g., heteroaryl) or substituted heterocyclo (e.g., substituted heteroaryl), halo, CN, R^1OC=O, R^4C=O, R^5R^6NC=O, HO$CR^7R^{7'}$, nitro, R^1OCH_2, R^1O, NH_2, C=OSR^1, SO_2R^1 or NR^4R^5;

Q_2 is H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocycloalkyl or substituted heterocycloalkyl, arylalkyl or substituted arylalkyl, alkynyl or substituted alkynyl, aryl or substituted aryl, heterocyclo (e.g., heteroaryl) or substituted heterocyclo (e.g., substituted heteroaryl), halo, CN, R^1OC=O, R^4C=O, R^5R^6NC=O, HO$CR^7R^{7'}$, nitro, R^1OCH_2, R^1O, NH_2, C=OSR^1, SO_2R^1 or NR^4R^5;

L is a bond, $(CR^7R^{7'})n$, NH, NR^5, NH $(CR^7R^{7'})n$, or $NR^5(CR^7R^{7'})n$, where n = 0-3;

R^1 and $R^{1'}$ are each independently H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkyalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl;

R^2 is alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl;

R^3 and $R^{3'}$ are each independently H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, halo, CN, hydroxylamine, hydroxamide, alkoxy or substituted alkoxy, amino, NR^1R^2, thiol, alkylthio or substituted alkylthio;

R^4 is H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, $R^1C{=}O$, $R^1OC{=}O$, $R^1NHC{=}O$, SO_2OR^1, SO_2R^1 or $SO_2NR^1R^{1'}$;

R^5 is alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl,

heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, $R^1C{=}O$, $R^1NHC{=}O$, SO_2R^1, SO_2OR^1, or $SO_2NR^1R^{1'}$;

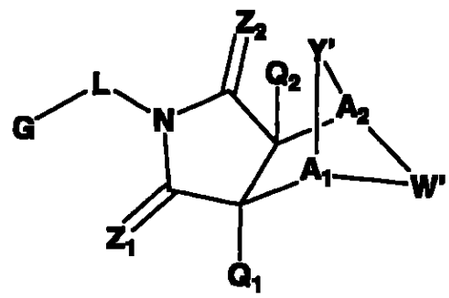
R^6 is alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, CN, OH, OR^1, $R^1C{=}O$, $R^1NHC{=}O$, SO_2R^1, SO_2OR^1, or $SO_2NR^1R^{1'}$;

R^7 and $R^{7'}$ are each independently H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, halo, CN, OR^4, nitro, hydroxylamine, hydroxylamide, amino, NHR^4, NR^2R^5, NR^5R^5, NOR^1, thiol, alkylthio or substituted alkylthio, $HOC{=}O$, $R^1C{=}O$, $R^1(C{=}O)O$, $R^1OC{=}O$, $R^1NHC{=}O$, $NH_2C{=}O$, SO_2R^1, SOR^1, $PO_3R^1R^{1'}$, $R^1R^{1'}NC{=}O$, $C{=}OSR^1$, SO_2R^1, SO_2OR^1, or $SO_2NR^1R^{1'}$, or, wherein A_1 or A_2 contains a group R^7 and W contains a group R^7, said R^7 groups of A_1 or A_2 and W together form a heterocyclic ring;

R^8 and $R^{8'}$ are each independently H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkyalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, nitro, halo, CN, OR^1, amino, NHR^4, NR^2R^5, NOR^1, alkylthio or substituted alkylthio, $C{=}OSR^1$, $R^1OC{=}O$, $R^1C{=}O$, $R^1NHC{=}O$, $R^1R^{1'}NC{=}O$, SO_2OR^1, $S{=}OR^1$, SO_2R^1, $PO_3R^1R^{1'}$, or $SO_2NR^1R^{1'}$; and

R^9 and $R^{9'}$ are each independently H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, CN, OH, OR^1, $R^1C{=}O$, $R^1OC{=}O$, $R^1NHC{=}O$, SO_2R^1, SO_2OR^1, or $SO_2NR^1R^{1'}$.

Compounds within formula I are novel, a preferred subgenus of which is the following formula Ia:



(Ia)

where G, L, Z_1, Z_2, A_1, A_2, Q_1 and Q_2 are as defined above;

Y' is J-J'-J" where J is $(CR^7R^{7'})n$ and n = 0-3, J' is a bond or O, S, S=O, SO_2, NH, NR^7, $CR^7R^{7'}$, $R^2P{=}O$, $R^2P{=}S$, $R^2OP{=}O$, $R^2NHP{=}O$, $OP{=}OOR^2$, $OP{=}ONHR^2$, OSO_2, NHNH, $NHNR^6$, NR^6NH, N=N, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, or heterocyclo or substituted heterocyclo, and J" is $(CR^7R^{7'})n$ and n = 0-3, where Y is not a bond; and

W' is $CR^7R^{7'}$—$CR^7R^{7'}$, $CR^7R^{7'}$—C=O, C=O—C=O, $CR^7R^{7'}$—$C{=}CH_2$, $C{=}CH_2$—$C{=}CH_2$, $CR^7R^{7'}$—$C{=}NR^1$, $C{=}NR^1$—$C{=}NR^1$, NR^9—$CR^7R^{7'}$, $N{=}CR^8$, N=N, NR^9—$NR^{9'}$, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, or aryl or substituted aryl, wherein when W' is not NR^9—$CR^7R^{7'}$, $N{=}CR^8$, N=N, NR^9—$NR^{9'}$, or heterocyclo or substituted heterocyclo, then J' must be O, S, S=O, SO_2, NH, NR^7, $OP{=}OOR^2$, $OP{=}ONHR^2$, OSO_2, NHNH, $NHNR^6$, NR^6NH, or N=N; or

when W' is $CR^7R^{7'}$—$CR^7R^{7'}$, the R^7 and $R^{7'}$ substituents in each occurrence may be taken together to form a substituted or unsubstituted carbocyclic or substituted or unsubstituted heterocyclic ring system which can be formed by any combination of R^7 and $R^{7'}$ attached to the same carbon atom; or alternatively, Y' is NR^7—$CR^7R^{7'}$ and W' is CR^8=$CR^{8'}$; or, alternatively, Y' is $CR^7R^{7'}$—C=O and W' is NR^9—$CR^7R^{7'}$;

where R^2, R^6, R^7, $R^{7'}$, R^8, R^9 and $R^{9'}$ are as defined above and with the provisos that

(1) when Y' is -O-, Q_1 and Q_2 are hydrogen, Z_1 and Z_2 are O, W' is $-CH_2-CH_2-$, and A_1 and A_2 are CH, then G-L is not phenyl, monosubstituted phenyl or phenyl which is substituted with two or more of the following groups: methoxy, halo, NO_2, methyl, CH_3-S-, OH, CO_2H, trifluoromethyl, -C(O)-C_6H_5, NH_2, 4-7-epoxy, hexahydro-1H-isoindole-1,3(2H)dione, or -C(O)-CH_3;

(2) when Y' is -O-, Q_1 and Q_2 are hydrogen, Z_1 and Z_2 are O, W' is CH_2-CH_2, and one of A_1 and A_2 is CH and the other is CR^7, then G-L is not unsubstituted phenyl;

(3) when Y' is -O-, Q_1 and Q_2 are hydrogen, Z_1 and Z_2 are O, W' is CH_2-CH_2, and one of A_1 and A_2 is CH and the other is C-CH_3, then G-L is not phenyl substituted with chloro and/or methyl;

(4) when Y' is -O- or -S-, Q_1 and Q_2 are hydrogen, Z_1 and Z_2 are O, W' is CH_2-CH_2, and one of A_1 and A_2 is CH and the other is CH or C-alkyl, then G-L is not N-substituted piperazine-alkyl- or N-substituted imidazolidine-alkyl-;

(5) when Y' is -O-; Q_1 and Q_2 are hydrogen, Z_1 and Z_2 are O, W' is CH_2-CH_2, and A_1 and A_2 are CH, then G-L is not oxazole or triazole;

(6) when Y' is -O-; Q_1 and Q_2 are hydrogen or methyl, Z_1 and Z_2 are O, W' is CH_2-CH_2, and A_1 and A_2 are CH or C-CH_3, then G-L is not thiazole or substituted thiazole (in addition such compounds where G-L is optionally substituted thiadiazole or partially saturated thiazole are optionally removed by proviso where A_1 and A_2 are both CH);

(7) when Y' contains a group J' selected from S, S=O, SO_2, NH, NR^7, R^2P=O, R^2P=S, R^2OP=O, R^2NHP=O, OP=OOR^2, OP=$ONHR^2$, OSO_2, NHNH, NHR^6,

NR^6NH or N=N, W' is $CR^7R^{7'}$- $CR^7R^{7'}$, and Z_1 and Z_2 are O, then G-L is not unsubstituted phenyl;

(8) when Y' is NR^7, W' is unsubstituted or substituted phenyl, and Q_1 and Q_2 are hydrogen, then Z_1 and Z_2 are not O;

(9) when Y' is -O-, Q_1 and Q_2 are hydrogen, Z_1 and Z_2 are O, W' is dihydroisoxazole bearing an optionally substituted phenyl group, and A_1 and A_2 are CH, then G-L is not unsubstituted phenyl or dichlorophenyl;

(10) when Y' is O, Q_1 and Q_2 are hydrogen, Z_1 and Z_2 are O, W' is ethylene oxide, and A_1 and A_2 are CH, then G-L is not methylphenyl or chlorophenyl;

(11) when Y' is NR^7—$CR^7R^{7'}$, W' is CR^8=$CR^{8'}$, Q_1 and Q_2 are hydrogen, A_1 and A_2 are CH, C-CH_3, C-CH_2-C_6H_5 or C-CH_2-CH_3, and Z_1 and Z_2 are O, then G-L is not unsubstituted phenyl, monosubstituted phenyl or methylpyridinyl;

(12) when Y' is $CR^7R^{7'}$—C=O, W' is NR^9—$CR^7R^{7'}$, Q_1 and Q_2 are hydrogen, A_1 and A_2 are CH, and Z_1 and Z_2 are O, then G-L is not unsubstituted phenyl;

(13) when Y' is $CHR^{7'}$—NR^7 where $R^{7'}$ is unsubstituted phenyl, methoxy or ethoxy and R^7 is unsubstituted phenyl, methyl or -C(O)-C_6H_5, W' is dimethoxyphenylene or unsubstituted phenylene, Z_1 and Z_2 are O, Q_1 and Q_2 are hydrogen, and A_1 and A_2 are CH, C-CN, C-C(O)-C_6H_5, or -C(O)-dimethoxyphenyl, then G-L is not unsubstituted phenyl;

(14) the compound of formula Ia is not 6,10-epithio-4H-thieno-[3',4':5,6]cyclooct[1,2-*f*]isoindole-7,9(5H,8H)-dione, 8-(3,5-dichlorophenyl)-6,6a,9a,10,11,12,-hexahydro-1,3,6,10-tetramethyl-2,2,13-trioxide, (6R,6aR,9aS,10S);

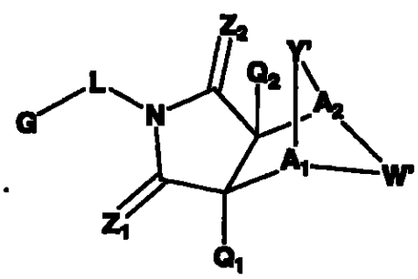
(15) when Y' is O, W' is –CH_2-CH_2-, Q_1 and Q_2 are methyl, Z_1 and Z_2 are O, and A_1 and A_2 are CH, then G-L is not unsubstituted phenyl, phenyl substituted with methoxy, phenyl-alkyl-, or morpholine-alkyl, nor is the compound bridged to itself through a group L which is alkylene to form a bis compound;

(16) when Y' is –O-, Q_1 and Q_2 are hydrogen, Z_1 and Z_2 are O, W' is $CR^7R^{7'}$-$CR^7R^{7'}$, and A_1 and A_2 are CH, then G-L is not an unsubstituted phenyl group; and

(17) when Y' is –O-, Q_1 and Q_2 are hydrogen, Z_1 and Z_2 are O, W' is cyclopentyl, cyclohexyl, 3-phenyl-2-isoxazoline or $CR^7R^{7'}$-$CR^7R^{7'}$ where R^7 and $R^{7'}$ are each independently defined as Cl, Br, H and 4-butyrolactone and R^7 and $R^{7'}$ are not all simultaneously H, and A_1 and A_2 are CH, then G-L is not an unsubstituted naphthyl ring or a monosubstituted phenyl ring, where said substituent is methoxy, Br, Cl, NO_2, methyl, ethyl, CH_2-phenyl, S-phenyl, or O-phenyl.

Preferably, compounds of formula I are monomeric, and are not comprised within other oligomers or polymers.

Another preferred novel subgenus is that of the following formula Ib:



Ib

where G, Z_1, Z_2, Q_1 and Q_2 are as defined above;

Y' is J-J'-J" where J is $(CR^7R^{7'})n$ and n = 0-3, J' is a bond or O, S, S=O, SO_2, NH, NR^7, $CR^7R^{7'}$, R^2P=O, R^2P=S, R^2OP=O, R^2NHP=O, OP=OOR^2, OP=$ONHR^2$, OSO_2, NHNH, $NHNR^6$, NR^6NH, N=N, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, or heterocyclo or substituted heterocyclo, and J" is $(CR^7R^{7'})n$ and n = 0-3, where Y' is not a bond; and

W' is $CR^7R^{7'}$—$CR^7R^{7'}$, $CR^7R^{7'}$—C=O, C=O—C=O, $CR^7R^{7'}$—C=CH_2, C=CH_2—C=CH_2, $CR^7R^{7'}$—C=NR^1, C=NR^1—C=NR^1, NR^9—$CR^7R^{7'}$, N=CR^8, N=N, NR^9—$NR^{9'}$, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, or aryl or substituted aryl, wherein when W' is not NR^9—$CR^7R^{7'}$, N=CR^8, N=N, NR^9—$NR^{9'}$, or

heterocyclo or substituted heterocyclo, then J' must be O, S, S=O, SO_2, NH, NR^7, $OP{=}OOR^2$, $OP{=}ONHR^2$, OSO_2, NHNH, $NHNR^6$, NR^6NH, or N=N; or when W' is $CR^7R^{7'}$—$CR^7R^{7'}$, the R^7 and $R^{7'}$ substituents in each occurrence may be taken together to form a substituted or unsubstituted carbocyclic or substituted or unsubstituted heterocyclic ring system which can be formed by any combination of R^7 and $R^{7'}$ attached to the same carbon atom; or alternatively, Y' is $CR^7R^{7'}$-C=O and W' is NR^9- $CR^7R^{7'}$;

L is a bond; and

A_1 and A_2 are as defined above, especially where A_1 and/or A_2 are alkyl or optionally substituted alkyl (preferred such optional substituents being one or more groups V^1 defined below), with the proviso that, when Y' = O and W' = $-CH_2-CH_2-$, then at least one of A_1 or A_2 is not CH;

with the further provisos (2), (3), (6), (7) and (8) above.

The compounds of formula I and salts thereof comprise a core which can serve as a steroid mimic (and do not require the presence of a steroid-type (e.g., cyclo-pentanoperhydrophenanthrene analog) structure).

Further Description of the Invention

The following are definitions of terms used in the present specification. The initial definition provided for a group or term herein applies to that group or term throughout the present specification individually or as part of another group, unless otherwise indicated.

The terms "alkyl" and "alk" refers to a straight or branched chain alkane (hydrocarbon) radical containing from 1 to 12 carbon atoms, preferably 1 to 6 carbon atoms. Exemplary such groups include, but are not limited to, methyl, ethyl, propyl, isopropyl, n-butyl, t-butyl, isobutyl, pentyl, hexyl, isohexyl, heptyl, 4,4-dimethylpentyl, octyl, 2,2,4-trimethylpentyl, nonyl, decyl, undecyl, dodecyl, and the like. "Substituted alkyl" refers to an alkyl group substituted with one or more substituents, preferably 1 to 4 substituents, at any available point of attachment. Exemplary substituents include but are not limited to one or more of the following groups: halo (e.g., a single halo substituent or multiple halo substitutents forming, in

the latter case, groups such as a perfluoroalkyl group or an alkyl group bearing Cl_3 or CF_3), alkoxy, alkylthio, hydroxy, carboxy (i.e., -COOH), alkoxycarbonyl, alkylcarbonyloxy, amino (i.e., $-NH_2$), carbamoyl or substituted carbomoyl, carbamate or substituted carbamate, urea or substituted urea, amidinyl or substituted amidinyl, thiol (i.e., -SH), aryl, heterocycle, cycloalkyl, heterocycloalkyl, -S-aryl, -S-heterocycle, -S=O-aryl, -S=O-heterocycle, arylalkyl-O-, $-S(O)_2$-aryl, $-S(O)_2$-heterocycle, $-NHS(O)_2$-aryl, $-NHS(O)_2$-heterocycle, $-NHS(O)_2NH$-aryl, $-NHS(O)_2NH$-heterocycle, $-P(O)_2$-aryl, $-P(O)_2$-heterocycle, $-NHP(O)_2$-aryl, $-NHP(O)_2$-heterocycle, $-NHP(O)_2NH$-aryl, $-NHP(O)_2NH$-heterocycle, -O-aryl, -O-heterocycle, -NH-aryl, -NH-heterocycle, -NHC=O-aryl, -NHC=O-alkyl, -NHC=O-heterocycle, -OC=O-aryl, -OC=O-heterocycle, -NHC=ONH-aryl, -NHC=ONH-heterocycle, -OC=OO-aryl, -OC=OO-heterocycle, -OC=ONH-aryl, -OC=ONH-heterocycle, -NHC=OO-aryl, -NHC=OO-heterocycle, -NHC=OO-alkyl, -C=ONH-aryl, -C=ONH-heterocycle, -C=OO-aryl, -C=OO-heterocycle, $-N(alkyl)S(O)_2$-aryl, $-N(alkyl)S(O)_2$-heterocycle, $-N(alkyl)S(O)_2NH$-aryl, $-N(alkyl)S(O)_2NH$-heterocycle, $-N(alkyl)P(O)_2$-aryl, $-N(alkyl)P(O)_2$-heterocycle, $-N(alkyl)P(O)_2NH$-aryl, $-N(alkyl)P(O)_2NH$-heterocycle, -N(alkyl)-aryl, -N(alkyl)-heterocycle, -N(alkyl)C=O-aryl, -N(alkyl)C=O-heterocycle, -N(alkyl)C=ONH-aryl, -N(alkyl)C=ONH-heterocycle, -OC=ON(alkyl)-aryl, -OC=ON(alkyl)-heterocycle, -N(alkyl)C=OO-aryl, -N(alkyl)C=OO-heterocycle, -C=ON(alkyl)-aryl, -C=ON(alkyl)-heterocycle, $-NHS(O)_2N(alkyl)$-aryl, $-NHS(O)_2N(alkyl)$-heterocycle, $-NHP(O)_2N(alkyl)$-aryl, $NHP(O)_2N(alkyl)$-heterocycle, -NHC=ON(alkyl)-aryl, -NHC=ON(alkyl)-heterocycle, $-N(alkyl)S(O)_2N(alkyl)$-aryl, $-N(alkyl)S(O)_2N(alkyl)$-heterocycle, $-N(alkyl)P(O)_2N(alkyl)$-aryl, $-N(alkyl)P(O)_2N(alkyl)$-heterocycle, -N(alkyl)C=ON(alkyl)-aryl, and -N(alkyl)C=ON(alkyl)-heterocycle. In the aforementioned exemplary substitutents, in each instance, groups such as "alkyl", "aryl" and "heterocycle" can themselves be optionally substituted; for example, "alkyl" in the group "NCH=OO-alkyl" recited above can be optionally substituted so that both "NHC=OO-alkyl" and "NHC=OO-substituted alkyl" are exemplary substitutents. Exemplary alkyl substituents also

include groups such as "T" and "T-R^{12}" (which are defined below), especially for substituted alkyl groups within A_1 or A_2.

The term "alkenyl" refers to a straight or branched chain hydrocarbon radical containing from 2 to 12 carbon atoms and at least one carbon-carbon double bond. Exemplary such groups include ethenyl or allyl. "Substituted alkenyl" refers to an alkenyl group substituted with one or more substituents, preferably 1 to 4 substituents, at any available point of attachment. Exemplary substituents include, but are not limited to, alkyl or substituted alkyl, as well as those groups recited above as exemplary alkyl substituents.

The term "alkynyl" refers to a straight or branched chain hydrocarbon radical containing from 2 to 12 carbon atoms and at least one carbon to carbon triple bond. Exemplary such groups include ethynyl. "Substituted alkynyl" refers to an alkynyl group substituted with one or more substituents, preferably 1 to 4 substituents, at any available point of attachment. Exemplary substituents include, but are not limited to, alkyl or substituted alkyl, as well as those groups recited above as exemplary alkyl substituents.

The term "cycloalkyl" refers to a fully saturated cyclic hydrocarbon group containing from 1 to 4 rings and 3 to 8 carbons per ring. Exemplary such groups include cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, etc. "Substituted cycloalkyl" refers to a cycloalkyl group substituted with one or more substituents, preferably 1 to 4 substituents, at any available point of attachment. Exemplary substituents include, but are not limited to, nitro, cyano, alkyl or substituted alkyl, as well as those groups recited above as exemplary alkyl substituents, and as previously mentioned as preferred aryl substituents in the definition for G. Exemplary substituents also include spiro-attached or fused cyclic substituents, especially cycloalkenyl or substituted cycloalkenyl.

The term "cycloalkenyl" refers to a partially unsaturated cyclic hydrocarbon group containing 1 to 4 rings and 3 to 8 carbons per ring. Exemplary such groups include cyclobutenyl, cyclopentenyl, cyclohexenyl, etc. "Substituted cycloalkenyl" refers to a cycloalkenyl group substituted with one more substituents, preferably 1 to 4 substituents, at any available point of attachment. Exemplary substituents include but are not limited to nitro, cyano, alkyl or substituted alkyl, as well as those groups

recited above as exemplary alkyl substituents, and as previously mentioned as preferred aryl substituents in the definition for G. Exemplary substituents also include spiro-attached or fused cyclic substituents, especially cycloalkyl or substituted cycloalkyl.

The terms "alkoxy" or "alkylthio" refer to an alkyl group as described above bonded through an oxygen linkage (-O-) or a sulfur linkage (-S-), respectively. The terms "substituted alkoxy" or "substituted alkylthio" refer to a substituted alkyl group as described above bonded through an oxygen or sulfur linkage, respectively.

The term "alkoxycarbonyl" refers to an alkoxy group bonded through a carbonyl group.

The term "alkylcarbonyl" refers to an alkyl group bonded through a carbonyl group. The term "alkylcarbonyloxy" refers to an alkylcarbonyl group bonded through an oxygen linkage.

The terms "arylalkyl", "substituted arylalkyl," "cycloalkylalkyl," "substituted cycloalkylalkyl," "cycloalkenylalkyl", "substituted cycloalkenylalkyl", "heterocycloalkyl" and "substituted heterocycloalkyl" refer to aryl, cycloalkyl, cycloalkenyl and heterocyclo groups bonded through an alkyl group, substituted on the aryl, cycloalkyl, cycloalkenyl or heterocyclo and/or the alkyl group where indicated as "substituted."

The term "aryl" refers to cyclic, aromatic hydrocarbon groups which have 1 to 5 aromatic rings, especially monocyclic or bicyclic groups such as phenyl, biphenyl or naphthyl. Where containing two or more aromatic rings (bicyclic, etc.), the aromatic rings of the aryl group may be joined at a single point (e.g., biphenyl), or fused (e.g., naphthyl, phenanthrenyl and the like). "Substituted aryl" refers to an aryl group substituted by one or more substituents, preferably 1,2,3,4 or 5 substituents, at any point of attachment. Exemplary substituents include, but are not limited to, nitro, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, cyano, alkyl-$S(O)_m$- (m=0, 1 or 2), alkyl or substituted alkyl, as well as those groups recited above as exemplary alkyl substituents and as previously mentioned as preferred aryl substituents in the definition for G. Exemplary substituents also include fused cyclic substituents, such as heterocyclo or cycloalkenyl, or substituted heterocyclo or

cycloalkenyl, groups (e.g., thereby forming a fluoroenyl, tetrahydronapthalenyl, or dihydroindenyl group).

"Carbamoyl" refers to the group –CONH- which is bonded on one end to the remainder of the molecule and on the other to hydrogen or an organic moiety (such as alkyl, substituted alkyl, aryl, substituted aryl, heterocycle, alkylcarbonyl, hydroxyl and substituted nitrogen). "Carbamate" refers to the group –O-CO-NH- which is bonded on one end to the remainder of the molecule and on the other to hydrogen or an organic moiety (such as those listed above). "Urea" refers to the group -NH-CO-NH- which is bonded on one end to the remainder of the molecule and on the other to hydrogen or an organic moiety (such as those listed above). "Amidinyl" refers to the group –C(=NH)(NH_2). "Substituted carbamoyl," "substituted carbamate," "substituted urea" and "substituted amidinyl" refer to carbamoyl, carbamate, urea or amidinyl groups as described above in which one more of the hydrogen groups are replaced by an organic moiety (such as those listed above).

The terms "heterocycle", heterocyclic" and "heterocyclo" refer to fully saturated, or partially or fully unsaturated, including aromatic (i.e., "heteroaryl") cyclic groups (for example, 3 to 7 membered monocyclic, 7 to 11 membered bicyclic, or 10 to 16 membered tricyclic ring systems) which have at least one heteroatom in at least one carbon atom-containing ring. Each ring of the heterocyclic group containing a heteroatom may have 1, 2, 3, or 4 heteroatoms selected from nitrogen atoms, oxygen atoms and/or sulfur atoms, where the nitrogen and sulfur heteroatoms may optionally be oxidized and the nitrogen heteroatoms may optionally be quaternized. (The term "heteroarylium" refers to a heteroaryl group bearing a quaternary nitrogen atom and thus a positive charge.) The heterocyclic group may be attached to the remainder of the molecule at any heteroatom or carbon atom of the ring or ring system. It is understood that, where W or W' are cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, or aryl or substituted aryl, that A1 and A2 can be separately bonded to different (such as adjacent) ring atoms on said groups. Exemplary monocyclic heterocyclic groups include ethylene oxide, azetidinyl, pyrrolidinyl, pyrrolyl, pyrazolyl, oxetanyl, pyrazolinyl, imidazolyl, imidazolinyl, imidazolidinyl, oxazolyl, oxazolidinyl, isoxazolinyl, isoxazolyl, thiazolyl, thiadiazolyl, thiazolidinyl, isothiazolyl,

isothiazolidinyl, furyl, tetrahydrofuryl, thienyl, oxadiazolyl, piperidinyl, piperazinyl, 2-oxopiperazinyl, 2-oxopiperidinyl, 2-oxopyrrolodinyl, 2-oxoazepinyl, azepinyl, hexahydrodiazepinyl, 4-piperidonyl, pyridyl, pyrazinyl, pyrimidinyl, pyridazinyl, triazinyl, triazolyl, tetrazolyl, tetrahydropyranyl, morpholinyl, thiamorpholinyl, thiamorpholinyl sulfoxide, thiamorpholinyl sulfone, 1,3-dioxolane and tetrahydro-1,1-dioxothienyl, and the like. Exemplary bicyclic heterocyclic groups include indolyl, isoindolyl, benzothiazolyl, benzodioxolyl, benzoxazolyl, benzoxadiazolyl, benzothienyl, quinuclidinyl, quinolinyl, tetrahydroisoquinolinyl, isoquinolinyl, benzimidazolyl, benzopyranyl, indolizinyl, benzofuryl, benzofurazanyl, chromonyl, coumarinyl, benzopyranyl, cinnolinyl, quinoxalinyl, indazolyl, pyrrolopyridyl, furopyridinyl (such as furo[2,3-c]pyridinyl, furo[3,2-b]pyridinyl] or furo[2,3-b]pyridinyl), dihydrobenzodioxinyl, dihydrodioxidobenzothiophenyl, dihydroisoindolyl, dihydroindolyl, dihydroquinolinyl, dihydroquinazolinyl (such as 3,4-dihydro-4-oxo-quinazolinyl), triazinylazepinyl, tetrahydroquinolinyl and the like. Exemplary tricyclic heterocyclic groups include carbazolyl, benzidolyl, phenanthrolinyl, dibenzofuranyl, acridinyl, phenanthridinyl, xanthenyl and the like.

"Substituted heterocycle," "substituted heterocyclic," and "substituted heterocyclo" (such as "substituted heteroaryl") refer to heterocycle, heterocyclic or heterocyclo groups substituted with one or more substituents, preferably 1 to 4 substituents, at any available point of attachment. Exemplary substituents include, but are not limited to, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, nitro, oxo (i.e., = O), cyano, alkyl-$S(O)_m$- (m = 0, 1 or 2), alkyl or substituted alkyl, as well as those groups recited above as exemplary alkyl substituents, and as previously mentioned as preferred heterocyclo substituents in the definition for G.

The term "quaternary nitrogen" refers to a tetravalent positively charged nitrogen atom including, for example, the positively charged nitrogen in a tetraalkylammonium group (e.g., tetramethylammonium, N-methylpyridinium), the positively charged nitrogen in protonated ammonium species (e.g., trimethyl-hydroammonium, N-hydropyridinium), the positively charged nitrogen in amine N-oxides (e.g., N-methyl-morpholine-N-oxide, pyridine-N-oxide), and the positively charged nitrogen in an N-amino-ammonium group (e.g., N-aminopyridinium).

The terms "halogen" or "halo" refer to chlorine, bromine, fluorine or iodine.

The terms "hydroxylamine" and "hydroxylamide" refer to the groups OH-NH- and OH-NH-CO-, respectively.

When a functional group is termed "protected", this means that the group is in modified form to mitigate, especially preclude, undesired side reactions at the protected site. Suitable protecting groups for the methods and compounds described herein include, without limitation, those described in standard textbooks, such as Greene, T. W. et al., *Protective Groups in Organic Synthesis*, Wiley, N.Y. (1991).

When a term such as "(CRR)n" is used, it denotes an optionally substituted alkyl chain existing between the two fragments to which it is bonded, the length of which chain is defined by the range described for the term n. An example of this is n=0-3, implying from zero to three (CRR) units existing between the two fragments, which are attached to the primary and terminal (CRR) units. In the situation where the term n is set to zero (n = 0) then a bond exists between the two fragments attached to (CRR).

Unless otherwise indicated, any heteroatom with unsatisfied valences is assumed to have hydrogen atoms sufficient to satisfy the valences.

Divalent groups, such as those in the definition of W (e.g., NR^9-$CR^7R^{7'}$), may be bonded in either direction to the remainder of the molecule (e.g, -A_1-NR^9-$CR^7R^{7'}$-A_2- or, -A_1-$CR^7R^{7'}$-NR^9-A_2- for the aforementioned group within the definition of W).

Carboxylate anion refers to a negatively charged group -COO^-.

The compounds of formula I form salts which are also within the scope of this invention. Reference to a compound of the formula I herein is understood to include reference to salts thereof, unless otherwise indicated. The term "salt(s)", as employed herein, denotes acidic and/or basic salts formed with inorganic and/or organic acids and bases. In addition, when a compound of formula I contains both a basic moiety, such as but not limited to a pyridine or imidazole, and an acidic moiety such as but not limited to a carboxylic acid, zwitterions ("inner salts") may be formed and are included within the term "salt(s)" as used herein. Pharmaceutically acceptable (i.e., non-toxic, physiologically acceptable) salts are preferred, although other salts are also

useful, e.g., in isolation or purification steps which may be employed during preparation. Salts of the compounds of the formula I may be formed, for example, by reacting a compound I with an amount of acid or base, such as an equivalent amount, in a medium such as one in which the salt precipitates or in an aqueous medium followed by lyophilization.

The compounds of formula I which contain a basic moiety, such as but not limited to an amine or a pyridine or imidazole ring, may form salts with a variety of organic and inorganic acids. Exemplary acid addition salts include acetates (such as those formed with acetic acid or trihaloacetic acid, for example, trifluoroacetic acid), adipates, alginates, ascorbates, aspartates, benzoates, benzenesulfonates, bisulfates, borates, butyrates, citrates, camphorates, camphorsulfonates, cyclopentanepropionates, digluconates, dodecylsulfates, ethanesulfonates, fumarates, glucoheptanoates, glycerophosphates, hemisulfates, heptanoates, hexanoates, hydrochlorides, hydrobromides, hydroiodides, hydroxyethanesulfonates (e.g., 2-hydroxyethanesulfonates), lactates, maleates, methanesulfonates, naphthalenesulfonates (e.g., 2-naphthalenesulfonates), nicotinates, nitrates, oxalates, pectinates, persulfates, phenylpropionates (e.g., 3-phenylpropionates), phosphates, picrates, pivalates, propionates, salicylates, succinates, sulfates (such as those formed with sulfuric acid), sulfonates (such as those mentioned herein), tartrates, thiocyanates, toluenesulfonates such as tosylates, undecanoates, and the like.

The compounds of formula I which contain an acidic moiety, such but not limited to a carboxylic acid, may form salts with a variety of organic and inorganic bases. Exemplary basic salts include ammonium salts, alkali metal salts such as sodium, lithium and potassium salts, alkaline earth metal salts such as calcium and magnesium salts, salts with organic bases (for example, organic amines) such as benzathines, dicyclohexylamines, hydrabamines (formed with N,N-bis(dehydroabietyl)ethylenediamine), N-methyl-D-glucamines, N-methyl-D-glycamides, t-butyl amines, and salts with amino acids such as arginine, lysine and the like. Basic nitrogen-containing groups may be quaternized with agents such as lower alkyl halides (e.g. methyl, ethyl, propyl, and butyl chlorides, bromides and iodides), dialkyl sulfates (e.g. dimethyl, diethyl, dibutyl, and diamyl sulfates), long chain

halides (e.g. decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides), aralkyl halides (e.g. benzyl and phenethyl bromides), and others.

Prodrugs and solvates of the compounds of the invention are also contemplated herein. The term "prodrug" as employed herein denotes a compound which, upon administration to a subject, undergoes chemical conversion by metabolic or chemical processes to yield a compound of the formula I, or a salt and/or solvate thereof. Solvates of the compounds of formula I include, for example, hydrates.

Compounds of the formula I, and salts thereof, may exist in their tautomeric form (for example, as an amide or imino ether). All such tautomeric forms are contemplated herein as part of the present invention.

All stereoisomers of the present compounds (for example, those which may exist due to asymmetric carbons on various substituents), including enantiomeric forms and diastereomeric forms, are contemplated within the scope of this invention. Individual stereoisomers of the compounds of the invention may, for example, be substantially free of other isomers (e.g., as a pure or substantially pure optical isomer having a specified activity), or may be admixed, for example, as racemates or with all other, or other selected, stereoisomers. The chiral centers of the present invention may have the S or R configuration as defined by the IUPAC 1974 Recommendations. The racemic forms can be resolved by physical methods, such as, for example, fractional crystallization, separation or crystallization of diastereomeric derivatives or separation by chiral column chromatography. The individual optical isomers can be obtained from the racemates by any suitable method, including without limitation, conventional methods, such as, for example, salt formation with an optically active acid followed by crystallization.

All configurational isomers of the compounds of the present invention are contemplated, either in admixture or in pure or substantially pure form. The definition of compounds of the present invention embraces both cis (*Z*) and trans (*E*) alkene isomers, as well as cis and trans isomers of cyclic hydrocarbon or heterocyclo rings. In certain cases, for example, the exo or endo conformation can be preferred for the fused ring system bonded to G-L in formula I. For example, for androgen receptor antagonists (or selective androgen receptor modulators), where Y is O or NR^7, the exo configuration can be preferred, while for most other definitions of Y, the

endo configuration can be preferred. As can be appreciated, the preferred configuration can be a function of the particular compound and its preferred activity. Separation of configurational isomers can be achieved by any suitable method, such as column chromatography.

Throughout the specifications, groups and substituents thereof may be chosen to provide stable moieties and compounds.

Embodiments indicated herein as exemplary or preferred are intended to be illustrative and not limiting.

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Methods of Preparation

The compounds of the present invention may be prepared by methods such as those illustrated in the following Schemes I to XI. Solvents, temperatures, pressures, and other reaction conditions may readily be selected by one of ordinary skill in the art. Starting materials are commercially available or readily prepared by one of ordinary skill in the art. Combinatorial techniques may be employed in the preparation of compounds, for example, where the intermediates possess groups suitable for these techniques. See the following which describe other methods which may be employed in the preparation of compounds of the present invention: Li, *et al.*, *Eur. J. Org. Chem.* **9**, 1841-1850 (1998); Li, Y-Q, *Synlett.* **5**, 461-464 (1996); Thiemann, *et al.*, *Bull. Chem. Soc. Jpn.* **67**, 1886-1893 (1994); Tsuge *et al.*, *Heterocycles* **14**, 423-428 (1980); Ward *et al.*, *Can J. Chem.* **75**, 681-693 (1997); Ward *et al.*, *Can J. Chem.* **69**, 1487-1497 (1991); Ward *et al.*, *Tetrahedron Lett.* **31**, 845-848 (1990); Fleming *et al.*, *J. Org. Chem.* **44**, 2280-2282 (1979); Jankowski *et al.*, *J. Organomet. Chem.* **595**, 109-113 (2000); Keglevich *et al.*, *J. Organomet. Chem.* **579**, 182-189 (1999); Keglevich *et al.*, *J. Organomet. Chem.* **570**, 49-539 (1998); Jankowski *et al.*, *Hetroat. Chem.* **7**, 369-374 (1996); Jankowski *et al.*, *J. Am. Chem. Soc.* **113**, 7011-7017 (1991); Quin *et al.*, *Tetrahedron Lett.* **31**, 6473-6476 (1990); Quin *et al.*, *J. Org. Chem.* **59**, 120-129 (1994); Quin *et al.*, *J. Org. Chem.* **58**, 6212-6216 (1993); Quin *et al.*, *Phosphorous, Sulfur Silicon Relat. Elem.* **63**, 349-362 (1991); Quin *et al.*, *Hetroat. Chem.* **2**, 359-367 (1991); Hussong *et al.*, *Phosphorus Sulfur.* **25**, 201-212 (1985); Quin *et al.*, *J. Org. Chem.* **51**, 3341-3347 (1986); Myers *et al.*, *J. Am. Chem. Soc.* **114**, 5684-5692 (1992); Myers *et al.*, *J. Am. Chem. Soc.* **113**, 6682-6683 (1991); Shen *et al.*, US Patent No. 5817679; Cordone *et al.*, *J. Am. Chem. Soc.* **111**, 5969-5970 (1989); Jung *et al.*, *J. Chem. Soc. Commun.* 630-632 (1984); Lay *et al.*, *J. Am. Chem. Soc.* **104**, 7658-7659 (1982); Gonzalez *et al.*, *J. Am. Chem. Soc.* **117**, 3405-3421 (1995); Kreher *et al.*, *Chem Ber.* **125**, 183-189 (1992); Simig *et al.*, *Synlett.* **7**, 425-426 (1990); Sha *et al.*, *J. Org. Chem.* **55**, 2446-2450 (1990); Drew *et al.*, *J. Chem. Soc., Perkin Trans. 1* **7**, 1277-1284 (1985); Kreher *et al.*, *Anorg. Chem., Org Chem.* **31B**, 599-604 (1976); Avalos *et al.*, *Tetrahedron Lett.* **39**, 9301-9304 (1998); Gousse *et al.*, *Macromolecules* **31**, 314-321 (1998); Mikhailyuchenko *et*

al., Khim. Geterotsikl. Soedin. 6, 751-758 (1993); Lubowitz *et al.*, US Patent No. 4476184; Padwa *et al., J. Org. Chem.* 61, 3706-3714 (1996); Schlessinger *et al., J. Org. Chem.* 59, 3246-3247 (1994); Buchmeiser *et al.*, WO Publication No. 9827423; Tanabe *et al.*, Japanese Patent Document JP 07144477; Mochizucki *et al.*, Japanese Patent Document JP 63170383; Hosoda *et al.*, Japanese Patent Document JP 62053963; Onaka *et al.*, Japanese Patent Document JP 62053964; Kato *et al.*, Japanese Patent Document JP 53086035; Kato *et al.*, Japanese Patent Document JP 51088631; Tottori *et al.*, Japanese Patent Document JP 49124225; Augustin *et al.*, German Patent Document DD101271; Title *et al.*, French Patent Document FR 2031538; Gousse *et al., Polym. Int.* 48, 723-731 (1999); Padwa *et al., J. Org. Chem.* 62, 4088-4096 (1997); Theurillat-Moritz *et al., Tetrahedron: Asymmetry* 7, 3163-3168 (1996); Mathews *et al., J. Carbohydr. Chem.* 14, 287-97 (1995); Srivastava *et al., Natl. Acad. Sci. Lett. (India)* 15, 41-44 (1992); Mayorga *et al., Rev. Cubana Quim.* 4, 1-6 (1988); Kondoli *et al., J. Chem. Res., Synop.* 3, 76 (1987); Primelles *et al., Cent. Azucar* 7-14 (1985); Solov'eva *et al., Khim. Geterotsikl. Soedin.* 5, 613-15 (1984); Liu *et al., Yaoxue Xuebao* 18, 752-759 (1983); Joshi *et al., Indian J. Chem, Sect. B.* 22B, 131-135 (1983); Amos *et al.*, WO Publication No. 9829495; Odagiri *et al.*, US Patent No. 4670536; Gallucci *et al.*, European Patent Document EP 355435; Redmore, D. US Patent No. 3821232; Nakano *et al., Heterocycles* 35, 37-40 (1993); Tomisawa *et al., Chem. Pharm. Bull.* 36, 1692-1697 (1988); Krow *et al., J. Heterocycl. Chem.* 22, 131-135 (1985); Krow *et al., J. Org. Chem.* 47, 1989-1993 (1982); Liu *et al., Yaoxue Xuebao* 18, 752-759 (1983); Nishikawa *et al., Yaoxue Xuebao* JP 01061457; and/or Rice *et al., J. Med. Chem.* 11, 183-185 (1968).

All documents cited in the present specification, such as those cited in this "Methods of Preparation" as well as other sections herein, are incorporated herein by reference in their entirety. Reference to any document herein is not to be construed as an admission that such document is prior art.

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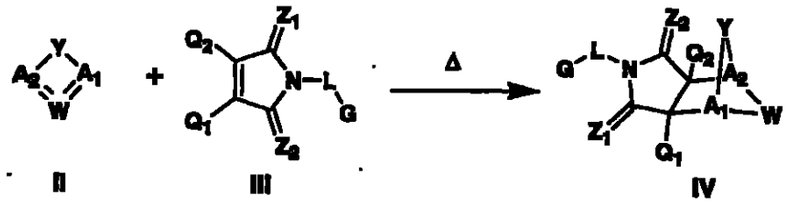
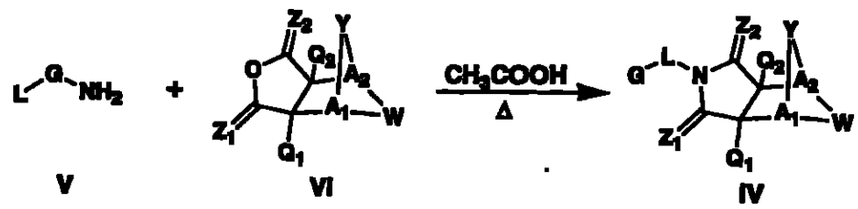
Scheme I



As illustrated in Scheme I, a diene of formula II can be reacted with a dienophile of formula III, under conditions readily selected by one skilled in the art (such as by the addition of heat ("Δ")), to obtain a compound of formula IV, which is a compound of formula I. An intermediate diene of formula II can be obtained from commercial sources or readily made by one skilled in the art, for example, in accordance with the following literature documents and the references found therein: Hofman *et al., J. Agric. Food Chem.* **45**, 898-906 (1997); Baciocchi *et al., J. Chem. Soc., Perkin Trans. 2* **8**, 821-824 (1975); Wu *et al., J. Heterocycles* **38**, 1507-1518 (1994); Yin *et al., Tetrahedron Lett.* **38**, 5953-5954 (1997); Mic'ovic' *et al.,Tetrahedron* **20**, 2279-2287 (1964); Gorbunova *et al., J. Org. Chem.*. **35**, 1557-1566 (1999); Rassu *et al., Chem. Soc. Rev.* **29**, 109-118 (2000); Kaberdin *et al., Russ. Chem . Rev..* **68**, 765-779 (1999); Barluenga *et al., Aldrichimica Acta* **32**, 4-15 (1999); Bogdanowicz-Szwed *et al., Pol. Wiad. Chem.* **52**, 821-842 (1998); Casiraghi *et al., Adv. Asymmetric Synth.* **3**, 113-189 (1998); and/or Baeckvall *et al., Chem. Rev.* **98**, 2291-2312 (1998). An intermediate dieneophile of formula III can be obtained from commercial sources or readily made by one skilled in the art, for example, in accordance with the following literature references and the references found therein: Deshpande *et al., Heterocycles* **51**, 2159-2162 (1999); Seijas *et al., J. Chem. Res., Synop.* **7**, 420-421 (1999); Langer *et al., Eur. J. Org. Chem.* **7**, 1467-1470 (1998); Kita *et al.*, Japanese Patent Document JP 09194458; Lopez-Alvarado *et al., J. Org. Chem.* **61**, 5865-5870 (1996); Condon *et al.*, US Patent No. 5523277; Sasakihara *et al.*, Japanese Patent Document JP 04290868; Igarashi *et al.*, Japanese Patent Document JP 04149173; Aoyama *et al.*, Japanese Patent Document JP 04134063; Aoyama *et al.*, Japanese Patent Document JP 04134062; Pastor *et al., J. Org. Chem.* **53**, 5776-5779 (1988); and/or Takahashi *et al., Chem. Lett.* **6**, 1229-1232 (1987).

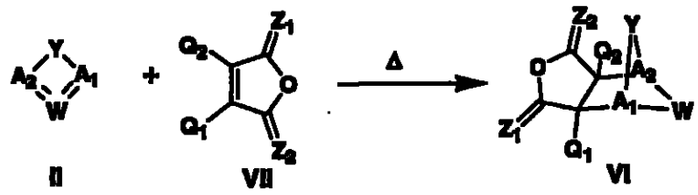
Scheme II



As illustrated in Scheme II, compounds of formula I can be obtained by reaction of a primary amine of formula V with a substituted anhydride-like intermediate of formula VI, for example, in a solvent such as acetic acid with or without heating, to yield a compound of formula IV, which is a compound of formula I. Primary amines of formula V can be obtained from commercial sources or readily synthesized by one skilled in the art. Anhydride-like agents of formula VI can be obtained from commercial sources or readily synthesized by one skilled in the art. The documents listed following describe exemplary approaches for the synthesis of intermediates of formula VI as well as synthetic approaches which can be applied to the synthesis of compounds of formula IV (all incorporated herein by reference in their entirety): Kohler, E. P.; Tishler, M.; Potter, H.; Thompson, H. T. *J. Am. Chem. Soc.* 1939, 1057-1061; Yur'ev, Y. K.; Zefirov, N. S. *J. Gen. Chem. U.S.S.R. (Engl. Transl.)* 1961, 31, 772-5; Norman G. Gaylord US Patent No. 3,995,099; Schueler, P. E.; Rhodes, Y. E. *J. Org. Chem.* 1974, 39, 2063-9; Ishitobi, H.; Tanida, H; Tsuji, T. *Bull. Chem. Soc. Japan* 1971, 44, 2993-3000; Stájer, G.; Virág, M.; Szabó, A. E.; Bernáth, G.; Sohár, P.; Sillanpää, R. *Acta. Chem. Scand.* 1996, 50, 922-30; Hart, H.; Ghosh, T. *Tetrahedron Lett.* 1988,29,881-884; Kato, M.; Yamamoto, S.; Yoshihara, T.; Furuichi, K; Miwa, T. *Chem. Lett.* 1987, 1823-1826; Kottwitz, J.; Vorbrüggen, H. *Synthesis* 1995, 636-637; Creary, X. *J. Org. Chem.* 1975, 40, 3326-3331; Alder, K.; Ache, H.-J.; Flock, F. H. *Chem. Ber.* 1960, 93, 1888-1895; Toder, B. H.; Branca, S. J.; Dieter, R. K.; Smith, A. B. III *Synth. Commun.* 1975, 5, 435-439; Sprague, P. W.; Heikes, J. E.; Gougoutas, J. Z.; Malley, M. F.; Harris, D. N.; and/or Greenberg, R. *J. Med. Chem.* 1985, 28, 1580-1590.

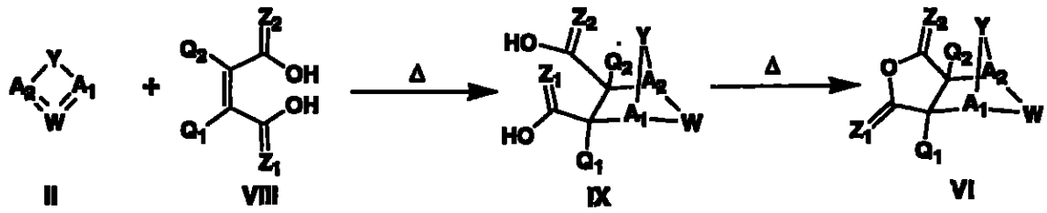
The aforementioned approach(es) can be applied in a combinatorial fashion, for example, by utilizing a multi-well reaction block such as is described in Waldemar Ruediger, Wen-Jeng Li, John W., Allen Jr., and Harold N. Weller III, US Patent No. 5,961,925, Apparatus for Synthesis of Multiple Organic Compounds With Pinch Valve Block (incorporated herein by reference in its entirety). By utilizing the above-mentioned multi-well reaction block, one can, for example, perform multiples of 96 reactions at a time. Solvent can then be removed from the reaction tubes without removal from the reaction block and the crude products can be precipitated using a base such as sodium bicarbonate. The precipitates can be collected by filtration of the reaction block and then the desired products can be transferred directly to 96 well plates for screening. In this fashion, a large array of compounds of formula I can be synthesized, and tests conducted as desired by an automated approach.

Scheme III



Scheme III describes a method for preparing an intermediate compound of formula VI which can be used to synthesize a compound of formula I, as described in Scheme II. As described in Scheme III, a diene of formula II can be reacted with a dieneophile of formula VII to yield the intermediate of formula VI. The methods applied to obtain such a transformation are analogous to those described in Scheme I.

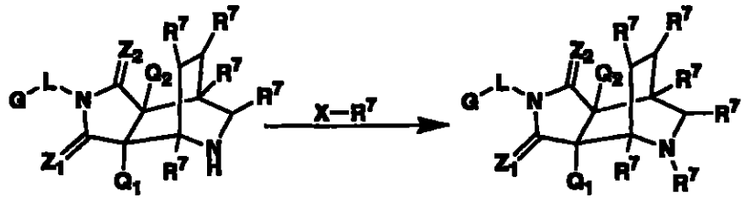
Scheme IV



Scheme IV describes a method for preparing an intermediate compound of formula VI which can be used to synthesize a compound of formula I, as described in Scheme II. As shown in Scheme IV, a diene of formula II can be reacted with a dieneophile of formula VIII to yield the intermediate of formula IX. The intermediate of formula IX can be dehydrated to an anhydride-like intermediate of formula VI. Dehydration of the bis-acid intermediate of formula IX to can be achieved by a variety of methods, such as those known to one skilled in the art and described in the following documents and the references embodied therein: Sprague *et al., J. Med. Chem.* **28**, 1580-1590 (1985); and/or Retemi *et al., J. Org. Chem.* **61**, 6296-6301 (1996).

Schemes I to IV describe general methods for the synthesis of compounds of formula I, and intermediates thereof, in which substitution about the ring system is incorporated directly, for example, at the level of the intermediate diene, dienophile, anhydride-like intermediate and amine groups. In addition to these approaches, additional substitution can be incorporated onto an already-prepared compound of formula I by a variety of approaches to prepare other compounds of the formula I. Exemplary methods for further substitution are described in Schemes V to XI.

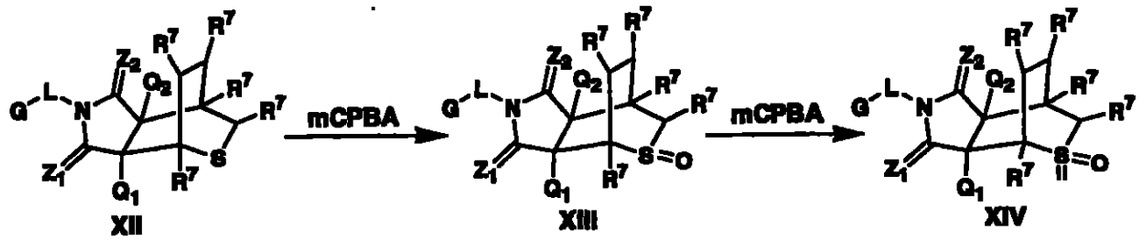
Scheme V



X XI

Scheme V describes one such approach to incorporating additional substitution into a structure of formula I. As illustrated in Scheme V, a compound of formula X, which is a compound of formula I where A_1 and A_2 are CR^7, W is NH—CHR^7 and Y is CHR^7—CHR^7, can be functionalized at the free amine of the group W by reaction with any of a variety of electrophilic agents such as acid halides or alkyl halides in the presence of base, for example, by methods known by one skilled in the art. In Scheme V, X is a leaving group, and a compound of formula XI is a compound of formula I where A_1 and A_2 are CR^7, W is NR^7—CHR^7 and Y is CHR^7—CHR^7.

Scheme VI



Scheme VI describes an additional approach for further incorporating substitution onto a compound of formula I. As illustrated in Scheme VI, a compound of formula XII, which is a compound of formula I where A_1 and A_2 are CR^7, W is S—CHR^7 and Y is CHR^7—CHR^7, can be partially oxidized with an oxidizing agent such as mCPBA or other agents such as those known to one skilled in the art, to give the sulfoxide analog of formula XIII, which is a compound of formula I where A_1 and A_2 are CR^7, W is SO—CHR^7 and Y is CHR^7—CHR^7. Further treatment of a compound of formula XIII with an oxidizing agent such as mCPBA or other agents such as those known to one skilled in the art, can yield the sulphone analog of formula XIV, which is a compound of formula I where A_1 and A_2 are CR^7, W is SO_2—CHR^7 and Y is CHR^7—CHR^7. Alternatively, a compound of formula XII can be converted directly to a compound of formula XIV by prolonged treatment with an oxidizing agent, such as mCPBA, or with other agents such as those known to one skilled in the art.

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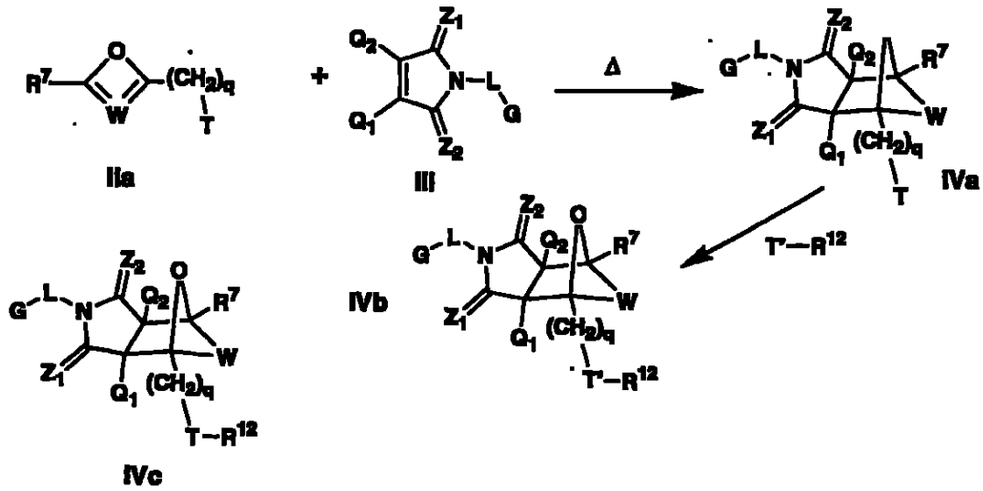
Scheme VII

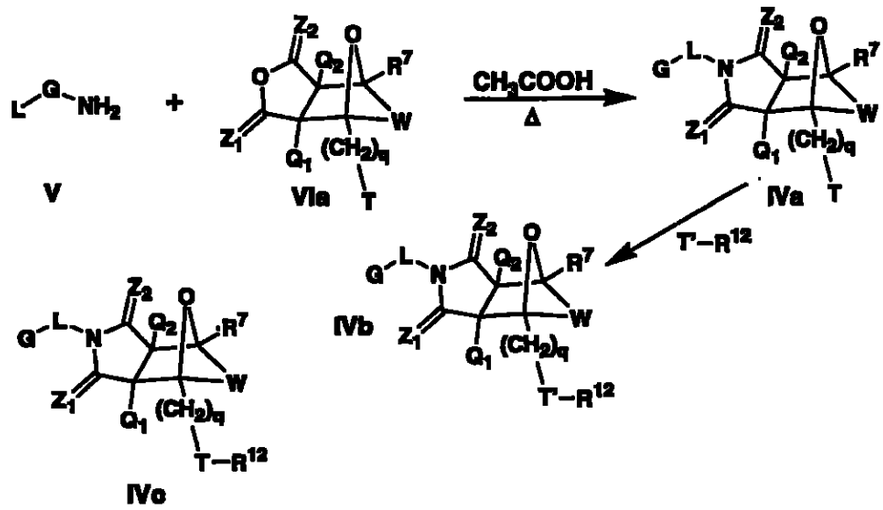


Scheme VII describes another approach to incorporating additional substitution onto a compound of formula I. As illustrated in Scheme VII, a diene of formula IIa can be reacted with a dienophile of formula III, as described in Scheme I, to yield a compound of formula IVa, which is a compound of formula I where Y is O, A_2 is CR^7 and A_1 is C—$(CH_2)_q$—T. The compound of formula IVa can be reacted with a reagent of formula R^{12}—T' to obtain a compound of formula IVb or IVc which are compounds of formula I where Y is O, A_2 is CR^7 and A_1 is C—$(CH_2)_q$—T'—R^{12} or C—$(CH_2)_q$—T—R^{12}, respectively. The reagent R^{12}—T' can be obtained from commercial sources or can readily be prepared by one skilled in the art.

In the above Scheme, R^{12} has the same definition as R^7 defined earlier, q is zero or an integer from 0-8, and T is defined either as (1) a nucleophilic center such as, but not limited, to a nitrogen, oxygen or sulfur-containing group, capable of undergoing a nucleophilic substitution reaction with the leaving group T' or (2) a leaving group capable undergoing a nucleophilic substitution reaction with a nucleophilic group T' (such as, but not limited, to a nitrogen, oxygen or sulfur-containing nucleophilic group). T' has the same definition as T. In the present case, for example, a nucleophilic substitution reaction occurs when the attacking reagent (the nucleophile) brings an electron pair to the substrate, using this pair to form the new bond, and the leaving group (the nucleofuge) comes away with the electron pair, leaving as an anionic intermediate. For a detailed discussion of the mechanism of aliphatic nucleophilic substitutions and a review of specific aliphatic nucleophilic

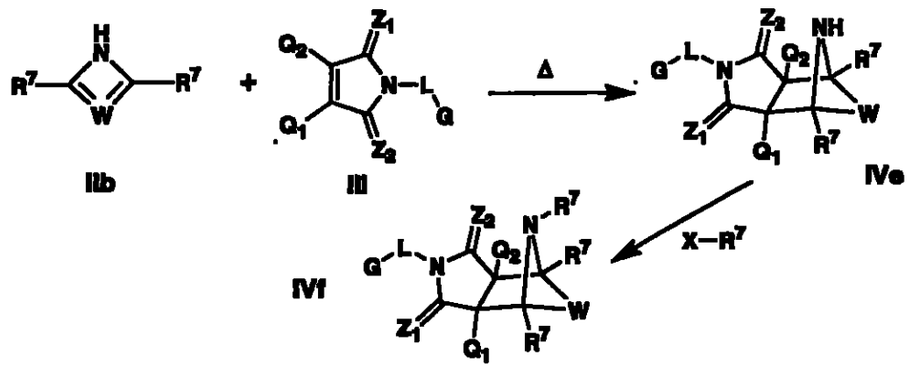
substitution reactions see *Advanced Organic Chemistry, Reactions, Mechanisms, and Structure, 4th Addition.* Jerry March (Ed.), John Wiley & Sons, New York (1992) 293-500 and the references therein. Compounds of the formulae **IVa**, **IVb**, or **IVc** may, of course, be employed in the methods described herein (especially, in the treatment of nuclear hormone receptor-associated conditions) without undergoing further reaction of T or T'.

Scheme VIII



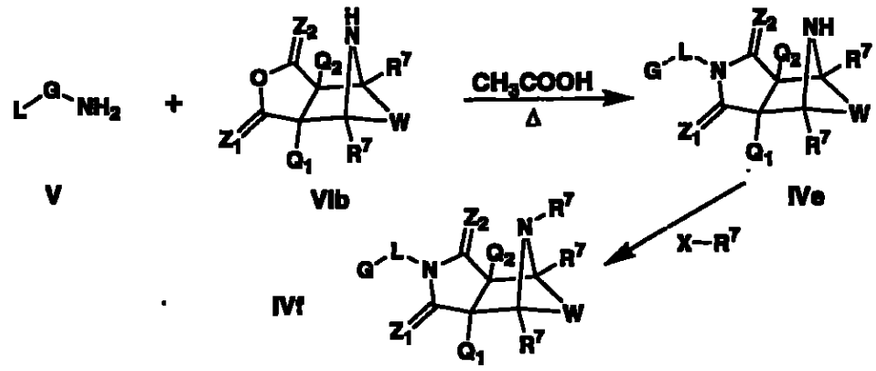
An alternate approach to compounds of formula IVa, IVb and IVc is illustrated in Scheme VIII. For this approach, techniques such as those described in Schemes II, III and IV can be applied to the preparation of an intermediate of formula VIa, where T and q are as defined in Scheme VII. The intermediate of formula VIa can be reacted with a substitited amine of formula V, as described in Scheme II, to yield the compound of formula IVa, which is a compound of formula I where Y is O, A_2 is CR^7 and A_1 is C—$(CH_2)_q$—T. The compound of formula IVa can be treated in the manner described in Scheme VII to obtain compounds of formula IVb or IVc which are compounds of formula I where Y is O, A_2 is CR^7 and A_1 is C—$(CH_2)_q$—T'—R^{12} or C—$(CH_2)_q$—T—R^{12}, respectively.

Scheme IX



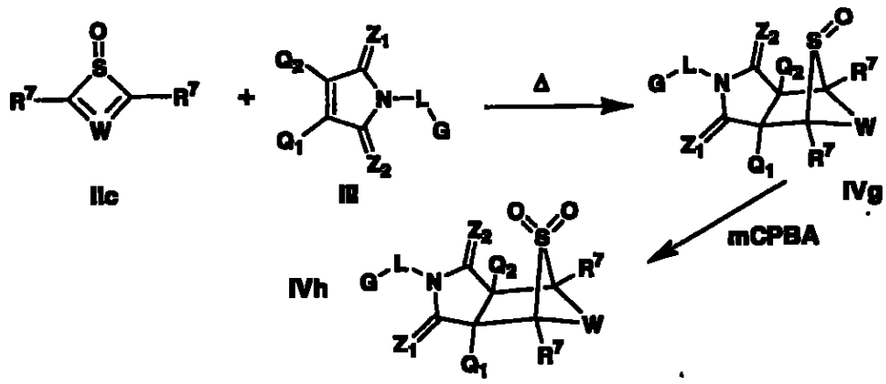
Scheme IX describes another approach to incorporating further substitution onto a compound of formula I. As illustrated in Scheme IX (where X is a leaving group), a diene of formula IIb can be reacted with a dienophile of formula III, as described in Scheme I, to yield a compound of formula IVe, which is a compound of formula I where Y is NH, and A_1 and A_2 are CR^7. The compound of formula IVe can be functionalized at the free amine by reacting with a variety of electrophilic agents such as acid halides or alkyl halides in the presence of base, for example by methods known by one skilled in the art and described in Scheme V, to yield a compound of formula IVf, which is a compound of formula I where Y is NR^7 and A_1 and A_2 are CR^7.

Scheme X



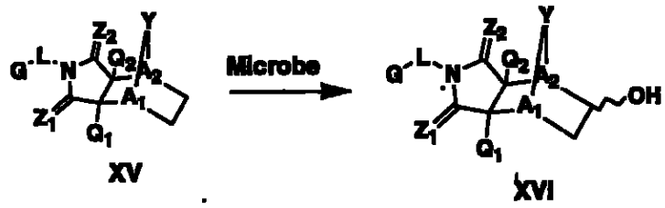
An alternate approach to compounds of formula IVe and IVf is illustrated in Scheme X. For this approach, techniques as described in Schemes II, III and IV can be applied to the preparation of an intermediate of formula VIb. The intermediate of formula VIb can be reacted with a substituted amine of formula V, as described in Scheme II, to yield a compound of formula IVe, which is a compound of formula I where Y is NH, and A_1 and A_2 are CR^7. The latter intermediate can be treated in the manner described in Scheme V to obtain a compound of formula IVf, which is a compound of formula I where Y is NR^7, and A_1 and A_2 are CR^7.

Scheme XI



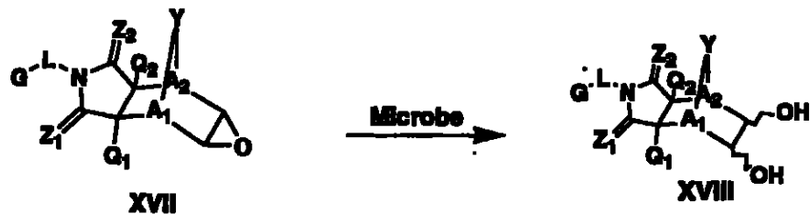
Scheme XI describes another approach to incorporating additional substitution onto a compound of formula I. As illustrated in Scheme XI, a diene of formula IIc can be reacted with a dienophile of formula III, as described in Scheme I, to yield a compound of formula IVg, which is a compound of formula I where Y is SO and A_1 and A_2 are CR^7. A compound of formula IVg can be treated with an oxidizing agent such as mCPBA, as described in Scheme VI, to yield a compound of formula IVh, which is a compound of formula I where Y is SO_2 and A_1 and A_2 are CR^7.

Scheme XII



Scheme XII describes another approach to incorporating additional substitution onto a compound of formula I. As illustrated in Scheme XII, a compound of formula XV, which can be prepared in accordance with the above Schemes, can be incubated in the presence of a suitable enzyme or microorganism resulting in the formation of a hydroxylated analog of formula XVI. Such a process can be employed to yield regiospecific as well as enantiospecific incorporation of a hydroxyl group into a molecule of formula XV by a specific microorganism or by a series of different microorganisms. Such microorganisms can, for example, be bacterial, yeast or fungal in nature and can be obtained from distributors such as ATCC or identified for use in this method such as by methods known to one skilled in the art. Compound XVI is a compound of formula I where Y is as described above and A_1 and A_2 are preferably CR^7.

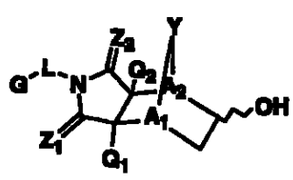
Scheme XIII



Scheme XIII describes another approach to incorporating additional substitution onto a compound of formula I. As illustrated in Scheme XIII, a compound of formula XVII, which can be prepared in accordance with the above Schemes, can be incubated in the presence of a suitable enzyme or microorganism resulting in the formation of a diol analog of formula XVIII. Such a process can be employed to yield regiospecific as well as enantiospecific transformation of a compound of formula XVII to a 1-2 diol of formula XVIII by a specific microorganism or by a series of different microorganisms. Such microorganisms can, for example, be bacterial, yeast or fungal in nature and can be obtained from distributors such as ATCC or identified for use in this method such as by methods known to one skilled in the art. Compound XVIII is a compound of formula I where Y is as described above and A_1 and A_2 are preferably CR^7.

The present invention also provides the methods of Schemes XII and XIII.

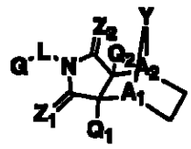
Thus, in one embodiment, the present invention provides a method for preparation of a compound of the following formula XVI, or salt thereof:



XVI

where the symbols are as defined herein,

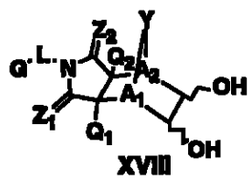
comprising the steps of contacting a compound of the following formula XV, or salt thereof:



XV

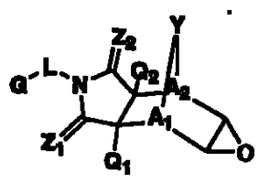
where the symbols are as defined above;
with an enzyme or microorganism capable of catalyzing the hydroxylation of said compound XV to form said compound XVI, and effecting said hydroxylation.

In another preferred embodiment, the present invention provides a method for preparation of a compound of the following formula XVIII, or salt thereof:



XVIII

where the symbols are as defined herein,
comprising the steps of contacting a compound of the following formula XVII, or salt thereof:



XVII

where the symbols are as defined above;
with an enzyme or microorganism capable of catalyzing the opening of the epoxide ring of compound XVII to form the diol of said compound XVIII, and effecting said ring opening and diol formation.

All stereoconfigurations of the unspecified chiral centers of the compounds of the formulae XV, XVI, XVII and XVIII are contemplated in the methods of the present invention, either alone (that is, substantially free of other stereoisomers) or in admixture with other stereoisomeric forms. Conversion of one isomer selectively

(e.g., hydroxylation of the exo isomer preferentially to hydroxylation of the endo isomer) when contacting an isomeric mixture is a preferred embodiment of the invention. Conversion to one isomer selectively (e.g., hydroxylation on the exo face "exo isomer" preferentially to the endo face "endo isomer" or regioselective opening of an epoxide to form only one of two possible regioisomers of a trans diol) is a preferred embodiment of the invention. Hydroxylation of an achiral intermediate to form a single optical isomer of the hydroxylated product is also a preferred embodiment of the invention. Resolution of a recemic mixture of an intermediate by selective hydroxylation, or epoxide ring opening and diol formation, to generate one of the two possible optical isomers is also a preferred embodiment of the invention. The term "resolution" as used herein denotes partial, as well as, preferably, complete resolution.

The terms "enzymatic process" or "enzymatic method", as used herein, denote a process or method of the present invention employing an enzyme or microorganism. The term "hydroxylation", as used herein, denotes the addition of a hydroxyl group to a methylene group as described above. Hydroxylation can be achieved, for example, by contact with molecular oxygen according to the methods of the present invention. Diol formation can be achieved, for example, by contact with water according to the methods of the present invention. Use of "an enzyme or microorganism" in the present methods includes use of two or more, as well as a single, enzyme or microorganism.

The enzyme or microorganism employed in the present invention can be any enzyme or microorganism capable of catalyzing the enzymatic conversions described herein. The enyzmatic or microbial materials, regardless of origin or purity, can be employed in the free state or immobilized on a support such as by physical adsorption or entrapment. Microorganisms or enzymes suitable for use in the present invention can be selected by screening for the desired activity, for example, by contacting a candidate microorganism or enzyme with a starting compound XV or XVII or salt thereof, and noting conversion to the corresponding compound XVI or XVIII or salt thereof. The enzyme may, for example, be in the form of animal or plant enzymes or mixtures thereof, cells of microorganisms, crushed cells, extracts of cells, or of synthetic origin.

Exemplary microorganisms include those within the genera: *Streptomyces* or *Amycolatopsis*. Particularly preferred microorganisms are those within the species *Streptomyces griseus*, especially *Streptomyces griseus* ATCC 10137, and *Amycolatopsis orientalis* such as ATCC 14930, ATCC 21425, ATCC 35165, ATCC 39444, ATCC 43333, ATCC 43490, ATCC 53550, ATCC 53630, and especially

ATCC 43491. The term "ATCC" as used herein refers to the accession number of the American Type Culture Collection, 10801 University Blvd., Manassas Virginia 20110-2209, the depository for the organism referred to. It should be understood that mutants of these organisms are also contemplated by the present invention, for use in the methods described herein, such as those modified by the use of chemical, physical (for example, X-rays) or biological means (for example, by molecular biology techniques).

Preferred enzymes include those derived from microorganisms, particularly those microorganisms described above. Enzymes may be isolated, for example, by extraction and purification methods such as by methods known to those of ordinary skill in the art. An enzyme may, for example, be used in its free state or in immobilized form. One embodiment of the invention is that where an enzyme is adsorbed onto a suitable carrier, e.g., diatomaceous earth (porous Celite Hyflo Supercel), microporous polypropylene (Enka Accurel® polypropylene powder), or a nonionic polymeric adsorbent such as Amberlite® XAD-2 (polystyrene) or XAD-7 (polyacrylate) from Rohm and Haas Co. When employed to immobilize an enzyme, a carrier may control the enzyme particle size and prevent aggregation of the enzyme particles when used in an organic solvent. Immobilization can be accomplished, for example, by precipitating an aqueous solution of the enzyme with cold acetone in the presence of the Celite Hyflo Supercel followed by vacuum drying, or in the case of a nonionic polymeric adsorbent, incubating enzyme solutions with adsorbent on a shaker, removing excess solution and drying enzyme-adsorbent resins under vacuum. While it is desirable to use the least amount of enzyme possible, the amount of enzyme required will vary depending upon the specific activity of the enzyme used.

Hydroxylation as described above can occur *in vivo*. For example, liver enzyme can selectively, relative to the endo isomer, hydroxylate the exo isomer of a compound of the present invention. In conducting the methods of the present invention outside the body, liver microsomal hydroxylase can be employed as the enzyme for catalysis.

These processes may also be carried out using microbial cells containing an enzyme having the ability to catalyze the conversions. When using a microorganism to perform the conversion, these procedures are conveniently carried out by adding the cells and the starting material to the desired reaction medium.

Where microorganisms are employed, the cells may be used in the form of intact wet cells or dried cells such as lyophilized, spray-dried or heat-dried cells, or in the form of treated cell material such as ruptured cells or cell extracts. Cell extracts immobilized on Celite® or Accurel® polypropylene as described earlier may also be

employed. The use of genetically engineered organisms is also contemplated. The host cell may be any cell, e.g. *Escherichia coli*, modified to contain a gene or genes for expressing one or more enzymes capable of catalysis as described herein.

Where one or more microorganisms are employed, the enzymatic methods of the present invention may be carried out subsequent to the fermentation of the microorganism (two-stage fermentation and conversion), or concurrently therewith, that is, in the latter case, by *in situ* fermentation and conversion (single-stage fermentation and conversion).

Growth of the microorganisms can be achieved by one of ordinary skill in the art by the use of an appropriate medium. Appropriate media for growing microorganisms include those which provide nutrients necessary for the growth of the microbial cells. A typical medium for growth includes necessary carbon sources, nitrogen sources, and elements (e.g. in trace amounts). Inducers may also be added. The term "inducer", as used herein, includes any compound enhancing formation of the desired enzymatic activity within the microbial cell.

Carbon sources can include sugars such as maltose, lactose, glucose, fructose, glycerol, sorbitol, sucrose, starch, mannitol, propylene glycol, and the like; organic acids such as sodium acetate, sodium citrate, and the like; and alcohols such as ethanol, propanol and the like.

Nitrogen sources can include N-Z amine A, corn steep liquor, soy bean meal, beef extracts, yeast extracts, molasses, baker's yeast, tryptone, nutrisoy, peptone, yeastamin, amino acids such as sodium glutamate and the like, sodium nitrate, ammonium sulfate and the like.

Trace elements can include magnesium, manganese, calcium, cobalt, nickel, iron, sodium and potassium salts. Phosphates may also be added in trace or, preferably, greater than trace amounts.

The medium employed can include more than one carbon or nitrogen source or other nutrient.

Preferred media for growth include aqueous media.

The agitation and aeration of the reaction mixture affects the amount of oxygen available during the conversion process when conducted, for example, in shake-flask cultures or fermentor tanks during growth of microorganisms.

Incubation of the reaction medium is preferably at a temperature between about 4 and about 60°C. The reaction time can be appropriately varied depending upon the amount of enzyme used and its specific activity. Reaction times may be reduced by increasing the reaction temperature and/or increasing the amount of enzyme added to the reaction solution.

It is also preferred to employ an aqueous liquid as the reaction medium, although an organic liquid, or a miscible or immiscible (biphasic) organic/aqueous liquid mixture, may also be employed. The amount of enzyme or microorganism employed relative to the starting material is selected to allow catalysis of the enzymatic conversions of the present invention.

Solvents for the organic phase of a biphasic solvent system may be any organic solvent immiscible in water, such as toluene, cyclohexane, xylene, trichlorotrifluoroethane and the like. The aqueous phase is conveniently of water, preferably deionized water, or a suitable aqueous buffer solution, especially a phosphate buffer solution. The biphasic solvent system preferably comprises between about 10 to 90 percent by volume of organic phase and between about 90 to 10 percent by volume of aqueous phase, and most preferably contains at or about 20 percent by volume of organic phase and at or about 80 percent by volume of the aqueous phase.

An exemplary embodiment of such processes starts with preparation of an aqueous solution of the enzyme(s) or microbes to be used. For example, the preferred enzyme(s) or microbes can be added to a suitable amount of an aqueous solvent, such as phosphate buffer or the like. This mixture is preferably adjusted to and maintained at a desired pH.

The compounds XVI and XVIII produced by the processes of the present invention can be isolated and purified, for example, by methods such as extraction, distillation, crystallization, and column chromatography.

Preferred Compounds

A preferred subgenus of the compounds of the present invention includes compounds of the formula I or salts thereof wherein one or more, preferably all, of the following substituents are as defined below:

G is an aryl or heterocyclo (e.g., heteroaryl) group, where said group is mono- or polycyclic, and which is optionally substituted at one or more positions, preferably with hydrogen, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, halo, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, aryl or substituted aryl, heterocyclo or substituted heterocyclo, arylalkyl or substituted arylalkyl, heterocycloalkyl or substituted heterocycloalkyl, CN, $R^1OC{=}O$, $R^1C{=}O$,

$R^1HNC{=}O$, $R^1R^2NC{=}O$, $HOCR^3R^{3'}$, nitro, R^1OCH_2, R^1O, NH_2, NR^4R^5, $S{=}OR^1$, SO_2R^1, $SO_2NR^1R^{1'}$, $(R^1)(R^{1'})P{=}O$, or $(R^{1'})(NHR^1)P{=}O$;

Z_1 is O, S, NH, or NR^6;

Z_2 is O, S, NH, or NR^6;

A_1 is CR^7 or N;

A_2 is CR^7 or N;

Y is J-J'-J" where J is $(CR^7R^{7'})n$ and n = 0-3, J' is a bond or O, S, S=O, SO_2, NH, OC=O, C=O, NR^7, $CR^7R^{7'}$, $R^2P{=}O$, $R^2P{=}S$, $R^2OP{=}O$, $R^2NHP{=}O$, $OP{=}OOR^2$, $OP{=}ONHR^2$, $OP{=}OR^2$, OSO_2, NHNH, $NHNR^6$, NR^6NH, N=N, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, or heterocyclo or substituted heterocyclo, and J" is $(CR^7R^{7'})n$ and n = 0-3, where Y is not a bond;

W is $CR^7R^{7'}{-}CR^7R^{7'}$, $CR^7R^{7'}{-}C{=}O$, $NR^9{-}CR^7R^{7'}$, $N{=}CR^8$, N=N, $NR^9{-}NR^{9'}$, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, or aryl or substituted aryl, wherein, when W is not $NR^9{-}CR^7R^{7'}$, $N{=}CR^8$, N=N, $NR^9{-}NR^{9'}$, or heterocyclo or substituted heterocyclo, then J' must be O, S, S=O, SO_2, NH, NR^7, $OP{=}OOR^2$, $OP{=}ONHR^2$, OSO_2, NHNH, $NHNR^6$, NR^6NH, or N=N;

Q_1 is H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocycloalkyl or substituted heterocycloalkyl, arylalkyl or substituted arylalkyl, alkynyl or substituted alkynyl, aryl or substituted aryl, heterocyclo (e.g., heteroaryl) or substituted heterocyclo (e.g., substituted heteroaryl), halo, CN, $R^1OC{=}O$, $R^4C{=}O$, $R^5R^6NC{=}O$, $HOCR^7R^{7'}$, nitro, R^1OCH_2, R^1O, NH_2, or NR^4R^5;

Q_2 is H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocycloalkyl or substituted heterocycloalkyl, arylalkyl or substituted arylalkyl, alkynyl or substituted alkynyl, aryl or substituted aryl, heterocyclo (e.g., heteroaryl) or substituted heterocyclo (e.g., substituted heteroaryl), halo,

CN, $R^1OC{=}O$, $R^4C{=}O$, $R^5R^6NC{=}O$, $HOCR^7R^{7'}$, nitro, R^1OCH_2, R^1O, NH_2, or NR^4R^5;

L is a bond, $(CR^7R^{7'})n$, NH, NR^5 or $NR^5(CR^7R^{7'})n$, where n = 0-3;

R^1 and $R^{1'}$ are each independently H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkyalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl;

R^2 is alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl;

R^3 and $R^{3'}$ are each independently H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, halo, CN, hydroxylamine, hydroxamide, alkoxy or substituted alkoxy, amino, NR^1R^2, thiol, alkylthio or substituted alkylthio;

R^4 is H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, $R^1C{=}O$, $R^1NHC{=}O$, or $SO_2NR^1R^{1'}$;

R^5 is alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, $R^1C{=}O$, $R^1NHC{=}O$, SO_2R^1, or $SO_2NR^1R^{1'}$;

R^6 is alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, CN, OH, OR^1, $R^1C{=}O$, $R^1NHC{=}O$, SO_2R^1, or $SO_2NR^1R^{1'}$;

R^7 and $R^{7'}$ are each independently H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, halo, CN, OR^4, nitro, hydroxylamine, hydroxylamide, amino, NHR^4, NR^2R^5, NOR^1, thiol, alkylthio or substituted alkylthio, $R^1C{=}O$, $R^1(C{=}O)O$, $R^1OC{=}O$, $R^1NHC{=}O$, SOR^1, $PO_3R^1R^{1'}$, $R^1R^{1'}NC{=}O$, $C{=}OSR^1$, SO_2R^1, or $SO_2NR^1R^{1'}$;

R^8 and $R^{8'}$ are each independently H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkyalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, nitro, halo, CN, OR^1, amino, NHR^4, NR^2R^5, NOR^1, alkylthio or substituted alkylthio, $C{=}OSR^1$, $R^1OC{=}O$, $R^1C{=}O$, $R^1NHC{=}O$, $R^1R^{1'}NC{=}O$, $S{=}OR^1$, SO_2R^1, $PO_3R^1R^{1'}$, or $SO_2NR^1R^{1'}$;

R^9 and $R^{9'}$ are each independently H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl; cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, CN, OH, OR^1, $R^1C{=}O$, $R^1OC{=}O$, $R^1NHC{=}O$, or $SO_2NR^1R^{1'}$;

especially where the groups W and Y of this preferred subgenus are also within the definitions of W' and Y' of formula Ia, with the provisos (1) to (14) of said formula Ia where appropriate to this subgenus, and most preferably where (i) when Y' is -O- and W' is $CR^7R^{7'}$—$CR^7R^{7'}$, A_1 and A_2 are not simultaneously CH; and (ii) when L is a bond, G is not an unsubstituted phenyl group.

Another, more preferred subgenus of the compounds of the invention includes compounds of the formula I or salts thereof wherein one or more, preferably all, of the following substituents are as defined below:

G is an aryl or heterocyclo (e.g., heteroaryl) group, where said group is mono- or polycyclic, and which is optionally substituted at one or more positions, preferably with hydrogen, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, halo, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, aryl or substituted aryl, heterocyclo or substituted heterocyclo, arylalkyl or substituted arylalkyl, heterocycloalkyl or substituted heterocycloalkyl, CN, $R^1C{=}O$, $R^1HNC{=}O$, $R^1R^2NC{=}O$, $HOCR^3R^{3'}$, nitro, R^1OCH_2, R^1O, NH_2, NR^4R^5, SO_2R^1, or $SO_2NR^1R^{1'}$;

Z_1 is O;

Z_2 is O;

A_1 is CR^7;

A_2 is CR^7;

Y is J-J'-J" where J is $(CR^7R^{7'})n$ and n = 0-3, J' is a bond or O, S, S=O, SO_2, NH, NR^7, $CR^7R^{7'}$, $R^2P{=}O$, $R^2P{=}S$, $R^2OP{=}O$, $R^2NHP{=}O$, $OP{=}OOR^2$, $OP{=}ONHR^2$,

$OP{=}OR^2$, OSO_2, NHNH, $NHNR^6$, NR^6NH, N=N, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, or heterocyclo or substituted heterocyclo, and J'' is $(CR^7R^{7'})n$ and n = 0-3, where Y is not a bond;

W is $CR^7R^{7'}$—$CR^7R^{7'}$, $CR^7R^{7'}$—C=O, NR^9—$CR^7R^{7'}$, $N{=}CR^8$, N=N, NR^9—$NR^{9'}$, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, or aryl or substituted aryl, wherein, when W is not NR^9—$CR^7R^{7'}$, $N{=}CR^8$, N=N, NR^9—$NR^{9'}$, or heterocyclo or substituted heterocyclo, then J' must be O, S, S=O, SO_2, NH, NR^7, $OP{=}OOR^2$, $OP{=}ONHR^2$, OSO_2, NHNH, $NHNR^6$, NR^6NH, or N=N;

Q_1 is H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocycloalkyl or substituted heterocycloalkyl, arylalkyl or substituted arylalkyl, alkynyl or substituted alkynyl, aryl or substituted aryl, heterocyclo (e.g., heteroaryl) or substituted heterocyclo (e.g., substituted heteroaryl), halo, CN, $R^4C{=}O$, $R^5R^6NC{=}O$, $HOCR^7R^{7'}$, nitro, R^1OCH_2, R^1O, NH_2, or NR^4R^5;

Q_2 is H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocycloalkyl or substituted heterocycloalkyl, arylalkyl or substituted arylalkyl, alkynyl or substituted alkynyl, aryl or substituted aryl, heterocyclo (e.g., heteroaryl) or substituted heterocyclo (e.g., substituted heteroaryl), halo, CN, $R^4C{=}O$, $R^5R^6NC{=}O$, $HOCR^7R^{7'}$, nitro, R^1OCH_2, R^1O, NH_2, or NR^4R^5;

L is a bond;

R^1 and $R^{1'}$ are each independently H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkyalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl;

R^2 is alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted

cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl;

R^3 and $R^{3'}$ are each independently H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, halo, CN, alkoxy or substituted alkoxy, amino, NR^1R^2, alkylthio or substituted alkylthio;

R^4 is H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, $R^1C{=}O$, $R^1NHC{=}O$, or $SO_2NR^1R^{1'}$;

R^5 is alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, $R^1C{=}O$, $R^1NHC{=}O$, SO_2R^1, or $SO_2NR^1R^{1'}$;

R^6 is alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl,

arylalkyl or substituted arylalkyl, CN, OH, OR^1, $R^1C{=}O$, $R^1NHC{=}O$, SO_2R^1, or $SO_2NR^1R^{1'}$;

R^7 and $R^{7'}$ are each independently H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, halo, CN, OR^4, nitro, amino, NHR^4, NR^2R^5, alkylthio or substituted alkylthio, $R^1C{=}O$, $R^1(C{=}O)O$, R1NHC=O, SO_2R^1, $R^1R^{1'}NC{=}O$, or $SO_2NR^1R^{1'}$;

R^8 and $R^{8'}$ are each independently H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkyalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, nitro, halo, CN, OR^1, amino, NHR^4, NR^2R^5, alkylthio or substituted alkylthio, $R^1C{=}O$, $R^1NHC{=}O$, $R^1R^{1'}NC{=}O$, SO_2R^1, or $SO_2NR^1R^{1'}$; and

R^9 and $R^{9'}$ are each independently H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, CN, OH, OR^1, $R^1C{=}O$, $R^1NHC{=}O$, or $SO_2NR^1R^{1'}$;

especially where the groups W and Y of this preferred subgenus are also within the definitions of W' and Y' of formula Ia, with the provisos (1) to (14) of said formula Ia where appropriate to this subgenus, and most preferably where (i) when Y' is -O- and W' is $CR^7R^{7'}$—$CR^7R^{7'}$, A_1 and A_2 are not simultaneously CH; and (ii) when L is a bond, G is not an unsubstituted phenyl group.

A particularly preferred subgenus of the compounds of the invention includes compounds of the formula I or salts thereof wherein one or more, preferably all, of the substituents are as defined below:

G is an aryl (especially, phenyl or naphthyl) or heterocyclo (especially those heterocyclo groups G of the compounds of the Examples herein) group, where said group is mono- or polycyclic, and which is optionally substituted at one or more positions, preferably with substituents as exemplified in any of the compounds of the Examples herein;

L is a bond, $(CR^{7}R^{7'})n$ (where n is 1 and R^{7} and $R^{7'}$ are each independently H, alkyl or substituted alkyl), or -CH2-NH-;

A_1 and A_2 are each independently CR^{7} where R^{7} (i) is hydrogen, alkyl or substituted alkyl, arylalkyl or substituted arylalkyl, alkenyl or substituted alkenyl (for example, alkenyl substituted with aryl (especially, phenyl or naphthyl) or substituted aryl, or alkenyl substituted with heterocyclo or substituted heterocyclo), aryl or substituted aryl, heterocyclo or substituted heterocyclo, heterocycloalkyl or substituted heterocycloalkyl, where, for each, preferred substituents are one or more groups selected from V^1 (especially A_1 and A_2 groups of the formula CR^{7} where R^{7} for each of A_1 and/or A_2 is independently selected from unsubstituted C_{1-4} alkyl, or C_{1-4} alkyl which alkyl is substituted by one or more groups V^1), or (ii) forms, together with R^{7} of a group W (especially where W is $CR^{7}R^{7''}$-$CR^{7}R^{7''}$), a heterocyclic ring;

V^1 is OH, CN, halo, -O-aryl, -O-substituted aryl, -O-heterocyclo (e.g., -O-(optionally substituted pyridinyl) or –O-(optionally substituted pyrimidinyl)), -O-substituted heterocyclo, -O-CO-alkyl, -O-CO-substituted alkyl, -O-(alkylsilyl), -O-arylalkyl, -O-substituted arylalkyl, -O-CO-alkyl, -O-CO-substituted alkyl, -O-CO-arylalkyl, -O-CO-substituted arylalkyl, -O-CO-aryl, -O-CO-substituted aryl, -O-CO-heterocyclo, -O-CO-substituted heterocyclo, -S-(optionally

substituted aryl)-NH-CO-(optionally substituted alkyl), -SO-(optionally substituted aryl)-NH-CO-(optionally substituted alkyl), -SO2-(optionally substituted aryl)-NH-CO-(optionally substituted alkyl), -NH-SO2-aryl, -NH-SO2-substituted aryl, -NH-CO-O-(optionally substituted arylalkyl), -NH-CO-O-alkyl, -NH-CO-O-substituted alkyl, -NH-CO-alkyl, -NH-CO-substituted alkyl, -NH-CO-aryl, -NH-CO-substituted aryl, -NH-CO-(optionally substituted arylalkyl), -NH-CO-(optionally substituted alkyl)-O-(optionally substituted aryl), -N(optionally substituted alkyl)(optionally substituted aryl), -N(optionally substituted alkyl)(optionally substituted arylalkyl), -COH, -COOH, -CO-O-alkyl, -CO-O-substituted alkyl, -CO-O-optionally substituted arylalkyl, -CO-aryl, -CO-substituted aryl, -O-CO-NH-aryl, -O-CO-NH-substituted aryl, -CO-NH-aryl, -CO-NH-substituted aryl, -CO-NH-arylalkyl, -CO-NH-substituted arylalkyl, -O-(optionally substituted aryl)-NH-CO-(optionally substituted alkyl);

Y is --O-, -SO-, -N(V^8)-, -CH_2-N(V^8)-, -CO-N(alkyl)-, -CH_2-S-, -CH_2-SO_2-;

V^8 is hydrogen, alkyl, arylalkyl, -CO-alkyl, -CO-O-aryl, -CO-O-arylalkyl;

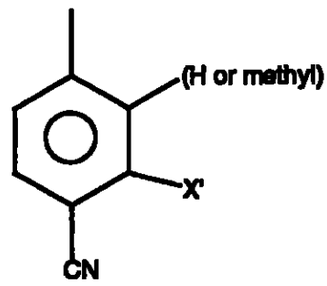
W is $CR^7R^{7'}$— $CR^7R^{7'}$ (where R^7 and $R^{7'}$ are each independently selected from H, OH, alkyl or substituted alkyl (such as hydroxyalkyl), or where R^7 forms a heterocyclic ring together with R^7 of A_1 or A_2), CR^8=$CR^{8'}$ (where R^8 and $R^{8'}$ are each independently selected from H, alkyl or substituted alkyl (such as hydroxyalkyl)), $CR^7R^{7'}$— C=O (where R^7 and $R^{7'}$ are each hydrogen, or where R^7 forms a heterocyclic ring together with R^7 of A_1 or A_2), N=CR^8 (where R^8 is alkyl), cycloalkyl or substituted cyclalkyl, or heterocyclo or substituted heterocyclo;

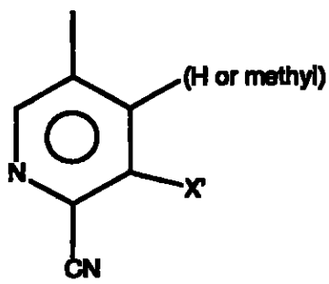
Z_1 and Z_2 are O; and

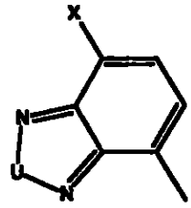
Q_1 and Q_2 are H.

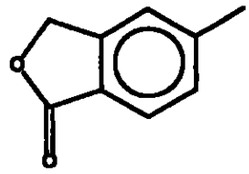
Preferred G-L groups are optionally substituted phenyl, optionally substituted naphthyl and optionally substituted fused bicyclic heterocyclic

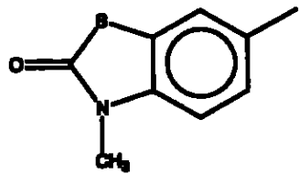
groups such as optionally substituted benzo-fused heterocyclic groups (e.g., bonded to the remainder of the molecule through the benzene portion), especially such groups wherein the heterocyclic ring bonded to benzene has 5 members exemplified by benzoxazole, benzothiazole, benzothiadiazole, benzoxadiazole or benzothiophene, for example:

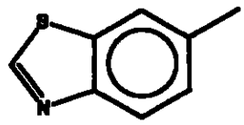


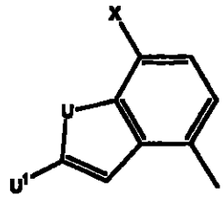


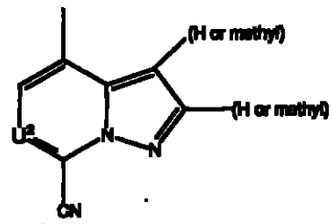

X
N
U
N

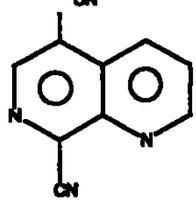

O
O

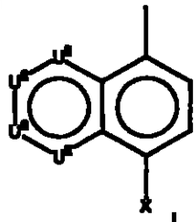

S
O
N
CH3


S
N









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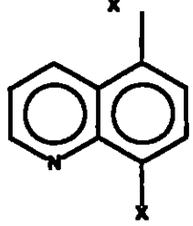
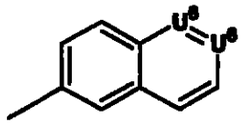
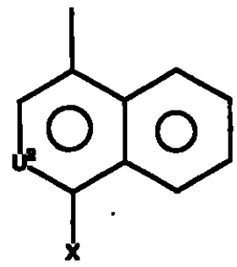
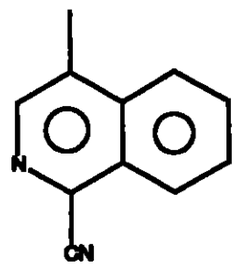


where X is OH or CN)

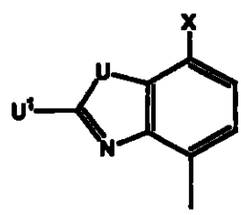
or





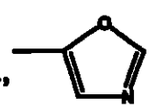
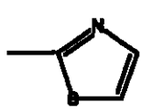
(e.g., )

or



where

X = halo (especially F), OH, CN, NO_2 or

(e.g.,  ,  or);

X' = halo (especially Cl, F, or I), CH_3, CF_3, CN or OCH_3;

U is O or S (where S can optionally be oxygenated, e.g., to SO);

U^1 is CH_3 or CF_3;

each U^2 is independently N, CH or CF;

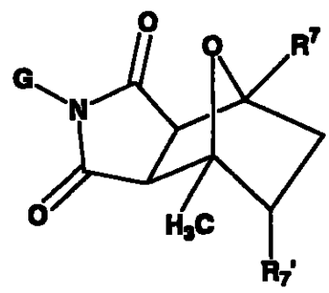
U^3 is N, O or S;

U^4 and U^5, together with the atoms to which they are bonded, form an optionally substituted 5-membered heterocyclic ring which can be partially unsaturated or aromatic and which contains 1 to 3 ring heteroatoms;

each U^6 is independently CH or N; and

(p) denotes optional double bond(s) within the ring formed by U^3, U^4 and U^5.

An especially preferred subgenus includes compounds of the formula I having the following structure, or salts thereof:



where G is an optionally substituted phenyl, naphthyl or benzo-fused bicyclic heterocyclic group, R^7 is CH_3 or C_{1-4}alkyl substituted by V^1, and one R^7 is H or hydroxyl and the other is H.

Preferred compounds of the invention include:

[3a*S*-(3aα,4β,6β,7β,7aα)]-4-(Octahydro-6-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

[3a*R*-(3aα,4β,6β,7β,7aα)]-4-(Octahydro-6-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

[3a*S*-(3aα,4β,5β,6α,7β,7aα)]-4-(Octahydro-5,6-dihydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

[3a*S*-(3aα,4β,5β,7β,7aα)]-5-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-3methyl-2-pyridinecarbonitrile;

[3a*S*-(3aα,4β,5β,7β,7aα)]-2-(2,1,3-Benzoxadiazol-5-yl)hexahydro-5-hydroxy-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione;

[3a*S*-(3aα,4β,5β,7β,7aα)]-5-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-3,4-dimethyl-2-pyridinecarbonitrile;

[3a*R*-(3aα,4β,5β,7β,7aα)]-5-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-3,4-dimethyl-2-pyridinecarbonitrile;

[3a*S*-(3aα,4β,5β,7β,7aα)]-2-(6-Benzothiazolyl)hexahydro-5-hydroxy-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione;

[3a*R*-(3aα,4β,5β,7β,7aα)]-2-(7-Chloro-2,1,3-benzoxadiazol-4-yl)hexahydro-5-hydroxy-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione;

[3a*R*-(3aα,4β,5α,7β,7aα)]-5-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-3-(trifluoromethyl)-2-pyridinecarbonitrile;

[3a*R*-(3aα,4β,5α,7β,7aα)]-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-iodobenzonitrile;

(3aα,4β,5α,6β,7β,7aα)-2-(4-Cyano-3-(trifluoromethyl)phenyl)hexahydro-6-cyano-4,7-dimethyl-1,3-dioxo-4,7-epoxy-1H-isoindole-5-carboxylic acid, methyl ester;

(3aα,4β,7β,7aα)-4-(Octahydro-4,7,8-trimethyl-1,3-dioxo-4,7-imino-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

[3a*R*-(3aα,4β,5β,6α,7β,7aα)]-4-(Octahydro-5,6-dichloro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

[3a*S*-(3aα,4β,5β,6α,7β,7aα)]-4-(Octahydro-5,6-dichloro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

(3aα,4β,7β,7aα)-4-(Octahydro-4,7-dimethyl-1,3,5-trioxo-4,7-epoxy-2H-isoindol-2-yl)-2-iodobenzonitrile;

(3aα,4β,5α,7β,7aα)-4-(Octahydro-5-[[[difluoromethyl]oxy]methyl]-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

(3aα,4β,5α,7β,7aα)-4-(Octahydro-5-[[phenylmethoxycarbonyl]amino]-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

(3aα,4β,5α,7β,7aα)-4-(Octahydro-5-[[propyloxycarbonyl]amino]-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

(3aα,4β,5α,7β,7aα)-4-(Octahydro-5-[[[cyclopropylmethyloxy]carbonyl]amino]-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

(3aα,4β,5α,7β,7aα)-4-(Octahydro-5-[[methoxycarbonyl]amino]-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

[3a*R*-(3aα,4β,5β,7β,7aα)]-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2,3-dichlorobenzonitrile;

[3a*R*-(3aα,4β,4aα,5aα,6β,7aα)]-4-(Octahydro-4a-hydroxy-4,6-dimethyl-1,3-dioxo-4,6-epoxycycloprop[f]isoindol-2(1H)-yl)-2-(trifluoromethyl)benzonitrile;

(3aα,4β,5α,7β,7aα)-2-(4-Cyano-3-(trifluoromethyl)phenyl)hexahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-*N*,*N*-dimethyl-1H-isoindole-5-carboxamide;

[3a*R*-(3aα,4β,5β,6β,7β,7aα)]-4-(Octahydro-5-chloro-6-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

[3a*S*-(3aα,4β,5β,6β,7β,7aα)]-4-(Octahydro-5-chloro-6-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

(3aα,4β,5α,7β,7aα)-4-(Octahydro-5-[[[6-(trifluoromethyl)-4-pyrimidinyl]oxy]methyl]-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

(3aα,4β,5α,7β,7aα)-4-(Octahydro-5-[[[5-chloro-2-pyridinyl]oxy]methyl]-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

[3a*R*-(3aα,4β,5α,7β,7aα)]-4-(Octahydro-5-[[[phenylamino]carbonyl]amino]-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

[3a*R*-(3aα,4β,5α,7β,7aα)]-4-(Octahydro-5-[[(1-methylethyloxy)carbonyl]amino]-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

(3aα,4β,5α,7β,7aα)-4-(Octahydro-5-[[[5-fluoro-4-pyrimidinyl]oxy]methyl]-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

[3a*R*-(3aα,4β,5α,7β,7aα)]-4-(Octahydro-5-[[ethyloxycarbonyl]amino]-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

[3a*R*-(3aα,4β,5α,7β,7aα)]-2-(4-Cyano-3-(trifluoromethyl)phenyl)-hexahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-1H-isoindole-5-carboxylic acid, 4-pyridinylmethyl ester;

[3a*R*-(3aα,4β,5α,7β,7aα)]-4-(Octahydro-5-[[4-pyridinylmethoxycarbonyl]amino]-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

3aα,4β,5β,7β,7aα)-4-(Octahydro-5-[[[2-methyl-5-(trifluoromethyl)-2H-pyrazol-3-yl]oxy]methyl]-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

(3aα,4β,5α,7β,7aα)-2-(4-Cyano-3-(trifluoromethyl)phenyl)hexahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-1H-isoindole-5-carboxylic acid, methyl ester;

[3a*R*-(3aα,4β,5β,7β,7aα)]-4-(Octahydro-5-cyclopropylmethoxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

(3aα,4β,5α,7β,7aα)-4-(Octahydro-5-[[((phenylmethyl)amino)carbonyl]oxy]-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile; and

[3a*R*-(3aα,4β,5β,7β,7aα)]-4-(Octahydro-5-cyclopropyloxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

or pharmaceutically acceptable salts, solvates, prodrugs or stereoisomers thereof.

More preferred compounds of the invention include:

[3a*R*-(3aα,4β,5β,7β,7aα)]-5-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-3-(trifluoromethyl)-2-pyridinecarbonitrile;

[3a*S*-(3aα,4β,5β,7β,7aα)]-5-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-3-(trifluoromethyl)-2-pyridinecarbonitrile;

[3a*R*-(3aα,4β,5β,7β,7aα)]-2-(4-Chloro-3-iodophenyl)hexahydro-5-hydroxy-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione;

[3a*S*-(3aα,4β,5β,6α,7β,7aα)]-4-(Octahydro-5,6-dihydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

[3a*R*-(3aα,4β,7β,7aα)]-4-(Octahydro-4,7-dimethyl-1,3,5-trioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

[3a*R*-(3aα,4β,5α,7β,7aα)]-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

[3a*S*-(3aα,4β,5α,7β,7aα)]-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

[3a*S*-(3aα,4β,6β,7β,7aα)]-4-(Octahydro-6-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

[3a*R*-(3aα,4β,5β,7β,7aα)]-2-(4-Chloro-3-(trifluoromethyl)phenyl)hexahydro-5-hydroxy-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione;

[3a*S*-(3aα,4β,5β,7β,7aα)]-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-iodobenzonitrile;

[3a*R*-(3aα,4β,5β,7β,7aα)]-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-iodobenzonitrile;

[3a*S*-(3aα,4β,5β,7β,7aα)]-2-(4-Chloro-3-(trifluoromethyl)pyridinyl)hexahydro-5-hydroxy-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione;

[3a*R*-(3aα,4β,5β,7β,7aα)]-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-3-methyl-2-(trifluoromethyl)benzonitrile;

[3a*R*-(3aα,4β,5β,7β,7aα)]-4-(Octahydro-5-methoxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

[3a*R*-(3aα,4β,5α,7β,7aα)]-5-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-3-(trifluoromethyl)-2-pyridinecarbonitrile;

[3a*S*-(3aα,4β,5β,7β,7aα)]-4-(Octahydro-5-methoxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

[3a*S*-(3aα,4β,6β,7β,7aα)]-4-(Octahydro-6-fluoro-5,5-dihydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

[3a*R*-(3aα,4β,7β,7aα)]-5-(Octahydro-4,7-dimethyl-1,3,5-trioxo-4,7-epoxy-2H-isoindol-2-yl)-3-(trifluoromethyl)-2-pyridinecarbonitrile;

[3a*S*-(3aα,4β,5β,7β,7aα)]-2-(4-Chloro-2-methyl-3-(trifluoromethyl)phenyl)hexahydro-5-hydroxy-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione;

[3a*R*-(3aα,4β,5β,7β,7aα)]-2-(4-Chloro-2-methyl-3-(trifluoromethyl)phenyl)hexahydro-5-hydroxy-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione;

(3aα,4β,6β,7β,7aα)-4-(Octahydro-6-fluoro-5,5-dihydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-iodobenzonitrile;

(3aα,4β,5α,7β,7aα)-2-(4-Cyano-3-(trifluoromethyl)phenyl)-hexahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-1H-isoindole-5-carboxylic acid, methyl ester;

[3a*S*-(3aα,4β,6β,7β,7aα)]-4-(Octahydro-6-fluoro-5,5-dihydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-iodobenzonitrile;

(3aα,4β,5α,7β,7aα)-4-(Octahydro-5-ethylsulfonamido-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

[3a*R*-(3aα,4β,5α,7β,7aα)]-4-(Octahydro-5-[[(4-fluorophenylamino)carbonyl]oxy]-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

[3a*R*-(3aα,4β,5α,7β,7aα)]-4-(Octahydro-5-[[(1-methylethylamino)carbonyl]oxy]-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

[3a*S*-(3aα,4β,5α,7β,7aα)]-4-(Octahydro-5-[[(1-methylethoxy)carbonyl]amino]-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

[3a*R*-(3aα,4β,6β,7β,7aα)]-4-(Octahydro-6-fluoro-5,5-dihydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-iodobenzonitrile;

[3a*R*-(3aα,4β,5α,7β,7aα)]-2-(4-Cyano-3-(trifluoromethyl)phenyl)hexahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-*N*-methyl-*N*-phenyl-1H-isoindole-5-carboxamide;

[3a*R*-(3aα,4β,5β,7β,7aα)]-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-chloro-3-methylbenzonitrile;

[3a*R*-(3aα,4β,5α,7β,7aα)]-4-(Octahydro-5-[[ethoxycarbonyl]amino]-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

(3aα,4β,5α,7β,7aα)-4-(Octahydro-5-[[[2-methyl-5-(trifluoromethyl)-2H-pyrazol-3-yl]oxy]methyl]-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

[3a*S*-(3aα,4β,5α,6β,7β,7aα)]-2-(4-Cyano-3-(trifluoromethyl)phenyl)-hexahydro-6-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-1H-isoindole-5-carboxylic acid, methyl ester;

(3aα,4β,5α,7β,7aα)-4-(Octahydro-5-[[[6-(trifluoromethyl)-4-pyrimidinyl]oxy]methyl]-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

[3a*R*-(3aα,4β,5α,7β,7aα)]-4-(Octahydro-5-methoxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

(3aα,4β,5α,7β,7aα)-2-(4-Cyano-3-(trifluoromethyl)phenyl)-hexahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-1H-isoindole-5-carbonitrile;

[3a*R*-(3aα,4β,5β,6α,7β,7aα)]-4-(Octahydro-5,6-dihydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-3-methyl-2-(trifluoromethyl)benzonitrile;

[3a*R*-(3aα,4β,5α,7β,7aα)]-4-(Octahydro-5-[[[(cyclopropylmethyl)amino]carbonyl]amino]-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

[3a*R*-(3aα,4β,5α,7β,7aα)]-4-(Octahydro-5-[[(dimethylamino)sulfonyl]amino]-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

(3aα,4β,5α,7β,7aα)-4-(Octahydro-5-benzenesulfonamido-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

[3a*R*-(3aα,4β,6β,7β,7aα)]-4-(Octahydro-6-fluoro-5,5-dihydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

[3a*R*-(3aα,4β,5α,6β,7β,7aα)]-2-(4-Cyano-3-(trifluoromethyl)phenyl)-hexahydro-6-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-1H-isoindole-5-carboxylic acid, methyl ester; and

[3a*R*-(3aα,4β,5α,7β,7aα)]-4-(Octahydro-5-[[(dimethylamino)sulfonyl]amino]-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

or pharmaceutically acceptable salts, solvates, prodrugs or stereoisomers thereof.

Compounds where $R^{7'}$ is hydroxyl can provide enhanced water solubility and metabolic stability, relative to the corresponding compounds where $R^{7'}$ is H, in addition to having good permeability and high systemic blood levels. These hydroxyl-bearing compounds can be obtained *in vivo* by metabolism of the corresponding compound where $R^{7'}$ is H, as well as by synthetic preparative methods such as those described herein.

Use and Utility

The compounds of the present invention modulate the function of nuclear hormone receptors (NHR), and include compounds which are, for example, agonists, partial agonists, antagonists or partial antagonists of the androgen receptor (AR), the estrogen receptor (ER), the progesterone receptor (PR), the glucocorticoid receptor (GR), the mineralocorticoid receptor (MR), the steroid and xenobiotic receptor (SXR), other steroid binding NHR's, the Orphan receptors or other NHR's. Selective modulation of one such NHR relative to others within the NHR family is preferred. "Modulation" includes, for example, activation (e.g., agonist activity such as selective androgen receptor agonist activity) or inhibition (e.g., antagonist activity).

The present compounds are thus useful in the treatment of NHR-associated conditions. A "NHR-associated condition", as used herein, denotes a condition or disorder which can be treated by modulating the function of a NHR in a subject, wherein treatment comprises prevention (e.g., prophylactic treatment), partial alleviation or cure of the condition or disorder. Modulation may occur locally, for example, within certain tissues of the subject, or more extensively throughout a subject being treated for such a condition disorder.

The compounds of the present invention are useful for the treatment of a variety of conditions and disorders including, but not limited to, those described following:

Compounds of formula I can be applied as agonists, partial agonists, antagonists, or partial antagonists of the estrogen receptor, preferably selectively to that receptor, in an array of medical conditions which involve modulation of the estrogen receptor pathway. Applications of said compounds include but are not

limited to: osteoporosis, hot flushes, vaginal dryness, prostate cancer, breast cancer, endometrial cancer, cancers expressing the estrogen receptor such as the aforementioned cancers and others, contraception, pregnancy termination, menopause, amennoreahea, and dysmennoreahea.

Compounds of formula I can be applied as agonists, partial agonists, antagonists or partial antagonists of the progesterone receptor, preferably selectively to that receptor, in an array of medical conditions which involve modulation of the progesterone receptor pathway. Applications of said compounds include but are not limited to: breast cancer, other cancers containing the progesterone receptor, endometriosis, cachexia, contraception, menopause, cyclesynchrony, meniginoma, dysmennoreahea, fibroids, pregnancy termination, labor induction and osteoporosis.

Compounds of formula I can be applied as agonists, partial agonists, antagonists or partial antagonists of the glucocorticoid receptor, preferably selectively to that receptor, in an array of medical conditions which involve modulation of the glucocorticoid receptor pathway. Applications of said compounds include but are not limited to: inflammatory diseases, autoimmune diseases, prostate cancer, breast cancer, Alzheimer's disease, psychotic disorders, drug dependence, non-insulin dependent Diabetes Mellitus, and as dopamine receptor blocking agents or otherwise as agents for the treatment of dopamine receptor mediated disorders.

Compounds of formula I can be applied as agonists, partial agonists, antagonists or partial antagonists of the mineralocorticoid receptor, preferably selectively to that receptor, in an array of medical conditions which involve modulation of the mineralocorticoid receptor pathway. Applications of said compounds include but are not limited to: drug withdrawal syndrome and inflammatory diseases.

Compounds of formula I can be applied as agonists, partial agonists, antagonists or partial antagonists of the aldosterone receptor, preferably selectively to that receptor, in an array of medical conditions which involve modulation of the aldosterone receptor pathway. One application of said compounds includes but is not limited to: congestive heart failure.

Compounds of formula I can be applied as agonists, partial agonists, antagonists or partial antagonists of the androgen receptor, preferably selectively to

that receptor, in an array of medical conditions which involve modulation of the androgen receptor pathway. Applications of said compounds include but are not limited to: hirsutism, acné, seborrhea, Alzheimer's disease, androgenic alopecia, hypogonadism, hyperpilosity, benign prostate hypertrophia, adenomas and neoplasies of the prostate (such as advanced metastatic prostate cancer), treatment of benign or malignant tumor cells containing the androgen receptor such as is the case for breast, brain, skin, ovarian, bladder, lymphatic, liver and kidney cancers, pancreatic cancers modulation of VCAM expression and applications therein for the treatment of heart disease, inflammation and immune modulations, modulation of VEGF expression and the applications therein for use as antiangiogenic agents, osteoporosis, suppressing spermatogenesis, libido, cachexia, endometriosis, polycystic ovary syndrome, anorexia, androgen supplement for age related decreased testosterone levels in men, male menopause, male hormone replacement, male and female sexual dysfunction, and inhibition of muscular atrophy in ambulatory patients. For example, pan AR modulation is contemplated, with prostate selective AR modulation ("SARM") being particularly preferred, such as for the treatment of early stage prostate cancers. .

Compounds of formula I can be applied as (preferably, selective) antagonists of the mutated androgen receptor, for example, found in many tumor lines. Examples of such mutants are those found in representative prostate tumor cell lines such as LNCap, (T877A mutation, Biophys. Acta, 187, 1052 (1990)), PCa2b, (L701H & T877A mutations, J. Urol., 162, 2192 (1999)) and CWR22, (H874Y mutation, Mol. Endo., 11, 450 (1997)). Applications of said compounds include but are not limited to: adenomas and neoplasies of the prostate, breast cancer and endometrial cancer.

Compounds of formula I can be applied as agonists, partial agonists, antagonists or partial antagonists of the steroid and xenobiotic receptor, preferably selectively to that receptor, in an array of medical conditions which involve modulation of the steroid and xenobiotic receptor pathway. Applications of said compounds include but are not limited to: treatment of disregulation of cholesterol homeostasis, attenuation of metabolism of pharmaceutical agents by co-administration of an agent (compound of the present invention) which modulates the P450 regulator effects of SXR.

Along with the aforementioned NHR, there also exist a number of NHR for which the activating or deactivating ligands may not be characterized. These proteins are classified as NHR due to strong sequence homology to other NHR, and are known as the Orphan receptors. Because the Orphan receptors demonstrate strong sequence homology to other NHR, compounds of formula I include those which serve as modulators of the function of the Orphan NHR. Orphan receptors which are modulated by NHR modulators such as compounds within the scope of formula I are exemplified, but not limited to, those listed in Table 1. Exemplary therapeutic applications of modulators of said Orphan receptors are also listed in Table 1, but are not limited to the examples therein.

Table 1. Exemplary Orphan nuclear hormone receptors, form (M = monomeric, D = heterodimeric, H = homodimeric), tissue expression and target therapeutic applications. (CNS=central nervous system)

Receptor	Form	Tissue Expression	Target Therapeutic Application
NURR1	M/D	Dopaminergic Neurons	Parkinson's Disease
RZRβ	M	Brain (Pituitary), Muscle	Sleep Disorders
RORα	M	Cerebellum, Purkinje Cells	Arthritis, Cerebellar Ataxia
NOR-1	M	Brain, Muscle , Heart, Adrenal, Thymus	CNS Disorders, Cancer
NGFI-Bβ	M/D	Brain	CNS Disorders
COUP-Tfα	H	Brain	CNS Disorders
COUP-TFβ	H	Brain	CNS Disorders
COUP-TFγχ	H	Brain	CNS Disorders
Nur77	H	Brain, Thymus, Adrenals	CNS Disorders
Rev-ErbAα	H	Muscle, Brain (Ubiquitous)	Obesity
HNF4α	H	Liver, Kidney, Intestine	Diabetes
SF-1	M	Gonads, Pituitary	Metabolic Disorders
LXRα,β	D	Kidney (Ubiquitous)	Metabolic Disorders
GCNF	M/H	Testes, Ovary	Infertility
ERRα,β	M	Placenta, Bone	Infertility, Osteoporosis

FXR	D	Liver, Kidney	Metabolic Disorders
CARα	H	Liver, Kidney	Metabolic Disorders
PXR	H	Liver, Intestine	Metabolic Disorders
COUP-TF2 (ARP1)	D	Testis	Oncology/angiogenesis
RORbeta	M	CNS, retina, pineal gland	Metabolic Disorders

The present invention thus provides methods for the treatment of NHR-associated conditions, comprising the step of administering to a subject in need thereof at least one compound of formula I in an amount effective therefor. Other therapeutic agents such as those described below may be employed with the inventive compounds in the present methods (for example, separately, or formulated together as a fixed dose). In the methods of the present invention, such other therapeutic agent(s) can be administered prior to, simultaneously with or following the administration of the compound(s) of the present invention.

The present invention also provides pharmaceutical compositions comprising at least one of the compounds of the formula I capable of treating a NHR-associated condition in an amount effective therefor, and a pharmaceutically acceptable carrier (vehicle or diluent). The compositions of the present invention can contain other therapeutic agents as described below, and can be formulated, for example, by employing conventional solid or liquid vehicles or diluents, as well as pharmaceutical additives of a type appropriate to the mode of desired administration (for example, excipients, binders, preservatives, stabilizers, flavors, etc.) according to techniques such as those well known in the art of pharmaceutical formulation.

It should be noted that the compounds of the present invention are, without limitation as to their mechanism of action, useful in treating any of the conditions or disorders listed or described herein such as inflammatory diseases or cancers, or other proliferate diseases, and in compositions for treating such conditions or disorders. Such conditions and disorders include, without limitation, any of those described previously, as well as those described following such as: maintenance of muscle strength and function (e.g., in the elderly); reversal or prevention of frailty or

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age-related functional decline ("ARFD") in the elderly (e.g., sarcopenia); treatment of catabolic side effects of glucocorticoids; prevention and/or treatment of reduced bone mass, density or growth (e.g., osteoporosis and osteopenia); treatment of chronic fatigue syndrome (CFS); chronic malagia; treatment of acute fatigue syndrome and muscle loss following elective surgery (e.g., post-surgical rehabilitation); acceleration of wound healing; accelerating bone fracture repair (such as accelerating the recovery of hip fracture patients); accelerating healing of complicated fractures, e.g. distraction osteogenesis; in joint replacement; prevention of post-surgical adhesion formation; acceleration of tooth repair or growth; maintenance of sensory function (e.g., hearing, sight, olefaction and taste); treatment of periodontal disease; treatment of wasting secondary to fractures and wasting in connection with chronic obstructive pulmonary disease (COPD), chronic liver disease, AIDS, weightlessness, cancer cachexia, burn and trauma recovery, chronic catabolic state (e.g., coma), eating disorders (e.g., anorexia) and chemotherapy; treatment of cardiomyopathy; treatment of thrombocytopenia; treatment of growth retardation in connection with Crohn's disease; treatment of short bowel syndrome; treatment of irritable bowel syndrome; treatment of inflammatory bowel disease; treatment of Crohn's disease and ulcerative colits; treatment of complications associated with transplantation; treatment of physiological short stature including growth hormone deficient children and short stature associated with chronic illness; treatment of obesity and growth retardation associated with obesity; treatment of anorexia (e.g., associated with cachexia or aging); treatment of hypercortisolism and Cushing's syndrome; Paget's disease; treatment of osteoarthritis; induction of pulsatile growth hormone release; treatment of osteochondrodysplasias; treatment of depression, nervousness, irritability and stress; treatment of reduced mental energy and low self-esteem (e.g., motivation/assertiveness); improvement of cognitive function (e.g., the

treatment of dementia, including Alzheimer's disease and short term memory loss); treatment of catabolism in connection with pulmonary dysfunction and ventilator dependency; treatment of cardiac dysfunction (e.g., associated with valvular disease, myocardial infarction, cardiac hypertrophy or congestive heart failure); lowering blood pressure; protection against ventricular dysfunction or prevention of reperfusion events; treatment of adults in chronic dialysis; reversal or slowing of the catabolic state of aging; attenuation or reversal of protein catabolic responses following trauma (e.g., reversal of the catabolic state associated with surgery, congestive heart failure, cardiac myopathy, burns, cancer, COPD etc.); reducing cachexia and protein loss due to chronic illness such as cancer or AIDS; treatment of hyperinsulinemia including nesidioblastosis; treatment of immunosuppressed patients; treatment of wasting in connection with multiple sclerosis or other neurodegenerative disorders; promotion of myelin repair; maintenance of skin thickness; treatment of metabolic homeostasis and renal homeostasis (e.g., in the frail elderly); stimulation of osteoblasts, bone remodeling and cartilage growth; regulation of food intake; treatment of insulin resistance, including NIDDM, in mammals (e.g., humans); treatment of insulin resistance in the heart; improvement of sleep quality and correction of the relative hyposomatotropism of senescence due to high increase in REM sleep and a decrease in REM latency; treatment of hypothermia; treatment of congestive heart failure; treatment of lipodystrophy (e.g., in patients taking HIV or AIDS therapies such as protease inhibitors); treatment of muscular atrophy (e.g., due to physical inactivity, bed rest or reduced weight-bearing conditions); treatment of musculoskeletal impairment (e.g., in the elderly); improvement of the overall pulmonary function; treatment of sleep disorders; and the treatment of the catabolic state of prolonged critical illness; treatment of hirsutism, acne, seborrhea, androgenic alopecia, anemia, hyperpilosity, benign prostate hypertrophy, adenomas and neoplasies of the

prostate (e.g., advanced metastatic prostate cancer) and malignant tumor cells containing the androgen receptor, such as is the case for breast, brain, skin, ovarian, bladder, lymphatic, liver and kidney cancers; cancers of the skin, pancreas, endometrium, lung and colon; osteosarcoma; hypercalcemia of malignancy; metastatic bone disease; treatment of spermatogenesis, endometriosis and polycystic ovary syndrome; conteracting preeclampsia, eclampsia of pregnancy and preterm labor; treatment of premenstrual syndrome; treatment of vaginal dryness; age related decreased testosterone levels in men, male menopause, hypogonadism, male hormone replacement, male and female sexual dysfunction (e.g., erectile dysfunction, decreased sex drive, sexual well-being, decreased libido), male and female contraception, hair loss, Reaven's Syndrome and the enhancement of bone and muscle performance/strength; and the conditions, diseases, and maladies collectively referenced to as "Syndrome X" or Metabolic Syndrome as detailed in Johannsson *J. Clin. Endocrinol. Metab.*, 82, 727-34 (1997).

The present compounds have therapeutic utility in the modulation of immune cell activation/proliferation, e.g., as competitive inhibitors of intercellular ligand/receptor binding reactions involving CAMs (Cellular Adhesion Molecules) and Leukointegrins. For example, the present compounds modulate LFA-ICAM 1, and are particularly useful as LFA-ICAM 1 antagonists, and in the treatment of all conditions associated with LFA-ICAM 1 such as immunological disorders. Preferred utilities for the present compounds include, but are not limited to: inflammatory conditions such as those resulting from a response of the non-specific immune system in a mammal (e.g., adult respiratory distress syndrome, shock, oxygen toxicity, multiple organ injury syndrome secondary to septicemia, multiple organ injury syndrome secondary to trauma, reperfusion injury of tissue due to cardiopulmonary bypass, myocardial infarction or use with thrombolysis agents, acute glomerulonephritis, vasculitis, reactive arthritis, dermatosis with acute inflammatory components, stroke, thermal injury, hemodialysis, leukapheresis, ulcerative colitis,

necrotizing enterocolitis and granulocyte transfusion associated syndrome) and conditions resulting from a response of the specific immune system in a mammal (e.g., psoriasis, organ/tissue transplant rejection, graft vs. host reactions and autoimmune diseases including Raynaud's syndrome, autoimmune thyroiditis, dermatitis, multiple sclerosis, rheumatoid arthritis, insulin-dependent diabetes mellitus, uveitis, inflammatory bowel disease including Crohn's disease and ulcerative colitis, and systemic lupus erythematosus). The present compounds can be used in treating asthma or as an adjunct to minimize toxicity with cytokine therapy in the treatment of cancers. The present compounds can be employed in the treatment of all diseases currently treatable through steroid therapy. The present compounds may be employed for the treatment of these and other disorders alone or with other immunosuppressive or antiinflammatory agents. In accordance with the invention, a compound of the formula I can be administered prior to the onset of inflammation (so as to suppress an anticipated inflammation) or after the initiation of inflammation. When provided prophylactically, the immunosupressive compound(s) are preferably provided in advance of any inflammatory response or symptom (for example, prior to, at, or shortly after the time of an organ or tissue transplant but in advance of any symptoms or organ rejection). The prophylactic administration of a compound of the formula I prevents or attenuates any subsequent inflammatory response (such as, for example, rejection of a transplanted organ or tissue, etc.) Administration of a compound of the formula I attenuates any actual inflammation (such as, for example, the rejection of a transplanted organ or tissue).

The compounds of the formula I can be administered for any of the uses described herein by any suitable means, for example, orally, such as in the form of tablets, capsules, granules or powders; sublingually; bucally; parenterally, such as by subcutaneous, intravenous, intramuscular, or intrasternal injection or infusion techniques (e.g., as sterile injectable aqueous or non-aqueous solutions or suspensions); nasally, including administration to the nasal membranes, such as by inhalation spray; topically, such as in the form of a cream or ointment; or rectally such as in the form of suppositories; in dosage unit formulations containing non-toxic, pharmaceutically acceptable vehicles or diluents. The present compounds can, for example, be administered in a form suitable for immediate release or extended

release. Immediate release or extended release can be achieved by the use of suitable pharmaceutical compositions comprising the present compounds, or, particularly in the case of extended release, by the use of devices such as subcutaneous implants or osmotic pumps. The present compounds can also be administered liposomally.

Exemplary compositions for oral administration include suspensions which can contain, for example, microcrystalline cellulose for imparting bulk, alginic acid or sodium alginate as a suspending agent, methylcellulose as a viscosity enhancer, and sweeteners or flavoring agents such as those known in the art; and immediate release tablets which can contain, for example, microcrystalline cellulose, dicalcium phosphate, starch, magnesium stearate and/or lactose and/or other excipients, binders, extenders, disintegrants, diluents and lubricants such as those known in the art. The compounds of formula I can also be delivered through the oral cavity by sublingual and/or buccal administration. Molded tablets, compressed tablets or freeze-dried tablets are exemplary forms which may be used. Exemplary compositions include those formulating the present compound(s) with fast dissolving diluents such as mannitol, lactose, sucrose and/or cyclodextrins. Also included in such formulations may be high molecular weight excipients such as celluloses (avicel) or polyethylene glycols (PEG). Such formulations can also include an excipient to aid mucosal adhesion such as hydroxy propyl cellulose (HPC), hydroxy propyl methyl cellulose (HPMC), sodium carboxy methyl cellulose (SCMC), maleic anhydride copolymer (e.g., Gantrez), and agents to control release such as polyacrylic copolymer (e.g. Carbopol 934). Lubricants, glidants, flavors, coloring agents and stabilizers may also be added for ease of fabrication and use.

Exemplary compositions for nasal aerosol or inhalation administration include solutions in saline which can contain, for example, benzyl alcohol or other suitable preservatives, absorption promoters to enhance bioavailability, and/or other solubilizing or dispersing agents such as those known in the art.

Exemplary compositions for parenteral administration include injectable solutions or suspensions which can contain, for example, suitable non-toxic, parenterally acceptable diluents or solvents, such as mannitol, 1,3-butanediol, water, Ringer's solution, an isotonic sodium chloride solution, or other suitable dispersing or

wetting and suspending agents, including synthetic mono- or diglycerides, and fatty acids, including oleic acid, or Cremaphor.

Exemplary compositions for rectal administration include suppositories which can contain, for example, a suitable non-irritating excipient, such as cocoa butter, synthetic glyceride esters or polyethylene glycols, which are solid at ordinary temperatures, but liquify and/or dissolve in the rectal cavity to release the drug.

Exemplary compositions for topical administration include a topical carrier such as Plastibase (mineral oil gelled with polyethylene).

The effective amount of a compound of the present invention can be determined by one of ordinary skill in the art, and includes exemplary dosage amounts for an adult human of from about 1 to 100 (for example, 15 or lower, especially 1 to 3 or less) mg/kg of body weight of active compound per day, which can be administered in a single dose or in the form of individual divided doses, such as from 1 to 4 times per day. It will be understood that the specific dose level and frequency of dosage for any particular subject can be varied and will depend upon a variety of factors including the activity of the specific compound employed, the metabolic stability and length of action of that compound, the species, age, body weight, general health, sex and diet of the subject, the mode and time of administration, rate of excretion, drug combination, and severity of the particular condition. Preferred subjects for treatment include animals, most preferably mammalian species such as humans, and domestic animals such as dogs, cats and the like, subject to NHR-associated conditions.

As mentioned above, the compounds of the present invention can be employed alone or in combination with each other and/or other suitable therapeutic agents useful in the treatment of NHR-associated conditions, e.g., an antibiotic or other pharmaceutically active material.

For example, the compounds of the present invention can be combined with growth promoting agents, such as, but not limited to, TRH, diethylstilbesterol, theophylline, enkephalins, E series prostaglandins, compounds disclosed in U.S. Patent No. 3,239,345, e.g., zeranol, and compounds disclosed in U.S. Patent No. 4,036,979, e.g., sulbenox or peptides disclosed in U.S. Patent No. 4,411,890.

The compounds of the invention can also be used in combination with growth hormone secretagogues such as GHRP-6, GHRP-1 (as described in U.S. Patent No. 4,411,890 and publications WO 89/07110 and WO 89/07111), GHRP-2 (as described in WO 93/04081), NN703 (Novo Nordisk), LY444711 (Lilly), MK-677 (Merck), CP424391 (Pfizer) and B-HT920, or with growth hormone releasing factor and its analogs or growth hormone and its analogs or somatomedins including IGF-1 and IGF-2, or with alpha-adrenergic agonists, such as clonidine or serotinin 5-HT_D agonists, such as sumatriptan, or agents which inhibit somatostatin or its release, such as physostigmine and pyridostigmine. A still further use of the disclosed compounds of the invention is in combination with parathyroid hormone, PTH(1-34) or bisphosphonates, such as MK-217 (alendronate).

A still further use of the compounds of the invention is in combination with estrogen, testosterone, a selective estrogen receptor modulator, such as tamoxifen or raloxifene, or other androgen receptor modulators, such as those disclosed in Edwards, J. P. et al., *Bio. Med. Chem. Let.*, 9, 1003-1008 (1999) and Hamann, L. G. et al., *J. Med. Chem.*, 42, 210-212 (1999).

A further use of the compounds of this invention is in combination with progesterone receptor agonists ("PRA"), such as levonorgestrel, medroxyprogesterone acetate (MPA).

The compounds of the present invention can be employed alone or in combination with each other and/or other modulators of nuclear hormone receptors or other suitable therapeutic agents useful in the treatment of the aforementioned disorders including: anti-diabetic agents; anti-osteoporosis agents; anti-obesity agents; anti-inflammatory agents; anti-anxiety agents; anti-depressants; anti-hypertensive agents; anti-platelet agents; anti-thrombotic and thrombolytic agents; cardiac glycosides; cholesterol/lipid lowering agents; mineralocorticoid receptor antagonists; phospodiesterase inhibitors; protein tyrosine kinase inhibitors; thyroid mimetics (including thyroid receptor agonists); anabolic agents; HIV or AIDS

therapies; therapies useful in the treatment of Alzheimer's disease and other cognitive disorders; therapies useful in the treatment of sleeping disorders; anti-proliferative agents; and anti-tumor agents.

Examples of suitable anti-diabetic agents for use in combination with the compounds of the present invention include biguanides (e.g., metformin), glucosidase inhibitors (e.g,. acarbose), insulins (including insulin secretagogues or insulin sensitizers), meglitinides (e.g., repaglinide), sulfonylureas (e.g., glimepiride, glyburide and glipizide), biguanide/glyburide combinations (e.g., Glucovance®), thiazolidinediones (e.g., troglitazone, rosiglitazone and pioglitazone), PPAR-alpha agonists, PPAR-gamma agonists, PPAR alpha/gamma dual agonists, SGLT2 inhibitors, glycogen phosphorylase inhibitors, inhibitors of fatty acid binding protein (aP2) such as those disclosed in U.S. Serial No. 09/519,079 filed March 6, 2000, glucagon-like peptide-1 (GLP-1), and dipeptidyl peptidase IV (DP4) inhibitors.

Examples of suitable anti-osteoporosis agents for use in combination with the compounds of the present invention include alendronate, risedronate, PTH, PTH fragment, raloxifene, calcitonin, steroidal or non-steroidal progesterone receptor agonists, RANK ligand antagonists, calcium sensing receptor antagonists, TRAP inhibitors, selective estrogen receptor modulators (SERM), estrogen and AP-1 inhibitors.

Examples of suitable anti-obesity agents for use in combination with the compounds of the present invention include aP2 inhibitors, such as those disclosed in U.S. Serial No. 09/519,079 filed March 6, 2000, PPAR gamma antagonists, PPAR delta agonists, beta 3 adrenergic agonists, such as AJ9677 (Takeda/Dainippon), L750355 (Merck), or CP331648 (Pfizer) or other known beta 3 agonists as disclosed in U.S. Patent Nos. 5,541,204, 5,770,615, 5,491,134, 5,776,983 and 5,488,064, a lipase inhibitor, such as orlistat or ATL-962 (Alizyme), a serotonin (and dopamine) reuptake inhibitor, such as sibutramine, topiramate (Johnson & Johnson) or axokine (Regeneron), a thyroid receptor beta drug, such as a thyroid receptor ligand as

disclosed in WO 97/21993 (U. Cal SF), WO 99/00353 (KaroBio) and GB98/284425 (KaroBio), and/or an anorectic agent, such as dexamphetamine, phentermine, phenylpropanolamine or mazindol.

Examples of suitable anti-inflammatory agents for use in combination with the compounds of the present invention include prednisone, dexamethasone, Enbrel®, cyclooxygenase inhibitors (i.e., COX-1 and/or COX-2 inhibitors such as NSAIDs, aspirin, indomethacin, ibuprofen, piroxicam, Naproxen®, Celebrex®, Vioxx®), CTLA4-Ig agonists/antagonists, CD40 ligand antagonists, IMPDH inhibitors, such as mycophenolate (CellCept®) integrin antagonists, alpha-4 beta-7 integrin antagonists, cell adhesion inhibitors, interferon gamma antagonists, ICAM-1, tumor necrosis factor (TNF) antagonists (e.g., infliximab, OR1384), prostaglandin synthesis inhibitors, budesonide, clofazimine, CNI-1493, CD4 antagonists (e.g., priliximab), p38 mitogen-activated protein kinase inhibitors, protein tyrosine kinase (PTK) inhibitors, IKK inhibitors, and therapies for the treatment of irritable bowel syndrome (e.g., Zelmac® and Maxi-K® openers such as those disclosed in U.S. Patent No. 6,184,231 B1).

Example of suitable anti-anxiety agents for use in combination with the compounds of the present invention include diazepam, lorazepam, buspirone, oxazepam, and hydroxyzine pamoate.

Examples of suitable anti-depressants for use in combination with the compounds of the present invention include citalopram, fluoxetine, nefazodone, sertraline, and paroxetine.

Examples of suitable anti-hypertensive agents for use in combination with the compounds of the present invention include beta adrenergic blockers, calcium channel blockers (L-type and T-type; e.g. diltiazem, verapamil, nifedipine, amlodipine and mybefradil), diuretics (e.g., chlorothiazide, hydrochlorothiazide, flumethiazide, hydroflumethiazide, bendroflumethiazide, methylchlorothiazide, trichloromethiazide, polythiazide, benzthiazide, ethacrynic acid tricrynafen, chlorthalidone, furosemide,

musolimine, bumetanide, triamtrenene, amiloride, spironolactone), renin inhibitors, ACE inhibitors (e.g., captopril, zofenopril, fosinopril, enalapril, ceranopril, cilazopril, delapril, pentopril, quinapril, ramipril, lisinopril), AT-1 receptor antagonists (e.g., losartan, irbesartan, valsartan), ET receptor antagonists (e.g., sitaxsentan, atrsentan and compounds disclosed in U.S. Patent Nos. 5,612,359 and 6,043,265), Dual ET/AII antagonist (e.g., compounds disclosed in WO 00/01389), neutral endopeptidase (NEP) inhibitors, vasopepsidase inhibitors (dual NEP-ACE inhibitors) (e.g., omapatrilat and gemopatrilat), and nitrates.

Examples of suitable anti-platelet agents for use in combination with the compounds of the present invention include GPIIb/IIIa blockers (e.g., abciximab, eptifibatide, tirofiban), P2Y12 antagonists (e.g., clopidogrel, ticlopidine, CS-747), thromboxane receptor antagonists (e.g., ifetroban), aspirin, and PDE-III inhibitors (e.g., dipyridamole) with or without aspirin.

Examples of suitable cardiac glycosides for use in combination with the compounds of the present invention include digitalis and ouabain.

Examples of suitable cholesterol/lipid lowering agents for use in combination with the compounds of the present invention include HMG-CoA reductase inhibitors (e.g., pravastatin, lovastatin, atorvastatin, simvastatin, NK-104 (a.k.a. itavastatin, or nisvastatin or nisbastatin) and ZD-4522 (a.k.a. rosuvastatin, or stavastatin or visastatin)), squalene synthetase inhibitors, fibrates, bile acid sequestrants, ACAT inhibitors, MTP inhibitors, lipooxygenase inhibitors, cholesterol absorption inhibitors, and cholesterol ester transfer protein inhibitors (e.g., CP-529414).

Examples of suitable mineralocorticoid receptor antagonists for use in combination with the compounds of the present invention include spironolactone and eplerinone.

Examples of suitable phospodiesterase inhibitors for use in combination with the compounds of the present invention include PDEIII inhibitors such as cilostazol, and PDE V inhibitors such as sildenafil.

Examples of suitable thyroid mimetics for use in combination with the compounds of the present invention include thyrotropin, polythyroid, KB-130015, and dronedarone.

Examples of suitable anabolic agents for use in combination with the compounds of the present invention include testosterone, TRH diethylstilbesterol, estrogens, β-agonists, theophylline, anabolic steroids, dehydroepiandrosterone, enkephalins, E-series prostagladins, retinoic acid and compounds as disclosed in U.S. Pat. No. 3,239,345, e.g., Zeranol®; U.S. Patent No. 4,036,979, e.g., Sulbenox® or peptides as disclosed in U.S. Pat. No. 4,411,890.

Examples of suitable HIV or AIDS therapies for use in combination with the compounds of the present invention include indinavir sulfate, saquinavir, saquinavir mesylate, ritonavir, lamivudine, zidovudine, lamivudine/zidovudine combinations, zalcitabine, didanosine, stavudine, and megestrol acetate.

Examples of suitable therapies for treatment of Alzheimer's disease and cognitive disorders for use in combination with the compounds of the present invention include donepezil, tacrine, revastigmine, 5HT6, gamma secretase inhibitors, beta secretase inhibitors, SK channel blockers, Maxi-K blockers, and KCNQs blockers.

Examples of suitable therapies for treatment of sleeping disorders for use in combination with the compounds of the present invention include melatonin analogs, melatonin receptor antagonists, ML1B agonists, and GABA/NMDA receptor antagonists.

Examples of suitable anti-proliferative agents for use in combination with the compounds of the present invention include cyclosporin A, paclitaxel, FK 506, and adriamycin.

Examples of suitable anti-tumor agents for use in combination with the compounds of the present invention include paclitaxel, adriamycin, epothilones, cisplatin and carboplatin.

Compounds of the present invention can further be used in combination with nutritional supplements such as those described in U.S. 5,179,080, especially in combination with whey protein or casin, amino acids (such as leucine, branched amino acids and hydroxymethylbutyrate), triglycerides, vitamins (e.g., A, B6, B12, folate, C, D and E), minerals (e.g., selenium, magnesium, zinc, chromium, calcium and potassium), carnitine, lipoic acid, creatine, and coenzyme Q-10.

In addition, compounds of the present invention can be used in combination with therapeutic agents used in the treatment of sexual dysfunction, including but not limited to PDE5 inhibitors, such as sildenafil or IC-351; with an antiresorptive agent, hormone replacement therapies, vitamin D analogues, calcitonins, elemental calcium and calcium supplements, cathepsin K inhibitors, MMP inhibitors, vitronectin receptor antagonists, Src SH_2 antagonists, vacular $-H^+$- ATPase inhibitors, progesterone receptor agonists, ipriflavone, fluoride, RANK antagonists, PTH and its analogues and fragments, Tibolone, HMG-CoA reductase inhibitors, SERM's, p38 inhibitors, prostanoids, 17-beta hydroxysteroid dehydrogenase inhibitors and Src kinase inhibitors.

Compounds of the present invention can be used in combination with male contraceptives, such as nonoxynol 9 or therapeutic agents for the treatment of hair loss, such as minoxidil and finasteride or chemotherapeutic agents, such as with LHRH agonists.

For their preferred anticancer or antiangiogenic use, the compounds of the present invention can be administered either alone or in combination with other anti-cancer and cytotoxic agents and treatments useful in the treatment of cancer or other proliferative diseases, for example, where the second drug has the same or different mechanism of action than the present compounds of formula I. Examples of classes of anti-cancer and cytotoxic agents useful in combination with the present compounds include but are not limited to: alkylating agents such as nitrogen mustards, alkyl sulfonates, nitrosoureas, ethylenimines, and triazenes; EGFR inhibitors such as small molecule EGFR inhibitors, EGFR antibodies such as C225 (Erbitux); antimetabolites such as folate antagonists, purine analogues, and pyrimidine analogues; antibiotics

such as anthracyclines, bleomycins, mitomycin, dactinomycin, and plicamycin; enzymes such as L-asparaginase; farnesyl-protein transferase inhibitors; 5α reductase inhibitors; inhibitors of 17β-hydroxy steroid dehydrogenase type 3 or type 1; hormonal agents such as glucocorticoids, estrogens/ antiestrogens, androgens/ antiandrogens, progestins, and luteinizing hormone-releasing hormone antagonists, octreotide acetate; microtubule-disruptor agents, such as ecteinascidins or their analogs and derivatives; microtubule-stabilizing agents such as taxanes, for example, paclitaxel (Taxol®), docetaxel (Taxotere®), and their analogs, and epothilones, such as epothilones A-F and their analogs; plant-derived products, such as vinca alkaloids, epipodophyllotoxins, taxanes; and topiosomerase inhibitors; prenyl-protein transferase inhibitors; and miscellaneous agents such as hydroxyurea, procarbazine, mitotane, hexamethylmelamine, platinum coordination complexes such as cisplatin and carboplatin; and other agents used as anti-cancer and cytotoxic agents such as biological response modifiers, growth factors; immune modulators and monoclonal antibodies. The compounds of the invention may also be used in conjunction with radiation therapy.

Representative examples of these classes of anti-cancer and cytotoxic agents include but are not limited to mechlorethamine hydrochloride, cyclophosphamide, chlorambucil, melphalan, ifosfamide, busulfan, carmustin, lomustine, semustine, streptozocin, thiotepa, dacarbazine, methotrexate, thioguanine, mercaptopurine, fludarabine, pentastatin, cladribin, cytarabine, fluorouracil, doxorubicin hydrochloride, daunorubicin, idarubicin, bleomycin sulfate, mitomycin C, actinomycin D, safracins, saframycins, quinocarcins, discodermolides, vincristine, vinblastine, vinorelbine tartrate, etoposide, etoposide phosphate, teniposide, paclitaxel, tamoxifen, estramustine, estramustine phosphate sodium, flutamide, buserelin, leuprolide, pteridines, diyneses, levamisole, aflacon, interferon, interleukins, aldesleukin, filgrastim, sargramostim, rituximab, BCG, tretinoin, irinotecan hydrochloride, betamethosone, gemcitabine hydrochloride, altretamine, and topoteca and any analogs or derivatives thereof.

Preferred member of these classes include, but are not limited to, paclitaxel, cisplatin, carboplatin, doxorubicin, carminomycin, daunorubicin, aminopterin, methotrexate, methopterin, mitomycin C, ecteinascidin 743, or porfiromycin, 5-

fluorouracil, 6-mercaptopurine, gemcitabine, cytosine arabinoside, podophyllotoxin or podophyllotoxin derivatives such as etoposide, etoposide phosphate or teniposide, melphalan, vinblastine, vincristine, leurosidine, vindesine and leurosine.

Examples of anticancer and other cytotoxic agents include the following: epothilone derivatives as found in German Patent No. 4138042.8; WO 97/19086, WO 98/22461, WO 98/25929, WO 98/38192, WO 99/01124, WO 99/02224, WO 99/02514, WO 99/03848, WO 99/07692, WO 99/27890, WO 99/28324, WO 99/43653, WO 99/54330, WO 99/54318, WO 99/54319, WO 99/65913, WO 99/67252, WO 99/67253 and WO 00/00485; cyclin dependent kinase inhibitors as found in WO 99/24416 (see also U.S. Patent No. 6,040,321); and prenyl-protein transferase inhibitors as found in WO 97/30992 and WO 98/54966; and agents such as those described generically and specifically in U.S. Patent No. 6,011,029 (the compounds of which U.S. Patent can be employed together with any NHR modulators (including, but not limited to, those of present invention) such as AR modulators, ER modulators, with LHRH modulators, or with surgical castration, especially in the treatment of cancer).

The combinations of the present invention can also be formulated or co-administered with other therapeutic agents that are selected for their particular usefulness in administering therapies associated with the aforementioned conditions. For example, the compounds of the invention may be formulated with agents to prevent nausea, hypersensitivity and gastric irritation, such as antiemetics, and H_1 and H_2 antihistaminics.

As it pertains to the treatment of cancer, the compounds of this invention are most preferably used alone or in combination with anti-cancer treatments such as radiation therapy and/or with cytostatic and/or cytotoxic agents, such as, but not limited to, DNA interactive agents, such as cisplatin or doxorubicin; inhibitors of farnesyl protein transferase, such as those described in U.S. Patent No. 6,011,029; topoisomerase II inhibitors, such as etoposide; topoisomerase I inhibitors, such as CPT-11 or topotecan; tubulin stabilizing agents, such as paclitaxel, docetaxel, other taxanes, or epothilones; hormonal agents, such as tamoxifen; thymidilate synthase inhibitors, such as 5-fluorouracil; antimetabolites, such as methoxtrexate; antiangiogenic agents, such as angiostatin, ZD6474, ZD6126 and comberstatin A2;

kinase inhibitors, such as her2 specific antibodies, Iressa and CDK inhibitors; histone deacetylase inhibitors, such as CI-994 and MS-27-275. Such compounds may also be combined with agents which suppress the production of circulating testosterone such as LHRH agonists or antagonists or with surgical castration. Exemplary combination therapies (e.g., for the treatment of prostate cancer) for use with a compound of the present invention include an LHRH modulator or prednisone.

The present invention also contemplates kits, for example, for the treatment of prostate cancer, comprising a first container (such as a vial) containing a pharmaceutical formulation comprising a compound of the present invention, said compound optionally in a pharmaceutically acceptable carrier, and a second container (such as a vial) containing a pharmaceutical formulation comprising one or more agents (such as an LHRH modulator) to be used in combination with said compound of the present invention, said agent(s) optionally in a pharmaceutically acceptable carrier.

For example, known therapies for advanced metastatic prostate cancer include "complete androgen ablation therapy" wherein tumor growth is inhibited by controlling the supply of androgen to the prostate tissues via chemical castration (castration serves to inhibit the production of circulating testosterone (T) and dihydrotestosterone (DHT)) followed by the administration of androgen receptor (AR) antagonists (which inhibit the function T/DHT derived from the conversion of circulating androgen precursors to T/DHT by the prostate tissue). The compounds of the present invention can be employed as AR antagonists in complete ablation therapy, alone or in combination with other AR antagonists such as Flutamide, Casodex, Nilutamide, or Cyproterone acetate.

The present invention provides compounds which can be used to treat patients suffering from prostate cancer resistant to androgen receptor antagonists which are not within formula I of the invention (or salts thereof), such as bicalutimide. The invention thus further contemplates a method of treating prostate cancer resistant to an androgen receptor antagonist other than those of formula I or salts thereof, comprising the step of administering to a patient in need thereof a compound capable of reducing the growth rate of the tumor mass of said cancer in an amount effective therefor. The term "reducing the growth rate of said tumor mass" denotes reduction in the growth

rate (including, of course, stabilization or reduction in size) of said tumor mass upon treatment relative to the growth rate upon treatment with said androgen receptor antagonist other than those of formula I or salts thereof. Compounds of the formula I and pharmaceutically acceptable salts thereof of the present invention are preferred such compounds.

The present invention also contemplates use of an antiestrogen and/or aromatase inhibitor in combination with a compound of the present invention, for example, to assist in mitigating side effects associated with antiandrogen therapy such as gynecomastia. Exemplary antiestrogen and/or aromatase inhibitors include anastrozole (Arimidex), tamoxifen citrate (Nolvadex), exemestane (Aromasin), toremifene citrate (Fareston), letrozole (Femara), raloxifene hydrochloride (Evista), Faslodex, or 923 (Wyeth Ayerst).

The compounds of the present invention may be employed adjuvant to surgery.

Another application of the present compounds is in combination with antibody therapy such as but not limited to antibody therapy against PSCA. An additional application is in concert with vaccine / immune modulating agents for the treatment of cancer.

Compounds of the present invention can be employed in accordance with the methods described in U.S. Provisional Patent Application Serial No. 60/284,438, entitled "Selective Androgen Receptor Modulators and Methods for Their Identification, Design and Use" filed April 18, 2001 by Mark E. Salvati *et al.* (Attorney Docket No. LD0250(PSP)), which Provisional Patent Application is incorporated herein by reference in its entirety (including, but not limited to, reference to all specific compounds within formula I of the present invention), and U.S. Patent Application Serial No. 09/885,827, entitled "Selective Androgen Receptor Modulators and Methods for Their Identification, Design and Use" filed June 20, 2001 by Mark E. Salvati *et al.* (Attorney Docket No. LD0250(NP)), which Patent Application is incorporated herein by reference in its entirety (including, but not limited to, reference to all specific compounds within formula I of the present invention).

For racemates of compounds of the present invention, one enantiomer can, for example be a full AR antagonist while the other can be an AR antagonist in tumor tissue while having no activity or agonist activity in nontumor tissue containing the androgen receptor.

The above other therapeutic agents, when employed in combination with the compounds of the present invention, can be used, for example, in those amounts indicated in the Physicians' Desk Reference (PDR) or as otherwise determined by one of ordinary skill in the art.

The following assays can be employed in ascertaining the activity of a compound as a NHR modulator. Preferred are those compounds with an activity greater than 20μm for binding or transactivation in any of these assays. Various compounds of the present invention were determined to have AR modulator activity utilizing the transactivation assay, and standard AR binding assays as described following.

Transactivation Assays:

AR Specific Assay:

Compounds of the present invention were tested in transactivation assays of a transfected reporter construct and using the endogenous androgen receptor of the host cells. The transactivation assay provides a method for identifying functional agonists and partial agonists that mimic, or antagonists that inhibit, the effect of native hormones, in this case, dihydrotestosterone (DHT). This assay can be used to predict *in vivo* activity as there is a good correlation in both series of data. See, e.g. T. Berger et al., *J. Steroid Biochem. Molec. Biol.* 773 (1992), the disclosure of which is herein incorporated by reference.

For the transactivation assay a reporter plasmid is introduced by transfection (a procedure to induce cells to take foreign genes) into the respective cells. This reporter plasmid, comprising the cDNA for a reporter protein, such as secreted alkaline phosphatase (SEAP), controlled by prostate specific antigen (PSA) upstream sequences containing androgen response elements (AREs). This reporter plasmid functions as a reporter for the transcription-modulating activity of the AR.

Thus, the reporter acts as a surrogate for the products (mRNA then protein) normally expressed by a gene under control of the AR and its native hormone. In order to detect antagonists, the transactivation assay is carried out in the presence of constant concentration of the natural AR hormone (DHT) known to induce a defined reporter signal. Increasing concentrations of a suspected antagonist will decrease the reporter signal (e.g., SEAP production). On the other hand, exposing the transfected cells to increasing concentrations of a suspected agonist will increase the production of the reporter signal.

For this assay, LNCaP and MDA 453 cells were obtained from the American Type Culture Collection (Rockville, MD), and maintained in RPMI 1640 or DMEM medium supplemented with 10% fetal bovine serum (FBS; Gibco) respectively. The respective cells were transiently transfected by electroporation according to the optimized procedure described by Heiser, 130 Methods Mol. Biol., 117 (2000), with the pSEAP2/PSA540/Enhancer reporter plasmid. The reporter plasmid, was constructed as follows: commercial human placental genomic DNA was used to generate by Polymerase Cycle Reaction (PCR) a fragment containing the BglII site (position 5284) and the Hind III site at position 5831 of the human prostate specific antigen promoter (Accession # U37672), Schuur, et al., *J. Biol. Chem.*, 271 (12): 7043-51 (1996). This fragment was subcloned into the pSEAP2/basic (Clontech) previously digested with BglII and HindIII to generate the pSEAP2/PSA540 construct. Then a fragment bearing the fragment of human PSA upstream sequence between positions –5322 and –3873 was amplified by PCR from human placental genomic DNA. A XhoI and a BglII sites were introduced with the primers. The resulting fragment was subcloned into pSEAP2/PSA540 digested with XhoI and BglII respectively, to generate the pSEAP2/PSA540/Enhancer construct. LNCaP and MDA 453 cells were collected in media containing 10% charcoal stripped FBS. Each cell suspension was distributed into two Gene Pulser Cuvetts (Bio-Rad) which then received 8 μg of the reporter construct, and electoporated using a Bio-Rad Gene Pulser at 210 volts and 960 μFaraday. Following the transfections the cells were washed and incubated with media containing charcoal stripped fetal bovine serum in the absence (blank) or presence (control) of 1 nM dihydrotestosterone (DHT; Sigma Chemical) and in the presence or absence of the standard anti-androgen

bicalutamide or compounds of the present invention in concentrations ranging from 10-10 to 10-5 M (sample). Duplicates were used for each sample. The compound dilutions were performed on a Biomek 2000 laboratory workstation.

After 48 hours, a fraction of the supernatant was assayed for SEAP activity using the Phospha-Light Chemiluminescent Reporter Gene Assay System (Tropix, Inc). Viability of the remaining cells was determined using the CellTiter 96 Aqueous Non-Radioactive Cell Proliferation Assay (MTS Assay, Promega). Briefly, a mix of a tetrazolium compound (3-(4,5-dimethylthiazol-2-yl)-5-(3-carboxymethoxyphenyl)- 2-(4-sulfophenyl)-2H-tetrazolium, inner salt; MTS) and an electron coupling reagent (phenazine methosulfate; PMS) are added to the cells. MTS (Owen's reagent) is bioreduced by cells into a formazan that is soluble in tissue culture medium, and therefore its absorbance at 490nm can be measured directly from 96 well assay plates without additional processing. The quantity of formazan product as measured by the amount of 490nm absorbance is directly proportional to the number of living cells in culture. For each replicate the SEAP reading was normalized by the Abs490 value derived from the MTS assay. For the antagonist mode, the % Inhibition was calculated as:

% Inhibition = 100 x (1 – [average control – average blank / average sample – average blank])

Data was plotted and the concentration of compound that inhibited 50% of the normalized SEAP was quantified (IC_{50}).

For the agonist mode % Control was referred as the effect of the tested compound compared to the maximal effect observed with the natural hormone, in this case DHT, and was calculated as:

% Control = 100 x average sample – average blank/ average control – average blank

Data was plotted and the concentration of compound that activates to levels 50% of the normalized SEAP for the control was quantified (EC_{50}).

GR Specificity Assay:

The reporter plasmid utilized was comprised of the cDNA for the reporter SEAP protein, as described for the AR specific transactivation assay. Expression of the reporter SEAP protein was controlled by the mouse mammary tumor virus long terminal repeat (MMTV LTR) sequences that contains three hormone response elements (HREs) that can be regulated by both GR and PR see, e.g. G. Chalepakis et al., Cell, 53(3), 371 (1988). This plasmid was transfected into A549 cells, which expresses endogenous GR, to obtain a GR specific transactivation assay. A549 cells were obtained from the American Type Culture Collection (Rockville, MD), and maintained in RPMI 1640 supplemented with 10% fetal bovine serum (FBS; Gibco). Determination of the GR specific antagonist activity of the compounds of the present invention was identical to that described for the AR specific transactivation assay, except that the DHT was replaced with 5 nM dexamethasone (Sigma Chemicals), a specific agonist for GR. Determination of the GR specific agonist activity of the compounds of the present invention was performed as described for the AR transactivation assay, wherein one measures the activation of the GR specific reporter system by the addition of a test compound, in the absence of a known GR specific agonists ligand.

PR Specific Assay:

The reporter plasmid utilized was comprised of the cDNA for the reporter SEAP protein, as described for the AR specific transactivation assay. Expression of the reporter SEAP protein was controlled by the mouse mammary tumor virus long terminal repeat (MMTV LTR) sequences that contains three hormone response elements (HREs) that can be regulated by both GR and PR. This plasmid was transfected into T47D, which expresses endogenous PR, to obtain a PR specific transactivation assay. T47D cells were obtained from the American Type Culture Collection (Rockville, MD), and maintained in DMEM medium supplemented with 10% fetal bovine serum (FBS; Gibco). Determination of the PR specific antagonist activity of the compounds of the present invention was identical to that described for the AR specific transactivation assay, except that the DHT was

replaced with 1 nM Promegastone (NEN), a specific agonist for PR. Determination of the PR specific agonist activity of the compounds of the present invention was performed as described for the AR transactivation assay, wherein one measures the activation of the PR specific reporter system by the addition of a test compound, in the absence of a known PR specific agonists ligand.

AR Binding Assay:

For the whole cell binding assay, human LNCaP cells (T877A mutant AR) or MDA 453 (wild type AR) in 96-well microtiter plates containing RPMI 1640 or DMEM supplemented with 10% charcoal stripped CA-FBS (Cocaleco Biologicals) respectively, were incubated at 37°C to remove any endogenous ligand that might be complexed with the receptor in the cells. After 48 hours, either a saturation analysis to determine the K_d for tritiated dihydrotestosterone, [^{3}H]-DHT, or a competitive binding assay to evaluate the ability of test compounds to compete with [^{3}H]-DHT were performed. For the saturation analysis, media (RPMI 1640 or DMEM – 0.2% CA-FBS) containing [^{3}H]-DHT (in concentrations ranging from 0.1 nM to 16 nM) in the absence (total binding) or presence (non-specific binding) of a 500-fold molar excess of unlabeled DHT were added to the cells. After 4 hours at 37°C, an aliquot of the total binding media at each concentration of [^{3}H]-DHT was removed to estimate the amount of free [^{3}H]-DHT. The remaining media was removed, cells were washed three times with PBS and harvested onto UniFilter GF/B plates (Packard), Microscint (Packard) was added and plates counted in a Top-Counter (Packard) to evaluate the amount of bound [^{3}H]-DHT.

For the saturation analysis, the difference between the total binding and the non-specific binding, was defined as specific binding. The specific binding was evaluated by Scatchard analysis to determine the K_d for [^{3}H]-DHT. See e.g. D. Rodbard, Mathematics and statistics of ligand assays: an illustrated guide: In: J. Langon and J. J. Clapp, eds., Ligand Assay, Masson Publishing U.S.A., Inc., New York, pp. 45-99, (1981), the disclosure of which is herein incorporated by reference.

For the competition studies, media containing 1 nM [^{3}H]-DHT and compounds of the invention ("test compounds") in concentrations ranging from 10^{-10} to 10^{-5} M were added to the cells. Two replicates were used for each sample. After 4

hours at 37°C, cells were washed, harvested and counted as described above. The data was plotted as the amount of [^{3}H]-DHT (% of control in the absence of test compound) remaining over the range of the dose response curve for a given compound. The concentration of test compound that inhibited 50% of the amount of [^{3}H]-DHT bound in the absence of competing ligand was quantified (IC_{50}) after log-logit transformation. The K_I values were determined by application of the Cheng-Prusoff equation to the IC_{50} values, where:

$$K_I = \frac{IC_{50}}{(1 + (^3\text{H-DHT}) / K_d \text{ for } ^3\text{H-DHT})}.$$

After correcting for non-specific binding, IC_{50} values were determined. The IC_{50} is defined as the concentration of competing ligand needed to reduce specific binding by 50%. The K_ds for [^{3}H]-DHT for MDA 453 and LNCaP were 0.7 and 0.2 nM respectively.

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Human Prostate Cell Proliferation Assay:

Compounds of the present invention were tested ("test compounds") on the proliferation of human prostate cancer cell lines. For that, MDA PCa2b cells, a cell line derived from the metastasis of a patient that failed castration, Navone et al., *Clin. Cancer Res.*, 3, 2493-500 (1997), were incubated with or without the test compounds for 72 hours and the amount of [^{3}H]-thymidine incorporated into DNA was quantified as a way to assess number of cells and therefore proliferation. The MDA PCa2b cell line was maintained in BRFF-HPC1 media (Biological Research Faculty & Facility Inc., MD) supplemented with 10% FBS. For the assay, cells were plated in Biocoated 96-well microplates and incubated at 37°C in 10% FBS (charcoal-stripped)/BRFF-BMZERO (without androgens). After 24 hours, the cells were treated in the absence (blank) or presence of 1 nM DHT (control) or with test compounds (sample) of the present invention in concentrations ranging from 10^{-10} to 10^{-5} M. Duplicates were used for each sample. The compound dilutions were performed on a Biomek 2000 laboratory work station. Seventy two hours later 0.44 uCi. of [^{3}H]-Thymidine (Amersham) was added per well and incubated for another 24 h followed by tripsinization, harvesting of the cells onto GF/B filters. Micro-scint PS were added to the filters before counting them on a Beckman TopCount.

The % Inhibition was calculated as:

% Inhibition = 100 x (1 – [average$_{control}$ – average$_{blank}$ / average$_{sample}$ – average$_{blank}$])

Data was plotted and the concentration of compound that inhibited 50% of the [^{3}H]-Thymidine incorporation was quantified (IC_{50}).

C2C12 Mouse Myoblast Transactivation Assay:

Two functional transactivation assays were developed to assess the efficacy of androgen agonists in a muscle cell background using a luciferase reporter. The first assay (ARTA Stable 1) uses a cell line, Stable 1 (clone #72), which stably expresses the full length rat androgen receptor but requires the transient transfection of an enhancer/reporter. This cell line was derived from C2C12 mouse moyoblast cells. The second assay (ARTA Stable 2) uses a cell line, Stable 2 (clone #133), derived from Stable 1 which stably expresses both rAR and the enhancer/luciferase reporter.

The enhancer/reporter construct used in this system is pGL3/2XDR-1/luciferase. 2XDR-1 was reported to be an AR specific response element in CV-1 cells, Brown et. al. *The Journal of Biological Chemisty* 272, 8227-8235, (1997). It was developed by random mutagenesis of an AR/GR consensus enhancer sequence.

ARTA Stable 1:

1. Stable 1 cells are plated in 96 well format at 6,000 cells/well in high glucose DMEM without phenol red (Gibco BRL, Cat. No.: 21063-029) containing 10% charcoal and dextran treated FBS (HyClone Cat. No.: SH30068.02), 50 mM HEPES Buffer (Gibco BRL, Cat. No.: 15630-080), 1X MEM Na Pyruvate (Gibco BRL, Cat. No.: 11360-070), 0.5X Antibiotic-Antimycotic, and 800 μg/ml Geneticin (Gibco BRL, Cat. No.: 10131-035).
2. 48 hours later, cells are transfected with pGL3/2XDR-1/luciferase using LipofectAMINE Plus™ Reagent (Gibco BRL, Cat. No.: 10964-013). Specifically, 5 ng/well pGL3/2XDR-1/luciferase DNA and 50 ng/well Salmon Sperm DNA (as carrier) are diluted with 5 μl/well Opti-MEMem media (Gibco BRL, Cat. No.: 31985-070). To this, 0.5 μl/well Plus reagent is added. This mixture is incubated for 15 minutes at room temperature. In a separate vessel, 0.385 μl/well LipofectAMINE reagent is diluted with 5 μl/well Opti-MEM. The DNA mixture is then combined with the LipofectAMINE mixture and incubated for an additional 15 minutes at room temperature. During this time, the media from the cells is removed and replaced with 60 μl/well of Opti-MEM. To this is added 10 μl/well of the DNA/LipofectAMINE transfection mixture. The cells are incubated for 4 hours.
3. The transfection mixture is removed from the cells and replaced with 90 μl of media as in #1 above.
4. 10 μl/well of appropriate drug dilution is placed in each well.
5. 24 hours later, the Steady-Glo™ Luciferase Assay System is used to detect activity according to the manufacturer's instructions (Promega, Cat. No.: E2520).

ARTA stable 2

1. Stable 2 cells are plated in 96 well format at 6,000 cells/well in high glucose DMEM without phenol red (Gibco BRL, Cat. No.: 21063-029) containing 10% charcoal and dextran treated FBS (HyClone Cat. No.: SH30068.02), 50 mM HEPES Buffer (Gibco BRL, Cat. No.: 15630-080), 1X MEM Na Pyruvate (Gibco BRL, Cat. No.: 11360-070), 0.5X Antibiotic-Antimycotic, 800 μg/ml Geneticin (Gibco BRL, Cat. No.: 10131-035) and 800 μg/ml Hygromycin β (Gibco BRL, Cat. No.: 10687-010).
2. 48 hours later, the media on the cells is removed and replaced with 90 μl fresh. 10 μl/well of appropriate drug dilution is placed in each well.
3. 24 hours later, the Steady-GloTM Luciferase Assay System is used to detect activity according to the manufacturer's instructions (Promega, Cat. No.: E2520).

See U.S. Patent Application Serial No. 09/885,831, entitled "Cell Lines and Cell-BasedAssays for Identification of Androgen Receptor Modulators" filed June 20, 2001 by Jacek Ostrowski *et al.* (Attorney Docket No. D0177), which Patent Application is incorporated herein by reference in its entirety.

Proliferation Assays

Murine Breast Cell Proliferation Assay:

The ability of compounds of the present invention ("test compounds") to modulate the function of the AR was determined by testing said compounds in a proliferation assay using the androgen responsive murine breast cell line derived from the Shionogi tumor, Hiraoka *et al., Cancer Res.*, 47, 6560-6564 (1987). Stable AR dependent clones of the parental Shionogi line were established by passing tumor fragments under the general procedures originally described in Tetuo, *et. al., Cancer Research* 25, 1168-1175 (1965). From the above procedure, one stable line, SC114, was isolated, characterized and utilized for the testing of example compounds. SC114 cells were incubated with or without the test compounds for 72 hours and the amount of [3H]-thymidine incorporated into DNA was quantified as a surrogate endpoint to assess the number of cells and therefore the proliferation rate as described in Suzuki *et. al., J. Steroid Biochem. Mol. Biol.* 37, 559-567 (1990). The SC114 cell line was

maintained in MEM containing 10^{-8} M testosterone and 2% DCC-treated FCS. For the assay, cells were plated in 96-well microplates in the maintenance media and incubated at 37°C. On the following day, the medium was changed to serum free medium [Ham's F-12:MEM (1;1, v/v) containing 0.1% BSA] with (antagonist mode) or without (agonist mode) 10^{-8} M testosterone and the test compounds of the present invention in concentrations ranging from 10^{-10} to 10^{-5} M. Duplicates were used for each sample. The compound dilutions were performed on a Biomek 2000 laboratory work station. Seventy two hours later 0.44uCi of [3H]-Thymidine (Amersham) was added per well and incubated for another 2 hr followed by tripsinization, and harvesting of the cells onto GF/B filters. Micro-scint PS were added to the filters before counting them on a Beckman TopCount.

For the antagonist mode, the % Inhibition was calculated as:

$$\% \text{ Inhibition} = 100 \times (1 - [\text{average}_{\text{sample}} - \text{average}_{\text{blank}} / \text{average}_{\text{control}} - \text{average}_{\text{blank}}])$$

Data was plotted and the concentration of compound that inhibited 50% of the [^{3}H]-Thymidine incorporation was quantified (IC_{50}).

For the agonist mode % Control was referred as the effect of the tested compound compared to the maximal effect observed with the natural hormone, in this case DHT, and was calculated as:

$$\% \text{ Control} = 100 \times (\text{average}_{\text{sample}} - \text{average}_{\text{blank}}) / (\text{average}_{\text{control}} - \text{average}_{\text{blank}})$$

Data was plotted and the concentration of compound that inhibited 50% of the [^{3}H]-Thymidine incorporation was quantified (EC_{50}).

In Vitro Assay to Measure GR Induced AP-1 Transrepression:

The AP-1 assay is a cell based luciferase reporter assay. A549 cells, which contain endogenous glucocorticoid receptor, were stably transfected with an AP-1 DNA binding site attached to the luciferase gene. Cells are

then grown in RPMI + 10% fetal calf serum (charcoal-treated) + Penicillin/Streptomycin with 0.5mg/ml geneticin. Cells are plated the day before the assay at approximately 40000 cells/well. On assay day, the media is removed by aspiration and 20 µl assay buffer (RPMI without phenol red + 10% FCS (charcoal-treated) + Pen/Strep) is added to each well. At this point either 20 µl assay buffer (control experiments), the compounds of the present invention ("test compounds") (dissolved in DMSO and added at varying concentrations) or dexamethasome (100 nM in DMSO, positive control) are added to each well. The plates are then pre-incubated for 15 minutes at 37°C, followed by stimulation of the cells with 10 ng/ml PMA. The plates are then incubated for 7 hrs at 37°C after which 40 µl luciferase substrate reagent is added to each well. Activity is measured by analysis in a luminometer as compared to control experiments treated with buffer or dexamethasome. Activity is designated as % inhibition of the reporter system as compared to the buffer control with 10 ng/ml PMA alone. The control, dexamethasone, at a concentration of ≤10 µM typically suppresses activity by 65%. Test compounds which demonstrate an inhibition of PMA induction of 50% or greater at a concentration of test compound of ≤10 µM are deemed active.

Wet Prostate Weight Assay AR Antagonist Assay:

The activity of compounds of the present invention as AR antagonists was investigated in an immature male rat model, a standard, recognized test of antiandrogen activity of a given compound, as described in L. G. Hershberger et al., *Proc. Soc. Expt. Biol. Med.*, 83, 175 (1953); P. C. Walsh and R. F. Gittes, "Inhibition of extratesticular stimuli to prostate growth in the castrated rat by antiandrogens", *Endocrinology*, 86, 624 (1970); and B. J. Furr et al., "ICI 176,334: A novel non-steroid, peripherally selective antiandrogen", *J. Endocrinol.*, 113, R7-9 (1987), the disclosures of which are herein incorporated by reference.

The basis of this assay is the fact that male sexual accessory organs, such as the prostate and seminal vesicles, play an important role in reproductive function.

These glands are stimulated to grow and are maintained in size and secretory function by the continued presence of serum testosterone (T), which is the major serum androgen (>95%) produced by the Leydig cells in the testis under the control of the pituitary luteinizing hormone (LH) and follicle stimulating hormone (FSH). Testosterone is converted to the more active form, dihydrotestosterone, (DHT), within the prostate by 5α-reductase. Adrenal androgens also contribute about 20% of total DHT in the rat prostate, compared to 40% of that in 65-year-old men. F. Labrie et al. Clin. Invest. Med., 16, 475-492 (1993). However, this is not a major pathway, since in both animals and humans, castration leads to almost complete involution of the prostate and seminal vesicles without concomitant adrenalectomy. Therefore, under normal conditions, the adrenals do not support significant growth of prostate tissues. M. C. Luke and D. S. Coffey, "*The Physiology of Reproduction*" ed. By E. Knobil and J. D. Neill, 1, 1435-1487 (1994). Since the male sex organs are the tissues most responsive to modulation of the androgen activity, this model is used to determine the androgen dependent growth of the sex accessory organs in immature castrated rats.

Male immature rats (19-20 days old Sprague-Dawley, Harlan Sprague-Dawely) were castrated under metofane ansestesia. Five days after surgery these castrated rats (60-70g, 23-25 day-old) were dosed for 3 days. Animals were dosed sub-cutaneously (s.c.) 1mg/kg with Testosterone Proprionate (TP) in arachis oil vehicle and anti-androgen test compounds (compounds of the present invention) were dosed orally by gavage (p.o.) in dissolved/suspensions of 80% PEG 400 and 20% Tween 80 (PEGTW). Animals were dosed (v/w) at 0.5 ml of vehicle /100g body weight. Experimental groups were as follows:

1. Control vehicle
2. Testosterone Propionate (TP) (3 mg/rat/day, subcutaneous)
3. TP plus Casodex (administered p.o. in PEGTW, QD) , a recognized antiandrogen, as a reference compound.
4. To demonstrate antagonist activity, a compound of the present invention ("test compound") was administered (p.o. in PEGTW, QD) with TP (s.c. as administered in group 2) in a range of doses.

5. To demonstrate agonist activity a compound of the present invention ("test compound") was administered alone (p.o.. in PEGTW, QD) in a range of doses.

At the end of the 3-day treatment, the animals were sacrificed, and the ventral prostate weighed. To compare data from different experiments, the sexual organs weights were first standardized as mg per 100 g of body weight, and the increase in organ weight induced by TP was considered as the maximum increase (100%). ANOVA followed by one-tailed Student or Fischer's exact test was used for statistical analysis.

The gain and loss of sexual organ weight reflect the changes of the cell number (DNA content) and cell mass (protein content), depending upon the serum androgen concentration. See Y. Okuda et al., *J. Urol.*, **145**, 188-191 (1991), the disclosure of which is herein incorporated by reference. Therefore, measurement of organ wet weight is sufficient to indicate the bioactivity of androgens and androgen antagonist. In immature castrated rats, replacement of exogenous androgens increases seminal vesicles (SV) and the ventral prostate (VP) in a dose dependent manner.

The maximum increase in organ weight was 4 to 5-fold when dosing 3 mg/rat/day of testosterone (T) or 1 mg/rat/day of testosterone propionate (TP) for 3 days. The EC_{50} of T and TP were about 1 mg and 0.03 mg, respectively. The increase in the weight of the VP and SV also correlated with the increase in the serum T and DHT concentration. Although administration of T showed 5-times higher serum concentrations of T and DHT at 2 hours after subcutaneous injection than that of TP, thereafter, these high levels declined very rapidly. In contrast, the serum concentrations of T and DHT in TP-treated animals were fairly consistent during the 24 hours, and therefore, TP showed about 10-30-fold higher potency than free T.

In this immature castrated rat model, a known AR antagonist (Casodex) was also administered simultaneously with 0.1 mg of TP (ED_{80}), inhibiting the testosterone-mediated increase in the weights of the VP and SV in a dose dependent manner. The antagonist effects were similar when dosing orally or subcutaneously. Compounds of the invention also exhibited AR antagonist activity by suppressing the testosterone-mediated increase in the weights of VP and SV.

Levator Ani & Wet Prostate Weight Assay AR Agonist Assay:

The activity of compounds of the present invention as AR agonists was investigated in an immature male rat model, a recognized test of anabolic effects in muscle and sustaining effects in sex organs for a given compound, as described in L. G. Hershberger et al., *Proc. Soc. Expt. Biol. Med.*, 83, 175 (1953); B. L. Beyler et al, "Methods for evaluating anabolic and catabolic agents in laboratory animals", *J. Amer. Med. Women's Ass.*, 23, 708 (1968); H. Fukuda et al., "Investigations of the levator ani muscle as an anabolic steroid assay", *Nago Dai. Yak. Ken. Nem.* 14, 84 (1966) the disclosures of which are herein incorporated by reference.

The basis of this assay lies in the well-defined action of androgenic agents on the maintenance and growth of muscle tissues and sexual accessory organs in animals and man. Androgenic steroids, such as testosterone (T), have been well characterized for their ability to maintain muscle mass. Treatment of animals or humans after castrations with an exogenous source of T results in a reversal of muscular atrophy. The effects of T on muscular atrophy in the rat levator ani muscle have been well characterized. M. Masuoka et al., "Constant cell population in normal, testosterone deprived and testosterone stimulated levator ani muscles" *Am. J. Anat.* 119, 263 (1966); Z. Gori et al., "Testosterone hypertrophy of levator ani muscle of castrated rats. I. Quantitative data" *Boll. –Soc. Ital. Biol. Sper.* 42, 1596 (1966); Z. Gori et al., "Testosterone hypertrophy of levator ani muscle of castrated rats. II. Electron-microscopic observations" *Boll. –Soc. Ital. Biol. Sper.* 42, 1600 (1966); A. Boris et al., *Steroids* 15, 61 (1970). As described above, the effects of androgens on maintenance of male sexual accessory organs, such as the prostate and seminal vesicles, is well described. Castration results in rapid involution and atrophy of the prostate and seminal vesicles. This effect can be reversed by exogenous addition of androgens. Since both the levator ani muscle and the male sex organs are the tissues most responsive to the effects of androgenic agents, this model is used to determine the androgen dependent reversal of atrophy in the levator ani muscle and the sex accessory organs in immature castrated rats. Sexually mature rats (200-250 g, 6-8 weeks-old, Sprague-Dawley, Harlan) were acquired castrated from the vendor (Taconic). The rats were divided into groups and treated daily for 7 to 14 days with one of the following:

1. Control vehicle
2. Testosterone Propionate (TP) (3 mg/rat/day, subcutaneous)
3. TP plus Casodex (administered p.o. in PEGTW, QD) , a recognized antiandrogen, as a reference compound.
4. To demonstrate antagonist activity, a compound of the present invention ("test compound") was administered (p.o. in PEGTW, QD) with TP (s.c. as administered in group 2) in a range of doses.
5. To demonstrate agonist activity a compound of the present invention ("test compound") was administered alone (p.o. in PEGTW, QD) in a range of doses.

At the end of the 7-14-day treatment, the animals were sacrificed by carbon dioxide, and the levator ani, seminal vesicle and ventral prostate weighed. To compare data from different experiments, the levator ani muscle and sexual organ weights were first standardized as mg per 100 g of body weight, and the increase in organ weight induced by TP was considered as the maximum increase (100%). Super-anova (one factor) was used for statistical analysis.

The gain and loss of sexual organ weight reflect the changes of the cell number (DNA content) and cell mass (protein content), depending upon the serum androgen concentration. See Y. Okuda et al., *J. Urol.*, 145, 188-191 (1991), the disclosure of which is herein incorporated by reference. Therefore, measurement of organ wet weight is sufficient to indicate the bioactivity of androgens and androgen antagonist. In immature castrated rats, replacement of exogenous androgens increases levator ani, seminal vesicles (SV) and prostate in a dose dependent manner.

The maximum increase in organ weight was 4 to 5-fold when dosing 3 mg/rat/day of testosterone (T) or 1 mg/rat/day of testosterone propionate (TP) for 3 days. The EC_{50} of T and TP were about 1 mg and 0.03 mg, respectively. The increase in the weight of the VP and SV also correlated with the increase in the serum T and DHT concentration. Although administration of T showed 5-times higher serum concentrations of T and DHT at 2 hours after subcutaneous injection than that of TP, thereafter, these high levels declined very rapidly. In contrast, the serum concentrations of T and DHT in TP-treated animals were fairly consistent during the 24 hours, and therefore, TP showed about 10-30-fold higher potency than free T.

MDA PCa2b Human Prostate Zenograft Assay:

In Vivo Antitumor Testing: MDA-PCa-2b human prostate tumors were maintained in Balb/c nu/nu nude mice. Tumors were propagated as subcutaneous transplants in adult male nude mice (4-6 weeks old) using tumor fragments obtained from donor mice. Tumor passage occurred every 5-6 weeks.

For antitumor efficacy trial, the required number of animals needed to detect a meaningful response were pooled at the start of the experiment and each was given a subcutaneous implant of a tumor fragment (~50 mg) with a 13-gauge trocar. Tumors were allowed to grow to approx. 100-200 mg (tumors outside the range were excluded) and animals were evenly distributed to various treatment and control groups. Treatment of each animal was based on individual body weight. Treated animals were checked daily for treatment related toxicity/mortality. Each group of animals was weighed before the initiation of treatment (Wt1) and then again following the last treatment dose (Wt2). The difference in body weight (Wt2-Wt1) provides a measure of treatment-related toxicity.

Tumor response was determined by measurement of tumors with a caliper twice a week, until the tumors reach a predetermined "target" size of 0.5 gm. Tumor weights (mg) were estimated from the formula: Tumor weight = (length x width2) ÷ 2

Tumor response end-point was expressed in terms of tumor growth inhibition (%T/C), defined as the ratio of median tumor weights of the treated tumors (T) to that of the control group (C).

To estimate tumor cell kill, the tumor volume doubling time was first calculated with the formula:

TVDT = Median time (days) for control tumors to reach target size – Median time (days) for control tumors to reach half the target size s

And, Log cell kill = (T-C) ÷ (3.32 x TVDT)

Statistical evaluations of data were performed using Gehan's generalized Wilcoxon test.

Dunning Prostate Tumor:

Dunning R3327H prostate tumor is a spontaneously derived, well differentiated androgen responsive adenocarcinoma of the prostate

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responsive to modulation of the androgen activity, this model is used to determine the activity of compounds that modulate the androgen receptor pathway in mature rats.

Along with its mitogenic activity on tissues such as prostate, seminal vesicle and muscle, testosterone also serves as a negative regulator for its own biosynthesis. Testosterone production in the Leydig cells of the testis is controlled by the level of circulating LH released from the pituitary gland. LH levels are themselves controlled by the level of LHRH produced in the hypothalmic region. Testosterone levels in the blood serve to inhibit the secretion of LHRH and subsequently reduce levels of LH and ultimately the levels of circulating testosterone levels. By measuring blood levels of LH as they are effected by compounds of the present invention ("test compounds"), it is possible to determine the level of agonist or antagonist activity of said compounds at the hypothalamic axis of this endocrine cycle.

Matched sets of Harlan Sprague-Dawely rats (40-42 days old, 180-220 g), were dosed orally by gavage (p.o.) with the test compounds in dissolved/suspensions of 80% PEG 400 and 20% Tween 20 (PEGTW) for 14 days. Two control groups, one intact and one castrated were dose orally only with the PEGTW vehicle. Animals were dosed (v/w) at 0.5 ml of vehicle /100g body weight. Experimental groups were as follows:

1. Intact vehicle (p.o., PEGTW, QD)
2. Control vehicle (p.o., PEGTW, QD)
3. Bicalutamide (Casodex, a recognized antiandrogen, as a reference compound) or a compound of the present invention, p.o. in PEGTW QD. (in a range of doses).

At the end of the 14-day treatment, the animals were sacrificed, and the ventral prostate, the seminal vesicles, and the levator ani were removed surgically and weighed. To compare data from different experiments, the organs weights were first standardized as mg per 100 g of body weight, and expressed as a percentage of the value of the respective organ in the intact group.

Rat luteinizing hormone (rLH) is quantitatively determined with the Biotrak [125 I] kit (Amersham Pharmacia Biotek), following the manufacturer directions. The assay is based on the competition by the LH present in the serum of the binding of [^{125}I] rLH to an Amerlex-M bead/antibody suspension. The radioactivity that

remains after incubation with the serum and subsequent washes is extrapolated into a standard curve to obtain a reading in ng/ml.

The gain and loss of sexual organ and levator ani weight reflect the changes of the cell number (DNA content) and cell mass (protein content), depending upon the serum androgen concentration, see Y. Okuda *et al.*, *J. Urol.*, 145, 188-191 (1991), the disclosure of which in herein incorporated by reference. Therefore, measurement of organ wet weight is sufficient to indicate the bioactivity of androgens and androgen antagonist. In the mature rats assay, active agonist agents will have no effect or will increase the weight of one or more of the androgen responsive organs (levator ani, prostate, seminal vessicle) and will have no effect or a suppressive effect on LH secretion. Compounds with antagonist activity will decrease the weight of one or more of the androgen responsive organs (levator ani, prostate, seminal vesicle) and will have no effect or a reduced suppressive effect on LH secretion.

CWR22 Human Prostate Zenograft Assay:

In Vivo Antitumor Testing: CWR22 human prostate tumors were maintained in Balb/c nu/nu nude mice. Tumors were propagated as subcutaneous transplants in adult male nude mice (4-6 weeks old) using tumor fragments obtained from donor mice. Tumor passage occurred every 5-6 weeks.

For antitumor efficacy trial, the required number of animals needed to detect a meaningful response were pooled at the start of the experiment and each was given a subcutaneous implant of a tumor fragment (~50 mg) with a 13-gauge trocar. Tumors were allowed to grow to approx. 100-200 mg (tumors outside the range were excluded) and animals were evenly distributed to various treatment and control groups. Treatment of each animal was based on individual body weight. Treated animals were checked daily for treatment related toxicity/mortality. Each group of animals was weighed before the initiation of treatment (Wt1) and then again following the last treatment dose (Wt2). The difference in body weight (Wt2-Wt1) provides a measure of treatment-related toxicity.

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Tumor response was determined by measurement of tumors with a caliper twice a week, until the tumors reach a predetermined "target" size of 0.5 gm. Tumor weights (mg) were estimated from the formula: Tumor weight = (length x width2) ÷ 2.

Tumor response end-point was expressed in terms of tumor growth inhibition (%T/C), defined as the ratio of median tumor weights of the treated tumors (T) to that of the control group (C).

To estimate tumor cell kill, the tumor volume doubling time was first calculated with the formula:

TVDT = Median time (days) for control tumors to reach target size – Median time (days) for control tumors to reach half the target size

And, Log cell kill = (T-C) ÷ (3.32 x TVDT)

Statistical evaluations of data were performed using Gehan's generalized Wilcoxon test.

The following Examples illustrate embodiments of the present invention, and are not intended to limit the scope of the claims. Within certain Examples, one compound of the formula I is prepared and then employed to further prepare one or more additional compounds of the formula I or salts thereof. Methods employed to prepare one compound of the formula I or salt thereof as described herein can be employed as appropriate to prepare other compounds of the invention.

Abbreviations

The following abbreviations are used herein:

DBU = 1,8-diazabicyclo[5.4.0]undec-7-ene

4-DMAP = 4-dimethylaminopyridine

ee = enantiomeric excess

DMF = dimethylformamide

EtOAc = ethyl acetate

LDA = lithium diisopropylamide

Hünig's Base = N,N-diisopropylethylamine

Me = methyl

RT = retention time

TFA = trifluoroacetic acid

THF = tetrahydrofuran

TLC = thin layer chromatography

TMS = trimethylsilyl

pTSA = para-toluenesulfonic acid

Δ = heat

t-Bu = *tert*-butyl

$PhCH_3$ = toluene

Pd/C = palladium on activated charcoal

TsCl = tosyl chloride

TBSOTf = *tert*-butyldimethylsilyl trifluoromethane sulfonate

TBS = *tert*-butyldimethylsilane

MeI = methyl iodide

$(BOC)_2O$ = di-*tert*-butyl dicarbonate

TEA = triethylamine

n-BuLi = *n*-butyllithium

rt = room temperature

LC = liquid chromatography

Ts = tosyl

Ph = phenyl

EtOH = ethanol

DCE = dichloroethane

DMSO = dimethylsulfoxide

Ra-Ni = Raney Nickel

MS = molecular sieves

MS(ES) = Electro-Spray Mass Spectrometry

mCPBA = m-chloroperoxybenzoic acid

sat = saturated

AcOH = acetic acid

MeOH = methanol

Et_2O = diethyl ether

Ac = acetyl

DEAD = diethyl azodicarboxylate

h = hours

Et = ethyl

WSDCC = water soluble dicarbonyl diimide, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride

TBAF = tetrabutylammonium fluoride

DBAD = di-terbutylazodicarboxylate

DCC = Dicyclohexylcarbodiimide

Wilkinson's catalyst = RhCl(PPh3)3

ADDP = 1,1-[azodicarbonyl]dipiperidine

DMA = dimethylacetamide

DME = 1,2-dimethoxyethane

BOP = benzotriazol-1-yloxytris(dimethylamino)-phosphonium hexafluorophosphate

HRMS = high resolution mass spectrometry

TBME = MTBE = methyl *tert*-butyl ether (i.e., 2-methoxy-2-methyl-propane)

$TiCl_2Cp_2$ = bis(cyclopentadienyl)titanium dichloride

DPPA = diphenylphosphoryl azide

HMPA = hexamethylphosphoryl amide

V% = volume percent

$BH_3 \cdot DMS$ = borane dimethylsulfate

vvm = volume gas per volume liquid per minute

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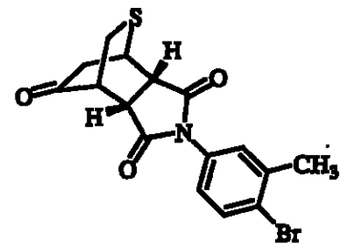
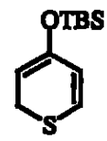
Example 1

(3aα,4α,7α,7aα)-2-(4-Bromo-3-methylphenyl)tetrahydro-4,7-ethanothiopyrano[3,4-c]pyrrole-1,3,8(2H,4H)-trione (1C)

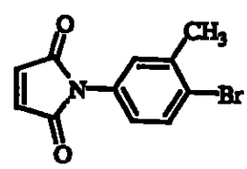


A. 4-(tert-Butyldimethylsiloxy)-2H-thiopyran (1A)



2,3-Dihydro-4H-thiopyran-4-one (1.50 g, 13.1 mmol, synthesized as described in Richards et al. *J. Org. Chem.* 46, 4836-4842 (1981)) was dissolved in CH_2Cl_2 (130 mL) and triethylamine (5.47 mL, 39.4 mmol) was added. *tert*-Butyldimethylsilyl trifluoromethanesulfonate (3.62 mL, 15.8 mmol) was then added. After 10 minutes, the volatiles were removed *in vacuo* at 25°C. The resulting yellow oil was passed through a short column of SiO_2 eluting with 3% TEA in hexanes to yield 1.82 g (7.97 mmol, 61%) of compound 1A as an orange oil.

B. 1-[4-bromo-3-methylphenyl]-1H-pyrrole-2,5-dione (1B)



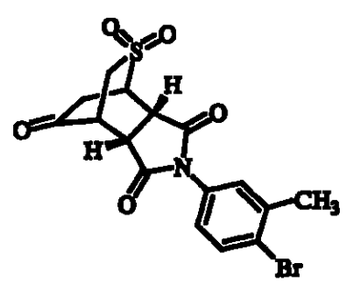
4-Bromo-3-methylaniline (1.55 g, 8.33 mmol) and maleic anhydride (0.898 g, 9.16 mmol) were dissolved in acetic acid (10 mL) and heated at 115 °C for 12 h. The reaction was then cooled to 25°C and the acetic acid was removed *in vacuo*. The resulting residue was suspended in 5% K_2CO_3 (100 mL), stirred for 25 minutes, filtered and rinsed with water. The material was then dried *in vacuo* to give 1.65 g (6.20 mmol, 74%) of compound 1B as a light brown solid. HPLC: 100% at 2.96 min

(retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm).

C. (3aα,4α,7α,7aα)-2-(4-Bromo-3-methylphenyl)tetrahydro-4,7-ethanothiopyrano[3,4-c]pyrrole-1,3,8(2H,4H)-trione (1C)

Compound 1A (0.313 g, 1.41 mmol) and compound 1B (0.250 g, 0.940 mmol) were dissolved in toluene and heated to reflux for 5 h. The toluene was then removed by passing a stream of argon through the reaction flask. The residue was then purified by flash chromatography on SiO_2 eluting with 20% hexane in chloroform. This gave 0.168 g of the enol ether intermediate as a yellow solid. The enol ether intermediate was dissolved in dichloroethane (2.0 mL) and TFA (0.25 mL) was added. After 0.5 h, the reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with CH_2Cl_2 (2 x 30 mL). The organics were dried over anhydrous sodium sulfate and evaporated to give 0.079 g (0.21 mmol, 22%) of compound 1C as a white solid. HPLC: 99% at 3.010 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 396.9 $[M+NH_4]^+$.

Example 2
(3aα,4α,7α,7aα)-2-(4-Bromo-3-methylphenyl)tetrahydro-4,7-ethanothiopyrano[3,4-c]pyrrole-1,3,8(2H,4H)-trione 5,5-dioxide (2)

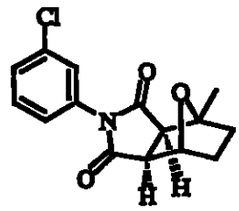


Compound 1C (0.040 g, 0.11 mmol) was dissolved in CH_2Cl_2 (4.0 mL) and cooled to 0°C. *m*-CPBA (60% purity, 0.061 g, 0.21 mmol) was added and the reaction was then warmed to 25°C. After 1 h, a 1:1 mixture of saturated $NaHCO_3$ and saturated sodium sulfite (20 mL) was added with vigorous stirring. After 15 minutes,

the mixture was extracted with CH_2Cl_2 (2 x 30 mL) and the organics were dried over anhydrous sodium sulfate to yield 0.031 g (0.075 mmol, 71%) of compound 2 as a white solid. No purification was necessary. HPLC: 78% at 2.290 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 429.8 $[M+NH_4]^+$.

Example 3

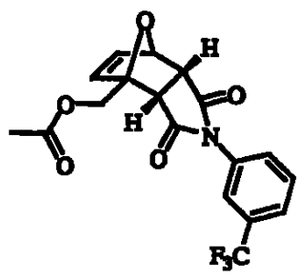
(3aα,4β,7β,7aα)-2-(3-Chlorophenyl)hexahydro-4-methyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione (3)

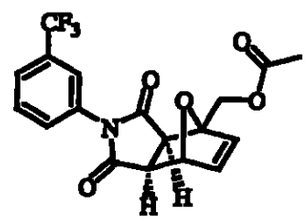


3-Chloroaniline (0.100 g, 0.787 mmol) and 3,6-endoxo-3-methylhexahydrophthalic anhydride (0.172 g, 0.945 mmol) were dissolved in AcOH (2.0 mL) and heated at 110°C for 11 h. The reaction was then cooled to 25°C, poured into cold saturated aq. K_2CO_3 and stirred vigorously for 10 min. The solution was then filtered and rinsed with water. The resulting filtrate was dried *in vacuo* to give 0.118 g (0.404 mmol, 51%) of compound 3 as a white solid. No further purification was needed. HPLC: 99% at 2.510 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 292.32 $[M+H]^+$.

Example 4

(3aα,4α,7α,7aα)- and (3aα,4β,7β,7aα)-4-[(Acetyloxy)methyl]-3a,4,7,7a-tetrahydro-2-[3-(trifluoromethyl)phenyl]-4,7-epoxy-1H-isoindole-1,3(2H)-dione (4i and 4ii, respectively)

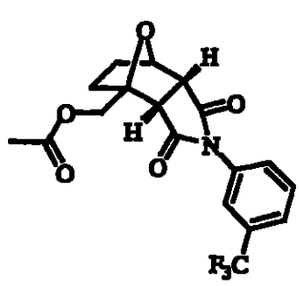


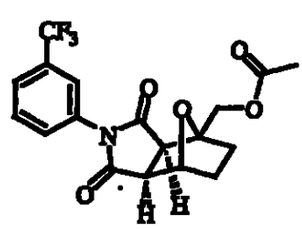


2-Acetoxymethylfuran (0.599 mL, 4.78 mmol) and 1-[3-(trifluoromethyl)-phenyl]-1H-pyrrole-2,5-dione (0.500 g, 2.39 mmol, prepared as described in Example 1B) were dissolved in methylene chloride (3.0 mL) at 25°C. After 22 h, the volatiles were removed *in vacuo* and the resulting residue was purified by flash chromatography on SiO_2 eluting with 0-15% acetone in methylene chloride to give 0.438 g (1.15 mmol, 48%) of a yellow oil as a 2:1 mixture of compound 4i and compound 4ii, which was not separated. HPLC: 100% at 3.093 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 398.9 $[M+NH_4]^+$.

Example 5

(3aα,4α,7α,7aα)- and (3aα,4β,7β,7aα)-4-[(Acetyloxy)methyl]-Hexahydro-2-[3-(trifluoromethyl)phenyl]-4,7-epoxy-1H-isoindole-1,3(2H)-dione (5i and 5ii, respectively)

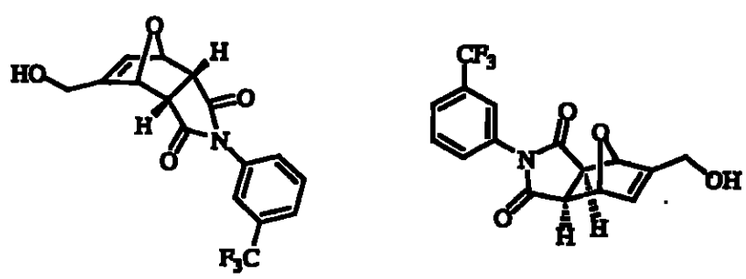




The 2:1 mixture of compounds 4i and 4ii (0.361 g, 0.948 mmol) was dissolved in ethyl acetate (25 mL) and Pd/C (10% Pd, 0.2 g) was added. Hydrogen was introduced via a balloon and the reaction was stirred at 25°C for 4 h, followed by filtration through Celite and rinsing with ethyl acetate. Concentration *in vacuo* gave 0.348 g (0.908 mmol, 96%) of a yellow oil that was determined to be a 2:1 mixture of compound 5i and compound 5ii (which was not separated). HPLC: 100% at 2.900 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 401.0 $[M+NH_4]^+$.

Example 6

(3aα,4α,7α,7aα)- and (3aα,4β,7β,7aα)-3a,4,7,7a-Tetrahydro-5-(hydroxymethyl)-2-[3-(trifluoromethyl)phenyl]-4,7-epoxy-1H-isoindole-1,3(2H)-dione (6i and 6ii, respectively)

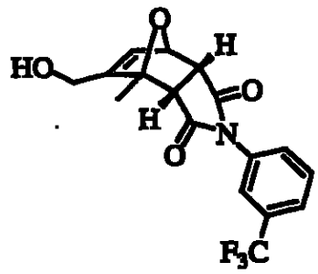


1-[3-(Trifluoromethyl)phenyl]-1H-pyrrole-2,5-dione (0.500 g, 2.39 mmol, prepared as described in Example 1B) and 3-furanmethanol (0.412 mL, 4.78 mmol) were dissolved in methylene chloride (3.0 mL) and stirred at 25°C for 20 h. The volatiles were then removed *in vacuo* and the resulting material purified by flash chromatography on SiO_2 eluting with chloroform/acetone to give 0.379 g (1.12 mmol, 47%) of compound 6i and 0.220 g of compound 6ii, both as white solids. Compound 6i: HPLC: 100% at 2.197 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 338.0 $[M-H]^-$. Compound 6ii: HPLC: 100% at 2.477 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with

10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 338.0 [M-H]⁻.

Example 7

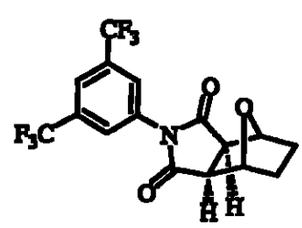
(3aα,4α,7α,7aα)-3a,4,7,7a-Tetrahydro-5-(hydroxymethyl)-4-methyl-2-[3-(trifluoromethyl)phenyl]-4,7-epoxy-1H-isoindole-1,3(2H)-dione (7)



2-Methyl-3-furanmethanol (0.537 g, 4.78 mmol) and 1-[3-(trifluoromethyl)-phenyl]-1H-pyrrole-2,5-dione (0.500 g, 2.39 mmol, prepared as described in Example 1B) were dissolved in dichloroethane (2.0 mL) and stirred at 25°C for 20 h. The reaction was then concentrated *in vacuo* and purified by flash chromatography in SiO_2 eluting with ethyl acetate/methylene chloride to give 0.317 g (0.897 mmol, 37.5%) of compound 7 as a white solid. No other possible isomer was isolated after chromatography. HPLC: 100% at 2.197 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 351.9 [M-H]⁻.

Example 8

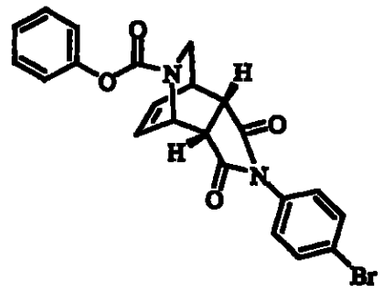
(3aα,4β,7β,7aα)-2-[3,5-Bis(trifluoromethyl)phenyl]hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione (8)



3,5-Bis(trifluoromethyl)aniline (0.017 g, 0.075 mmol) was dissolved in acetic acid (0.300 mL) and transferred to a 1.5 mL conical vial with a septa cap. Stock solutions of an additional 95 amines were prepared as described above. To each of

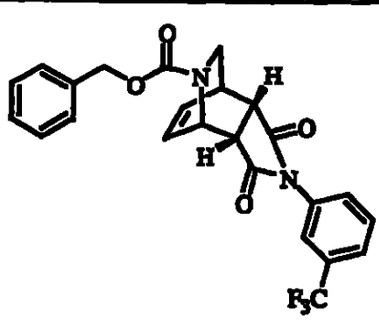
the above vials was added 0.40 mL (0.12 mmol) of a stock solution of exo-7-oxabicyclo[2.2.1]heptane-2,3-dicarboxylic anhydride in acetic acid. The vials were then sealed and heated at 110°C for 11 h. Upon cooling to 25°C, the caps were removed from the vials and the acetic acid was removed *in vacuo*. To each vial was added 1 mL of 2:1 acetone/methylene chloride and the vials were heated at 40°C for 1 h. Once all products were in solution, they were transferred via robot to filter tubes with coarse frits pre-wetted with 0.2 mL of water. Nitrogen was blown through each tube until the volatile organics were removed. 1.5 mL of 10% aq. K_2CO_3 was then added to each tube followed by vigorous shaking at 25°C for 15 min. The tubes were then drained, resealed and 1.0 mL of water was added to each tube followed by shaking. The tubes were drained again and washed with water a second time. The resulting residues in each tube were then dried *in vacuo* for 48 h. After drying, 1.0 mL of 20% TFA in methylene chloride was added to each tube and the racks were shaken for 30 min. The tubes were then drained into a 96-well plate with pre-tared custom micro-tubes present. Each tube was assayed for product purity (analytical LC) and identity (LC-MS). The tubes were then concentrated *in vacuo* and weighed for yields. The tube containing the reaction of 3,5-bistrifluoromethylaniline and exo-7-oxabicyclo[2.2.1]heptane-2,3-dicarboxylic anhydride, yielded 0.022 g (0.058 mmol, 77%) of compound **8** as a white solid. HPLC: 94% at 4.03 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 434.2 $[M+Na+MeOH]^+$. Of the remaining 95 additional reactions run, a total of 80 final compounds were obtained in >70% purity and >5 mg yield. Several samples needed further purification which was performed by short SiO_2 column eluting with methylene chloride/acetone. See Table 2 below.

Example 9
(3aα,4α,7α,7aα)-2-(4-Bromophenyl)octahydro-1,3-dioxo-4,7-etheno-5H-pyrrolo[3,4-c]pyridine-5-carboxylic acid phenyl ester (9)



1-[4-Bromophenyl]-1H-pyrrole-2,5-dione (0.250 g, 0.992 mmol, prepared as described in Example 1B) and 1(2H)-pyridinecarboxylic acid phenylmethyl ester (0.299 g, 1.49 mmol, synthesized as described in Richard et al. *J. Org. Chem.* 46, 4836-4842 (1981)) were dissolved in toluene and heated at 85°C for 1 h. Upon cooling to 25°C, the toluene was removed *in vacuo*. The resulting residue was dissolved in a minimum amount of chloroform and the product was precipitated by addition of hexanes. After 1 h at 25°C, the product was filtered and rinsed with cold 20% hexanes in chloroform giving 0.243 g (0.536 mmol, 54%) of compound **9** as a white solid (single isomer). HPLC: 100% at 3.393 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 454.98 $[M+H]^+$.

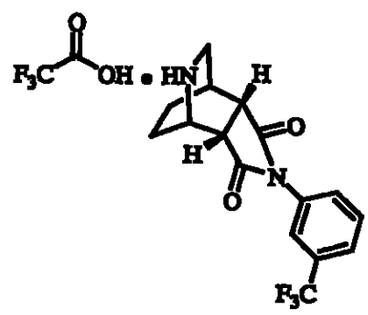
Example 10
(3aα,4α,7α,7aα)-2-(4-Bromophenyl)octahydro-1,3-dioxo-4,7-etheno-5H-pyrrolo[3,4-c]pyridine-5-carboxylic acid phenylmethyl ester (10)



1-[3-(Trifluoromethyl)phenyl]-1H-pyrrole-2,5-dione (3.78 g, 15.7 mmol, prepared as described in Example 1B) and 1(2H)-pyridinecarboxylic acid phenylmethyl ester (4.00 g, 18.8 mmol, synthesized as described in Richard et al. *J. Org. Chem.* 46, 4836-4842 (1981)) were dissolved in toluene and heated at 80°C for 3 h. After cooling to 25°C, the toluene was removed *in vacuo* and the resulting residue was purified by flash chromatography on SiO_2 eluting with methanol/methylene chloride to give 3.20 g (7.01 mmol, 45%) of compound **10** as a yellow oil. HPLC: 95% at 3.510 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 457.2 $[M+H]^+$.

Example 11

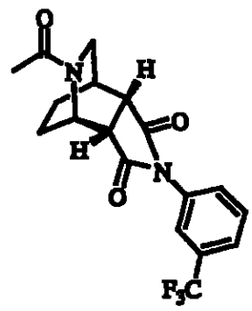
(3aα,4α,7α,7aα)-Hexahydro-2-[3-(trifluoromethyl)phenyl]-4,7-ethano-1H-pyrrolo[3,4-c]pyridine-1,3(2H)-dione trifluoroacetate (11)



Compound **10** (3.20 g, 7.01 mmol) was dissolved in 100 mL of MeOH and 10% Pd/C Degussa catalyst (2.00 g, cat.) was added. Hydrogen was then introduced via a balloon. After 1 h, the reaction was filtered through Celite and rinsed with MeOH. The volatiles were removed *in vacuo* and the resulting crude material was purified by reverse phase preparative HPLC to yield 2.50 g (5.70 mmol, 81%) of compound **11** as the TFA salt (white solid). HPLC: 99% at 1.843 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 325.12 $[M+H]^+$.

Example 12

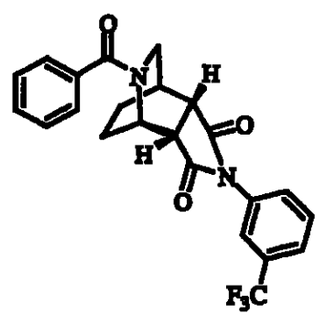
(3aα,4α,7α,7aα)-5-Acetylhexahydro-2-[3-(trifluoromethyl)phenyl]-4,7-ethano-1H-pyrrolo[3,4-c]pyridine-1,3(2H)-dione (12)



Compound 11 (0.10 g, 0.23 mmol) was suspended in THF (5.0 mL) and TEA (0.097 mL, 0.46 mmol) was added resulting in a homogeneous solution. Acetyl chloride (0.033 mL, 0.46 mmol) was then added. After 2 h, the reaction was quenched with saturated aqueous $NaHCO_3$ and extracted with methylene chloride (3 x 15 mL). The crude material was purified by preparative TLC eluting with chloroform/acetone to give 0.067 g (0.18 mmol, 79%) of compound 12 as a colorless oil. HPLC: 99% at 2.66 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 367.0 $[M+H]^+$.

Example 13

(3aα,4α,7α,7aα)-5-Benzoylhexahydro-2-[3-(trifluoromethyl)phenyl]-4,7-ethano-1H-pyrrolo[3,4-c]pyridine-1,3(2H)-dione (13)

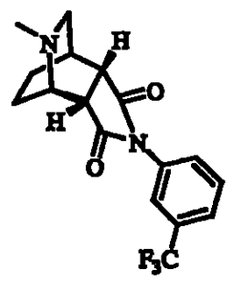


Compound 11 (0.10 g, 0.23 mmol) was suspended in THF (5.0 mL) and TEA (0.097 mL, 0.46 mmol) was added resulting in a homogeneous solution. Benzoyl chloride (0.053 mL, 0.46 mmol) was then added. After 2 h, the reaction was

quenched with saturated aqueous $NaHCO_3$ and extracted with methylene chloride (3 x 15 mL). The crude material was purified by reverse phase preparative HPLC to give 0.020 g (0.047 mmol, 20%) of compound 13 as a white foam. HPLC: 99% at 3.183 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 429.1 $[M+H]^+$.

Example 14

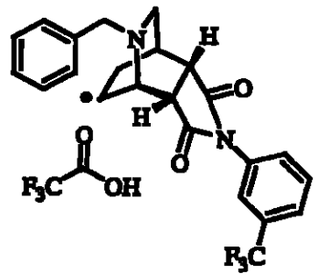
(3aα,4α,7α,7aα)-Hexahydro-5-methyl-2-[3-(trifluoromethyl)phenyl]-4,7-ethano-1H-pyrrolo[3,4-c]pyridine-1,3(2H)-dione (14)



Compound 11 (0.10 g, 0.23 mmol) was suspended in THF (5.0 mL) and TEA (0.097 mL, 0.46 mmol) was added resulting in a homogeneous solution. Dimethyl sulfate (0.043 mL, 0.46 mmol) was added and the reaction was stirred at 25°C. After 14 h, the reaction was concentrated *in vacuo* and the crude material was purified by preparative TLC eluting with 10% MeOH in methylene chloride to give 0.030 g (0.088 mmol, 39%) of compound 14 as a white solid. HPLC: 100% at 1.797 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 339.21 $[M+H]^+$.

Example 15

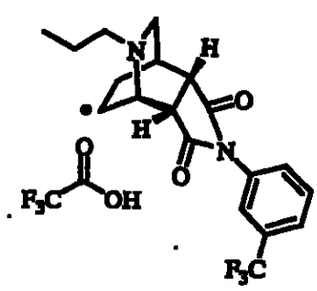
(3aα,4α,7α,7aα)-Hexahydro-5-(phenylmethyl)-2-[3-(trifluoromethyl)phenyl]-4,7-ethano-1H-pyrrolo[3,4-c]pyridine-1,3(2H)-dione trifluoroacetate (15)



Compound 11 (0.10 g, 0.23 mmol) was dissolved in DMF (5.0 mL) and K_2CO_3 (0.063 g, 0.46 mmol) was added. Benzyl bromide (0.041 mL, 0.35 mmol) was then added. The reaction was stirred at 25°C for 1 h, filtered and concentrated *in vacuo*. The crude material was purified by reverse phase preparative HPLC to give 0.055 g (0.10 mmol, 43%) of compound 15 as a white solid. HPLC: 100% at 2.31 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 415.36 $[M+H]^+$.

Example 16

(3aα,4α,7α,7aα)-Hexahydro-5-propyl-2-[3-(trifluoromethyl)phenyl]-4,7-ethano-1H-pyrrolo[3,4-c]pyridine-1,3(2H)-dione trifluoroacetate (16)



Compound 11 (0.10 g, 0.23 mmol) was dissolved in DMF (5.0 mL) and K_2CO_3 (0.079 g, 0.57 mmol) was added, followed by 1-bromopropane (0.031 mL, 0.34 mmol). The reaction was stirred at 25°C for 6 h, then filtered and concentrated *in vacuo*. The crude material was purified by reverse phase preparative HPLC to give

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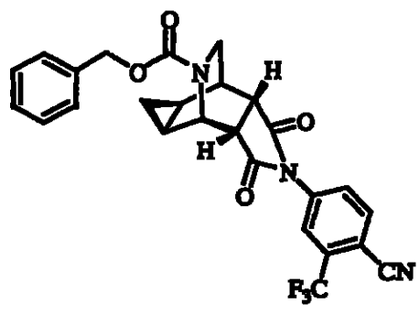
0.070 g (0.15 mmol, 63%) of compound 16 as a white solid. HPLC: 100% at 1.907 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 340.22 $[M+H]^+$.

Example 17

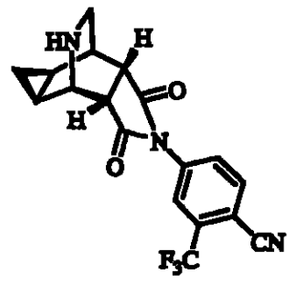
(3aα,4α,4aβ,5aβ,6α,6aα)-2-[4-Cyano-3-(trifluoromethyl)phenyl]decahydro-1,3-dioxo-4,6-(iminomethano)cycloprop[f]isoindole-7-carboxylic acid phenylmethyl ester (17)



1-Methyl-3-nitro-1-nitrosoguanidine (2.5 g, 17 mmol) was added portionwise to a solution of 40% KOH/H_2O (15 mL) and Et_2O (25 mL) at 0°C. The ether layer turned yellow once addition was complete. After 30 min at 0°C, the ether layer was poured into a solution of (3aα,4α,7α,7aα)-2-[4-cyano-3-(trifluoromethyl)phenyl]-octahydro-1,3-dioxo-4,7-etheno-5H-pyrrolo[3,4-c]pyridine-5-carboxylic acid phenylmethyl ester (0.500 g, 1.09 mmol, prepared as described in Example 10) and $Pd(OAc)_2$ (0.010 g) in THF (10 mL) at 0°C. The reaction was then warmed slowly to 25°C, stirred for 24 h and then filtered through Celite rinsing with THF. The crude material was then purified by flash chromatography on SiO_2 eluting with MeOH/CH_2Cl_2 to give 0.34 g (0.69 mmol, 63%) of compound 17 as a white solid and a single isomer. HPLC: 100% at 3.61 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 496.25 $[M+H]^+$.

Example 18

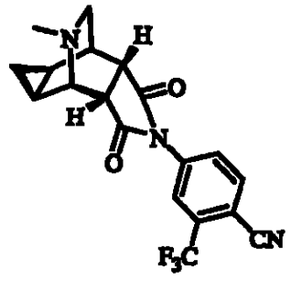
(3aα,4α,4aβ,5aβ,6α,6aα)-4-[Decahydro-1,3-dioxo-4,6-(iminomethano)cycloprop[f]isoindol-2-yl]-2-(trifluoromethyl)benzonitrile (18)



Compound 17 (0.200 g, 0.404 mmol) was dissolved in MeOH (20 mL) and 5% Pd/C (0.200 g) was added. Hydrogen was then introduced via balloon. After 3 h, the reaction was filtered through Celite, rinsed with MeOH and the volatiles were removed *in vacuo* to yield 0.130 g (0.360 mmol, 89%) compound 18 as a white solid. HPLC: 100% at 1.80 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 362.09 $[M+H]^+$.

Example 19

(3aα,4α,4aβ,5aβ,6α,6aα)-4-[Decahydro-7-methyl-1,3-dioxo-4,6-(iminomethano)cycloprop[f]isoindol-2-yl]-2-(trifluoromethyl)benzonitrile (19)

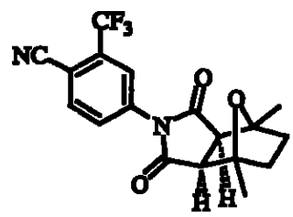


Compound 18 (0.100 g, 0.277 mmol) was dissolved in CH_3CN (2.0 mL). TEA (0.19 mL, 1.4 mmol) and MeI (0.052 mL, 0.83 mmol) were then added and the reaction was stirred at 25°C for 14 h. The reaction was concentrated under reduced

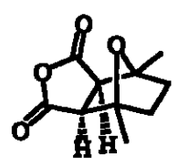
pressure and the crude material was partioned between CH_2Cl_2/water and the aqueous layer was extracted with CH_2Cl_2 (3 x 15 mL). The combined organics were dried over anhydrous Na_2SO_4. The crude material was purified by flash chromatography eluting with 3% MeOH/CH_2Cl_2 to give 0.030 g (0.080 mmol, 29%) of compound **19** as a light yellow solid. HPLC: 100% at 1.720 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 376.11 $[M+H]^+$.

Example 20

(3aα,4β,7β,7aα)-4-(Octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (20B)



A. (3aα,4β,7β,7aα)-Hexahydro-4,7-epoxyisobenzofuran-1,3-dione (20A)



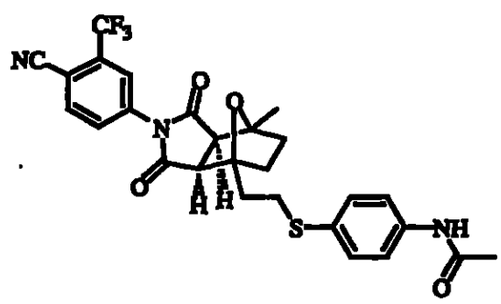
Freshly distilled dimethyl furan (1.60 mL, 15.3 mmol) was dissolved in CH_2Cl_2 (2.0 mL) and maleic anhydride (1.00 g, 10.2 mmol) was added. The reaction was stirred at 25°C for 16 h and was then concentrated *in vacuo* to give a yellow solid. This solid was dissolved in ethyl acetate (30 mL) and 10% Pd/C (0.200 g, cat.) was added. Hydrogen was then introduced via a balloon and the reaction stirred for 24 h. The reaction mixture was filtered through Celite rinsing with EtOAc followed by concentration *in vacuo* to give 1.69 g (8.61 mmol, 84%) of compound **20A** as a white solid. 2-Dimensional NOE experiments confirmed the structural assignment to be that of compound **20A**.

B. (3aα,4β,7β,7aα)-4-(Octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (20B)

A solution of compound 20A (603 mg, 3.21 mmol), 5-amino-2-cyanobenzotrifluoride (640 mg, 3.44 mmol) and TsOH (10 mg, cat.) in toluene (5 mL) was heated in a sealed tube for 2 days. The reaction mixture was cooled to room temperature and then concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with 50% EtOAc/hexanes gave 400 mg (1.10 mmol, 34%) of compound 20B as a white solid. HPLC: 99% at 3.04 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ESI): m/z 382.2 $[M+NH_4]^+$.

Example 21

(3aα,4β,7β,7aα)-*N*-[4-[[2-[2-[4-Cyano-3-(trifluoromethyl)phenyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindol-4-yl]ethyl]thio]phenyl]acetamide (21E)



A. 5-Methyl-2-furanethanol (21A)

A solution of *n*-BuLi (83.0 mL, 133 mmol, 1.6 M in hexanes) was added to a stirred solution of 2-methylfuran (10.0 mL, 111 mmol) in THF (85 mL) at 0°C under inert atmosphere. The reaction mixture was stirred for 4 h at room temperature then cooled to 0°C. Ethylene oxide (8.30 mL, 166 mmol) was added dropwise and the reaction mixture was allowed to warm to room temperature overnight. After quenching with saturated aqueous NH_4Cl, the resulting layers were separated and the aqueous layer was extracted with Et_2O (2 X 250 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Distillation at

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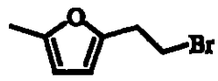
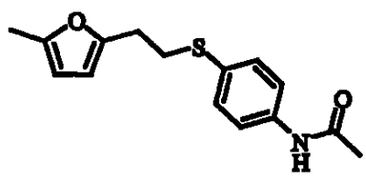
atmospheric pressure (170-185 °C) gave 10.1 g (80.3 mmol, 72%) of compound **21A** as a light yellow oil.

B. 2-(2-Bromoethyl)-5-methylfuran (21B)



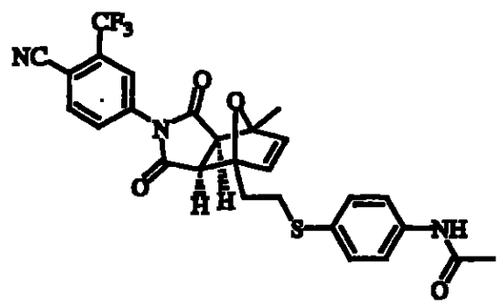
Ph_3Br_2 (3.68 g, 8.72 mmol) was added to a solution of compound **21A** (1.00 g, 7.93 mmol) in DMF (8 mL) and the reaction mixture was stirred at room temperature for 1 h. The reaction mixture was added to H_2O and extracted with EtOAc (3 X). The combined organic layers were washed with H_2O (2 X), dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with 10% EtOAc/hexanes gave 0.507 g (2.68 mmol, 34%) of compound **21B**.

C. *N*-[4-[[2-(5-Methyl-2-furanyl)ethyl]thio]phenyl]acetamide (21C)



To a solution of 4-acetamidothiophenol (442 mg, 2.64 mmol) in THF (1 mL) at 0°C under inert atmosphere was added a solution of *n*-BuLi (2.00 mL, 3.17 mmol, 1.6 M in hexanes) in THF (1 mL). The reaction solution was stirred at room temperature for 10 min then a solution of compound **21B** (500 mg, 2.64 mmol) in THF (3 mL) was added. After the starting material was consumed (as determined by TLC), the reaction was quenched with H_2O and the mixture was extracted with EtOAc (2X), dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with 50% EtOAc/hexanes gave 0.644 g (2.34 mmol, 88%) of compound **21C**. MS (ESI): m/z 276.09 $[M+H]^+$.

D. (8aα,4β,7β,7aα)-*N*-[4-[[2-[2-[4-Cyano-3-(trifluoromethyl)phenyl]-1,2,3,3a,7,7a-hexahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindol-4-yl]ethyl]thio]phenyl]acetamide (21D)



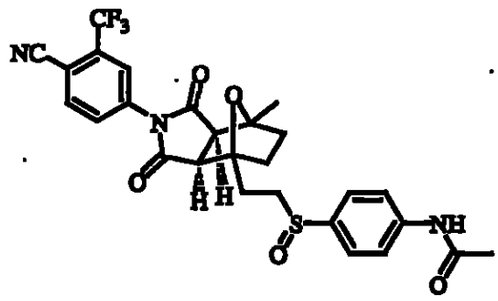
A solution of compound 21C (195 mg, 0.708 mmol) and 4-(2,5-dihydro-2,5-dioxo-1H-pyrrol-1-yl)-2-trifluoromethylbenzonitrile (377 mg, 1.416 mmol, prepared as described for Example 1B) in CH_2Cl_2 (1.5 mL) was stirred at room temperature for two days. The reaction mixture was concentrated under reduced pressure to yield compound 21D as determined by NMR analysis. Compound 21D was used directly in the next step without purification.

E. (3aα,4β,7β,7aα)-*N*-[4-[[2-[2-[4-Cyano-3-(trifluoromethyl)phenyl]-octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindol-4-yl]ethyl]thio]-phenyl]acetamide (21E)

A solution of crude compound 21D (0.708 mmol) and 10% Pd/C (200 mg) in MeOH (20 mL) was stirred under a hydrogen atmosphere overnight. Purification by reverse phase HPLC [34.4 min (retention time) (YMC S5 ODS column 20 x 250 mm, 0-100% aqueous methanol over 30 minutes containing 0.1% TFA, 10 mL/min, monitoring at 220 nm)] followed by flash chromatography on silica gel eluting with 1% MeOH/CH_2Cl_2 gave 29 mg (0.053 mmol, 7.5%) of compound 21E as a yellow powder. HPLC: 99% at 3.44 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ESI): m/z 544.01 $[M+H]^+$.

Example 22

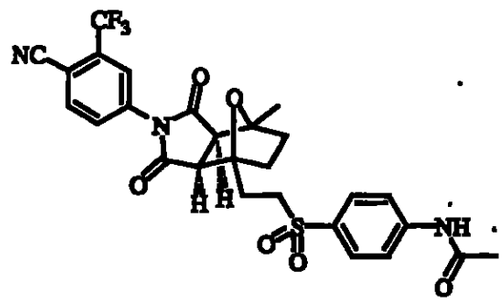
(3aα,4β,7β,7aα)-*N*-[4-[[2-[2-[4-Cyano-3-(trifluoromethyl)phenyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindol-4-yl]ethyl]sulfinyl]phenyl]acetamide (22)



*m*CPBA (12 mg, 0.050 mmol) was added portionwise to a solution of crude compound **21E** (65 mg, 0.12 mmol) in CH_2Cl_2 (6 mL) until the starting material was consumed. Purification by reverse phase HPLC [30.5 min (retention time) (YMC S5 ODS column 30 x 250 mm, 0-100% aqueous methanol over 30 minutes containing 0.1% TFA, 25 mL/min, monitoring at 220 nm)] gave 27.5 mg (0.0491 mmol, 41%) of compound **22** as a tan solid (~1:1 mixture of diastereomers). HPLC: 96% at 2.88 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ESI): m/z 559.97 $[M+H]^+$.

Example 23

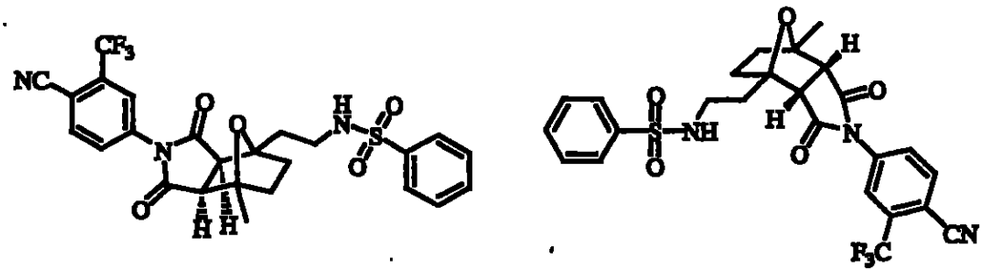
(8aα,4β,7β,7aα)-*N*-[4-[[2-[2-[4-Cyano-3-(trifluoromethyl)phenyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindol-4-yl]ethyl]sulfonyl]phenyl]acetamide (23)



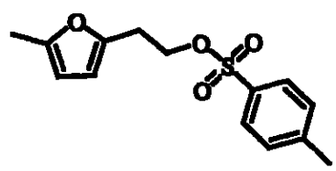
*m*CPBA (26 mg, 0.11 mmol) was added to a solution of compound 21E (19 mg, 0.035 mmol) in CH_2Cl_2 (6 mL) and the reaction was stirred at rt until starting material and the intermediate sulfoxide (compound 22) were consumed as was apparent by TLC. Purification by reverse phase preparative HPLC [53.3 min (retention time) (YMC S5 ODS column 30 x 250 mm, 0-70% aqueous methanol over 45 minutes containing 0.1% TFA, 25 mL/min, monitoring at 220 nm)] gave 8.0 mg mg (0.014 mmol, 40%) of compound 23 as a white solid. HPLC: 99% at 2.94 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ESI): m/z 575.95 $[M+H]^+$.

Example 24

(3aα,4β,7β,7aα)- and (3aα,4α,7α,7aα)-*N*-[2-[2-[4-Cyano-3-(trifluoromethyl)phenyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindol-4-yl]ethyl]benzenesulfonamide (24Cl and 24Cll, respectively)

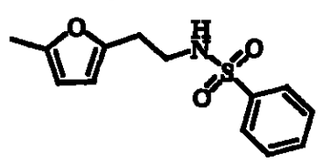


A. 5-Methyl-2-furanethanol 4-methylbenzenesulfonate (24A)



4-Methylbenzenesulfonyl chloride (907 mg, 4.76 mmol) was added to a solution of compound **21A** (500 mg, 3.96 mmol) in 6 mL of dry pyridine. The reaction was stirred at room temperature for 4 h and then quenched with ice. The reaction mixture was extracted with CH_2Cl_2 and the combined organic layers were washed with saturated aqueous sodium bicarbonate and water, dried and concentrated under reduced pressure to give 900 mg (81%) of compound **24A** as a yellow oil.

B. *N*-[2-(5-Methyl-2-furanyl)ethyl]benzenesulfonamide (24B)



Benzenesulfonamide (157 mg, 1.00 mmol) was added to a 10% aqueous solution of sodium hydroxide (0.40 mL, 1.0 mmol). A solution of compound **24A** (280 mg, 1.00 mmol) in acetone (1 mL) was then added. The reaction mixture was heated at 90°C for 8 h then cooled to room temperature. Ice was added and the

mixture was extracted with CH_2Cl_2. The combined organic layers were washed with water, dried and concentrated under reduced pressure. Purification by flash chromatography on silica gel, eluting with CH_2Cl_2 gave 60 mg (0.23 mmol, 23%) of compound **24B** as yellow oil.

C. (3aα,4β,7β,7aα)- and (3aα,4α,7α,7aα)-*N*-[2-[2-[4-Cyano-3-(trifluoromethyl)phenyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindol-4-yl]ethyl]benzenesulfonamide (24Ci and 24Cii, respectively)

4-(2,5-Dihydro-2,5-dioxo-1H-pyrrol-1-yl)-2-trifluoromethylbenzonitrile (129 mg, 0.485 mmol, prepared as described in Example 1B) was added to a solution of compound **24B** (60 mg, 0.23 mmol) in CH_2Cl_2 (2 mL). The reaction mixture was stirred at room temperature for 2 days, concentrated under reduced pressure and purified by flash chromatography on silica gel, eluting with 70% EtOAc/hexanes, to give 20 mg (0.038 mmol, 16%) of the unsaturated Diels-Alder product. The unsaturated product (20 mg) was immediately dissolved in ethanol (2 mL) and 10% Pd/C (10 mg, cat.) was added. The solution was stirred at room temperature overnight under a hydrogen atmosphere. The mixture was filtered and the filtrate was concentrated under reduced pressure. Purification by reverse phase preparative HPLC gave 7.0 mg (0.013 mmol, 34%) of compound **24Ci** and 2.0 mg (0.0037 mmol, 10%) of compound **24Cii**. Compound **24Ci**: HPLC: 96% at 3.17 min (retention time) (YMC ODSA S5 C18 4.6 x 50 mm, 10%-90% aqueous methanol over 4 min gradient with 0.1% TFA, monitoring at 220 nm). MS (ES): m/z: 533.99 $[M+H]^+$. Compound **24Cii**: HPLC: 99% at 38.95 min (retention time) (YMC ODS S5 20X250 mm, 10%-90% aqueous methanol over 40 min gradient with 0.1% TFA, monitoring at 220 nm). MS (ES): m/z 533.99 $[M+H]^+$.

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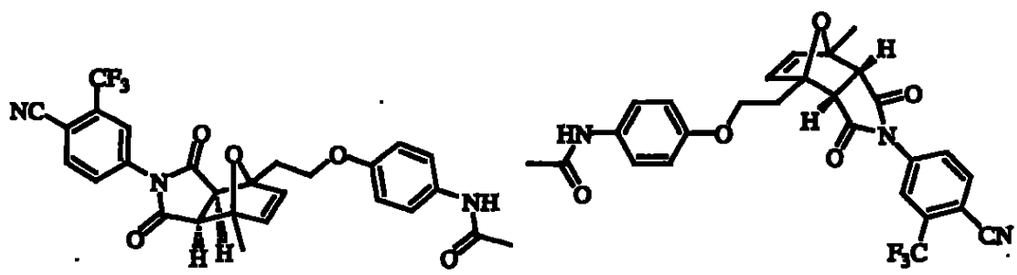
CH_2Cl_2 (4 mL). THF (5 mL) was added to make the reaction mixture homogeneous and the mixture was then cooled to 0°C. DEAD (0.41 mL, 2.6 mmol) was added dropwise and the reaction mixture was stirred at room temperature overnight, then concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with 60% EtOAc/hexanes followed by reverse phase preparative HPLC gave 270 mg (1.04 mmol, 52%) of compound **26A** as a light brown solid. MS (ESI): m/z 260.09 $[M+H]^+$.

B. (3aα,4β,7β,7aα)- and (3aα,4α,7α,7aα)-*N*-[4-[2-[2-[4-Cyano-3-(trifluoromethyl)phenyl]-1,2,3,3a,7,7a-hexahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindol-4-yl]ethoxy]phenyl]acetamide (26Bi and 26Bii, respectively)

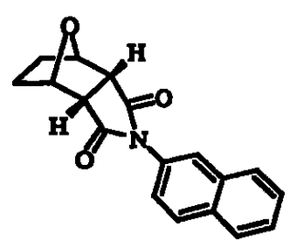


A solution of compound **26A** (40 mg, 0.15 mmol) and 4-(2,5-dihydro-2,5-dioxo-1H-pyrrol-1-yl)-2-trifluoromethylbenzonitrile (88 mg, 0.31 mmol) in CH_2Cl_2 (2 mL) was stirred at room temperature for 2 days. The reaction mixture was concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with 75% EtOAc/hexanes gave 55 mg (0.105 mmol, 68%) of a 5:1 mixture of compounds **26Bi** and **26Bii** as a white solid, which was used directly in the next step. HPLC: 90% at 3.28 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm).

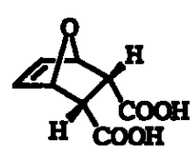
C. (3aα,4β,7β,7aα)- and (3aα,4α,7α,7aα)-*N*-[4-[2-[2-[4-Cyano-3-(trifluoromethyl)phenyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindol-4-yl]ethoxy]phenyl]acetamide (26Ci and 26Cii, respectively)

A solution of a mixture of compounds **26BI** and **26BII** (55 mg, 0.105 mmol) and 10% Pd/C (12 mg, cat.) in EtOH (3 mL) was stirred under a hydrogen atmosphere at room temperature overnight. The reaction mixture was filtered through Celite and concentrated under reduced pressure to give 50 mg of crude product. Purification by flash chromatography on silica gel eluting with 70% EtOAc/hexanes gave 18 mg (0.034 mmol, 32%) of compound **26CI** [HPLC: 96% at 3.33 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 528.01 $[M+H]^+$]; and 2.3 mg (0.0044 mmols, 4%) of an 85:15 mixture of **26CII** and **26CI** respectively as determined by ^{1}H NMR. HPLC: 90% at 3.35 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ESI): m/z 528.12 $[M+H]^+$.

Example 27
(3aα,4α,7α,7aα)-Hexahydro-2-(2-naphthalenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione (27D)



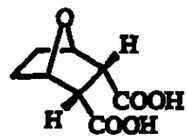
A. (endo, endo)-7-Oxabicyclo[2.2.1]hept-5-ene-2,3-dicarboxylic acid (27A)



Compounds **27A**, **27B** and **27C** were synthesized in accordance with the approaches described in Sprague et al. *J. Med. Chem.* **28**, 1580-1590 (1985). A mixture of furan (100 mL, 1.38 mol) and maleic acid (160 g, 1.38 mol) in H_2O (340 mL) was stirred at room temperature for 5 days. The mixture was placed in a separatory funnel and the aqueous layer was separated from the layer containing the

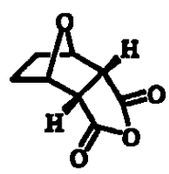
unreacted furan. The aqueous layer was treated with charcoal, filtered through Celite and placed in the refrigerator. The desired product crystallized from solution upon seeding, was filtered, washed with cold water and dried over P_2O_5 to give 70 g (0.38 mol, 28%) of compound 27A as a white solid.

B. (endo, endo)-7-Oxabicyclo[2.2.1]heptane-2,3-dicarboxylic acid (27B)



To a solution of compound 27A (69.0 g, 0.375 mol) in EtOH (700 mL) was added 10% Pd/C (4.5 g, cat.) and the mixture was shaken under a hydrogen atmosphere at 55 psi until gas uptake ceased. The mixture was filtered through Celite and concentrated *in vacuo* to give 66.0 g (0.355 mol, 95%) of compound 27B as a white solid.

C. (3aα,4α,7α,7aα)-Hexahydro-4,7-epoxyisobenzofuran-1,3-dione (27C)



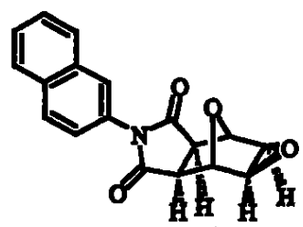
A solution of compound 27B (66.0 g, 355 mol) in acetyl chloride (300 mL) was refluxed for 1 h. The reaction solution was concentrated *in vacuo* and the resulting residue was recrystallized from benzene to give 49.2 g (0.292 mol, 82%) of compound 27C as a white solid (>99% endo by ^{1}H NMR).

D. (3aα,4α,7α,7aα)-Hexahydro-2-(2-naphthalenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione (27D)

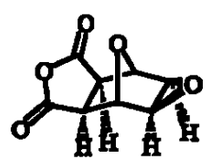
Compound 27C (45 mg, 0.30 mmol) was combined with 2-aminonaphthalene (47 mg, 0.33 mmol) in acetic acid (1 mL) and heated at 115°C overnight. After the

reaction was cooled to rt, a drop of water was added, and the resulting precipitate was filtered. The material was washed with methanol and dried to provide 65.7 mg (0.224 mmol, 74.7%) of compound 27D as a white crystalline solid. HPLC: 99% at 2.68 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ESI): m/z 294.0 $[M+H]^+$.

Example 28
(1aα,2β,2aα,5aα,6β,6aα)-Hexahydro-4-(2-naphthalenyl)-2,6-epoxy-3H-oxireno[f]isoindole-3,5(4H)-dione (28B)



A. (1aα,2β,2aα,5aα,6β,6aα)-Tetrahydro-2,6-epoxyoxireno[f]isobenzofuran-3,5(2aH,5aH)-dione (28A)

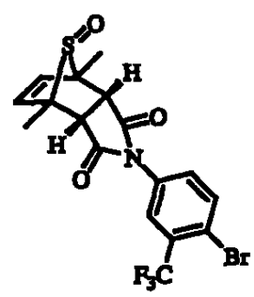


As described in Yur'ev et al. *J. Gen. Chem. U.S.S.R. (Engl. Transl.)* **31**, 772-775 (1961), a solution of exo-7-oxabicyclo[2.2.1]heptane-2,3-dicarboxylic anhydride (5.00 g, 30.1 mmol), formic acid (10 mL) and hydrogen peroxide (6 mL) was stirred at room temperature. After 30 min, the reaction was placed in an ice bath (it became exothermic along with gas evolution) and was allowed to warm to room temperature slowly. After stirring overnight, the resulting precipitate was collected by filtration and washed with glacial acetic acid and dried to yield 3.02 g of a white powder. The crude solid was boiled in acetyl chloride (100 mL) for 10 hours and the mixture was concentrated to ~20 mL under reduced pressure. The resulting precipitate was filtered, washed with dioxanes and dried to give 2.37 g (13.0 mmol, 43%) of compound 28A as a white powder.

B. (1aα,2β,2aα,5aα,6β,6aα)-Hexahydro-4-(2-naphthalenyl)-2,6-epoxy-3H-oxireno[f]isoindole-3,5(4H)-dione (28B)

Compound 28A (100 mg, 0.520 mmol) was combined with 2-aminonaphthalene (62.1 mg, 0.434 mmol) in acetic acid (2 mL) and heated at 115°C overnight. After the reaction was allowed to cool to rt, water was added, and the resulting precipitate was filtered. The material was washed sequentially with aqueous K_2CO_3 and water and then dried in a vacuum oven to provide 113.7 mg (0.371 mmol, 85.5%) of compound 28B as an off-white crystalline solid. HPLC: 99% at 1.76 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ESI): m/z 308.0 $[M+H]^+$.

Example 29
(3aα,4α,7α,7aα)-2-[4-Bromo-3-(trifluoromethyl)phenyl]-3a,4,7,7a-tetrahydro-4,7-dimethyl-4,7-epithio-1H-isoindole-1,3(2H)-dione 8-oxide (29)

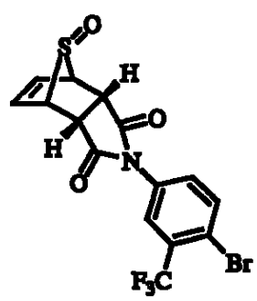


2,5-Dimethylthiophene (0.048 mL, 0.42 mmol) and 4-(2,5-dihydro-2,5-dioxo-1H-pyrrol-1-yl)-2-trifluoromethylbenzonitrile (0.290 g, 0.625 mmol, prepared as described for Example 1B) were dissolved in CH_2Cl_2 (8.0 mL) and cooled to –20 °C. $BF_3 \cdot Et_2O$ (0.412 mL, 3.36 mmol) was added slowly followed by addition of *m*CPBA (~50%, 0.29 g, 0.84 mmol). After 2 h at –20 °C, the reaction mixture was poured into saturated aq. $NaHCO_3$ and extracted with CH_2Cl_2 (3 x 20 mL) and the organics dried over anhydrous Na_2SO_4. The crude product was purified by flash chromatography on SiO_2 eluting with 5%-10%-20% EtOAc in CH_2Cl_2 to give 0.119 g (0.265 mmol, 63%)

of compound 29 as a white solid. HPLC: 91% at 3.303 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ESI): m/z 480.2 $[M+H]^+$.

Example 30

(3aα,4α,7α,7aα)-2-[4-Bromo-3-(trifluoromethyl)phenyl]-3a,4,7,7a-tetrahydro-4,7-epithio-1H-isoindole-1,3(2H)-dione 8-oxide (30)



Thiophene (0.375 mL, 4.69 mmol) and 4-(2,5-dihydro-2,5-dioxo-1H-pyrrol-1-yl)-2-trifluoromethylbenzonitrile (0.100 g, 0.313 mmol, prepared as described for Example 1B) were dissolved in CH_2Cl_2 (50 mL), *m*CPBA (~50%, 1.62 g, 4.69 mmol) was added and the resulting mixture was stirred at 25°C for 3 h. Triphenylphosphine (2.0 g) was then added. After 15 min, the volatiles were removed *in vacuo* and the resulting residue was dissolved in CH_2Cl_2 (200 mL) and washed with saturated aq. $NaHCO_3$ (3 x 50 mL) and dried over Na_2SO_4. The crude material was then purified by flash chromatography on SiO_2 eluting with 1% - 3% - 5% methanol in CH_2Cl_2 to give 0.059 g (0.14 mmol, 45%) compound 30 as a white powder. NMR and LC analysis showed a single diastereomer. HPLC: 100% at 3.437 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ESI): m/z 443.2 $[M+H]^+$.

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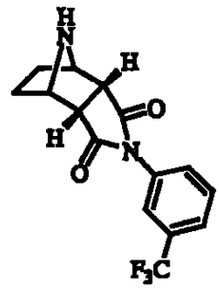
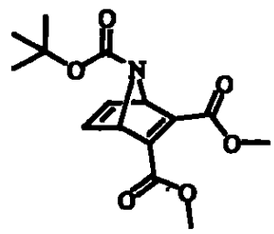
Example 31
(3aα,4α,7α,7aα)-Hexahydro-2-[3-(trifluoromethyl)phenyl]-4,7-imino-1H-isoindole-1,3(2H)-dione (31D)

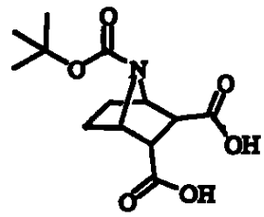


A. 7-Azabicyclo[2.2.1]hepta-2,5-diene-2,3,7-tricarboxylic acid 2,3-dimethyl 7-(1,1-dimethylethyl) ester (31A)



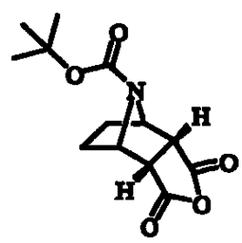
Freshly distilled acetylenedicarboxylic acid dimethyl ester (6.7 mL, 54 mmol) and *N*-(*tert*-butyloxycarbonyl)-1H-pyrrole (9.0 mL, 54 mmol) were combined and heated at 120°C for 3 h. Purification by flash chromatography on SiO_2 eluting with EtOAc/CH_2Cl_2 gave 8.3 g (27 mmol, 50%) of compound 31A as a yellow solid.

B. (exo,endo)-7-Azabicyclo[2.2.1]hept-2,5-diene-2,3,7-tricarboxylic acid 7-(1,1-dimethylethyl) ester (31B)



Compound 31A (1.0 g, 3.5 mmol) was dissolved in MeOH (2.0 mL) and aq. KOH (1 g in 5 mL H_2O) was added. The reaction was heated at 50°C for 1 h. The reaction was then cooled to 25°C and 10% Pd/C (0.5 g, cat.) was added and the mixture was placed in a Parr apparatus for 14 h at 25°C. The reaction was then filtered through Celite rinsing with water. The aqueous solution was acidified to pH 2 by addition of 1 N HCl and then extracted with EtOAc (2 x 100 mL). Concentration of the organics gave the compound 31B as a pale yellow solid.

C. (3aα,4α,7α,7aα)-Hexahydro-1,3-dioxo-4,7-iminoisobenzofuran-8-carboxylic acid 1,1-dimethylethyl ester (31C)



Crude compound, 31B, was heated to 120°C *in vacuo* in a sublimation chamber, resulting in sublimation of 0.051 g (0.19 mmol, 5.4%) of compound 31C as a white solid, which was collected directly and used in the next step without further purification.

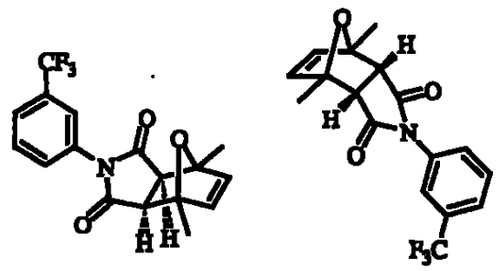
D. (3aα,4α,7α,7aα)-Hexahydro-2-[3-(trifluoromethyl)phenyl]-4,7-imino-1H-isoindole-1,3(2H)-dione (31D)

Compound 31C (0.050 g, 0.19 mmol) and the 1-amino-3-(trifluoromethyl)benzene (0.030 g, 0.19 mmol) were dissolved in AcOH (2.5 mL) and heated at 115°C for 4.5 h. The reaction was quenched by addition of saturated aqueous $NaHCO_3$ and the mixture was extracted with methylene chloride (3 x 15 mL). The crude material was purified by reverse phase preparative HPLC to give 0.030 g (0.097 mmol, 51%)of compound 31D as a white solid. HPLC: 99% at 2.33 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol

over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ESI): m/z 311.15 $[M+H]^+$.

Example 32

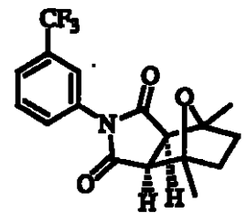
(3aα,4β,7β,7aα)- and (3aα,4α,7α,7aα)-3a,4,7,7a-Tetrahydro-4,7-dimethyl-2-[3-(trifluoromethyl)phenyl]-4,7-epoxy-1H-isoindole-1,3(2H)-dione (32i and 32ii, respectively)



Freshly distilled 2,5-dimethylfuran (0.32 mL, 2.6 mmol) was dissolved in CH_2Cl_2 (2.0 mL) and 1-[3-(trifluoromethyl)phenyl]-1H-pyrrole-2,5-dione (0.5 g, 2.5 mmol, prepared as described in Example 1B) was added. The reaction was stirred at 25°C for 16 h and was then concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with 0.5% $MeOH/CH_2Cl_2$ gave 250 mg (0.741 mmol, 30%) of compound **32i**, and 50 mg (0.15 mmol, 6%) of compound **32ii** as white solids. Compound **32i**: HPLC: 98% at 3.080 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 338.30 $[M+H]^+$. Compound **32ii**: HPLC: 92% at 3.047 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm), MS (ES): m/z: 338.15 $[M+H]^+$.

Example 33

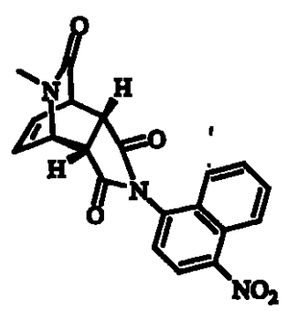
(3aα,4β,7β,7a α)-Hexahydro-4,7-dimethyl-2-[3-(trifluoromethyl)phenyl]-4,7-epoxy-1H-isoindole-1,3(2H)-dione (33)



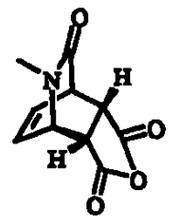
Compound 32i (0.080 g, 0.24 mmol) was dissolved in EtOAc (2 mL) and EtOH (1 mL) and 10% Pd/C (0.050 g, cat.) was added. Hydrogen was then introduced by a balloon and the reaction was stirred for 24 h. The mixture was filtered through Celite, rinsed with EtOAc and concentrated *in vacuo* to give 0.075 g (0.22 mmol, 93%) of compound 33 as a white solid. No further purification was needed. HPLC: 90% at 3.233 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 340.40 $[M+H]^+$.

Example 34

(3aα,4β,7β,7aα)-Tetrahydro-5-methyl-2-(4-nitro-1-naphthalenyl)-4,7-etheno-1H-pyrrolo[3,4-c]pyridine-1,3,6(2H,5H)-trione (34B)



A. **4,5,7,7a-Tetrahydro-5-methyl-4,7-ethenofuro[3,4-c]pyridine-1,3,6(3aH)-trione (34A)**



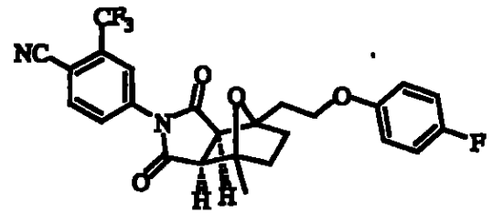
Compound **34A** was synthesized by a modification of the methods described by Tomisawa et al. *Heterocycles* **6**, 1765-1766 (1977) & *Tetrahedron Lett.* **29**, 2465-2468 (1969). Maleic anhydride (2.00 g, 20.4 mmol) and 1-methyl-2-pyridone (2.22 g, 20.4 mmol) were suspended in 30 mL of anhydrous toluene. The reaction vessel was fitted with a Dean Stark trap and refluxed for 48 hours. The dark colored solution was allowed to cool to rt and then the volatiles were removed *in vacuo*. The resulting brown paste (4 g) was dissolved in 10 mL of boiling toluene and the hot solution was filtered under a nitrogen flow to remove particulates. On standing at 25°C the desired product precipitated from solution. The solid was isolated by filtration and washed with cold toluene to give 1.0 g (4.8 mmol, 24%) of compound **34A**, which was used without further purification.

B. (3aα,4α,7α,7aα)-Tetrahydro-5-methyl-2-(4-nitro-1-naphthalenyl)-4,7-etheno-1H-pyrrolo[3,4-c]pyridine-1,3,6(2H,5H)-trione (34B)

1-Amino-4-nitronaphthalene (0.094 g, 0.50 mmol) and compound **34A** (0.130 g, 0.627 mmol) were dissolved in AcOH (2.0 mL) and heated at 110°C for 11 h. The reaction was then cooled to 25°C and poured into cold saturated aqueous K_2CO_3 and stirred vigorously for 10 min. The solution was filtered and rinsed with water. The resulting filtrate was concentrated *in vacuo* and purified by flash chromatography on silica gel eluting with 4:6 EtOAc/hexanes to give 0.172 g (0.456 mmol, 91%) of compound **34B** as a white solid. HPLC: 92% at 2.472 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 378.29 $[M+H]^+$.

Example 35

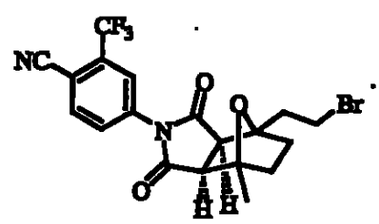
(3aα,4β,7β,7aα)-4-[4-[2-(4-Fluorophenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile (35)



DEAD (0.060 mL, 0.38 mmol) was added to a solution of triphenylphosphine (100 mg, 0.380 mmol) in THF (1.3 mL) at room temperature under an inert atmosphere. After stirring for 10 min, 4-fluorophenol (43 mg, 0.380 mmol) was added in one portion. The reaction mixture was stirred for 5 min, compound 25B (100 mg, 0.254 mmol) was added and stirring was continued for 3.5 h. Purification by flash chromatography on silica gel eluting with 50% EtOAc/hexanes followed by reverse phase preparative HPLC [11.93 min (retention time) (YMC S5 ODS column 20 x 100 mm, 0-100% aqueous methanol over 10 minutes containing 0.1% TFA, 20 mL/min, monitoring at 220 nm)] gave 72 mg (58%) of compound 35 as a solid. HPLC: 99% at 3.74 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ESI): m/z 487.1 $[M-H]^-$.

Example 36

(3aα,4β,7β,7aα)-4-[4-(2-Bromoethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile (36)

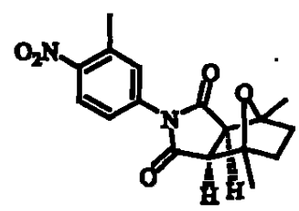


A solution of 25B (495 mg, 1.26 mmol) and pyridine (100 μL, 1.26 mmol) in CH_2Cl_2 (2 mL) was added to a solution of Ph_3PBr_2 (636 mg, 1.51 mmol) in CH_2Cl_2 (2 mL) at 0°C. The reaction mixture was stirred at room temperature for 3 hr, then

the solvent was removed under reduced pressure. The resulting residue was washed 2X with 10 mL portions of EtOAc-hexane (6:4) and the combined washings were purified by flash chromatography on silica gel eluting with 60% EtOAc/hexane to give 390 mg (0.853 mmol, 67.7%) of compound **36** as a white solid. HPLC: 99% at 3.51 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ESI): m/z 456.7 $[M-H]^-$.

Example 37

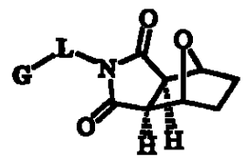
(3aα,4β,7β,7aα)-Hexahydro-4,7-dimethyl-2-(3-methyl-4-nitrophenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione (37)



A combination of 4-nitro-3-methylaniline (0.050 g, 0.33 mmol), compound **20A** (0.083 g, 0.43 mmol), TEA (0.2 mL), $MgSO_4$ (0.075 g) and toluene (0.8 mL) were combined in a sealed tube and the mixture was heated at 120°C for 14 h. After cooling to 25°C, the reaction was filtered, rinsed with CH_2Cl_2 and concentrated under reduced pressure. The crude product was purified by preparative TLC on SiO_2 eluting with CH_2Cl_2 to give 0.075 g (0.23 mmol, 69%) of compound **37** as a pale yellow solid. HPLC: 100% at 2.733 min (retention time) (YMC S5 ODS column, 4.6 X 50 mm; 10-90% $MeOH/H_2O$ gradient,+ 0.1% TFA; 4 mL/min, 220 nm detection). MS (ES): m/z 348.2 $[M+NH_4]^+$.

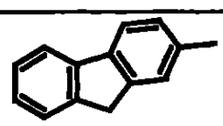
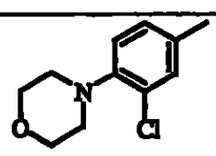
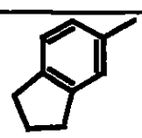
Examples 38 to 121

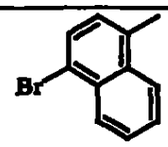
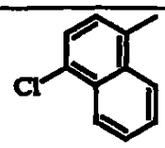
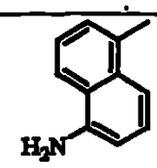
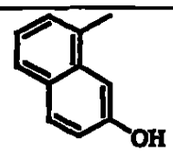
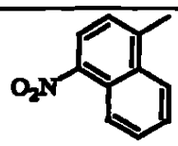
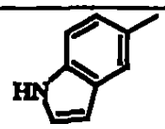
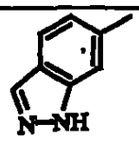
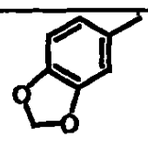
Additional compounds of the present invention were prepared by procedures analogous to those described above. The compounds of Examples 38 to 121 have the following structure (L is a bond):

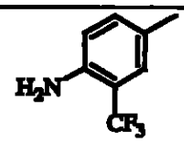
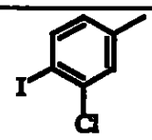
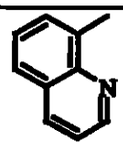
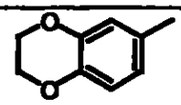
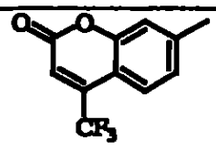
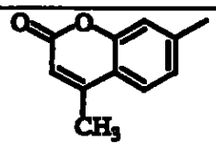
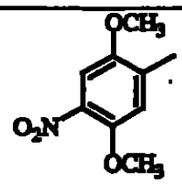
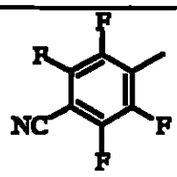


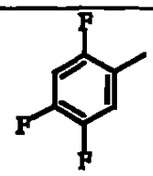
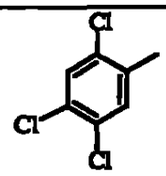
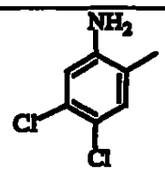
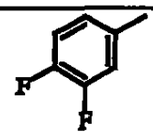
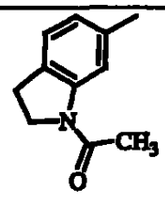
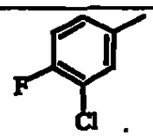
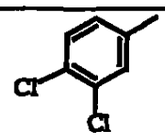
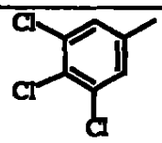
where G, the compound name, retention time, molecular mass, and the procedure employed, are set forth in Table 2. The chromatography techniques used to determine the compound retention times of Table 2 are as follows: LCMS = YMC S5 ODS column, 4.6 X 50 mm eluting with 10-90% MeOH/H_2O over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm. The molecular mass of the compounds listed in Table 2, where provided, were determined by MS (ES) by the formula m/z.

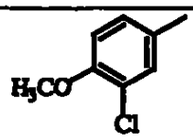
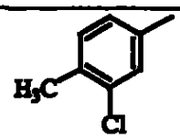
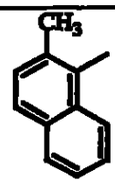
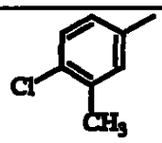
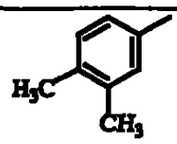
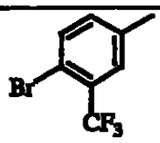
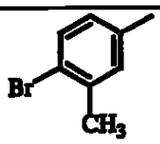
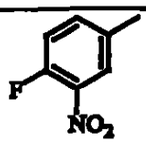
Table 2

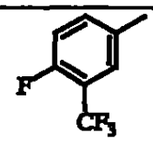
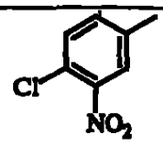
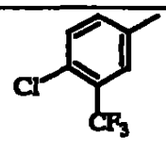
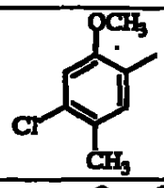
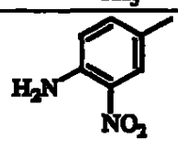
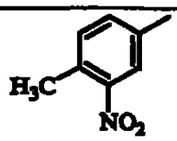
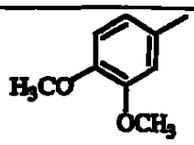
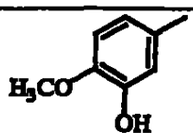
Ex. No.	G	Compound Name	Retention Time (Min.)/ Molecular Mass	Pro. of Ex.
38		(3aα,4β,7β,7aα)-2-(2-Fluorenyl)hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.72 LCMS/ 332.20 $[M+H]^+$	8
39		(3aα,4β,7β,7aα)-2-[3-Chloro-4-(4-morpholinyl)phenyl]hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.20 LCMS/ 363.20 $[M+H]^+$	8
40		(3aα,4β,7β,7aα)-2-(2,3-Dihydro-1H-inden-5-yl)hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.26 LCMS/ 284.22 $[M+H]^+$	8

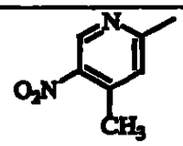
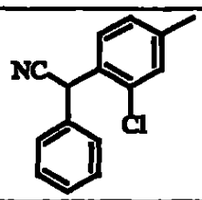
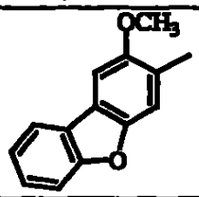
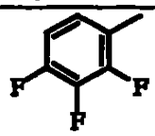
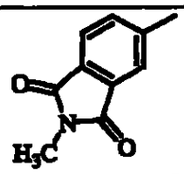
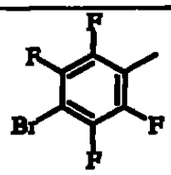
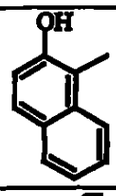
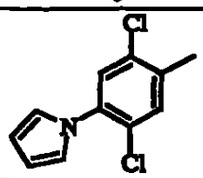
Ex. No.	G	Compound Name	Retention Time (Min.)/ Molecular Mass	Pro. of Ex.
41		(3aα,4β,7β,7aα)-2-(4-Bromo-1-naphthalenyl)hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.73 LCMS/ 404.11 $[M+CH_3OH+H]^+$	8
42		(3aα,4β,7β,7aα)-2-(4-Chloro-1-naphthalenyl)hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.63 LCMS/ 328.14 $[M+H]^+$	8
43		(3aα,4β,7β,7aα)-2-(5-Amino-1-naphthalenyl)hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	1.64 LCMS/	8
44		(3aα,4β,7β,7aα)-Hexahydro-2-(7-hydroxy-1-naphthalenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione	2.54 LCMS/ 308.23 $[M-H]^-$	8
45		(3aα,4β,7β,7aα)-Hexahydro-2-(4-nitro-1-naphthalenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.117 LCMS/ 404.11 $[M+CH_3OH+H]^+$	8
46		(3aα,4β,7β,7aα)-Hexahydro-2-(1H-indol-5-yl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione	2.39 LCMS/ 283.23 $[M+H]^+$	8
47		(3aα,4β,7β,7aα)-Hexahydro-2-(1H-indazol-6-yl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione	2.35 LCMS/ 282.23 $[M-H]^-$	8
48		(3aα,4β,7β,7aα)-2-(1,3-Benzodioxol-5-yl)hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	2.47 LCMS/ 288.20 $[M+H]^+$	8

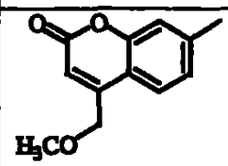
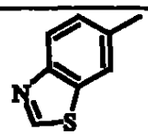
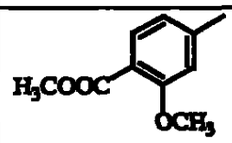
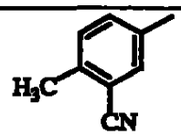
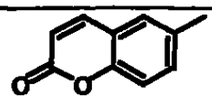
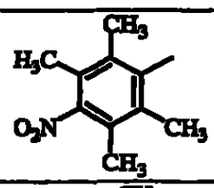
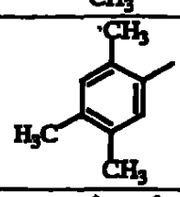
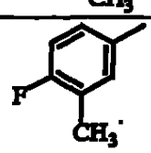
Ex. No.	G	Compound Name	Retention Time (Min.)/ Molecular Mass	Pro. of Ex.
49		(3aα,4β,7β,7aα)-2-[4-Amino-3-(trifluoromethyl)phenyl]hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	2.71 LCMS/ 327.20 $[M+H]^+$	8
50		(3aα,4β,7β,7aα)-2-(3-Chloro-4-iodophenyl)hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.70 LCMS/ 435.2 $[M+CH_3OH]^+$	8
51		(3aα,4β,7β,7aα)-Hexahydro-2-(8-quinolinyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione	2.28 LCMS/ 295.22 $[M+H]^+$	8
52		(3aα,4β,7β,7aα)-2-(2,3-Dihydro-1,4-benzodioxin-6-yl)hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	2.55 LCMS/ 302.23 $[M+H]^+$	8
53		(3aα,4β,7β,7aα)-Hexahydro-2-[2-oxo-4-(trifluoromethyl)-2H-1-benzopyran-7-yl]-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.38 LCMS/ 412.17 $[M+CH_3OH+H]^+$	8
54		(3aα,4β,7β,7aα)-Hexahydro-2-(4-methyl-2-oxo-2H-1-benzopyran-7-yl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione	2.74 LCMS/ 326.20 $[M+H]^+$	8
55		(3aα,4β,7β,7aα)-2-(2,5-Dimethoxy-4-nitrophenyl)hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	2.70 LCMS/ 349.23 $[M+H]^+$	8
56		(3aα,4β,7β,7aα)-2,3,5,6-Tetrafluoro-4-(octahydro-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)benzonitrile	2.97 LCMS	8

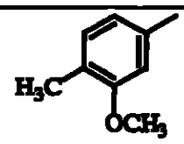
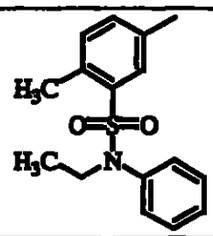
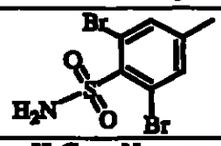
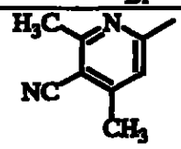
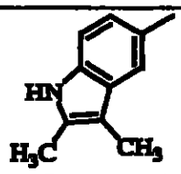
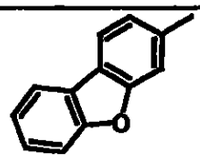
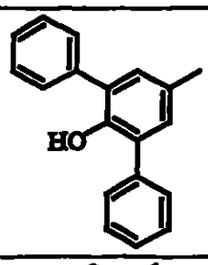
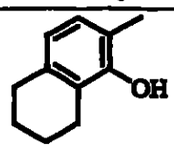
Ex. No.	G	Compound Name	Retention Time (Min.)/ Molecular Mass	Pro. of Ex.
57		(3aα,4β,7β,7aα)-Hexahydro-2-(2,4,5-trifluorophenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione	2.90 LCMS	8
58		(3aα,4β,7β,7aα)-Hexahydro-2-(2,4,5-trichlorophenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.64 LCMS/ 346.39 $[M]^{+\cdot}$	8
59		(3aα,4β,7β,7aα)-2-(2-Amino-4,5-dichlorophenyl)hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.23 LCMS	8
60		(3aα,4β,7β,7aα)-2-(3,4-Difluorophenyl)hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	2.91 LCMS/ 280.23 $[M+H]^+$	8
61		(3aα,4β,7β,7aα)-1-Acetyl-2,3-dihydro-6-(octahydro-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-1H-indole	2.43 LCMS/ 359.26 $[M+CH_3OH+H]^+$	8
62		(3aα,4β,7β,7aα)-2-(3-Chloro-4-fluorophenyl)hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.21 LCMS/ 328.14 $[M+CH_3OH+H]^+$	8
63		(3aα,4β,7β,7aα)-2-(3,4-Dichlorophenyl)hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.54 LCMS/ 311.79 $[M-H]^-$	8
64		(3aα,4β,7β,7aα)-Hexahydro-2-(3,4,5-trichlorophenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione	4.05 LCMS/ 378.10 $[M+CH_3OH+H]^+$	8

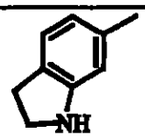
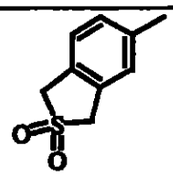
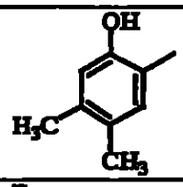
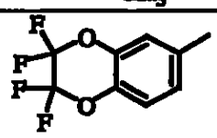
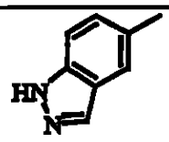
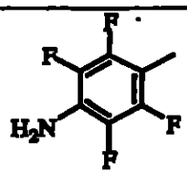
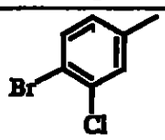
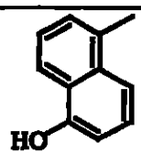
Ex. No.	G	Compound Name	Retention Time (Min.)/ Molecular Mass	Pro. of Ex.
65		(3aα,4β,7β,7aα)-2-(3-Chloro-4-methoxyphenyl)hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	2.99 LCMS/ 308.11 $[M+H]^+$	8
66		(3aα,4β,7β,7aα)-2-(3-Chloro-4-methylphenyl)hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.39 LCMS/ 292.20 $[M+H]^+$	8
67		(3aα,4β,7β,7aα)-Hexahydro-2-(2-methyl-1-naphthalenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.28 LCMS/ 308.23 $[M+H]^+$	8
68		(3aα,4β,7β,7aα)-2-(4-Chloro-3-methylphenyl)hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.40 LCMS/ 292.20 $[M+H]^+$	8
69		(3aα,4β,7β,7aα)-2-(3,4-Dimethylphenyl)hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.11 LCMS/ 272.23 $[M+H]^+$	8
70		(3aα,4β,7β,7aα)-2-[4-Bromo-3-(trifluoromethyl)phenyl]hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.76 LCMS/ 421.98 $[M+CH_3OH+H]^+$	8
71		(3aα,4β,7β,7aα)-2-(4-Bromo-3-methylphenyl)hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.50 LCMS/ 336.05 $[M+H]^+$	8
72		(3aα,4β,7β,7aα)-2-(4-Fluoro-3-nitrophenyl)hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	2.80 LCMS/ 305.25 $[M-H]^-$	8

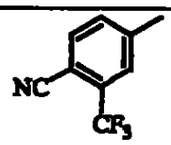
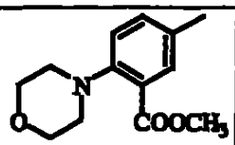
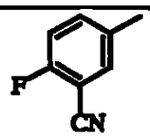
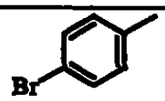
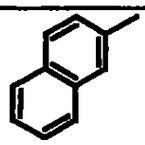
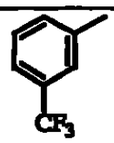
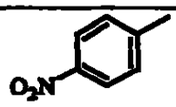
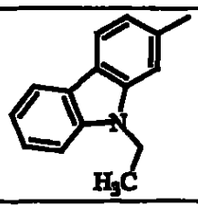
Ex. No.	G	Compound Name	Retention Time (Min.)/ Molecular Mass	Pro. of Ex.
73		(3aα,4β,7β,7aα)-2-[4-Fluoro-3-(trifluoromethyl)phenyl]hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.45 LCMS/ 362.26 $[M+CH_3OH+H]^+$	8
74		(3aα,4β,7β,7aα)-2-(4-Chloro-3-nitrophenyl)hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.19 LCMS/ 322.86 $[M]^{+\cdot}$	8
75		(3aα,4β,7β,7aα)-2-[4-Chloro-3-(trifluoromethyl)phenyl]hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.68 LCMS/ 345.83 $[M]^{+\cdot}$	8
76		(3aα,4β,7β,7aα)-2-(4-Chloro-2-methoxy-5-methylphenyl)hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.31 LCMS/ 322.20 $[M+H]^+$	8
77		(3aα,4β,7β,7aα)-2-(4-Amino-3-nitrophenyl)hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	2.34 LCMS/ 302.27 $[M-H]^-$	8
78		(3aα,4β,7β,7aα)-Hexahydro-2-(4-methyl-3-nitrophenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.02 LCMS/ 335.20 $[M+CH_3OH+H]^+$	8
79		(3aα,4β,7β,7aα)-2-(3,4-Dimethoxyphenyl)hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	2.35 LCMS/ 304.25 $[M+H]^+$	8
80		(3aα,4β,7β,7aα)-Hexahydro-2-(3-hydroxy-4-methoxyphenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione	0.98 LCMS/ 321.19 $[M+CH_3OH]^{+\cdot}$	8

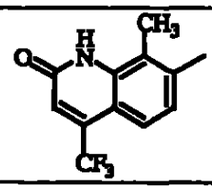
Ex. No.	G	Compound Name	Retention Time (Min.)/ Molecular Mass	Pro. of Ex.
81		(3aα,4β,7β,7aα)-Hexahydro-2-(4-methyl-5-nitro-2-pyridinyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione	0.54 LCMS/ 304.20 $[M+H]^+$	8
82		(3aα,4β,7β,7aα)-2-Chloro-4-(octahydro-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-α-phenylbenzeneacetonitrile	3.67 LCMS/ 423.8 $[M+CH_3OH]^{+\cdot}$	8
83		(3aα,4β,7β,7aα)-Hexahydro-2-(2-methoxy-3-dibenzofuranyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.66 LCMS/ 364.25 $[M+H]^+$	8
84		(3aα,4β,7β,7aα)-Hexahydro-2-(2,3,4-trifluorophenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.06 LCMS/ 298.14 $[M+H]^+$	8
85		(3aα,4β,7β,7aα)-2-(2,3-Dihydro-2-methyl-1,3-dioxo-1H-isoindol-5-yl)hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	2.70 LCMS/ 359.22 $[M+CH_3OH+H]^+$	8
86		(3aα,4β,7β,7aα)-2-(4-Bromo-2,3,5,6-tetrafluorophenyl)hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.72 LCMS/ 426.07 $[M+CH_3OH+H]^+$	8
87		(3aα,4β,7β,7aα)-Hexahydro-2-(2-hydroxy-1-naphthalenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione	2.52 LCMS/ 308.26 $[M-H]^-$	8
88		(3aα,4β,7β,7aα)-2-[2,5-Dichloro-4-(1H-pyrrol-1-yl)phenyl]hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.70 LCMS/ 376.64 $[M-H]^-$	8

Ex. No.	G	Compound Name	Retention Time (Min.)/ Molecular Mass	Pro. of Ex.
89		(3aα,4β,7β,7aα)-Hexahydro-2-[4-(methoxymethyl)-2-oxo-2H-1-benzopyran-7-yl]-4,7-epoxy-1H-isoindole-1,3(2H)-dione	2.79 LCMS/ 356.26 $[M+H]^+$	8
90		(3aα,4β,7β,7aα)-2-(6-Benzothiazolyl)hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	2.46 LCMS/ 301.19 $[M+H]^+$	8
91		(3aα,4β,7β,7aα)-2-Methoxy-4-(octahydro-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)benzoic acid methyl ester	2.75 LCMS/ 332.25 $[M+H]^+$	8
92		(3aα,4β,7β,7aα)-2-Methyl-5-(octahydro-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)benzonitrile	2.80 LCMS/ 315.26 $[M+CH_3OH+H]^+$	8
93		(3aα,4β,7β,7aα)-Hexahydro-2-(2-oxo-2H-1-benzopyran-6-yl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione	2.45 LCMS/ 312.20 $[M+H]^+$	8
94		(3aα,4β,7β,7aα)-Hexahydro-2-(2,3,5,6-tetramethyl-4-nitrophenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.59 LCMS/ 377.25 $[M+CH_3OH+H]^+$	8
95		(3aα,4β,7β,7aα)-Hexahydro-2-(2,4,5-trimethylphenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.33 LCMS/ 286.30 $[M+H]^+$	8
96		(3aα,4β,7β,7aα)-2-(4-Fluoro-3-methylphenyl)hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.00 LCMS/ 276.23 $[M+H]^+$	8

Ex. No.	G	Compound Name	Retention Time (Min.)/ Molecular Mass	Pro. of Ex.
97		(3aα,4β,7β,7aα)-Hexahydro-2-(3-methoxy-4-methylphenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.05 LCMS/ 288.23 $[M+H]^+$	8
98		(3aα,4β,7β,7aα)-*N*-Ethyl-2-methyl-5-(octahydro-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-*N*-phenylbenzenesulfonamide	3.56 LCMS/ 441.26 $[M+H]^+$	8
99		(3aα,4β,7β,7aα)-2,6-Dibromo-4-(octahydro-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)benzenesulfonamide	2.25 LCMS	8
100		(3aα,4β,7β,7aα)-2,4-Dimethyl-6-(octahydro-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-3-pyridinecarbonitrile	2.75 LCMS/ 298.23 $[M+H]^+$	8
101		(3aα,4β,7β,7aα)-2-(2,3-Dimethyl-1H-indol-5-yl)hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.00 LCMS/ 311.26 $[M+H]^+$	8
102		(3aα,4β,7β,7aα)-2-(3-Dibenzofuranyl)hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.72 LCMS/ 366.23 $[M+CH_3OH+H]^+$	8
103		(3aα,4β,7β,7aα)-Hexahydro-2-(2'-hydroxy[1,1':3',1"-terphenyl]-5'-yl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.70 LCMS/ 412.23 $[M+H]^+$	8
104		(3aα,4β,7β,7aα)-Hexahydro-2-(5,6,7,8-tetrahydro-3-hydroxy-2-naphthalenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.24 LCMS/ 312.32 $[M+H]^+$	8

Ex. No.	G	Compound Name	Retention Time (Min.)/ Molecular Mass	Pro. of Ex.
105		(3aα,4β,7β,7aα)-2-(2,3-Dihydro-1H-indol-6-yl)hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	2.42 LCMS/ 285.29 $[M+H]^+$	8
106		(3aα,4β,7β,7aα)-2-(1,3-Dihydro-2,2-dioxidobenzo[c]thiophen-5-yl)hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	1.99 LCMS/ 366.26 $[M+CH_3OH+H]^+$	8
107		(3aα,4β,7β,7aα)-Hexahydro-2-(2-hydroxy-4,5-dimethylphenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione	2.78 LCMS/ 286.32 $[M-H]^-$	8
108		(3aα,4β,7β,7aα)-2-(2,3-Dihydro-2,2,3,3-tetrafluoro-1,4-benzodioxin-6-yl)hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.82 LCMS/ 406.19 $[M+CH_3OH+H]^+$	8
109		(3aα,4β,7β,7aα)-Hexahydro-2-(1H-indazol-5-yl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione	2.13 LCMS/ 284.23 $[M+H]^+$	8
110		(3aα,4β,7β,7aα)-2-(4-Amino-2,3,5,6-tetrafluorophenyl)-hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	2.60 LCMS/ 363.22 $[M+CH_3OH+H]^+$	8
111		(3aα,4β,7β,7aα)-2-(4-Bromo-3-chlorophenyl)hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.64 LCMS/ 389.64 $[M+CH_3OH+H]^+$	8
112		(3aα,4β,7β,7aα)-Hexahydro-2-(5-hydroxy-1-naphthalenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione	2.48 LCMS/ 308.27 $[M-H]^-$	8

Ex. No.	G	Compound Name	Retention Time (Min.)/ Molecular Mass	Pro. of Ex.
113		(3aα,4β,7β,7aα)-4-(Octahydro-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile	3.28 LCMS/ 337.16 $[M+H]^+$	8
114		(3aα,4β,7β,7aα)-2-(4-Morpholinyl)-5-(octahydro-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)benzoic acid methyl ester	2.72 LCMS/ 387.17 $[M+H]^+$	8
115		(3aα,4β,7β,7aα)-2-Fluoro-5-(octahydro-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)benzonitrile	2.69 LCMS/ 319.26 $[M+CH_3OH+H]^+$	8
116		(3aα,4β,7β,7aα)-2-(4-Bromophenyl)hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	5.80 LCMS/ 393.0 $[M+H]^+$	8
117		(3aα,4β,7β,7aα)-Hexahydro-2-(2-naphthalenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione	6.92 LCMS/ 333.7 $[M+H]^+$	8
118		(3aα,4β,7β,7aα)-Hexahydro-2-[3-(trifluoromethyl)phenyl]-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.27 LCMS/ 312.2 $[M+H]^+$	8
119		(3aα,4β,7β,7aα)-Hexahydro-2-(4-nitrophenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione	2.88 LCMS/ 343.2 $[M+H]^+$	8
120		(3aα,4β,7β,7aα)-2-(9-Ethyl-9H-carbazol-3-yl)hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.73 LCMS/ 360.1 $[M+H]^+$	8

Ex. No.	G	Compound Name	Retention Time (Min.)/ Molecular Mass	Pro. of Ex.
121		(3aα,4β,7β,7aα)-2-[1,2-Dihydro-8-methyl-2-oxo-4-(trifluoromethyl)-7-quinolinyl]hexahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.11 LCMS/ 393.0 $[M+H]^+$	8

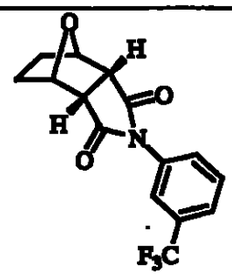
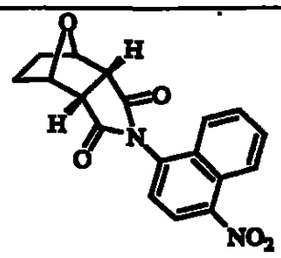
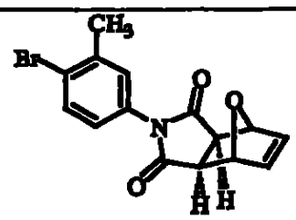
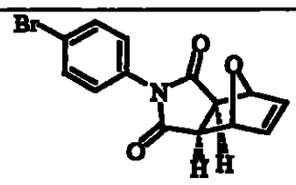
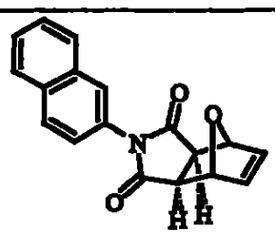
Examples 122 to 164

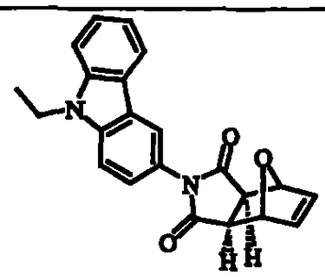
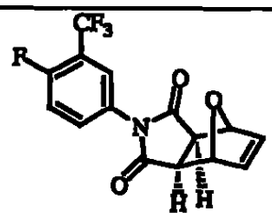
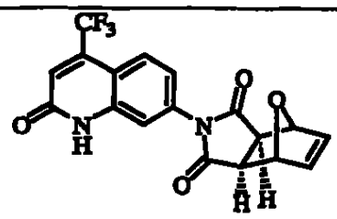
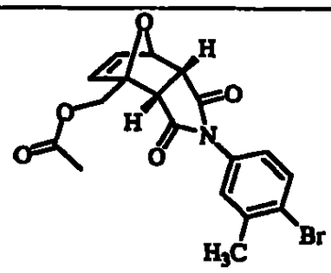
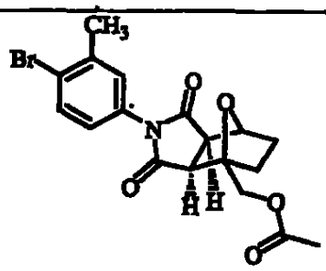
Further compounds of the present invention were prepared by procedures analogous to those described above. Table 3 provides the compound name and structure, retention time, as well as the Example number of the procedure on which the preparation of Table 3 was based, for the compounds of Examples 122 to 164. The chromatography techniques used to determine the compound retention times of Table 3 are as follows:

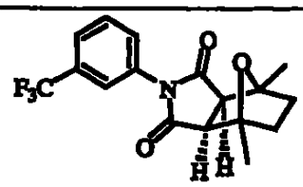
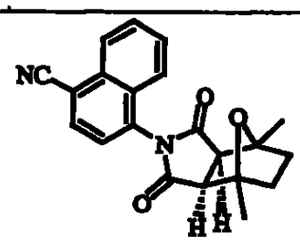
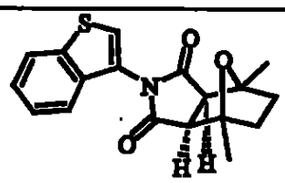
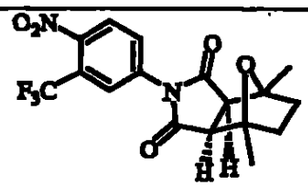
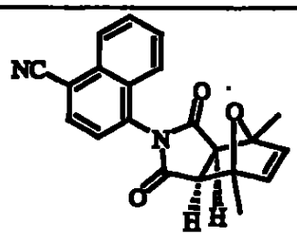
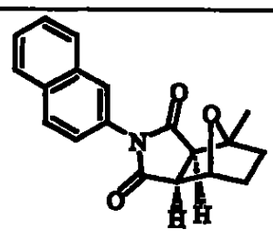
LCMS = YMC S5 ODS column, 4.6 X 50 mm eluting with 10-90% MeOH/H_2O over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm.

LC = YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% MeOH/H_2O over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm

Table 3

Ex. No.	Compound Structure	Compound Name	Retention Time Min./ Molecular Mass	Pro. of Ex.
122		(3aα,4α,7α,7aα)-Hexahydro-2-[3-(trifluoromethyl)phenyl]-4,7-epoxy-1H-isoindole-1,3(2H)-dione	2.66 LCMS	27
123		(3aα,4α,7α,7aα)-Hexahydro-2-(4-nitro-1-naphthalenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione	2.76 LCMS	27
124		(3aα,4β,7β,7aα)-2-(4-Bromo-3-methylphenyl)-3a,4,7,7a-tetrahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	6.36 LCMS	8
125		(3aα,4β,7β,7aα)-2-(4-Bromophenyl)-3a,4,7,7a-tetrahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	5.72 LCMS	8
126		(3aα,4β,7β,7aα)-3a,4,7,7a-Tetrahydro-2-(2-naphthalenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione	5.92 LCMS	8

Ex. No.	Compound Structure	Compound Name	Retention Time Min./ Molecular Mass	Pro. of Ex.
127		(3aα,4β,7β,7aα)-2-(9-Ethyl-9H-carbazol-3-yl)-3a,4,7,7a-tetrahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.73 LCMS	8
128		(3aα,4β,7β,7aα)-2-[4-Fluoro-3-(trifluoromethyl)phenyl]-3a,4,7,7a-tetrahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.40 LCMS	8
129		(3aα,4β,7β,7aα)-2-[1,2-Dihydro-8-methyl-2-oxo-4-(trifluoromethyl)-7-quinolinyl]-3a,4,7,7a-tetrahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.14 LCMS	8
130		(3aα,4α,7α,7aα)-4-[(Acetyloxy)methyl]-2-(4-bromo-3-methylphenyl)-3a,4,7,7a-tetrahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	2.95 LC	4
131		(3aα,4β,7β,7aα)-4-[(Acetyloxy)methyl]-2-(4-bromo-3-methylphenyl)-3a,4,7,7a-tetrahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione.	2.97 LCMS	5

Ex. No.	Compound Structure	Compound Name	Retention Time Min./ Molecular Mass	Pro. of Ex.
132		(3aα,4β,7β,7aα)-Hexahydro-4,7-dimethyl-2-[3-(trifluoromethyl)phenyl]-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.08 LC	20
133		(3aα,4β,7β,7aα)-4-(Octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-1-naphthalenecarbonitrile	3.00 LC	20
134		(3aα,4β,7β,7aα)-(Benzo[b]thiophen-3-yl)hexahydro-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.61 LC	20
135		(3aα,4β,7β,7aα)-Hexahydro-4,7-dimethyl-2-[4-nitro-3-(trifluoromethyl)phenyl]-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.21 LC	20
136		(3aα,4β,7β,7aα)-4-(1,3,3a,4,7,7a-Hexahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-1-naphthalenecarbonitrile	2.94 LC	32
137		(3aα,4α,7α,7aα)-Hexahydro-4-methyl-2-(2-naphthalenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione	2.88 LC	3

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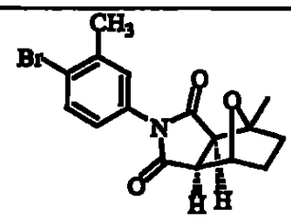
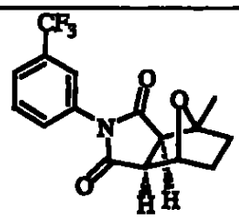
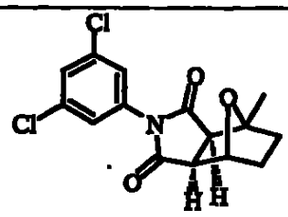
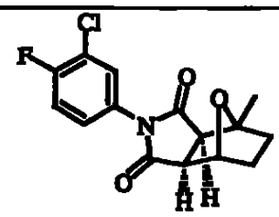
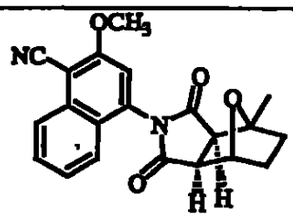
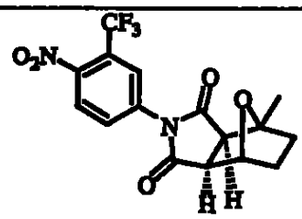
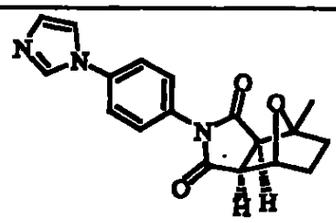
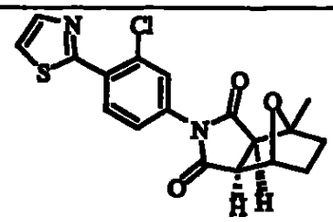
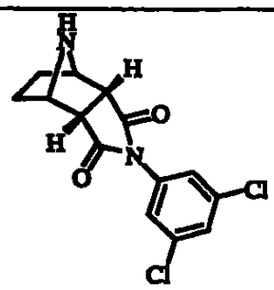
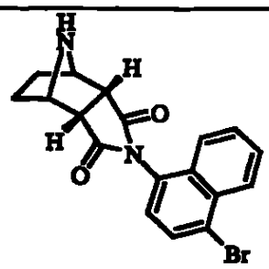
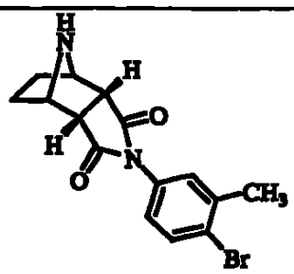
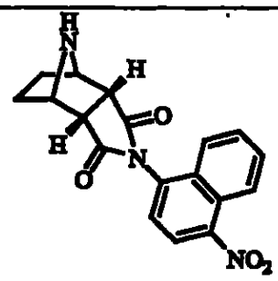
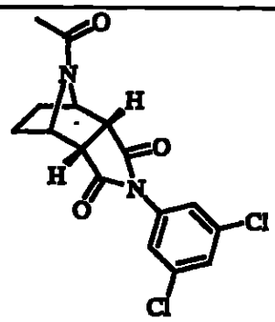
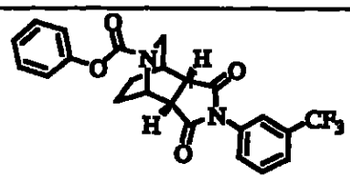
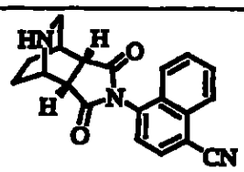
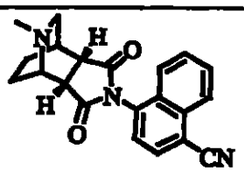
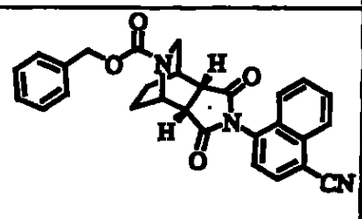
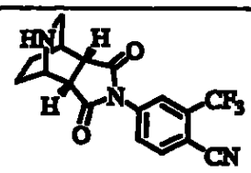
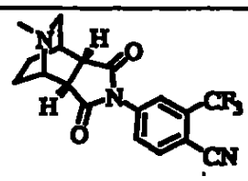
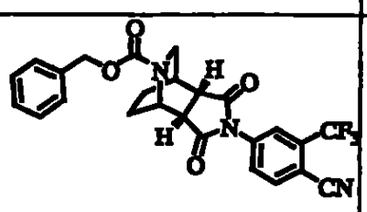
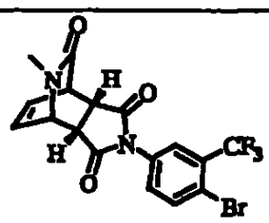
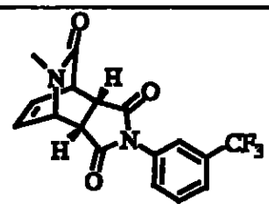
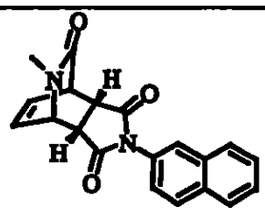
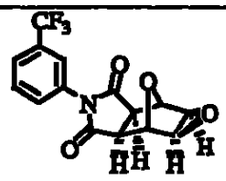
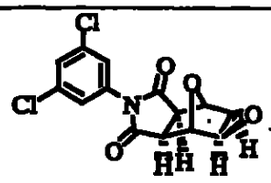
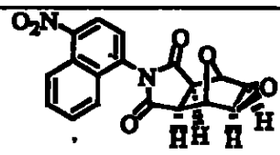
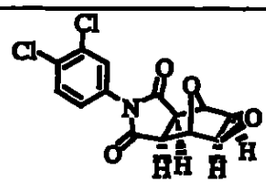
Ex. No.	Compound Structure	Compound Name	Retention Time Min./ Molecular Mass	Pro. of Ex.
138		(3aα,4β,7β,7aα)-2-(4-Bromo-3-methylphenyl)hexahydro-4-methyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.11 LC	3
139		(3aα,4β,7β,7aα)-Hexahydro-4-methyl-2-[3-(trifluoromethyl)phenyl]-4,7-epoxy-1H-isoindole-1,3(2H)-dione	2.90 LC	3
140		(3aα,4β,7β,7aα)-2-(3,5-Dichlorophenyl)hexahydro-4-methyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.31 LC	3
141		(3aα,4β,7β,7aα)-2-(3-Chloro-4-fluorophenyl)-hexahydro-4-methyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione	2.72 LC	3
142		(3aα,4β,7β,7aα)-2-Methoxy-4-(octahydro-1,3-dioxo-4-methyl-4,7-epoxy-2H-isoindol-2-yl)-1-naphthalenecarbonitrile	2.72 LC	3
143		(3aα,4β,7β,7aα)-Hexahydro-4-methyl-2-[4-nitro-3-(trifluoromethyl)phenyl]-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.10 LC	3

Ex. No.	Compound Structure	Compound Name	Retention Time Min./ Molecular Mass	Pro. of Ex.
144		(3aα,4β,7β,7aα)-Hexahydro-2-[4-(1H-imidazol-1-yl)phenyl]-4-methyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione	1.16 LC	3
145		(3aα,4β,7β,7aα)-2-[3-Chloro-4-(2-thiazolyl)phenyl]hexahydro-4-methyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione	2.81 LC	3
146		(3aα,4α,7α,7aα)-2-(3,5-Dichlorophenyl)hexahydro-4,7-imino-1H-isoindole-1,3(2H)-dione	2.72 LC	31
147		(3aα,4α,7α,7aα)-2-(4-Bromo-1-naphthalenyl)hexahydro-4,7-imino-1H-isoindole-1,3(2H)-dione	2.95 LC	31
148		(3aα,4α,7α,7aα)-2-(4-Bromo-3-methylphenyl)hexahydro-4,7-imino-1H-isoindole-1,3(2H)-dione	2.65 LC	31

Ex. No.	Compound Structure	Compound Name	Retention Time Min./ Molecular Mass	Pro. of Ex.
149		(3aα,4α,7α,7aα)-Hexahydro-2-(4-nitro-1-naphthalenyl)-4,7-imino-1H-isoindole-1,3(2H)-dione	2.49 LC	31
150		(3aα,4α,7α,7aα)-8-Acetyl-2-(3,5-dichlorophenyl)hexahydro-4,7-imino-1H-isoindole-1,3(2H)-dione	3.53 LC	31, 12
151		(3aα,4α,7α,7aα)-Octahydro-1,3-dioxo-2-[3-(trifluoromethyl)phenyl]-4,7-ethano-5H-pyrrolo[3,4-c]pyridine-5-carboxylic acid phenyl ester	3.397 LC	9
152		(3aα,4α,7α,7aα)-4-(Octahydro-1,3-dioxo-4,7-ethano-2H-pyrrolo[3,4-c]pyridin-2-yl)-1-naphthalenecarbonitrile	1.74 LC	11
153		(3aα,4α,7α,7aα)-4-(Octahydro-5-methyl-1,3-dioxo-4,7-ethano-2H-pyrrolo[3,4-c]pyridin-2-yl)-1-naphthalenecarbonitrile	1.71 LC	14

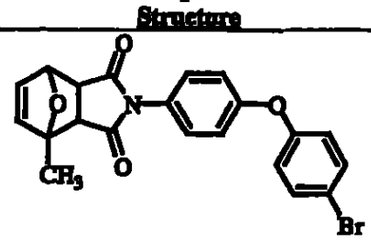
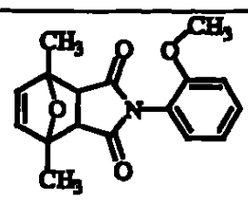
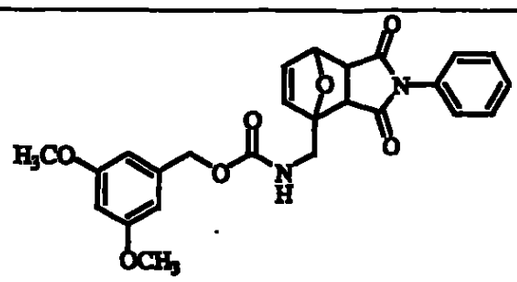
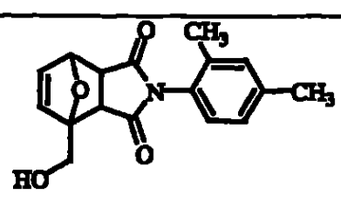
Ex. No.	Compound Structure	Compound Name	Retention Time Min./ Molecular Mass	Pro. of Ex.
154		(3aα,4α,7α,7aα)-2-(4-Cyano-1-naphthalenyl)octahydro-1,3-dioxo-4,7-etheno-5H-pyrrolo[3,4-c]pyridine-5-carboxylic acid phenylmethyl ester	3.40 LC	10
155		(3aα,4α,7α,7aα)-4-(Octahydro-1,3-dioxo-4,7-ethano-2H-pyrrolo[3,4-c]pyridin-2-yl)-2-(trifluoromethyl)benzonitrile	1.74 LC	11
156		(3aα,4α,7α,7aα)-4-(Octahydro-5-methyl-1,3-dioxo-4,7-ethano-2H-pyrrolo[3,4-c]pyridin-2-yl)-2-(trifluoromethyl)benzonitrile	1.65 LC	14
157		(3aα,4α,7α,7aα)-2-[4-Cyano-3-(trifluoromethyl)phenyl]octahydro-1,3-dioxo-4,7-etheno-5H-pyrrolo[3,4-c]pyridine-5-carboxylic acid phenylmethyl ester	3.53 LC	10
158		(3aα,4α,7α,7aα)-2-[4-Bromo-3-(trifluoromethyl)phenyl]tetrahydro-5-methyl-4,7-etheno-1H-pyrrolo[3,4-c]pyridine-1,3,6(2H,5H)-trione	2.95 LCMS	34

Ex. No.	Compound Structure	Compound Name	Retention Time Min./ Molecular Mass	Pro. of Ex.
159		(3aα,4α,7α,7aα)-Tetrahydro-5-methyl-2-[3-(trifluoromethyl)phenyl]-4,7-etheno-1H-pyrrolo[3,4-c]pyridine-1,3,6(2H,5H)-trione	2.53 LCMS	34
160		(3aα,4α,7α,7aα)-Tetrahydro-5-methyl-2-(2-naphthalenyl)-4,7-etheno-1H-pyrrolo[3,4-c]pyridine-1,3,6(2H,5H)-trione	2.58 LCMS	34
161		(1aα,2β,2aα,5aα,6β,6aα)-Hexahydro-4-[3-(trifluoromethyl)phenyl]-2,6-epoxy-3H-oxireno[f]iso-indole-3,5(4H)-dione	1.80 LCMS	28
162		(1aα,2β,2aα,5aα,6β,6aα)-4-(3,5-Dichlorophenyl)-hexahydro-2,6-epoxy-3H-oxireno[f]isoindole-3,5(4H)-dione	1.45 LCMS	28
163		(1aα,2β,2aα,5aα,6β,6aα)-Hexahydro-4-(4-nitro-1-naphthalenyl)-2,6-epoxy-3H-oxireno[f]isoindole-3,5(4H)-dione	1.52 LCMS	28
164		(1aα,2β,2aα,5aα,6β,6aα)-4-(3,4-Dichlorophenyl)-hexahydro-2,6-epoxy-3H-oxireno[f]isoindole-3,5(4H)-dione	3.21 LCMS	28

Examples 165 to 203

Additional compounds of the present invention were prepared and are described further below in Table 4. Table 4 sets forth the compound name and structure, as well as the Example number of the procedure on which the preparation of Table 4 was based, for the compounds of Examples 165 to 203.

Table 4

Ex. No.	Compound Structure	Compound Name	Pro. of Ex.
165		2-[4-(4-Bromo-phenoxy)phenyl]-3a,4,7,7a-tetrahydro-4-methyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione	32
166		3a,4,7,7a-Tetrahydro-2-(2-methoxyphenyl)-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione	32
167		[(1,2,3,3a,7,7a-Hexahydro-2-phenyl-4,7-epoxy-4H-isoindol-4-yl)methyl]carbamic acid (3,5-dimethoxyphenyl)methyl ester	21-26
168		2-(2,4-Dimethylphenyl)-3a,4,7,7a-tetrahydro-4-(hydroxymethyl)-4,7-epoxy-1H-	21-26

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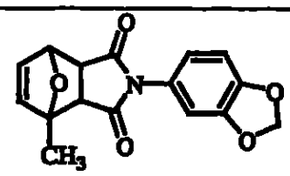
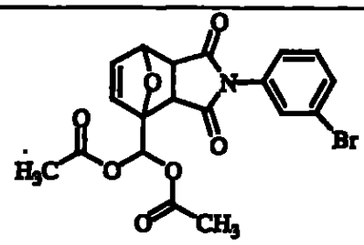
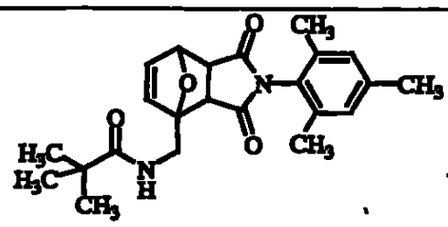
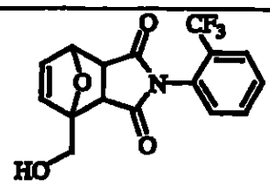
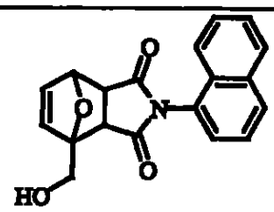
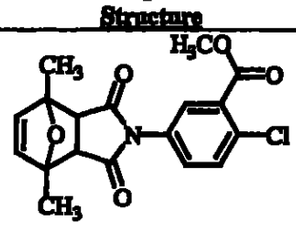
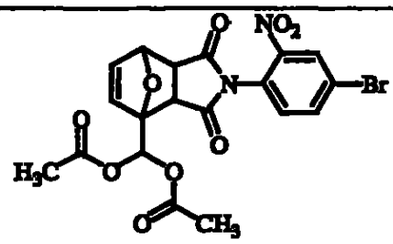
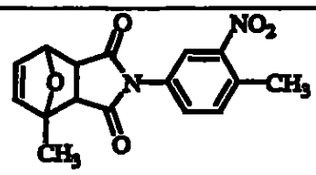
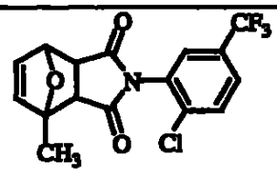
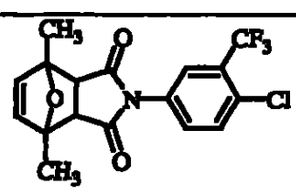
Ex. No.	Compound Structure	Compound Name	Pro. of Ex.
		isoindole-1,3(2H)-dione	
169		2-(1,3-Benzodioxol-5-yl)-3a,4,7,7a-tetrahydro-4-methyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione	32
170		4-[Bis(acetyloxy)methyl]-2-(3-bromophenyl)-3a,4,7,7a-tetrahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	21-26
171		*N*-[[1,2,3,3a,7,7a-Hexahydro-2-(2,4,6-trimethylphenyl)-4,7-epoxy-4H-isoindol-4-yl]methyl]-2,2-dimethylpropanamide	21-26
172		3a,4,7,7a-Tetrahydro-4-(hydroxymethyl)-2-[2-(trifluoromethyl)phenyl]-4,7-epoxy-1H-isoindole-1,3(2H)-dione	21-26
173		3a,4,7,7a-Tetrahydro-4-(hydroxymethyl)-2-(1-naphthalenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione	21-26

Ex. No.	Compound Structure	Compound Name	Pro. of Ex.
174		2-Chloro-5-(1,3,3a,4,7,7a-hexahydro-4,7-dimethyl-4,7-epoxy-2H-isoindol-2-yl)benzoic acid methyl ester	32
175		4-[Bis(acetyloxy)methyl]-2-(4-bromo-2-nitrophenyl)-3a,4,7,7a-tetrahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione	21-26
176		3a,4,7,7a-Tetrahydro-4-methyl-2-(4-methyl-3-nitrophenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione	32
177		2-[2-Chloro-5-(trifluoromethyl)phenyl]-3a,4,7,7a-tetrahydro-4-methyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione	32
178		2-[4-Chloro-3-(trifluoromethyl)phenyl]-3a,4,7,7a-tetrahydro-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione	32

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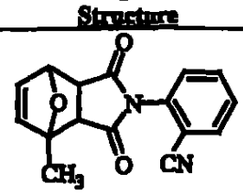
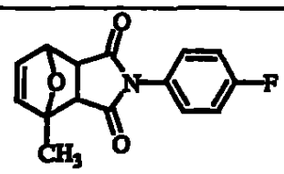
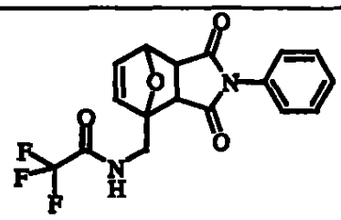
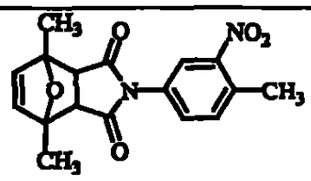
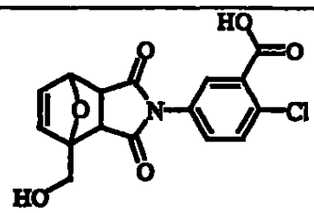
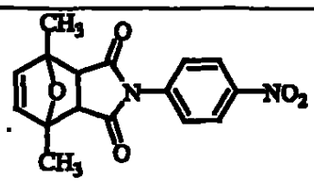
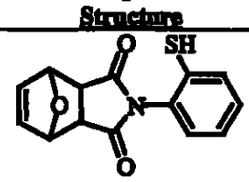
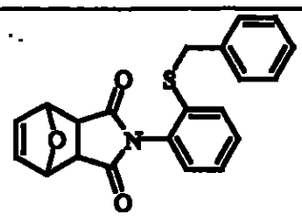
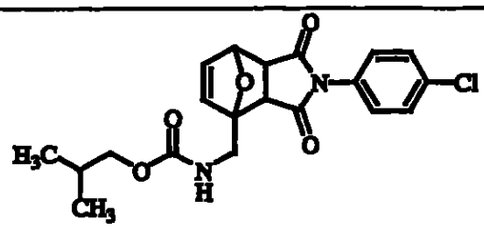
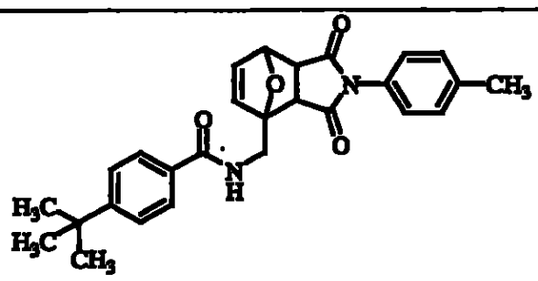
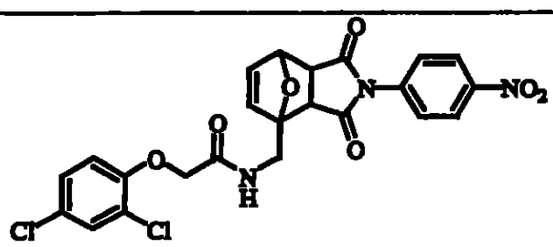
Ex. No.	Compound Structure	Compound Name	Pro. of Ex.
179		2-(1,3,3a,4,7,7a-Hexahydro-4-methyl-4,7-epoxy-2H-isoindol-2-yl)benzonitrile	32
180		2-(4-Fluorophenyl)-3a,4,7,7a-tetrahydro-4-methyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione	32
181		2,2,2-Trifluoro-*N*-[(1,2,3,3a,7,7a-hexahydro-2-phenyl-4,7-epoxy-4H-isoindol-4-yl)methyl]acetamide	21-26
182		3a,4,7,7a-Tetrahydro-4,7-dimethyl-2-(4-methyl-3-nitrophenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione	32
183		2-Chloro-5-[1,3,3a,4,7,7a-hexahydro-4-(hydroxymethyl)-4,7-epoxy-2H-isoindol-2-yl]benzoic acid	21-26
184		3a,4,7,7a-Tetrahydro-4,7-dimethyl-2-(4-nitrophenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione	32

Ex. No.	Compound Structure	Compound Name	Pro. of Ex.
185		3a,4,7,7a-Tetrahydro-2-(2-mercaptophenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione	32
186		3a,4,7,7a-Tetrahydro-2-[2-[(phenylmethyl)thio]phenyl]-4,7-epoxy-1H-isoindole-1,3(2H)-dione	32
187		[[2-(4-Chlorophenyl)-1,2,3,3a,7,7a-hexahydro-4,7-epoxy-4H-isoindol-4-yl]methyl]carbamic acid 2-methylpropyl ester	21-26
188		4-(1,1-Dimethylethyl)-*N*-[[1,2,3,3a,7,7a-hexahydro-2-(4-methylphenyl)-4,7-epoxy-4H-isoindol-4-yl]methyl]benzamide	21-26
189		2,4-Dichloro-*N*-[[1,2,3,3a,7,7a-hexahydro-2-(4-nitrophenyl)-4,7-epoxy-4H-isoindol-4-yl]methyl]benzamide	21-26

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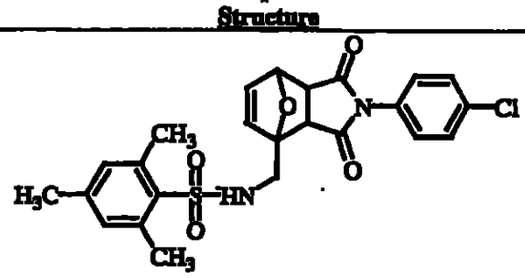
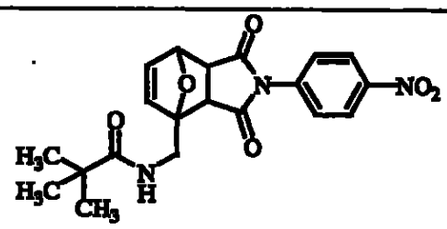
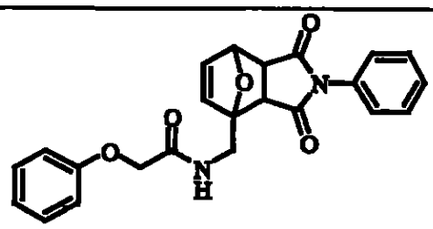
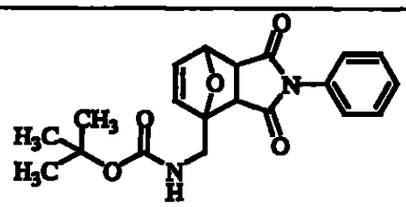
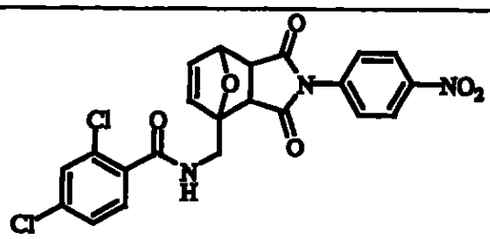
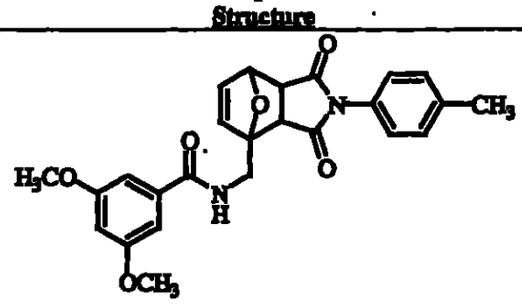
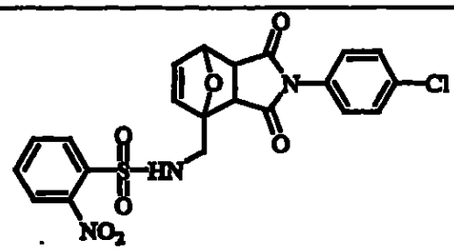
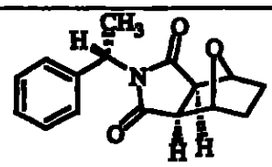
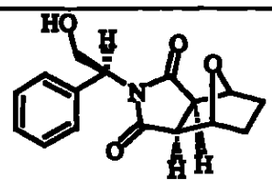
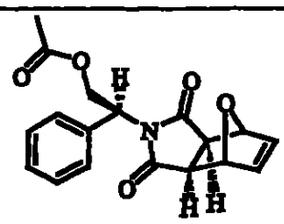
Ex. No.	Compound Structure	Compound Name	Pro. of Ex.
190		*N*-[[2-(4-Chlorophenyl)-1,2,3,3a,7,7a-hexahydro-4,7-epoxy-4H-isoindol-4-yl]methyl]-2,4,6-trimethylbenzenesulfonamide	21-26
191		*N*-[[1,2,3,3a,7,7a-Hexahydro-2-(4-nitrophenyl)-4,7-epoxy-4H-isoindol-4-yl]methyl]-2,2-dimethylpropanamide	21-26
192		*N*-[(1,2,3,3a,7,7a-Hexahydro-2-phenyl-4,7-epoxy-4H-isoindol-4-yl)methyl]-2-phenoxyacetamide	21-26
193		[(1,2,3,3a,7,7a-Hexahydro-2-phenyl-4,7-epoxy-4H-isoindol-4-yl)methyl]carbamic acid 1,1-dimethylethyl ester	21-26
194		2-(2,4-Dichlorophenoxy)-*N*-[[1,2,3,3a,7,7a-hexahydro-2-(4-nitrophenyl)-4,7-epoxy-4H-isoindol-4-yl]methyl]acetamide	21-26

Ex. No.	Compound Structure	Compound Name	Pro. of Ex.
195		*N*-[[1,2,3,3a,7,7a-Hexahydro-2-(4-methylphenyl)-4,7-epoxy-4H-isoindol-4-yl]methyl]-3,5-dimethoxybenzamide	21-26
196		*N*-[[2-(4-Chlorophenyl)-1,2,3,3a,7,7a-hexahydro-4,7-epoxy-4H-isoindol-4-yl]methyl]-2-nitrobenzenesulfonamide	21-26
197		(3aα,4β,7β,7aα)-Hexahydro-2-[(1*S*)-1-phenylethyl]-4,7-epoxy-1H-isoindole-1,3(2H)-dione.	8
198		(3aα,4β,7β,7aα)-Hexahydro-2-[(1*S*)-2-hydroxy-1-phenylethyl]-4,7-epoxy-1H-isoindole-1,3(2H)-dione.	8
199		(3aα,4β,7β,7aα)-2-[(1*S*)-2-(Acetyloxy)-1-phenylethyl]-3a,4,7,7a-tetrahydro-4,7-epoxy-1H-isoindole-1,3(2H)-dione.	8

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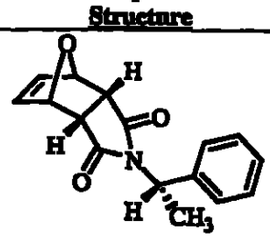
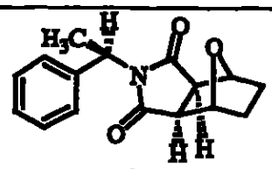
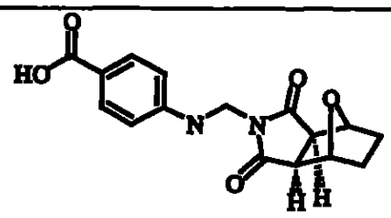
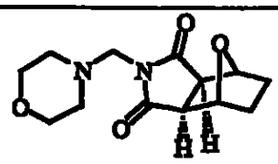
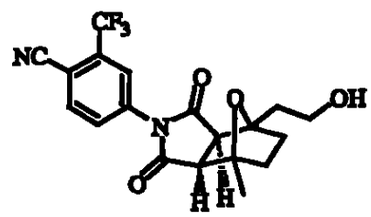
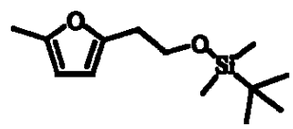
Ex. No.	Compound Structure	Compound Name	Pro. of Ex.
200		(3aα,4α,7α,7aα)-3a,4,7,7a-Tetrahydro-2-[(1*S*)-1-phenylethyl]-4,7-epoxy-1H-isoindole-1,3(2H)-dione.	8
201		(3aα,4β,7β,7aα)-Hexahydro-2-[(1*R*)-1-phenylethyl]-4,7-epoxy-1H-isoindole-1,3(2H)-dione.	8
202		(3aα,4β,7β,7aα)-4-[[(Octahydro-1,3-dioxo-4,7-epoxy-2H-Isoindol-2-yl)methyl]amino]benzoic acid.	8
203		(3aα,4β,7β,7aα)-Hexahydro-2-(4-morpholinylmethyl)-4,7-epoxy-1H-Isoindole-1,3(2H)-dione.	8

Example 204

(3aα,4β,7β,7aα)-4-[Octahydro-4-(2-hydroxyethyl)-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile (204D/25B)

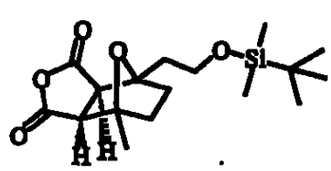


A. 2-[2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]-5-methylfuran (204A)



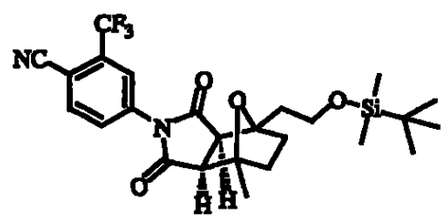
To a solution of compound 21A (2.00 g, 15.9 mmol) in DMF (50 mL) was added imidazole (1.62 g, 23.9 mmol), followed by *tert*-butyldimethylsilyl chloride (2.63 g, 17.5 mmol). After 2 h at 25°C, the reaction was poured into diethyl ether (300 mL) and washed with water (1 x 100 mL), 1 N HCl (1 x 100 mL), water (1 x 100 mL), brine (1 x 50 mL) and dried over anhydrous $MgSO_4$. Crude compound 204A was analyzed by LCMS and NMR and determined to be pure enough to be carried on directly to the next step. HPLC: 100% at 4.347 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm).

B. (3aα,4β,7β,7aα)-4-[2-[[(1,1-Dimethylethyl)dimethylsilyl]-oxy]ethyl]hexahydro-7-methyl-4,7-epoxy-1H-isobenzofuran-1,3(2H)-dione (204B)



Compound **204A** (4.0 g, 18.9 mmol) and maleic anhydride (1.42 g, 14.5 mmol) were dissolved in dichloroethane (10 mL) and stirred at 25°C for 60 hours. The volatiles were then removed *in vacuo* and the resulting orange oil was dissolved in absolute ethanol (50 mL) and 10% Pd/C (1.00 g, cat.) was added. Hydrogen was then introduced via a balloon. After 3 h, the reaction was filtered through Celite rinsing with EtOAc and concentrated *in vacuo*. The crude anhydride was purified by rapid flash chromatography on SiO_2 eluting with acetone/chloroform (0 – 2 – 4% acetone) to give 1.30 g (3.82 mmol, 20%) of compound **204B** as a clear oil, in addition to 3.00 g (12.5 mmol, 66%) of the starting compound **204A**. Characterization by proton NMR spectroscopy showed only the exo isomer. 1H NMR (400 MHz, $CDCl_3$) δ = 3.83 (2 H, t, J = 6.0 Hz), 3.22 (1 H, d, J = 8.2 Hz), 3.06 (1 H, d, J = 8.2 Hz), 1.70 – 2.25 (6 H, m), 1.55 (3 H, s), 0.82 (9 H, s), 0.00 (6 H, s).

C. (3aα,4β,7β,7aα)-4-[4-[2-[[(1,1-Dimethylethyl)dimethylsilyl]-oxy]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile (204C)



Compound **204B** (0.250 g, 0.734 mmol) and 4-amino-2-trifluoromethyl-benzonitrile (0.124 g, 0.668 mmol) were suspended in dry toluene (2.0 mL) in a sealed tube. $MgSO_4$ (0.200 g) and triethylamine (0.5 mL) were then added and the tube was sealed and placed in a oil bath at 125°C. After 40 h, the reaction was cooled to 25°C, filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography on SiO_2 eluting with CH_2Cl_2 to give 0.111 g (0.281 mmol, 30%) of compound **204C** as a yellow solid. HPLC: 92% at 4.203 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes

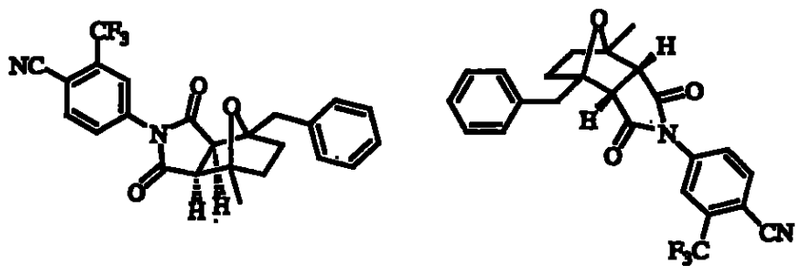
containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ESI): m/z 531.1 $[M+Na]^+$.

D. (3aα,4β,7β,7aα)-4-[Octahydro-4-(2-hydroxyethyl)-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile (204D)

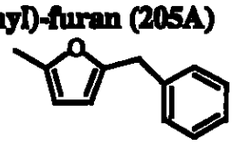
Compound 204C (0.031 g, 0.061 mmol) was dissolved in THF (0.5 mL) and transferred to a polypropylene container followed by cooling to 0°C. HF•pyridine (~47% HF, 0.1 mL) was then added. After 15 min, the reaction was complete as determined by LC and was poured into cold sat. aqueous $NaHCO_3$. The mixture was extracted with CH_2Cl_2 (3 x 10 mL). The combined organic layers were washed with 1 N HCl (1 x 20 mL) and dried over anhydrous Na_2SO_4. Compound 204D was isolated as a yellow oil and compared to the material prepared in Example 25. No purification was necessary.

Example 205

(3aα,4β,7β,7aα)- and (3aα,4α,7α,7aα)-4-[Octahydro-4-methyl-1,3-dioxo-7-(phenylmethyl)-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile (205Ci and 205Cii, respectively)



A. 2-Methyl-5-(phenylmethyl)-furan (205A)



n-BuLi (1.8 mL, 4.51 mmol, 2.5 M in hexane) was added to a solution of 2-methylfuran (0.37 mL, 4.10 mmol) in anhydrous THF (3 mL) at –25 °C. The resulting solution was stirred at room temperature for 3 h and then cooled to

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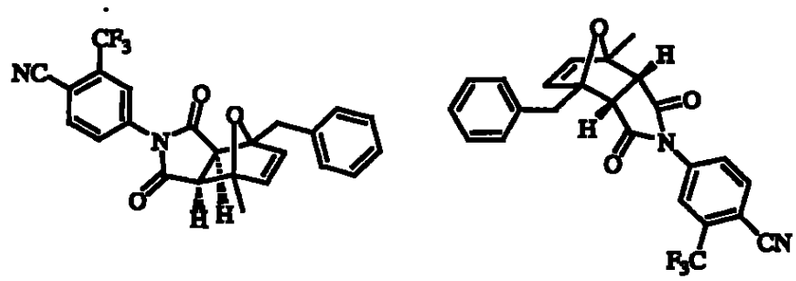
–15°C. Benzyl bromide (0.59 mL, 4.92 mmol), which was passed through a plug of aluminum oxide, was added and the solution was warmed to rt and stirred overnight. Saturated NH_4Cl solution (5 mL) was added and the mixture was stirred for 1 h. The reaction mixture was then extracted with ether (2 x 5 mL) and the combined organic extracts were dried and concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with hexanes gave 323 mg (1.88 mmol, 46%) of compound **205A** as colorless oil. HPLC: 95% at 3.72 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm) and about 400 mg mixture of product and benzyl bromide (~2:1 by HPLC).

B. (3aα,4β,7β,7aα)- and (3aα,4α,7α,7aα)-4-[Octahydro-4-methyl-1,3-dioxo-7-(phenylmethyl)-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl) benzonitrile (205Bi and 205Bii, respectively)



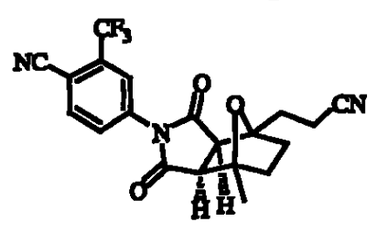
A solution of compound **205A** (124 mg, 0.72 mmol) and 4-(2,5-dihydro-2,5-dioxo-1H-pyrrol-1-yl)-2-trifluoromethylbenzonitrile (290 mg, 1.09 mmol) in CH_2Cl_2 (2 mL) was stirred at room temperature. After 4 days, the reaction mixture was concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with CH_2Cl_2 gave 62 mg (0.14 mmol, 20%) of a mixture of compounds **205Bi** and **205Bii** as a white solid, which was used directly in the next step. HPLC: 93% at 3.69 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm).

C. (3aα,4β,7β,7aα)- and (3aα,4α,7α,7aα)-4-[Octahydro-4-methyl-1,3-dioxo-7-(phenylmethyl)-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)-benzonitrile (205Ci and 205Cii, respectively)

A solution of a mixture of compounds 205Bi and 205Bii (62 mg, 0.14 mmol) and 10% Pd/C (12 mg, cat.) in EtOH (3.5 mL) was stirred under a hydrogen atmosphere at room temperature for 2 h. The reaction mixture was filtered through Celite and concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with 35% EtOAc/hexanes gave 22 mg (0.05 mmol, 35%) of compound 205Ci and 12 mg (0.027 mmols, 19%) of compound 205Cii. Compound 205Ci: HPLC: 98% at 3.75 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ESI): m/z 458.2 $[M+NH_4]^+$. Compound 205Cii: HPLC: 97% at 3.78 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ESI): m/z 473.45 $[M+CH_3OH]^+$.

Example 206

(3aα,4β,7β,7aα)-2-[4-Cyano-3-(trifluoromethyl)phenyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindole-4-propanenitrile (206)



A solution of compound 36 (34 mg, 0.074 mmol) and NaCN (24 mg, 0.49 mmol) in DMSO (1 mL) was heated at 100°C for 0.5 h. After cooling, the reaction mixture was poured into H_2O (5 mL) and the aqueous layer was extracted with EtOAc (2 x 5 mL). The combined organic layers were washed with H_2O (2 x 5 mL), dried over Na_2SO_4 and concentrated under

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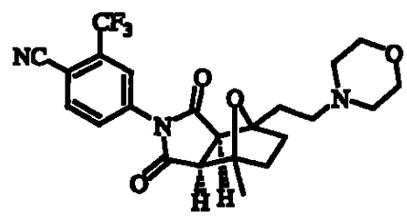
reduced pressure. Purification by flash chromatography on SiO_2 eluting with 50% EtOAc/hexanes followed by reverse phase preparative HPLC [30.41 min (retention time) (YMC S5 ODS 30 X 250 mm, 10-90% aqueous methanol over 30 minutes containing 0.1% TFA, 25 mL/min, monitoring at 220 nm)] gave 6.6 mg (0.016 mmol, 22%) of compound **206** as a white solid. HPLC: 99% at 2.89 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 402.1 $[M-H]^-$.

Example 207

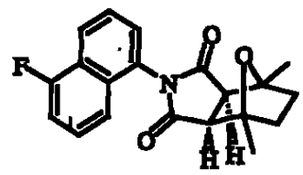
(3aα,4β,7β,7aα)-4-[Octahydro-4-methyl-7-[2-(4-morpholinyl)ethyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile, trifluoroacetate (1:1) (207)



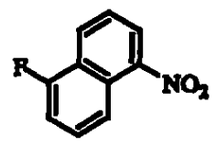
A solution of compound **36** (15.6 mg, 0.0341 mmol) and morpholine (6.0 μL, 0.068 mmol) in toluene (1 mL) was heated at 100°C overnight. After cooling, the reaction mixture was concentrated under reduced pressure. Purification by flash chromatography on SiO_2 eluting with 10% $MeOH/CH_2Cl_2$ followed by reverse phase preparative HPLC [23.96 min (retention time) (YMC S5 ODS 30 x 250 mm, 10-90% aqueous methanol over 30 minutes containing 0.1% TFA, 25 mL/min, monitoring at 220 nm)] gave 8.7 mg (0.015 mmol, 44%) of compound **207** (TFA salt) as a white solid. HPLC: 99% at 2.02 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 464.3 $[M+H]^+$.

Example 208

(3aα,4β,7β,7aα)-2-(5-Fluoro-1-naphthalenyl)hexahydro-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione (208C)



A. 1-Fluoro-5-nitronaphthalene (208A)

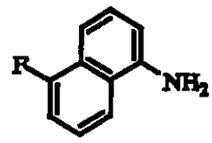


To a solution of 6 N HCl (12 mL) was added 1.47 g (7.83 mmol) of finely powdered 5-nitro-1-naphthylamine, as described in *J. Chem. Soc.* 1187 (1949). The mixture was cooled to 0°C and a cold solution of $NaNO_2$ (547 mg, 7.93 mmol) in 2 mL H_2O was added slowly so that the temperature was kept near 0°C. After the addition was complete, the reaction mixture was stirred for 30 min and filtered. The filtrate was cooled to 0°C and treated with cold 4.5 M $NaBF_4$ solution (5 mL) to give complete precipitation of the diazonium borofluoride. The mixture was kept at 0°C for 30 min before it was filtered and the precipitates were washed with cold 4.5 M $NaBF_4$ solution (5 mL), ice-cold ethanol (10 mL) and Et_2O (20 mL). The obtained solids were air dried to yield 1.74 g (77) of the corresponding diazonium salt.

To 1.70 g (5.92 mmol) of the above diazonium borofluoride was added 5 g of sand and the components were thoroughly mixed. The reaction mixture was heated cautiously under reduced pressure until decomposition set in. Toward the end of the reaction the flask was further heated for 30 min to 130°C to assure complete conversion. After cooling the reaction mixture was dissolved in acetone and the contents were preabsorbed on silica gel. Purification was achieved by flash

chromatography on silica gel, eluting with 0 to 10% EtOAc in hexanes to give 449 mg (2.35 mmol, 40%) of compound **208A** as a white solid.

B. 1-Amino-5-fluoronaphthalene (208B)



A solution of compound **208A** (62 mg, 0.32 mmol) in 1 mL EtOH containing 0.1 mL 12 N HCl was heated to reflux. Iron powder (62 mg, 1.11 mmol) was added in small portions and heating was continued for 2 h. The mixture was cooled, neutralized with 1 N NaOH solution and the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo* to leave a residue which was purified by flash chromatography on silica gel eluting with 40 to 80 EtOAc in hexanes to give 42 mg (0.26 mmol, 80%) of compound **208B** as a yellow solid.

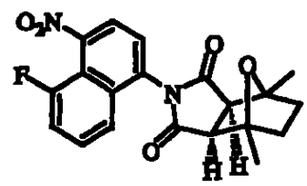
C. (3aα,4β,7β,7aα)-2-(5-Fluoro-1-naphthalenyl)hexahydro-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione (208C)

Compound **208B** (42 mg, 0.26 mmol), compound **20A** (54 mg, 0.27 mmol), $MgSO_4$ (69 mg, 0.58 mmol) and triethylamine (191 μL, 1.37 mmol) were taken up in 2 mL of toluene and placed in a sealed tube. The sealed tube was heated at 135°C for 14 h. The cooled reaction mixture was filtered through a short pad of Celite eluting with CH_2Cl_2 and the solvent was removed under reduced pressure. The residue was purified by reverse phase preparative HPLC (YMC S5 ODS 20 x 100 mm eluting with 30-100% aqueous methanol over 10 min containing 0.1% TFA, 20 mL/min) to give 15 mg (0.044 mmol, 17%) of compound **208C** as a light yellow solid. HPLC: 16% at 2.96 min & 77% at 3.06 min (atropisomers, retention time)

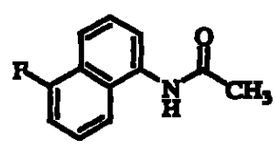
(YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 340.2 $[M+H]^+$.

Example 209

(3aα,4β,7β,7aα)-2-(5-Fluoro-4-nitro-1-naphthalenyl)hexahydro-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione (209C)

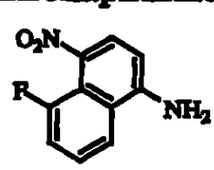


A. *N*-(5-Fluoro-1-naphthalenyl)acetamide (209A)



A solution of 141 mg (0.74 mmol) of compound 208A in 2 mL of AcOH was heated to reflux and treated with small portions of iron powder (118 mg, 2.11 mmol). The mixture was kept at reflux for 15 min before 73 μL (0.78 mmol) of Ac_2O was added. After an additional 15 min at reflux, the mixture was cooled and filtered eluting with CH_2Cl_2. The filtrate was then concentrated under reduced pressure and the residue was purified by flash chromatography on silica gel eluting with 20 to 50% EtOAc in to give 145 mg (0.71 mmol, 97%) of compound 209A as a white solid.

B. 1-Amino-5-fluoro-4-nitronaphthalene (209B)



Compound 209A (133 mg, 0.645 mmol) was dissolved in 1 mL AcOH and the resulting solution was cooled to 10°C. At this temperature, 80.0 μL (2.00 mmol) of red fuming HNO_3 was added and stirring was continued

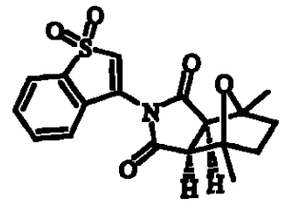
for 15 min before the reaction was quenched by the addition of crushed ice. The aqueous layer was extracted with CH_2Cl_2 and the combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The resulting residue was dissolved in 3 mL EtOH, heated to reflux and treated with 0.5 mL of 40% aqueous NaOH solution. Stirring was continued for 15 min before the reaction was cooled and diluted with H_2O. The aqueous layer was extracted with CH_2Cl_2 and the combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The resulting residue was purified by flash chromatography on silica gel, eluting with 40 to 70% EtOAc in hexane to afford 36 mg (0.17 mmol, 27%) of compound **209B** as a yellow solid.

C. 3aα,4β,7β,7aα)-2-(5-Fluoro-4-nitro-1-naphthalenyl)hexahydro-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione (209C)

Compound **209B** (36 mg, 0.18 mmol) was reacted in a sealed tube with compound **20A** (38 mg, 0.19 mmol), $MgSO_4$ (46 mg, 0.39 mmol) and Et_3N (128 μL, 0.920 mmol) in 250 μL toluene according to the above procedure described in example **208C** to give, after purification by reverse phase preparative HPLC (YMC S5 ODS 20 x 100 mm eluting with 30-100% aqueous methanol over 10 min containing 0.1% TFA, 20 mL/min), 27 mg (0.070 mmol, 39%) of compound **209C** as a yellow solid. HPLC: 8% at 2.88 min & 84% at 3.06 min (atropisomers, retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 402.0 $[M+H]^+$.

Example 210

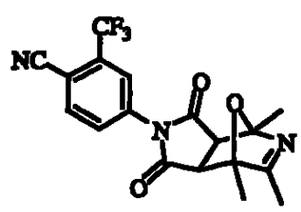
(3aα,4β,7β,7aα)-2-(1,1-Dioxidobenzo[b]thiophen-3-yl)hexahydro-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione (210)



*m*CPBA (160 mg, 0.641 mmol, 70% pure) was added to a solution of compound 134 (70.0 mg, 0.214 mmol) in CH_2Cl_2 (2 mL) at rt. After the starting material was consumed, the reaction was quenched with sat. $NaHCO_3$, and extracted with CH_2Cl_2. The organic layer was washed with 1 N NaOH, dried over Na_2SO_4 and concentrated under reduced pressure to give 63.9 mg (0.178 mmol, 83%) of compound 210 as a white solid. HPLC: 99% at 3.81 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2 phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 360.0 $[M+H]^+$.

Example 211

4-(1,3,3a,4,7,7a-Hexahydro-4,6,7-trimethyl-1,3-dioxo-4,7-epoxy-2H-pyrrolo[3,4-c]pyridin-2-yl)-2-(trifluoromethyl)benzonitrile (211)

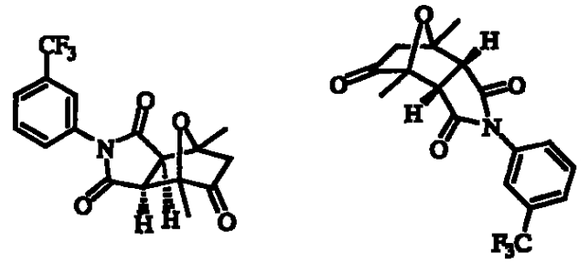


2,4,5-Trimethyl oxazole (0.48 mL, 4.14 mmol) was dissolved in toluene (2.0 mL) and 4-(2,5-dihydro-2,5-dioxo-1H-pyrrol-1-yl)-2-trifluoromethylbenzonitrile (1.00 g, 3.76 mmol) was added. The reaction mixture was stirred at 75°C under nitrogen for 2.5 hrs. The solution was cooled to room temperature and the resulting precipitate was filtered and rinsed with toluene to give 0.51 g (35%) of compound 211 as a light grey solid. NMR analysis revelaed that compound 211 was one isomer (exo/endo) however the identity of the isomer could not be determined by

NMR analysis. HPLC: 100% at 2.85 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90 aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 378.42 $[M+H]^+$.

Example 212

(3aα,4β,7β,7aα)-Tetrahydro-4,7-dimethyl-2-[3-(trifluoromethyl)phenyl]-4,7-epoxy-1H-isoindole-1,3,5(2H,4H)-trione & (3aα,4α,7α,7aα)-Tetrahydro-4,7-dimethyl-2-[3-(trifluoromethyl)phenyl]-4,7-epoxy-1H-isoindole-1,3,5(2H,4H)-trione (212i & 212ii, respectively)

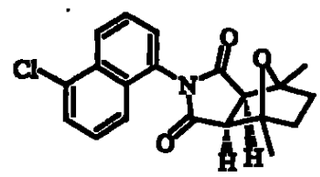


2,2-Dimethyl-3(H)-furanone (0.500 g, 4.46 mmol) and 1-[3-(trifluoromethyl)phenyl]-1H-pyrrole-2,5-dione (1.07 g, 4.46 mmol, prepared as described in Example 1B) were suspended in toluene (20 mL) in a sealed tube. The mixture was heated at 110°C for 4 h and then cooled to 25°C followed by concentration *in vacuo*. The resulting residue was purified by flash chromatography on SiO_2 eluting with methylene chloride to yield 0.411 g (26%) of compound **212i** as a white solid and 0.198 g (12) of compound **212ii** as a white solid. The structural assignments were confirmed by 1-D NOE proton NMR experiments. Compound **212i**: HPLC: 100% at 2.817 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 376.0 $[M + Na]^+$. Compound **212ii**: HPLC: 100% at 3.013 min (retention time) (YMC S5

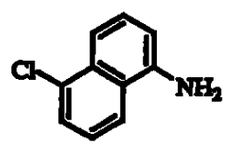
ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 354.02 $[M+H]^+$.

Example 213

(3aα,4β,7β,7aα)-2-(5-Chloro-1-naphthalenyl)hexahydro-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione (213B)



A. 1-Amino-5-chloronaphthalene (213A)



To a solution of 1.74 g (6.06 mmol) of the diazonium borofluoride (described in Example 208A) in acetone (7 mL) was added 693 mg (7.00 mmol) of CuCl in small portions. After the evolution of nitrogen had ceased the acetone was removed under reduced pressure and the residue was taken up in CH_2Cl_2 (30 mL). The organic phase was washed with H_2O (30 mL), dried over $MgSO_4$, concentrated *in vacuo* and finally purified by flash chromatography (silica gel, EtOAc in hexane 0 to 15%) to give 754 mg (70%) of 1-chloro-5-nitronaphthalene.

The above synthesized 1-chloro-5-nitronaphthalene (540 mg, 2.6 mmol) was dissolved in 10 mL AcOH, followed by treatment with 415 mg (7.43 mmol) iron powder and subsequently acylated with Ac_2O (0.26 mL, 2.73 mmol) according to the procedure described in Example 209A to give 543 mg (95%) of 1-acetamino-5-chloronaphthalene.

A solution of the above synthesized 1-acetamino-5-chloronaphthalene (52 mg, 0.24 mmol) in 3 mL EtOH was heated to reflux

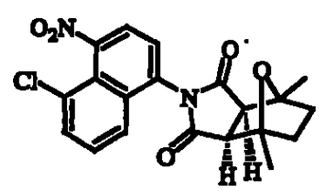
and treated with 0.5 mL 40% aqueous NaOH solution. The mixture was refluxed until no more starting material could be detected, cooled and concentrated under reduced pressure. The residue was taken up in CH_2Cl_2 (50 mL) and was washed with H_2O (25 mL). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo* to leave 41 mg (98%) of compound **213A** as a white solid.

B. (3aα,4β,7β,7aα)-2-(5-Chloro-1-naphthalenyl)hexahydro-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione (213B)

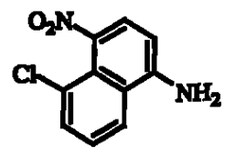
Compound **213A** (24 mg, 0.14 mmol) was reacted in a sealed tube with compound **20A** (29 mg, 0.15 mmol), $MgSO_4$ (36 mg, 0.30 mmol) and Et_3N (100 μL, 0.710 mmol) in 250 μL toluene according to the procedure described in Example **208C** to give, after purification by reverse phase preparative HPLC (YMC S5 ODS 20 x 100 mm eluting with 30-100% aqueous methanol over 10 min containing 0.1% TFA, 20 mL/min), 27 mg (40%) of compound **213B** as a white solid. HPLC: 98% at 1.82 min (retention time) (YMC S5 TurboPack Pro column 4.6 x 33 mm eluting with 10-90% aqueous methanol over 2 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 356.4 $[M+H]^+$.

Example 214

(3aα,4β,7β,7aα)-2-(5-Chloro-4-nitro-1-naphthalenyl)hexahydro-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione (214B)



A. 1-Amino-5-chloro-4-nitronaphthalene (214A)



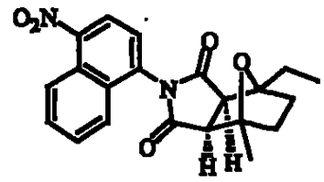
1-Acetamino-5-chloronaphthalene (150 mg, 0.68 mmol, prepared as described in Example 213A) was dissolved in 1 mL AcOH and treated with 82 μL of red fuming HNO_3 and subsequently deacylated with 1 mL 40% aqueous NaOH solution in 3 mL EtOH according to the procedure described in Example 209A to yield 49 mg (32%) of compound 214A as a yellow solid.

B. (3aα,4β,7β,7aα)-2-(5-Chloro-4-nitro-1-naphthalenyl)hexahydro-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione (214B)

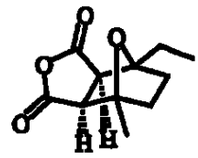
Compound 214A (27 mg, 0.12 mmol) was reacted in a sealed tube with compound 20A (26 mg, 0.13 mmol), $MgSO_4$ (32 mg, 0.27 mmol) and Et_3N (88 μL, 0.63 mmol) in 250 μL toluene according to the procedure described in Example 208C to give, after purification by reverse phase preparative HPLC (YMC S5 ODS 20 x 100 mm eluting with 30-100% aqueous methanol over 10 min containing 0.1% TFA, 20 mL/min) 22 mg (45%) of compound 214B as a yellow solid. HPLC: 24% at 3.06 min & 76 at 3.25 min (atropisomers, retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 418.0 $[M+NH_4]^+$.

Example 215

(3aα,4β,7β,7aα)-4-Ethylhexahydro-7-methyl-2-(4-nitro-1-naphthalenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione (215B)



A. **(3aα,4β,7β,7aα)-4-Ethylhexahydro-7-methyl-4,7-epoxyisobenzofuran-1,3-dione (215A)**



2-Ethyl-5-methylfuran (1.89 mL, 15.3 mmol) was dissolved in methylene chloride (10 mL) and maleic anhydride (1.00 g, 10.2 mmol) was added. The reaction was stirred at 25°C for 18 h and then concentrated *in vacuo*. The resulting crude bicycle was dissolved in EtOAc (50 mL) and 10% Pd/C (0.40 g) was added. Hydrogen was then introduced via a balloon. After 4 h, the reaction was filtered through Celite, rinsing with EtOAc. Concentration *in vacuo* gave the crude compound **215A** (1.93 g) as a white solid. This material was taken on directly to the next reaction without purification.

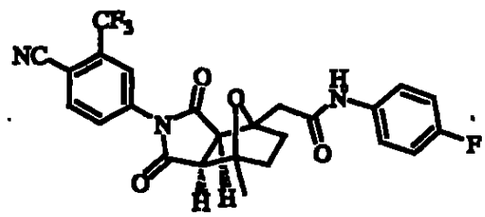
B. **(3aα,4β,7β,7aα)-4-Ethylhexahydro-7-methyl-2-(4-nitro-1-naphthalenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione (215B)**

Compound **215A** (0.168 g, 0.798 mmol) and 1-amino-4-nitronaphthalene (0.10 g, 0.53 mmol) were suspended in toluene (0.8 mL) and TEA (0.2 mL) and magnesim sulfate (0.1 g) were added. The mixture was heated at 135°C in a sealed tube for 18 h. The reaction was then cooled to rt and filtered, rinsing with chloroform. Concentration gave the crude product which was purified by preparative TLC on SiO_2 eluting with methylene chloride. This gave 0.077 g (0.20 mmol, 38%) of compound **215B** as a yellow solid. HPLC: 100% at 3.260 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over

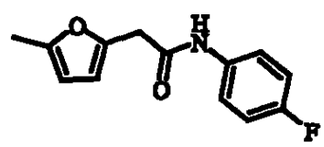
4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 381.05 $[M+H]^+$.

Example 216

(3aα,4β,7β,7aα)-2-(4-Cyano-1-naphthalenyl)-*N*-(4-fluorophenyl)octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindole-4-acetamide (216B)



A. *N*-(4-Fluorophenyl)-5-methyl-2-furanacetamide (216A)



5-Methyl-2-furanacetic acid (1.00 g, 7.14 mmol, synthesized as described WO 9507893, Example 19) was dissolved in CH_3CN/DMF (4:1, 25 mL), 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide (1.37 g, 7.14 mmol) and 1-hydroxy-7-azabenzotriazole (0.972 g, 7.14 mmol) were then added followed by 4-fluoroaniline (0.676 mL, 7.14 mmol). After 3 h, the reaction was diluted with EtOAc (150 mL) and washed with 1 N HCl (1 x 30 mL), sat. aq. $NaHCO_3$ (1 x 30 mL), brine (1 x 40 mL) and dried over sodium sulfate. Compound 216A (1.58 g, 95%)) was isolated as a yellow foam after concentration *in vacuo*. No further purification was necessary. HPLC: 78% at 2.647 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm).

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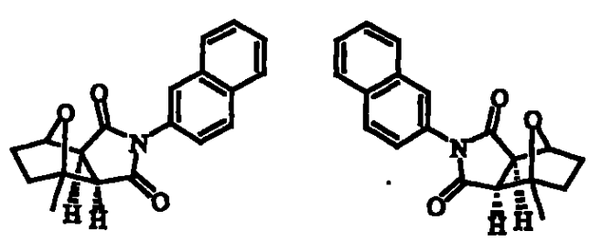
B. 3aα,4β,7β,7aα)-2-(4-Cyano-1-naphthalenyl)-*N*-(4-fluorophenyl)octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindole-4-acetamide (216B)

Compound 216A (0.200 g, 0.858 mmol) and 4-(2,5-dihydro-2,5-dioxo-1H-pyrrol-1-yl)-2-trifluoromethylbenzonitrile (0.164 g, 0.616 mmol) were dissolved in benzene and heated at 60°C for 14 h. The reaction was then cooled and concentrated *in vacuo*. The resulting orange oil was dissolved in EtOAc (15 mL) and 10% Pd/C (0.050 g) was added. Hydrogen was then introduced via a balloon. After 3 h, the reaction was filtered through Celite rinsing with EtOAc and concentrated *in vacuo*. The resulting crude material was purified by preparative TLC on silica eluting with 5% acetone in methylene chloride to give 0.166 g (54%) of compound 216B as a white solid. NMR spectroscopy showed only a single isomer which was determined to be exo by NOE experiments. HPLC: 95% at 3.200 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 484.0 $[M+H]^+$.

Example 217

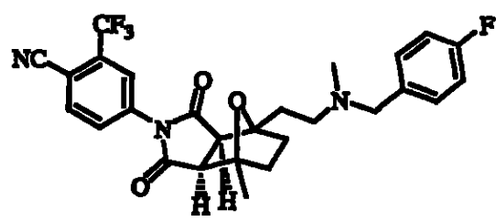
(3aα,4β,7β,7aα)-Hexahydro-4-methyl-2-(2-naphthalenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione, faster eluting enantiomer & (3aα,4β,7β,7aα)-Hexahydro-4-methyl-2-(2-naphthalenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione, slower eluting enantiomer (217i & 217ii, respectively)



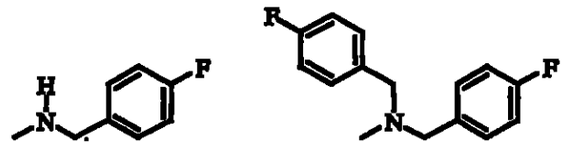
Racemic compound 137 was separated into the individual antipodes by chiral reverse phase liquid chromatography. A Chiralpak AD-R column (4.6 x 250 mm) was used eluting with 70% acetonitrile/30% water at 1 mL/min. UV detection at 220 nm was used. The faster eluting isomer, compound 217i (retention time = 15.66 min), was found to be 99.9% ee and the slower eluting isomer, compound 217ii (retention time = 15.66 min) was 99.6% ee by analytical chiral reverse phase chromatography.

Example 218

(3aα,4β,7β,7aα)-4-[4-[2-[[(4-Fluorophenyl)methyl]methylamino]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile (218B)



A. **(4-Fluorobenzyl)methylamine & Bis(4-fluorobenzyl)methylamine (218A & 218A')**



218A 218A'

Compounds 218A & 218A' were made in accordance with the procedure described by Singer et al. *J. Med. Chem.* 29, 40-44 (1986). 4-Fluorobenzyl bromide (189 mg, 1.00 mmol) was refluxed in a solution of ethanol (1.5 mL) and methylamine (5 mL, 2 M solution in MeOH) for 3 h. An additional portion of methylamine (2 mL) was added and the mixture was refluxed for an additional hour. The solution was cooled and

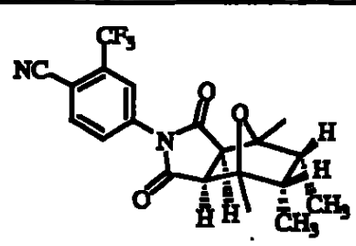
concentrated *in vacuo*, and the residue was dissolved in a mixture of 2 N HCl (3 mL) and ether (1.5 mL). The layers were separated and the aqueous layer was extracted with an additional portion of ether. The aqueous solution was chilled to 0°C, titrated to pH 11 with NaOH and extracted with CH_2Cl_2. The extracts were dried over $MgSO_4$ and concentrated *in vacuo* to give 120 mg of a 2.5:1 mixture of compounds 218A and compound 218A' respectively. The crude mixture was taken on without further purification.

B. (3aα,4β,7β,7aα)-4-[4-[2-[[(4-Fluorophenyl)methyl]-methylamino]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile (218B)

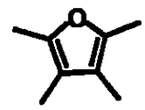
A solution of compound 36 (34.3 mg, 0.075 mmol) and compounds 218A & 218A' (21 mg, ~0.088 mmol (of 218A)) in toluene (0.4 mL) was heated at 100°C overnight. The reaction mixture was cooled to room temperature and then concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with 25% acetone/75% CH_2Cl_2 gave 30 mg (0.058 mmol, 78%) of 218B as a yellow solid. HPLC: 99% at 2.46 min (retention time) (YMC S5 ODS 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, monitoring at 220 nm). MS (ES): m/z 516.26 $[M+H]^+$.

Example 219

(3aα,4β,5β,6β,7β,7aα)-4-(Octahydro-4,5,6,7-tetramethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (219D)



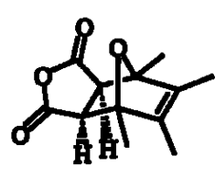
A. 2,3,4,5-Tetramethylfuran (219A)



Compound 219A was made in accordance with the procedures described in Hancock et al. *J. Org. Chem.* 42,1850-1856 (1977) & Amarnath et al. *J. Org. Chem.*, 60, 301-307 (1995). 2-Propanone (100 mL, 1.1 mol) was refluxed over PbO_2 (26.7 g, 0.112 mol) for 28 h. After cooling to rt, the reaction mixture was filtered and the residue was washed with acetone. The filtrate was concentrated under reduced pressure to remove the acetone and then distilled at 20 Torr. The fraction that came over between 100-120°C was collected to give 6.75 g (42.5%) of 3,4-dimethylhexane-2,5-dione as a light yellow oil.

A solution of 3,4-dimethylhexane-2,5-dione (3.00 g, 21.1 mmol) and *p*-toluenesulfonic acid (401 mg, 2.11 mmol) in benzene (30 mL) was heated to reflux in a Dean-Stark trap overnight. The reaction mixture was distilled at atmospheric pressure to remove the excess benzene. The remaining mixture was transferred to a smaller flask and distilled at atmospheric pressure. The fraction that came over between 80-100°C was collected to give 509 mg (19%) of compound 219A as a light yellow oil.

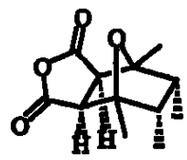
B. (3aα,4β,7β,7aα)-4-Ethyl-3a,4,7,7a-tetrahydro-4,5,6,7-tetramethyl-4,7-epoxyisobenzofuran-1,3-dione (219B)



A solution of compound 219A (400 mg, 3.22 mmol) and maleic anhydride (442 mg, 4.51 mmol) in Et_2O (1.5 mL) was stirred at rt overnight. The reaction mixture was then placed in freezer for 5 days, after which time the resulting crystals were collected and dried to give

0.26 g (37%) of compound **219B** as tan crystals. The crude compound **219B** was taken on to the next step without further purification.

C. (3aα,4β,5α,6α,7β,7aα)-4-Ethylhexahydro-4,5,6,7-tetramethyl-4,7-epoxyisobenzofuran-1,3-dione (219C)



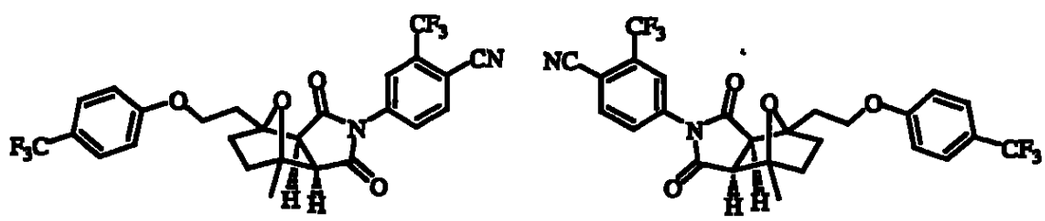
A solution of compound **219B** (120 mg, 0.545 mmol) and 10% Pd/C (24 mg, cat.) in EtOAc (2 mL) was stirred under a balloon of hydrogen at room temperature overnight. The reaction mixture was filtered through Celite and concentrated under reduced pressure to give 100 mg (0.446 mmol, 82%) of compound **219C** as a white solid, which was carried on with no further purification.

D. (3aα,4β,5β,6β,7β,7aα)-4-(Octahydro-4,5,6,7-tetramethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (219D)

A solution of compound **219C** (44.4 mg, 0.2 mmol), 5-amino-2-cyanobenzotrifluoride (45 mg, 0.24 mmol), TEA (0.04 mL) and $MgSO_4$ (20 mg) in toluene (0.2 mL) was heated at 135°C overnight. The reaction mixture was cooled to room temperature, filtered and then concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with 40% EtOAc/hexanes followed by washing the resulting solid with MeOH gave 17 mg (0.043 mmol, 22%) of compound **219D** as a white solid. HPLC: 90% at 3.11 min (retention time) (YMC S5 ODS 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, monitoring at 220 nm). MS (ES): m/z 391.2 $[M-H]^-$.

Example 220

(3aα,4β,7β,7aα)-4-[Octahydro-4-methyl-1,3-dioxo-7-[2-[4-(trifluoromethyl)phenoxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile, faster eluting antipode & (3aα,4β,7β,7aα)-4-[Octahydro-4-methyl-1,3-dioxo-7-[2-[4-(trifluoromethyl)phenoxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile, slower eluting enantiomer (220i & 220ii, respectively)



Racemic compound 35 was separated into the individual antipodes by chiral normal phase liquid chromatography. A Chiralpak AD column (50 x 500 mm) was used eluting with 85% hexanes/7.5% methanol/7.5% ethanol, at 50mL/min. UV detection at 220 nm was used. The faster eluting isomer compound 220i (retention time = 55.86 min) was found to have 95.8% ee ($[\alpha]_D^{25}$ = -53.02°, C = 3.134 mg/cc in CH_2Cl_2) and the slower eluting isomer compound 220ii (retention time = 62.86 min) was 86% ee ($[\alpha]_D^{25}$ = +48.74°, C = 2.242 mg/cc in CH_2Cl_2) by analytical chiral normal phase chromatography.

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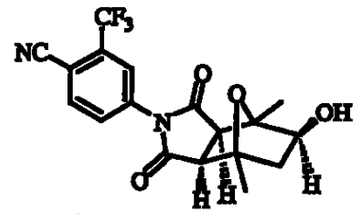
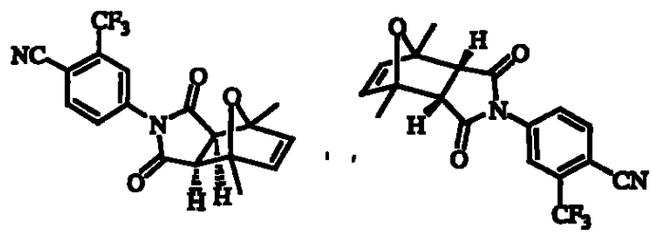
Example 221

(3aα,4β,5β,7β,7aα)-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (221B)



A. (3aα,4β,7β,7aα)-4-(hexahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (221Ai) & (3aα,4α,7α,7aα)-4-(hexahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (221Aii)



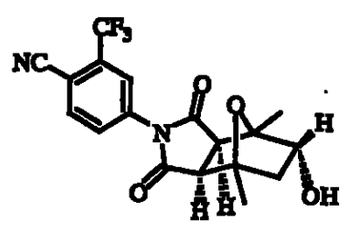
A solution of 2,5-dimethylfuran (0.800 mL, 7.51 mmol) and 4-(2,5-dihydro-2,5-dioxo-1H-pyrrol-1-yl)-2-trifluoromethylbenzonitrile (synthesized as described in Example 1B, using 4-cyano-3-trifluoromethylaniline in place of 4-bromo-3-methylaniline) (1.00 g, 3.75 mmol) in benzene (4 mL) was heated at 60°C overnight. The reaction mixture was concentrated under reduced pressure and placed on a high vacuum pump until the oil solidified to give a 3:1 mixture (determined by LC and NMR) of compounds 221Ai & 221Aii, respectively, as a brown solid, which was used directly in the next step without further purification.

B. (3aα,4β,5β,7β,7aα)-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (221B)

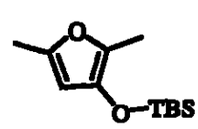
BH_3•THF (3.75 mL, 3.75 mmol, 1M in THF) was added to a solution of crude compounds 221Ai & 221Aii (3.75 mmol) in THF (12.5 mL) at 0°C. After the starting material was consumed the reaction mixture was concentrated under reduced pressure. The resulting residue was then dissolved in toluene (12.5 mL), Me_3NO (845 mg, 11.2 mmol) was added and the mixture was heated to reflux overnight. The reaction mixture was then cooled to rt, added to H_2O and extracted with EtOAc (3X). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on SiO_2 eluting with 75% EtOAc/hexanes gave 0.354 g (25%) of compound 221B as a tan powder. HPLC: 90% at 2.45 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 381.11 $[M+H]^+$.

Example 222

(3aα,4β,5α,7β,7aα)-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (222D)

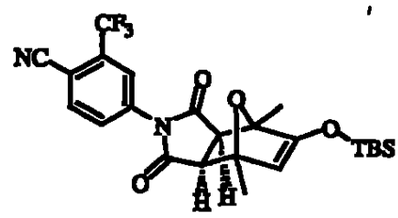


A. 3-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-2,5-dimethylfuran (222A)



2,5-Dimethyl-3(3H)-furanone (2.00 g, 17.8 mmol) was dissolved in methylene chloride (180 mL). TEA (7.43 mL, 53.5 mmol) was added followed by TBSOTf (4.92 mL, 21.4 mmol) at 25°C. After 1 h, the reaction was concentrated *in vacuo* and the resulting slurry was run through a silica gel column conditioned with 3% TEA in hexanes. The product was eluted with 3% TEA/hexanes to give 3.6 g (89%) of compound **222A** as an orange oil which was used directly in subsequent reactions.

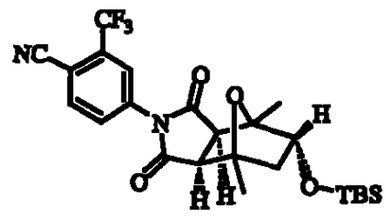
B. (3aα,4β,7β,7aα)-4-[5-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]-1,3,3a,4,7,7a-hexahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile (222B)



4-(2,5-Dihydro-2,5-dioxo-1H-pyrrol-1-yl)-2-trifluoromethylbenzonitrile (1.00 g, 3.85 mmol) was dissolved in benzene (5.0 mL) and the compound **222A** (1.30 g, 5.77 mmol) was added. The reaction mixture was warmed to 60°C for 2 h and then cooled to 25°C. The solution was then concentrated *in vacuo* to give compound **222B** as a yellow oil which was carried on to the next reaction without purification. HPLC: 60% at 4.013 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm).

C. (3aα,4β,5α,7β,7aα)-4-[5-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]octahydro-4,7-dimethyl-1,3-

dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile (222C)



Crude compound **222B** (3.85 mmol) was dissolved in ethyl acetate (75 mL) and 10% Pd/C (1.20 g) was added. Hydrogen was then introduced via a balloon. After 24 h, the reaction was filtered through Celite rinsing with ethyl acetate and concentrated *in vacuo* to give a yellow oil. The crude product was purified by flash chromatography on silica gel eluting with methylene chloride/acetone (0% - 1% - 2% acetone) to give 0.710 g (35%) compound **222C** as a yellow solid. HPLC: 100% at 4.160 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90 aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 517.6 $[M+Na]^+$.

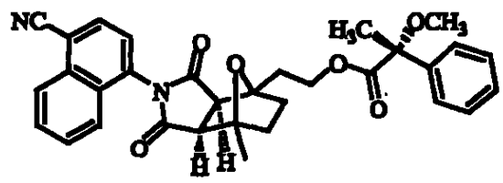
D. (3aα,4β,5α,7β,7aα)-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (222D)

Compound **222C** (0.040 g, 0.081 mmol) was dissolved in THF (1.0 mL) and HF•Pyridine (0.5 mL) was added. After 2 h, the reaction was carefully poured into cold saturated aq. $NaHCO_3$. The mixture was then extracted with methylene chloride (3 x 10 mL). The combined organics were washed with 1 N HCl (1 x 10 mL) and dried over anhydrous sodium sulfate. Concentration *in vacuo* gave 0.031 g (10%) compound **222D** as a yellow solid. NOE experiments confirmed the assigned isomer. HPLC:

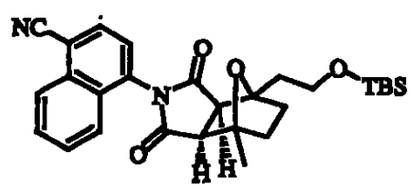
98% at 2.777 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 403.06 $[M+Na]^+$.

Example 223

(αR)-α-Methoxybenzeneacetic acid, 2-[(3aα,4β,7β,7aα)-2-(4-cyano-1-naphthalenyl)octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindol-4-ylethyl ester (223C)



A. **(3aα,4β,7β,7aα)-4-[4-[2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (223A)**

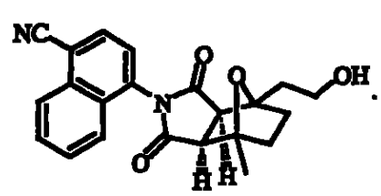


A solution of 4-amino-1-naphthalenecarbonitrile (19.2 g, 114 mmol) and maleic anhydride (14.0 g, 113 mmol) in AcOH (230 mL) was heated at 115°C for 12 h. After cooling to rt, the reaction mixture was concentrated under reduced pressure then diluted with CH_2Cl_2 (2.5 L). The organic layer was washed 3X with H_2O (3 L), 1X with sat. aq. Na_2CO_3 (1 L) and 1X with brine (1 L), dried over $MgSO_4$ and concentrated to ~200 mL under reduced pressure. Purification by flash chromatography on cation exchange resin (60 g, CUBX13M6 from United Chemical Technologies)

eluting with CH_2Cl_2 gave 25.0 g (88%) of 4-(2,5-dihydro-2,5-dioxo-1H-1-yl)-1-naphthalenecarbonitrile as a yellow solid. HPLC: 96% at 2.48 min (retention time) (Phenomenex-prime S5-C18 column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 249.25 $[M+H]^+$.

4-(2,5-Dihydro-2,5-dioxo-1H-1-yl)-1-naphthalenecarbonitrile (1.00 g, 4.03 mmol) was suspended in benzene (6.0 mL) in a sealed tube and compound **204A** (1.11 g, 5.24 mmol) was added. The reaction was heated at 60°C for 16 h and then cooled to 25°C. The benzene was removed *in vacuo* to give a yellow solid. The solid was dissolved in ethyl acetate (40 mL) and Pd/C (10% Pd, 0.300 g) was added. Hydrogen was then introduced via a balloon. After 4 h, the reaction was filtered through Celite rinsing with ethyl acetate. Concentration *in vacuo* gave a pale yellow solid which was purified by flash chromatography on silica gel eluting with acetone/chloroform (0% - 1.5% - 3% acetone) to give 1.53 g (77%) compound **223A** as a yellow foam. HPLC: 86% at 4.173 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm).

B. (3aα,4β,7β,7aα)-4-[Octahydro-4-(2-hydroxyethyl)-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (223B)



Compound **223A** (1.37 g, 2.97 mmol) was dissolved in THF (8.0 mL) and transferred to a polypropylene bottle and cooled to 0°C. HF•Pyridine

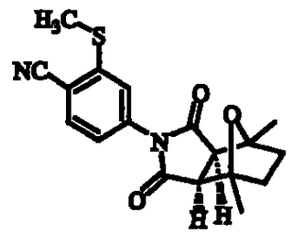
(2.0 mL) was then added. After 20 min, the reaction was carefully poured into cold sat. aq. sodium bicarbonate and extracted with methylene chloride (3 x 30 mL). The organics were then washed with 1 N HCl and dried over anhydrous sodium sulfate. Concentration *in vacuo* gave 0.99 g (89%) the compound **223B** as a yellow foam which was not purified further. HPLC: 96% at 2.443 and 2.597 min (atropisomers, retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 399.02 $[M+Na]^+$.

C. (αR)-α-Methoxybenzeneacetic acid, 2-[(3aα,4β,7β,7aα)-2-(4-cyano-1-naphthalenyl)octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindol-4-y]ethyl ester (223C)

Compound **223B** (0.200 g, 0.575 mmol) was added to a solution of WSDCC (0.138 g, 0.719 mmol) and (*R*)-mandelic acid (0.096 g, 0.57 mmol) in dichloromethane (6.0 mL). 4-DMAP (0.005 g) was then added and the reaction was stirred at 25°C for 4 h. The mixture was then diluted with dichloromethane, washed with 1 N HCl (2 x 10 mL) followed by sodium bicarbonate (1 x 10 mL) and dried over anhydrous sodium sulfate. Concentration *in vacuo* gave 0.220 g (71%) compound **223C** as a yellow solid which was not purified further. HPLC: 100% at 3.283 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 547.26 $[M+Na]^+$.

Example 224

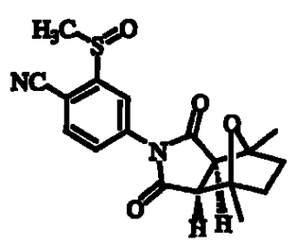
(3aα,4β,7β,7aα)-2-(Methylthio)-4-(octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)benzonitrile (224)



4-Amino-2-(methylthio)benzonitrile (100 mg, 0.609 mmol, synthesized as described in EP 40931 A1) was reacted in a sealed tube with compound **20A** (131 mg, 0.668 mmol), $MgSO_4$ (161 mg, 1.34 mmol) and Et_3N (0.440 mL, 3.17 mmol) in 0.50 mL toluene according to the procedure described in Example **208C** to give, after purification by reverse phase preparative HPLC (YMC S5 ODS 20 x 100 mm eluting with 30-100% aqueous methanol over 10 min containing 0.1% TFA, 20 mL/min), 137 mg (0.400 mmol, 66%) of compound **224** as a white solid. HPLC: 100% at 2.73 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 401.0 $[M-H+OAc]^-$.

Example 225

(3aα,4β,7β,7aα)-2-(Methylsulfinyl)-4-(octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)benzonitrile (225)

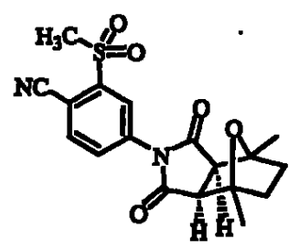


To an ice-cold suspension of compound **224** (30 mg, 0.088 mmol) in 2 mL of H_2O/MeOH (1:1) was added oxone (80 mg, 0.26 mmol) in one solid portion. The resulting mixture was stirred for 4 h at 0°C before it was

diluted with H_2O (10 mL) and extracted with CH_2Cl_2 (2 x 20 mL). The combined organic layers were dried and concentrated *in vacuo* to leave a residue which was purified by filtering the material through a short pad of silica gel eluting with CH_2Cl_2 to yield 32 mg (0.088 mmol, 100%) of compound **225** as a colorless oil. HPLC: 99% at 2.01 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 376.0 $[M+NH_4]^+$.

Example 226

(3aα,4β,7β,7aα)-2-(Methylsulfonyl)-4-(octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)benzonitrile (226)

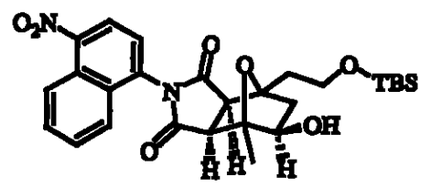


To a solution of compound **225** (48 mg, 0.14 mmol) in CH_2Cl_2 (2 mL) was added *m*CPBA (145 mg, 50% mixture, 0.420 mmol) in one solid portion. The resulting mixture was allowed to warm to room temperature and was stirred for 60 h at which time no more starting material could be detected by HPLC. The reaction was quenched by the addition of sat. $NaHCO_3$ solution (5 mL), the layers were separated and the aqueous layer was extracted with CH_2Cl_2 (20 mL). The combined organic phases were dried over $MgSO_4$ and concentrated *in vacuo*. The remaining residue was purified by reverse phase preparative HPLC (YMC S5 ODS 20 x 100 mm eluting with 30-100% aqueous methanol over 10 min containing 0.1% TFA, 20 mL/min) to afford 48 mg (0.13 mmol, 92%) of compound **226** as a white solid. HPLC: 100% at 2.07 min (retention time) (YMC S5 ODS

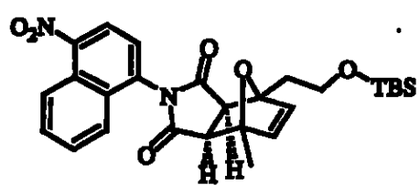
column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 392.0 $[M+NH_4]^+$.

Example 227

(3aα,4β,5β,7β,7aα)-7-[2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]hexahydro-5-hydroxy-4-methyl-2-(4-nitro-1-naphthalenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione (227B)



A. **(3aα,4β,7β,7aα)-4-[2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]-3a,4,7,7a-tetrahydro-7-methyl-2-(4-nitro-1-naphthalenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione (227A)**



A solution of compound **204A** (455 mg, 1.89 mmol) and 1-[4-nitronaphthalene]-1H-pyrrole-2,5-dione (254 mg, 0.947 mmol, prepared as described for 4-(2,5-dihydro-2,5-dioxo-1H-1-yl)-1-naphthalenecarbonitrile, Example 223A) in benzene (2 mL) was heated at 60°C overnight. The reaction mixture was concentrated under reduced pressure to give crude

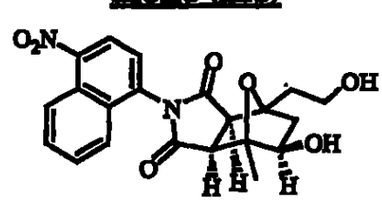
compound **227A** as a brown solid, which was used directly in the next step without further purification.

B. (3aα,4β,5β,7β,7aα)-7-[2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]hexahydro-5-hydroxy-4-methyl-2-(4-nitro-1-naphthalenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione (227B)

BH_3•THF (0.95 mL, 0.95 mmol, 1M in THF) was added to a solution of crude compound **227A** (0.48 g, 0.95 mmol) in THF (2 mL) at 0°C. After compound **227A** was consumed, as was evident by HPLC, the reaction mixture was concentrated under reduced pressure. The resulting residue was then dissolved in toluene (2 mL), Me_3NO (71.0 mg, 2.84 mmol) was added and the mixture was heated to reflux overnight. The reaction mixture was then cooled to rt, added to H_2O and extracted with EtOAc (3X). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on SiO_2 eluting with 75% EtOAc/hexanes, gave 130 mg (26%) of compound **227B** as a brown solid. HPLC: 94% at 3.92 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 527.5 $[M+H]^+$.

Example 228

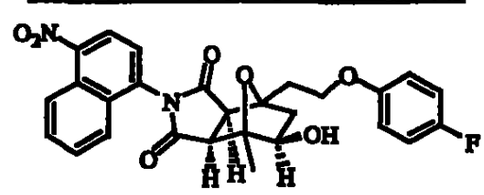
(3aα,4β,5β,7β,7aα)-Hexahydro-5-hydroxy-7-(2-hydroxyethyl)-4-methyl-2-(4-nitro-1-naphthalenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione (228)



A mixture of TBAF (0.3 mL, 0.3 mmol, 1 M solution in THF) and HF (0.3 mL, 50% in H_2O) in CH_3CN (6 mL) was added to a solution of **227B** (104 mg, 0.197 mmol) in THF (2 mL) at 0°C. The reaction mixture was stirred overnight at rt. After the starting material was consumed, as was evident by TLC, H_2O and EtOAc were added and the layers were separated. The aqueous layer was extracted with EtOAc (1X) and the combined organic layers were washed with H_2O (1X) and brine (1X), dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography on SiO_2 eluting with 5% $MeOH/CH_2Cl_2$ gave 61 mg (75%) of compound **228** as a yellow solid. HPLC: 99% at 2.47 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 411.2 $[M-H]^-$.

Example 229

(3aα,4β,5β,7β,7aα)-7-[2-(4-Fluorophenoxy)ethyl]hexahydro-5-hydroxy-4-methyl-2-(4-nitro-1-naphthalenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione (229)

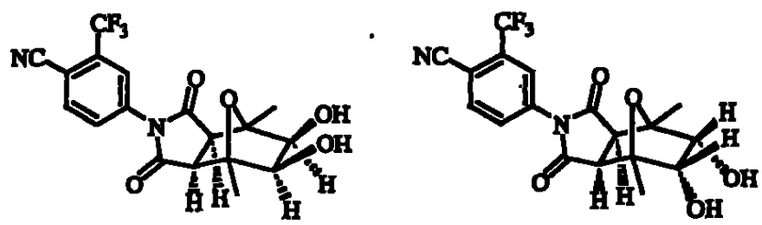


DBAD (37.7 mg, 0.164 mmol) was added to a solution of PPh_3 (43.0 mg, 0.164 mmol) in THF (1 mL). After stirring for 10 min, 4-fluorophenol (18.3 mg, 0.164 mmol) was added and the reaction mixture was stirred for a further 5 min. A solution of compound **228** (45.0 mg, 0.109 mmol) in THF (1 mL) was added and the mixture was stirred at rt overnight. HPLC showed the crude reaction mixture to contain mostly starting diol (compound **228**), so this mixture was added to a preformed mixture as before of PPh_3 (86 mg), DBAD (75.4 mg) and phenol (36.6 mg) in THF (4

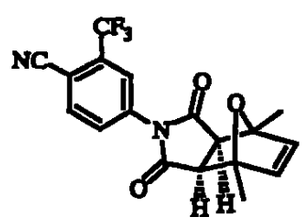
mL) at rt. Stirring was continued until all of compound **228** was consumed. The reaction was then concentrated under reduced pressure. Purification by reverse phase preparative HPLC [15.2 min (retention time) (YMC S5 ODS A column 20 x 100 mm, 10-90% aqueous methanol over 15 minutes containing 0.1% TFA, 20 mL/min, monitoring at 220 nm)] gave 25.0 mg (45%) of compound **229** as a light yellow solid. HPLC: 99 at 3.53 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2 phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 505.2 $[M-H]^-$.

Example 230

(3aα,4β,5β,6β,7β,7aα)-4-(Octahydro-5,6-dihydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile & (3aα,4β,5α,6α,7β,7aα)-4-(Octahydro-5,6-dihydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (230Bi & 230Bii, Respectively)



A. **(3aα,4β,7β,7aα)-4-(1,3,3a,4,7,7a-Hexahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (230A)**



2,5-Dimethyl furan (1.23 mL, 11.5 mmol) and 4-(2,5-dihydro-2,5-dioxo-1H-pyrrol-1-yl)-2-trifluoromethylbenzonitrile (2.00 g, 7.69 mmol) were dissolved in benzene (10 mL) and heated at 60°C for 18 h. The volatile organics were then removed *in vacuo*. The resulting crude compound **230A** was carried on without purification. HPLC: 71% at 3.007 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm).

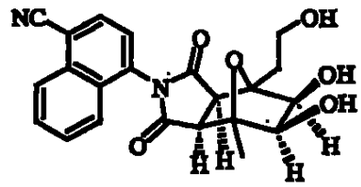
B. (3aα,4β,5β,6β,7β,7aα)-4-(Octahydro-5,6-dihydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile & (3aα,4β,5α,6α,7β,7aα)-4-(Octahydro-5,6-dihydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (230Bi & 230Bii)

Compound **230A** (0.100 g, 0.281 mmol) was dissolved in acetone and *N*-methylmorpholine-*N*-oxide (50% aq. solution, 0.10 mL, 0.42 mmol) was added. OsO_4 (4% aq. solution, 0.014 mmol) was then added. After 3 h at 25°C, the reaction was complete and sodium sulfite (0.250 g) was added with vigorous stirring. After 15 min, brine (10 mL) was added and the solution was extracted with EtOAc (3 x 15 mL). The organics were dried over anhydrous sodium sulfate and then concentrated *in vacuo*. The crude diol mixture was purified by preparative TLC eluting with 18% acetone in chloroform to give 0.038 g (34%) of compound **230Bi** (beta face) and 0.012 g (11%) of compound **230Bii** (alpha face) as pale yellow solids. Compound **230Bi**: HPLC: 100% at 2.567 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 397.08 $[M+H]^+$. Compound **230Bii**: HPLC: 100% at 2.417 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90%

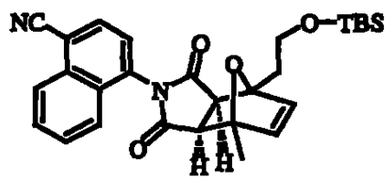
aqueous methanol over 4 minutes containing 0.2 phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 397.08 $[M+H]^+$.

Example 231

(3aα,4β,5β,6β,7β,7aα)-4-[Octahydro-5,6-dihydroxy-4-(hydroxyethyl)-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile. (231C)



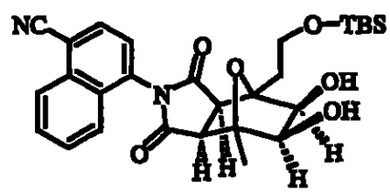
A. (3aα,4β,7β,7aα)-4-[4-[2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]-1,3,3a,4,7,7a-hexahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (231A)



Compound **204A** (29.0 g, 120 mmol) and 4-(2,5-dihydro-2,5-dioxo-1H-1-yl)-1-naphthalenecarbonitrile (20.0 g, 80.6 mmol) were suspended in benzene (80 mL) and heated at 60°C for 14 h. The mixture was then concentrated *in vacuo* at 40°C for 40 min. The resulting slurry was cooled to 25°C and then suspended in MeOH (200 mL) and stirred at rt for 30 min. The solution was then cooled to 0°C for 30 min and then filtered rinsing with cold MeOH. The resulting solid was dried *in vacuo* to give 26.1 g (55%) of crude compound **231A** as a white solid. The methanol solution was concentrated *in vacuo* and resuspended in MeOH (50 mL) and cooled to −20°C for 4 h. The solution was then filtered rinsing with cold MeOH. The resulting solid was dried *in vacuo* to give 3.8 g (10%) of

compound **231A** as a white solid. HPLC: 95% at 4.227 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm)

B. (3aα,4β,5β,6β,7β,7aα)-4-[4-[2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]octahydro-5,6-dihydroxy-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (231B)



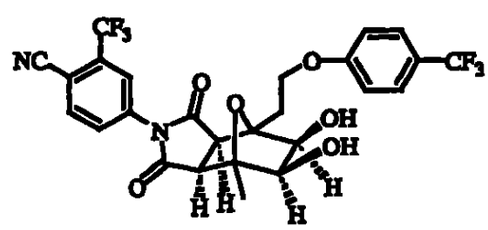
Compound **231A** (0.400 g, 0.851 mmol) was dissolved in acetone (9.0 mL) and *N*-methylmorpholine-*N*-oxide (50% aq. solution, 0.150 mL, 1.28 mmol) was added. OsO_4 (4% aq. solution, 0.043 mmol) was then added. After 3 h at 25°C, the reaction was complete and sodium sulfite (1.0 g) was added with vigorous stirring. After 15 minutes, brine (30 mL) was added and the solution extracted with EtOAc (3 x 50 mL). The organics were dried over anhydrous sodium sulfate and then concentrated *in vacuo*. The crude diol was purified by flash chromatography on silica eluting with 5-25% acetone in chloroform to give 0.355 g (80%) of compound **231B** as a yellow solid. HPLC: 93% at 3.903 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 522.00 $[M+H]^+$.

C. (3aα,4β,5β,6β,7β,7aα)-4-[Octahydro-5,6-dihydroxy-4-(hydroxyethyl)-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (231C)

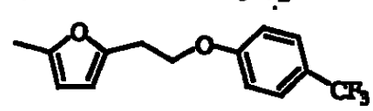
Compound 231B (0.400 g, 0.766 mmol) was dissolved in THF (5.0 mL) and transferred to a polypropylene bottle and cooled to 0°C. HF•Pyridine (1.0 mL) was then added. After 20 min, the reaction was carefully poured into cold sat. aq. sodium bicarbonate and extracted with methylene chloride (3 x 30 mL). The organics were then washed once with 1 N HCl and dried over anhydrous sodium sulfate. Concentration *in vacuo* gave 0.290 g (93%) compound 231C (0.290 g) as a yellow foam which was not purified further. HPLC: 92% at 2.278 and 2.423 min (atropisomers, retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 409.10 $[M+H]^+$.

Example 232

(3aα,4β,5β,6β,7β,7aα)-4-[Octahydro-5,6-dihydroxy-4-methyl-1,3-dioxo-7-[2-[4-(trifluoromethyl)phenoxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile, (232C)



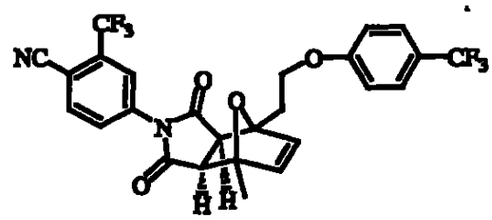
A. 2-Methyl-5-[2-[4-(trifluoromethyl)phenoxy]ethyl]furan (232A)



To a solution of triphenylphosphine (1.56 g, 5.95 mmol) in THF (40 mL) was added DBAD (1.37 g, 5.95 mmol). After 10 min, 4-

trifluoromethylphenol (0.964 g, 5.95 mmol) was added. After 10 additional minutes, compound 21A (0.500 g, 3.97 mmol) was added. After 14 h at 25°C, the reaction was concentrated *in vacuo* and purified by flash chromatography on silica eluting with chloroform to give 0.713 g (44%) of compound 232A as a clear oil.

B. (3aα,4β,7β,7aα)-4-[1,3,3a,4,7,7a-hexahydro-4-methyl-1,3-dioxo-7-[2-[4-(trifluoromethyl)phenoxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile (232B)



Compound 232A (0.301 g, 1.15 mmol) and 4-(2,5-dihydro-2,5-dioxo-1H-pyrrol-1-yl)-2-trifluoromethylbenzonitrile (0.220 g, 0.846 mmol) were suspended in benzene (1.5 mL) and heated at 60°C for 14 h. The mixture was then concentrated *in vacuo* at 40°C for 40 minutes. The crude product was purified by flash chromatography on silica eluting with 10 – 0% hexanes in methylene chloride to give 0.199 g (44%) of compound 232B as a yellow solid. Compound 232B was characterized as the exo diastereomer by NOE experiments. HPLC: 94% at 3.993 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm).

C. (3aα,4β,5β,6β,7β,7aα)-4-[Octahydro-5,6-dihydroxy-4-methyl-1,3-dioxo-7-[2-[4-(trifluoromethyl)phenoxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile, (232C)

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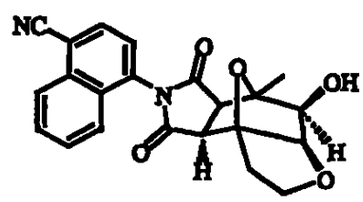
Compound **232B** (0.075 g, 0.14 mmol) was dissolved in acetone (2.0 mL) and *N*-methylmorpholine-*N*-oxide (50% aq. solution, 0.025 mL, 0.21 mmol) was added. OsO_4 (4% aq. solution, 0.007 mmol) was then added. After 3 h at 25°C, the reaction was complete and sodium sulfite (0.25 g) was added with vigorous stirring. After 15 minutes, brine (5 mL) was added and the solution extracted with EtOAc (3 x 10 mL). The organics were dried over anhydrous sodium sulfate and then concentrated *in vacuo*. The crude diol was purified by preparative TLC on silica gel, eluting with 10% acetone in chloroform to give 0.038 g (48%) of compound **232C** as a yellow solid. HPLC: 98% at 3.747 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 593.08 $[M+Na]^+$.

Example 233

(3aα,4β,5β,5aβ,8aβ,8bα)-4-(Decahydro-5-hydroxy-4-methyl-1,3-dioxo-4,8a-epoxy-2H-furo[3,2-e]isoindol-2-yl)-1-naphthalenecarbonitrile, (233)

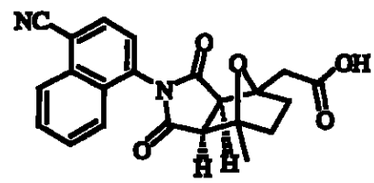


To a solution of triphenylphosphine (0.072 g, 0.28 mmol) in THF (3.0 mL) was added DBAD (0.068 g, 0.28 mmol). After 10 min, 4-cyanophenol (0.033 g, 0.28 mmol) was added. After 10 additional minutes, compound **231C** (0.075 g, 0.18 mmol) was added. After 3 h at 25°C, the reaction was concentrated *in vacuo* and purified by preparative TLC on silica gel, eluting with 15% acetone in chloroform to give 0.068 g (95%) of compound **233** as a white solid. HPLC: 95% at 2.430 and 2.560 min (atropisomers, retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90%

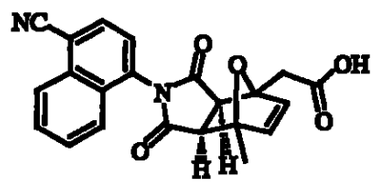
aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 391.09 $[M+H]^+$.

Example 234

(3aα,4β,7β,7aα)-2-(4-Cyano-1-naphthalenyl)octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindole-4-acetic acid, (234B)



A. (3aα,4β,7β,7aα)-2-(4-Cyano-1-naphthalenyl)-1,2,3,3a,7,7a-hexahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindole-4-acetic acid (234A)



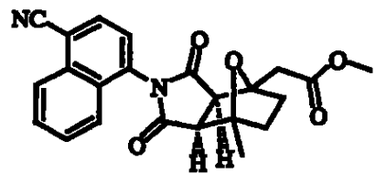
5-Methyl-2-furanacetic acid (0.500 g, 3.57 mmol) and 4-(2,5-dihydro-2,5-dioxo-1H-1-yl)-1-naphthalenecarbonitrile (0.899 g, 3.57 mmol) were dissolved in benzene (3.0 mL) and heated at 60°C for 2 h and then cooled to 25°C. After 12 h, a white solid precipitated out of solution which was collected and rinsed with diethyl ether to yield 1.20 g (87) of compound 234A as a light yellow solid. NMR analysis showed only one diastereomer. HPLC: 86% at 2.767 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 389.45 $[M+H]^+$.

B (3aα,4β,7β,7aα)-2-(4-Cyano-1-naphthalenyl)octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindole-4-acetic acid, (234B)

Compound **234A** (1.10 g, 2.82 mmol) was dissolved in EtOH/EtOAc (1:1, 50 mL) and 10% Pd/C (0.4 g, cat.) was added. H_2 was introduced via a balloon. After 5 h at 25°C, the reaction was filtered through Celite rinsing with EtOAc and concentrated *in vacuo* to yield 1.00 g (91%) of compound **234B** as a yellow solid. HPLC: 80% at 2.84 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 391.1 $[M+H]^+$.

Example 235

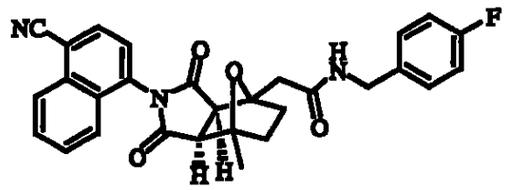
(3aα,4β,7β,7aα)-2-(4-Cyano-1-naphthalenyl)octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindole-4-acetic acid, methyl ester, (235)



Compound **234B** (0.050 g, 0.13 mmol) was dissolved in acetonitrile (2.0 mL), then DCC (0.025 g, 0.13 mmol) was added followed by HOAc (0.018 g, 0.13 mmol). 4-Fluorobenzyl alcohol (0.014 mL, 0.13 mmol) was then added and the reaction was stirred for 3 h. The reaction mixture was concentrated *in vacuo* and purified by reverse phase preparative HPLC (YMC S5 ODS 20 x 100 mm, 10-90% aqueous methanol over 15 min containing 0.1% TFA, 20 mL/min, monitoring at 220 nm). Purification yielded 0.040 g (82%) of compound **235** as a white solid, rather than the expected benzyl ester. None of the anticipated benzyl ester was observed by NMR or LC-MS. HPLC: 100% at 3.033 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 405.51 $[M+H]^+$.

Example 236

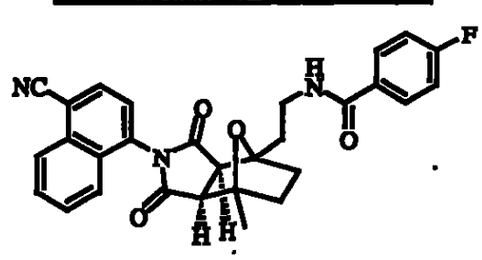
(3aα,4β,7β,7aα)-2-(4-Cyano-1-naphthalenyl)-*N*-[(4-fluorophenyl)methyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindole-4-acetamide, (236)



Compound **234B** (0.10 g, 0.27 mmol) was dissolved in acetonitrile (4.0 mL). HOAc (0.035 g, 0.27 mmol) and DCC (0.049 g, 0.27 mmol) were then added followed by 4-fluorobenzylamine (0.030 mL, 0.27 mmol). After 4 h at 25°C, the reaction was concentrated *in vacuo* and purified by reverse phase preparative HPLC (YMC S5 ODS 20 x 100 mm, 10-90% aqueous methanol over15 minutes containing 0.1% TFA, 20 mL/min, monitoring at 220 nm) to yield 0.085 g (67%) of compound **236** as a white solid. HPLC: 100% at 3.277 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 498.43 $[M+H]^+$.

Example 237

(3aα,4β,7β,7aα)-*N*-[2-[2-(4-Cyano-1-naphthalenyl)octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindol-4-yl]ethyl]-4-fluorobenzamide, (237B)



A. 4-Fluoro-*N*-[2-(5-methyl-2-furanyl)ethyl]benzamide (237A)

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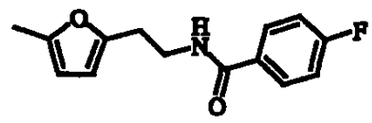


4-Fluorophenylacetyl chloride (0.290 mL, 2.44 mmol) was added dropwise to a solution of β-(5-methyl-2-furanyl)ethanamine (300 mg, 2.44 mmol, made according to the procedure of Yur'ev et al. *J. Gen. Chem. USSR (Engl. Transl.)* 33, 3444-8 (1963)) in THF (2.5 mL) at rt, followed by the dropwise addition of Et_3N (0.340 mL, 2.44 mmol). Once the starting material was consumed, as was evident by HPLC, the reaction was quenched with H_2O and extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with a gradient of 0-50% EtOAc/hexane gave 523 mg (95%) of compound **237A** as a white solid. HPLC: 99% at 2.84 min (retention time) (Phenomenex-prime S5-C18 column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 248.15 $[M+H]^+$.

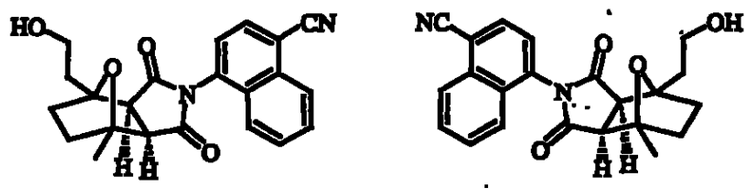
B. (3aα,4β,7β,7aα)-*N*-[2-[2-(4-Cyano-1-naphthalenyl)octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindol-4-yl]ethyl]-4-fluorobenzamide, (237B)

A solution of compound **237A** (221 mg, 0.896 mmol) and 4-(2,5-dihydro-2,5-dioxo-1H-1-yl)-1-naphthalenecarbonitrile (222 mg, 0.896 mmol) in benzene (4 mL) was heated at 60°C overnight. The reaction mixture was concentrated under reduced pressure and dissolved in EtOAc (30 mL). 10% Pd/C (50 mg) was added and the mixture was stirred under a hydrogen balloon overnight. The reaction mixture was filtered through a pad of Celite and concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with 25%-75% EtOAc/hexane (gradient) gave 160 mg (36%) of compound **237B** as an off-white solid. HPLC: 97 at 3.13 & 3.23 min (atropisomers, retention time) (Phenomenex-prime S5-C18 column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes

containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 498.11 $[M+H]^+$.

Example 238

[3a*R*-(3aα,4β,7β,7aα)]-4-[Octahydro-4-(2-hydroxyethyl)-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile & [3a*S*-(3aα,4β,7β,7aα)]-4-[Octahydro-4-(2-hydroxyethyl)-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile. (238i & 238ii)



Racemic compound **223B** was separated into its enantiomers by normal phase preparative chiral HPLC (CHIRALPAK AD 5 x 50 cm column; eluting with 20% MeOH/EtOH (1:1) in heptane (isocratic) at 50 mL/min, monitoring at 220 nm) to give the faster eluting compound **238i** (Chiral HPLC: 13.54 min; CHIRALPAK AD 4.6 x 250 mm column; eluting with 20% MeOH/EtOH (1:1) in heptane at 1 mL/min) and the slower eluting compound **238ii** (Chiral HPLC: 14.99 min; CHIRALPAK AD 4.6 x 250 mm column; eluting with 20% MeOH/EtOH (1:1) in heptane at 1 mL/min). The absolute conformation for compounds **238i** & **238ii** was not established. For simplicity in nomenclature, compound **238i** is designated herein as having an "R" configuration and compound **238ii** as having an "S" configuration. Enantiomerically pure products derived from compound **238i** are designated herein as having a "R" configuration and enantiomerically pure products derived from compound **238ii** are designated herein as having an "S" configuration.

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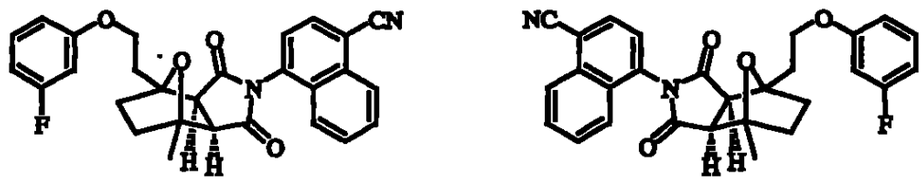
Example 239

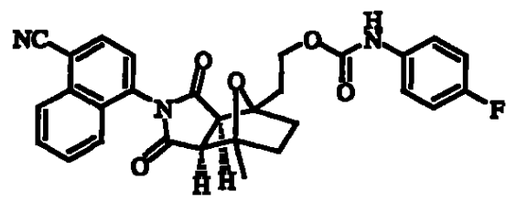
[3aR-(3aα,4β,7β,7aα)]-4-[4-[2-(3-Fluorophenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile & [3aS-(-(3aα,4β,7β,7aα)]-4-[4-[2-(3-Fluorophenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, (239i & 239ii)



To a solution of triphenylphosphine (0.052 g, 0.20 mmol) in THF (2.0 mL) was added DBAD (0.046 g, 0.20 mmol). After 10 min, 3-fluorophenol (0.018 mL, 0.20 mmol) was added. After 10 additional minutes, compound 238i (0.050 g, 0.18 mmol) was added. After 3 h at 25°C, the reaction was concentrated *in vacuo* and purified by reverse phase preparative HPLC (YMC S5 ODS 20 x 100 mm, 10-90% aqueous methanol over 15 minutes containing 0.2% TFA, 20 mL/min, monitoring at 220 nm) to give 0.031 g (33%) of compound 239i as a white solid. This process was repeated with compound 238ii to yield compound 239ii. Compound 239i: HPLC: 100% at 3.80 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 471.65 $[M+H]^+$, $[\alpha]_D^{25}$ = -47.371 (c = 4.412 mg/cc, CH_2Cl_2). Compound 239ii: HPLC: 100% at 3.80 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2 phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 471.65 $[M+H]^+$, $[\alpha]_D^{25}$ = +24.3 (c = 4.165 mg/cc, CH_2Cl_2).

Example 240

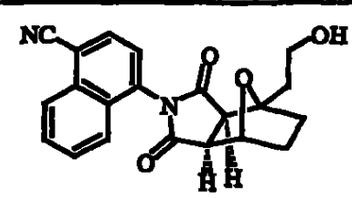
(4-Fluorophenyl)carbamic acid, 2-[(3aα,4β,7β,7aα)-2-(4-cyano-1-naphthalenyl)octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindol-4-ylethyl ester, (240)



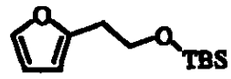
Compound **223B** (0.100 g, 0.279 mmol) was dissolved in dichloroethane (3.0 mL) and 4-fluorophenylisocyanate (0.048 mL, 0.42 mmol) was added followed by heating to 60°C. After 2 h, the reaction was cooled to 25°C and diluted with methylene chloride. The mixture was washed once with sat. aq. sodium bicarbonate (20 mL) and then the organics were dried over anhydrous sodium sulfate. The crude material was purified by flash chromatography on silica gel eluting with 15% acetone in chloroform to give 0.098 g (68%) of compound **240** as a yellow foam. HPLC: 98% at 3.320 & 3.457 min (atropisomers, retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 514.13 $[M+H]^+$.

Example 241

(3aα,4β,7β,7aα)-4-[Octahydro-4-(2-hydroxyethyl)-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, (241D)

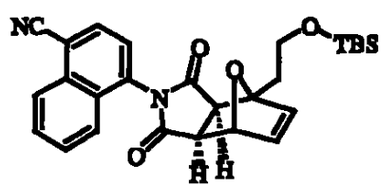


A. 2-[2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]furan (241A)



2-(2-Hydroxyethyl)furan (1.00 g, 8.93 mmol, Example 255A) was dissolved in DMF at 25°C and imidazole (0.790 g, 11.6 mmol) was added. TBSCl (1.35 g, 8.93 mmol) was then added in portions over 5 minutes. After 2 h, the reaction was poured into diethyl ether (300 mL) and washed sequentially with water (1 x 100 mL), 1 N HCl (1 x 100 mL), and brine (1 x 100 mL). The combined organics were then dried over magnesium sulfate and concentrated *in vacuo*. Compound 241A was isolated as a clear oil (1.77 g) and was taken on without purification. HPLC: 100% at 4.233 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm).

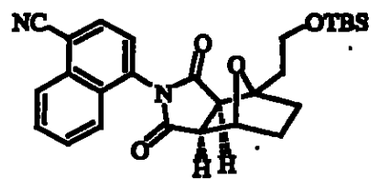
B. (3aα,4β,7β,7aα)-4-[4-[2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]-1,3,3a,4,7,7a-hexahydro-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (241B)



4-(2,5-Dihydro-2,5-dioxo-1H-1-yl)-1-naphthalenecarbonitrile (0.721 g, 3.40 mmol) was suspended in benzene (5.0 mL) in a sealed tube and compound 241A (1.00 g, 4.42 mmol) was added. The reaction was heated at 60°C for 16 h and then cooled to 25°C. The benzene was removed *in vacuo* to give a yellow solid. The crude material was purified by flash chromatography on silica gel eluting with 1-5% acetone in chloroform to

give 1.37 g (85%) of compound 241B as a yellow solid. NMR experiments confirmed the exo isomer assignment. HPLC: 100% at 4.030 & 4.110 min (atropsiomers, retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm).

C. (3aα,4β,7β,7aα)-4-[4-[2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]octahydro-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (241C)



Compound 241B (0.500 g, 1.14 mmol) was dissolved in ethyl acetate (40 mL) and 10% Pd/C (0.200 g) was added. Hydrogen was then introduced via a balloon. After 4 h, the reaction was filtered through Celite, rinsed with ethyl acetate and concentrated *in vacuo* to yield a pale yellow solid, which was purified by flash chromatography on silica gel eluting with acetone/chloroform (0% - 1.5% - 3% acetone) to give 0.450 g (83%) of compound 241C as a yellow foam.

D. (3aα,4β,7β,7aα)-4-[Octahydro-4-(2-hydroxyethyl)-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, (241D)

Compound 241C (0.283 g, 0.594 mmol) was dissolved in a solution of 2% conc. HCl in absolute ethanol (10 mL). After 1 h, the reaction was quenched with sat. aq. sodium bicarbonate and extracted with methylene chloride (4 x 20 mL). The combined organics were dried over sodium sulfate and concentrated *in vacuo* to give 0.211 g (98%) of compound 241D

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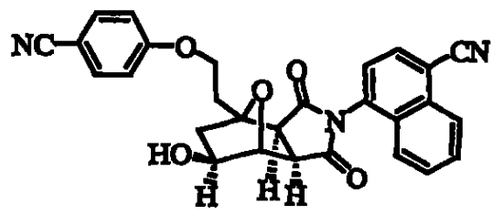
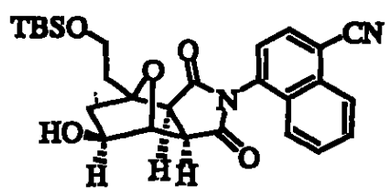
as a white solid. HPLC: 100% at 2.14 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 363.45 $[M+H]^+$.

Example 242

(3aα,4β,6β,7β,7aα)-4-[4-[2-(4-Cyanophenoxy)ethyl]octahydro-6-hydroxy-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, (242C)



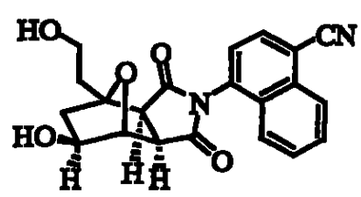
A. (3aα,4β,6β,7β,7aα)-4-[4-[2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]octahydro-6-hydroxy-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (242A)



Compound **241B** (1.00 g, 2.28 mmol) and Wilkinson's catalyst (0.105 g, 0.114 mmol) were stirred rapidly under vacuum at 25°C for 1 h and then purged with N_2. THF (30 mL) was then added followed by catecholborane (0.487 mL, 4.57 mmol) after the olefin was completely dissolved. After 1 h, the reaction was cooled to 0°C and a pH 7.2 phosphate buffer (33 mL) was added followed by EtOH (13 mL) and H_2O_2 (30% aq. soln, 3.0 g). After 3 h at 0°C the reaction was complete by LC

and the mixture was extracted with methylene chloride (3 x 50 mL). The combined organics were washed with a 1:1 mixture of 10% sodium sulfite/1 N NaOH (50 mL) and once with brine (50 mL). All aqueous phases were combined and extracted with methylene chloride (50 mL) and the organic phase combined with the previous extractions. All the organics were then dried over anhydrous sodium sulfate and then concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel eluting with 10-20% acetone in chloroform to give 0.634 g of compound **242A** as a white foam. HPLC: 96% at 3.797 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 493.13 $[M+H]^+$.

B. (3aα,4β,6β,7β,7aα)-4-[Octahydro-6-hydroxy-4-(2-hydroxyethyl)-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (242B)



Compound **242A** (0.400 g, 0.813 mmol) was dissolved in a solution of 2% 12 N HCl in absolute ethanol (10 mL). After 1 h, the reaction was quenched with sat. aq. sodium bicarbonate and extracted with EtOAc (4 x 20 mL). The combined organics were dried over sodium sulfate and concentrated *in vacuo* to give 0.305 g of compound **242B** as a white solid. HPLC: 90% at 2.043 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2%

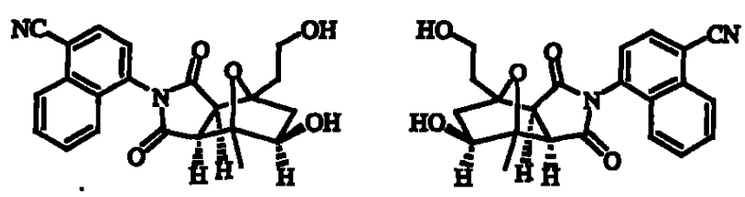
phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 379.09 $[M+H]^+$.

C. (3aα,4β,5β,7β,7aα)-4-[4-[2-(4-Cyanophenoxy)ethyl]octahydro-6-hydroxy-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, (242C)

To a solution of triphenylphosphine (0.054 g, 0.207 mmol) in THF (2.0 mL) was added DBAD (0.048 g, 0.207 mmol). After 10 min, 4-cyanophenol (0.025 g, 0.207 mmol) was added. After 10 additional minutes, compound 242B (0.050 g, 0.138 mmol) was added. After 3 h at 25°C, the reaction was concentrated *in vacuo* and purified by preparative TLC on silica eluting with 25% acetone/chloroform to give 0.056 g of compound 242C as a white solid. HPLC: 90% at 2.987 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 480.10 $[M+H]^+$.

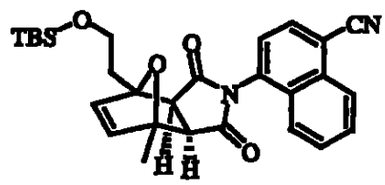
Example 243

[3a*S*-(3aα,4β,5β,7β,7aα)]-4-[Octahydro-5-hydroxy-7-(2-hydroxyethyl)-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile & [3a*R*-(3aα,4β,5β,7β,7aα)]-4-[Octahydro-5-hydroxy-7-(2-hydroxyethyl)-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, (243Di & 243Dii)



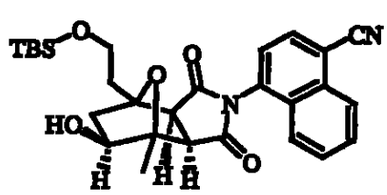
A. (3aα,4β,7β,7aα)-4-[4-[2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]-1,3,3a,4,7,7a-

hexahydro-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (243A)



4-(2,5-Dihydro-2,5-dioxo-1H-1-yl)-1-naphthalenecarbonitrile (18.3 g, 68.7 mmol) was added to a solution of compound **204A** (26.6 g, 110.6 mmol) in benzene (75 mL) and heated at 60°C overnight. After cooling to rt, the reaction mixture was concentrated under reduced pressure. The residue was treated with MeOH (250 mL) with stirring at 0°C for 10 min. The resulting solid was filtered, washed with cold MeOH (2 X 10 mL) and dried to give 26.7 g (79.5%) of compound **243A** as a yellow solid. HPLC analysis of the above solid revealed it to be 95% pure (HPLC conditions: 95% at 2.48 min (retention time) (Phenomenex-prime S5-C18 column, 4.6 x 50 mm, 10%-90% aqueous methanol over 4 minute gradient with 0.2% H_3PO_4, detecting at 220 nm)). The filtrate was then concentrated under reduced pressure and the resulting solid was chromatographed, eluting with 3% acetone/$CHCl_3$, to give an additional 4.36 g of compound **243A** (13%), giving a total final yield of 92.5%.

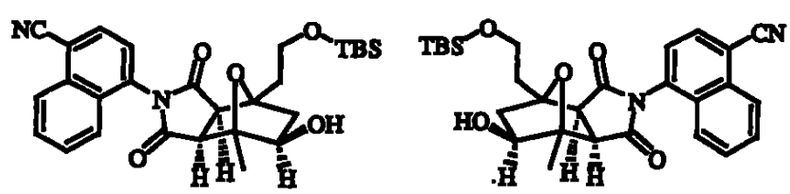
B. (3aα,4β,5β,7β,7aα)-4-[7-[2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (243B)



A mixture of **243A** (10 g, 20.46 mmol) and $RhCl(PPh_3)_3$ (0.947 mg, 1.02 mmol) was evacuated and filled with argon (3X). THF (200 mL) was

added and once all particulates had dissolved, catecholborane (4.4 mL, 40.93 mmol) was slowly added dropwise. When the formation of product ceased, as was determined by HPLC, the reaction mixture was cooled to 0°C and quenched with phosphate buffer (330 mL, pH 7.2) then EtOH (130 mL) and H_2O_2 (300 mL, 30% aq. sol) were added. Once boronate was consumed, the mixture was extracted with CH_2Cl_2 (3X) and the combined organic layers were washed with 1 N NaOH, 10% aq. $NaHSO_3$ (1:1, 1X) and brine (1X). The combined washes was extracted with CH_2Cl_2 (1X) and the combined organic layers were dried over Na_2SO_4. Purification by flash chromatography on silica gel eluting with 10% to 30% acetone/$CHCl_3$ gradient over 25 min gave 7.1 g (68%) of **243B** as a light yellow solid. HPLC conditions: 98% at 3.82 min (retention time) (Phenomenex-prime S5-C18 column 4.6 x 50 mm, 10%-90% aqueous methanol over 4 minute gradient with 0.2% H_3PO_4, detecting at 220 nm).

C. **[3a*R*-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile & [3a*S*-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (243Ci & 243Cii)**



The racemic compound **243B** was separated into the individual enantiomers by chiral normal phase liquid chromatography. A Chiralpak OD column (50 x 500 mm) was used, eluting with 13% EtOH/hexanes over 99 min at 50mL/min detecting at 220 nm. The faster eluting isomer

compound **243Ci** had a retention time = 45 min and the slower eluting isomer compound **243Cii** had a retention time = 66 min.

D. [3aS-(3aα,4β,5β,7β,7aα)]-4-[Octahydro-5-hydroxy-7-(2-hydroxyethyl)-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile & [3aR-(3aα,4β,5β,7β,7aα)]-4-[Octahydro-5-hydroxy-7-(2-hydroxyethyl)-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, (243Di & 243Dii)

Compound **243Ci** (0.84 g, 2.14 mmol) was dissolved in 2% 12 N HCl/EtOH (20 mL), stirred for 5 minutes and concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with 5-10% MeOH/CH_2Cl_2 gave 0.57 g (88%) of **243Di**. Compound **243Di** which came from the faster eluting isomer (**243Ci**) was found to be 99.7% ee by analytical normal phase chiral chromatography. HPLC conditions: 99.7 at 2.17 min (retention time) (Chiralcel OJ 44.6 X 250 mm, 10 micron, 40°C, isocratic 80% Heptane / 20% EtOH/MeOH (1:1), 1.0 mL/min., detection at 288 nm).

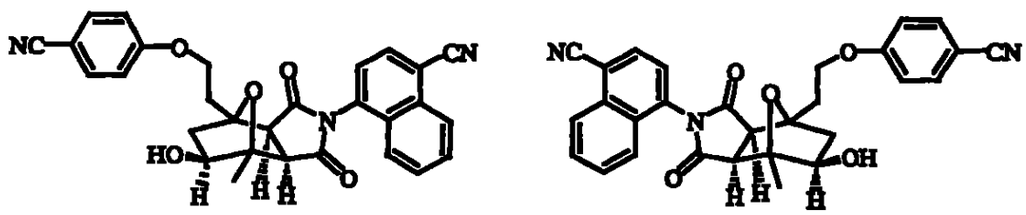
Compound **243Cii** (0.86 g, 2.19 mmol) was dissolved in 2% 12 N HCl/EtOH (20 mL), stirred for 5 minutes and concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with 5-10% MeOH/CH_2Cl_2 gave 0.60 g (90%) of **243Dii**. Compound **243Dii** which came from the slower eluting isomer (**243Cii**) was found to have 87.1% ee by analytical chiral phase chiral chromatography. HPLC conditions: 87.1% at 18.4 min (retention time) (Chiralcel OJ 44.6 X 250 mm, 10 micron, 40°C, isocratic 80% heptane / 20% EtOH/MeOH (1:1), 1.0 mL/min., detection at 288 nm).

The absolute conformation for compounds **243Di** & **243Dii** was not determined. For simplicity in nomenclature, compound **243Di** is designated herein as having an "S" configuration and compound **243Dii** as

having an "R" configuration. Enantiomerically pure products derived from compound **243Di** are designated herein as having an "S" configuration and enantiomerically pure products derived from compound **243Dii** are designated herein as having an "R" configuration

Example 244

[3aS-(3aα,4β,5β,7β,7aα)]-4-[7-[2-(4-Cyanophenoxy)ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile & [3aR-(3aα,4β,5β,7β,7aα)]-4-[7-[2-(4-Cyanophenoxy)ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, (244i & 244ii)



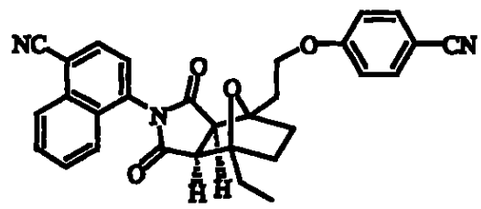
DBAD (26 mg, 0.115 mmol) was added to a solution of PPh_3 (30 mg, 0.115 mmol) in THF (0.65 mL). After stirring for 10 min, 4-cyanophenol (13.6 mg, 0.115 mmol) was added and the reaction mixture was stirred for a further 5 min. Compound **243Di** (30 mg, 0.076 mmol) was added and the mixture was stirred at rt for 1 h. The reaction was concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with 30% acetone/70% $CHCl_3$ gave 23.1 mg (0.047 mmol, 61.7) of compound **244i**. HPLC conditions: 95% at 3.06 min (retention time) (YMC S5 ODS 4.6 x 50 mm, 10%-90% aqueous methanol over 4 minute gradient with 0.2% H_3PO_4, detecting at 220 nm). MS (ES): m/z 494.09 $[M+H]^+$. $[\alpha]_D$ = 53.30°, C = 4.5 mg/cc in THF, @ 589 nm)

DBAD (26 mg, 0.115 mmol) was added to a solution of PPh_3 (30 mg, 0.115 mmol) in THF (0.65 mL). After stirring for 10 min, 4-cyanophenol (13.6 mg, 0.115 mmol) was added and the reaction mixture was stirred for a further 5 min. Compound **243Dii** (30 mg, 0.076 mmol) was added and the mixture was stirred at rt for 1 h. The reaction was concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with 30% acetone/70% $CHCl_3$ gave 20.3 mg (0.041 mmol, 54.2%) of compound **244ii**. HPLC conditions: 90 at 3.07 min (retention time)

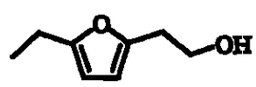
(YMC S5 ODS 4.6 x 50 mm, 10%-90 aqueous methanol over 4 minute gradient with 0.2% H_3PO_4, detecting at 220 nm). MS (ES): m/z 494.09 $[M+H]^+$. $[\alpha]_D$ = -42.87°, C = 6.6 mg/cc in THF, @ 589 nm)

Example 245

(3aα,4β,7β,7aα)-4-[4-[2-(4-Cyanophenoxy)ethyl]-7-ethyloctahydro-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile. (245D)

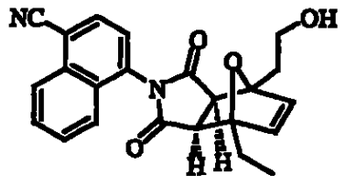


A. 2-Ethyl-5-(2-hydroxyethyl)furan (245A)



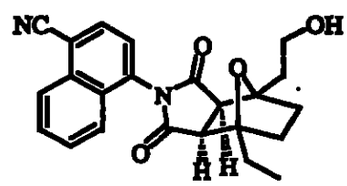
n-BuLi (2.5 M in hexane, 4.4 mL, 11 mmol) was added to a solution of 2-ethylfuran (1.05 mL, 10 mmol) in THF (10 mL) at –25°C. The solution was warmed to rt and stirred for 3 h. Ethylene oxide (0.75 mL) was added at –78°C. The reaction was stirred for 0.5 h at –15°C and overnight at rt. Aqueous sat. NH_4Cl was added and the mixture was extracted with ether (3X). The combined extracts were washed with water (1X) and brine (1X) and dried over Na_2SO_4. Purification by flash chromatography on silica gel eluting with 30% EtOAc/70% hexane gave 1.12 g (8.02 mmol, 80.2%) of compound 245A as a yellow oil.

B. (3aα,4β,7β,7aα)-4-[4-Ethyl-1,3,3a,4,7,7a-hexahydro-7-(2-hydroxyethyl)-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (245B)



A solution of compound **245A** (280 mg, 2.00 mmol) and the 4-(2,5-dihydro-2,5-dioxo-1H-1-yl)-1-naphthalenecarbonitrile (496 mg, 2.00 mmol) in benzene (2 mL) was stirred at 60°C for 2 h. The reaction mixture was concentrated under reduced pressure. The yellow solid, compound **245B**, was used directly in the next step.

C. (3aα,4β,7β,7aα)-4-[4-Ethyloctahydro-7-(2-hydroxyethyl)-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (245C)



A mixture of compound **245B** (764 mg, 1.97 mmol) and 10% Pd/C (115 mg, cat.) in EtOAc (36 mL) was stirred under a hydrogen atmosphere at rt for 2 h. The reaction mixture was filtered through Celite and concentrated under reduced pressure to give 779 mg of crude compound **245C**. Purification of this crude product by flash chromatography on silica gel eluting with 70% EtOAc/30% hexane gave 235 mg (0.6 mmol, 30.1%) of compound **245C**. HPLC conditions: 99% at 2.84 min (retention time) (YMC S5 ODS 4.6 x 50 mm, 10%-90% aqueous methanol over 4 minute gradient with 0.2% H_3PO_4, detecting at 220 nm). MS (ES): m/z 391.12 $[M+H]^+$.

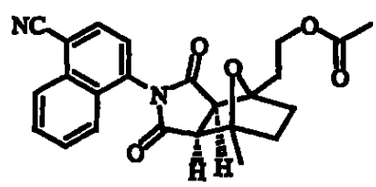
D. (3aα,4β,7β,7aα)-4-[4-[2-(4-Cyanophenoxy)ethyl]-7-ethyloctahydro-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (245D)

DBAD (44.2 mg, 0.192 mmol) was added to a solution of PPh_3 (50.4 mg, 0.192 mmol) in THF (1 mL). After stirring for 10 min, 4-cyanophenol

(23 mg, 0.192 mmol) was added and the reaction mixture was stirred for an additional 5 min. Compound **245C** (50 mg, 0.128 mmol) was added and the mixture was stirred at rt for 2 h. The reaction was concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with 40% EtOAc/60% hexane gave 43 mg (0.087 mmol, 68.4) of compound **245D** as a white solid. HPLC conditions: 99% at 3.65 min (retention time) (YMC S5 ODS 4.6 x 50 mm, 10%-90% aqueous methanol over 4 minute gradient with 0.2% H_3PO_4, detecting at 220 nm). MS (ES): m/z 492.16 $[M+H]^+$.

Example 246

(3aα,4β,7β,7aα)-4-[2-(Acetyloxy)ethyl]-2-(4-cyano-1-naphthalenyl)hexahydro-7-methyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione, (246)

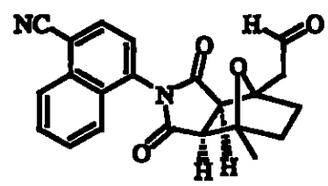


Compound **223B** (0.100 g, 0.279 mmol) was dissolved in methylene chloride (3.0 mL) at 25°C and pyridine (0.071 mL, 0.837 mmol) and 4-DMAP (1.0 mg) were added. Acetic anhydride (0.053 mL, 0.559 mmol) was then added and the reaction was stirred for 20 h at 25°C. After 20 h, sat. aq. sodium bicarbonate was added and the reaction was stirred for 30 min. The mixture was then extracted with methylene chloride (2 x 20 mL). The organics were then washed once with 1 N HCl (10 mL) and then dried over anhydrous sodium sulfate. After concentration *in vacuo*, the crude material was purified by preparative TLC on silica eluting with 12 acetone in chloroform to give 0.073 g of compound **246** as a yellow foam. HPLC: 95% at 2.837 and 3.027 min (atropisomers, retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes

containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 441.10 $[M+Na]^+$.

Example 247

(3aα,4β,7β,7aα)-4-[Octahydro-4-methyl-1,3-dioxo-7-(2-oxoethyl)-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, (247)



Oxalyl chloride (2.0 M soln, 1.73 mL, 3.5 mmol) was added to dry methylene chloride (10 mL) and cooled to –78°C. DMSO (0.283 mL, 3.99 mmol) was then added dropwise with the evolution of gas. After 15 min, compound **223B** (1.00 g, 2.66 mmol) was then added in methylene chloride (10 mL). After 15 min, TEA (1.10 mL, 7.98 mmol) was added and the reaction was slowly warmed to 25°C. Water (30 mL) was then added and the mixture was diluted with methylene chloride (100 mL). The organics were then washed once with 1 N HCl (30 mL), once with water (30 mL) and once with brine (30 mL) and then dried over anhydrous sodium sulfate. The crude product was isolated by concentration *in vacuo* to yield compound **247** as an orange foam. Crude compound **247** was taken on directly to the next reaction. HPLC: 100% at 2.70 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 483.65 $[M+H]^+$.

Example 248

[3aα,4β(E),7β,7aα]-4-[4-[3-(4-Cyanophenyl)-2-propenyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile & [3aα,4β(Z),7β,7aα]-4-[4-[3-(4-

(Smolev JK, Heston WD, Scott WW, and Coffey DS, *Cancer Treat Rep.* 61, 273-287 (1977)). The growth of the R3327H subline has been selected for its highly androgen-dependent and reproducible growth in intact male rats. Therefore, this model and other sublines of this tumor have been widely used to evaluate *in vivo* antitumor activities of antiandrogens such as flutamide and bacilutamide/Casodex (Maucher A., and von Angerer, *J. Cancer Res. Clin. Oncol.*, 119, 669-674 (1993), Furr B.J.A. *Euro. URL.* 18 (suppl. 3), 2-9 (1990), Shain S.A. and Huot RI. *J. Steriod Biochem.* 31, 711-718 (1988)).

At the beginning of the study, the Dunning tumor pieces (about 4 x 4 mm) are transplanted subcutaneously to the flank of mature male Copenhagen rats (6-7 weeks old, Harlan-Sprague Dawley, Indianapolis, MD). About 6 weeks after the implantation, the animals with tumors of measurable size (about 80 - 120 mm^3) are randomized into treatment groups (8-10 rats/group) and the treatments are initiated. One group of the rats are castrated to serve as the negative control of tumor growth. Animals are treated daily with compounds of the current invention, standard antiandrogens such as bacilutamide or vehicle (control) for an average of 10 to 14 weeks. Test compounds are dissolved in a vehicle of (2.5 ml/kg of body weight) 10% polyethylene glycol and 0.05% Tween-80 in 1% carboxymethyl cellulose, PEG/CMC, (Sigma, St Louis, MO). Typical therapeutic experiments would include three groups of three escalating doses for each standard or test compound (in a range of 300-3 mg/kg).

Tumors in the vehicle (control) group reach a size of 1500 to 2500 mm^3, whereas the castrated animal group typically shows tumor stasis over the 14 weeks of observation. Animals treated orally with 20 mg/kg of bicalutamide or flutamide would be expected to show a 40% reduction in tumor volumes compared to control after 14 weeks of treatment. The size of tumors are measured weekly by vernier caliper (Froboz, Switzerland), taking perpendicular measurements of length and width. Tumor volumes are measured in mm^3 using the formula: Length x Width x Height = Volume. Statistical differences between treatment groups and control are

evaluated using multiple ANOVA analysis followed by one tail non-parametric Student t test.

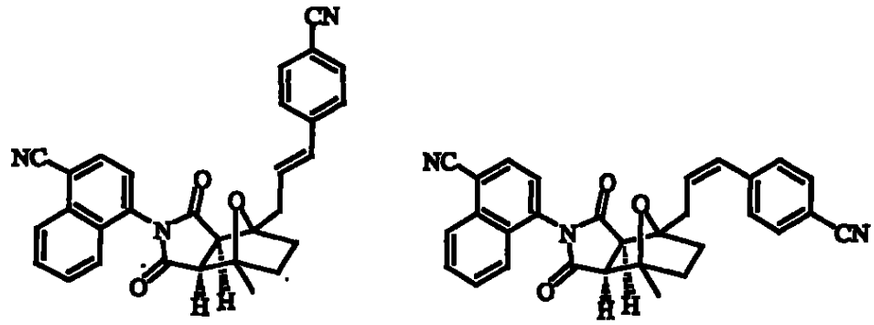
Mature Rat Prostate Weight Assay:

The activity of compounds of the present invention were investigated in a mature male rat model, which is a variation of the Levator ani & wet prostate weight assay described above. The above *in vivo* assays are recognized assays for determining the anabolic effects in muscle and sustaining effects in sex organs for a given compound, as described in L. G. Hershberger *et al., 83 Proc. Soc. Expt. Biol. Med.*, 175 (1953); B. L. Beyler *et al*, "Methods for evaluating anabolic and catabolic agents in laboratory animals", *23 J. Amer. Med. Women's Ass.*, 708 (1968); H. Fukuda *et al.*, "Investigations of the levator ani muscle as an anabolic steroid assay", *14 Nago Dai. Yak. Ken. Nem.* 84 (1966) the disclosures of which are herein incorporated by reference. The basis of this assay lies in the well-defined action of androgenic agents on the maintenance and growth of muscle tissues and sexual accessory organs in animals and man.

The male sexual accessory organs, such as the prostate and seminal vesicles, play an important role in reproductive function. These glands are stimulated to grow and are maintained in size and secretory function by the continued presence of serum testosterone (T), which is the major serum androgen (>95%) produced by the Leydig cells in the testis under the control of the pituitary luteinizing hormone (LH) and follicle stimulating hormone (FSH). Testosterone is converted to the more active form, dihydrotestosterone, (DHT), within the prostate by 5α-reductase. Adrenal androgens also contribute about 20% of total DHT in the rat prostate, compared to 40% of that in 65-year-old men. F. Labrie *et. al. 16 Clin. Invest. Med.*, 475-492 (1993). However, this is not a major pathway, since in both animals and humans, castration leads to almost complete involution of the prostate and seminal vesicles without concomitant adrenalectomy. Therefore, under normal conditions, the adrenals do not support significant growth of prostate tissues, M. C. Luke and D. S. Coffey, "The Physiology of Reproduction" ed. By E. Knobil and J. D. Neill, 1, 1435-1487 (1994). Since the male sex organs and the levator ani are the tissues most

126

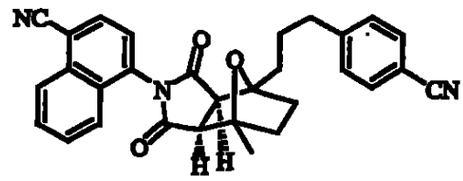
Cyanophenyl)-2-propenyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (248i & 248ii)



(4-cyanobenzyl)-triphenylphosphonium chloride (0.072 g, 0.174 mmol) was suspended in THF (2.0 mL) and cooled to 0°C. *n*-BuLi (1.6 M soln, 0.092 mL, 0.147 mmol) was then added dropwise resulting in a homogenous solution. The solution warmed to 25°C for 15 min and then cooled to 0°C. Compound **247** (0.050 g, 0.134 mmol) was then added in THF. After 1 h, the reaction was quenched with sat. aq. ammonium chloride and then extracted with methylene chloride (3 x 20 mL). The combined organics were dried over anhydrous sodium sulfate and then concentrated *in vacuo*. The crude material was purified by preparative TLC eluting with 5% acetone in chloroform to give 0.010 g of a mixture of compounds **248i** & **248ii** as a white solid. A 1:1 mixture of E and Z olefin isomers characterized by NMR spectroscopy. HPLC: 100% at 3.517 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 474.2 $[M+H]^+$.

Example 249

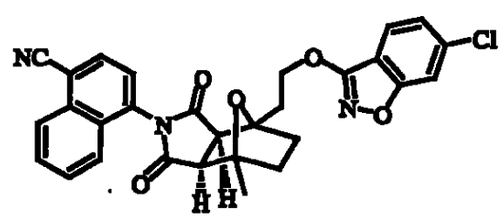
(3aα,4β,7β,7aα)-4-[4-[3-(4-Cyanophenyl)propyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, (249)



The mixture of compounds **248i** & **248ii** (0.008 g, 0.017 mmol) was dissolved in EtOH (3.0 mL) and Pd/C (10% Pd, 0.008 g) was added. H_2 was then introduced via a balloon. After 18 h, the reaction was filtered through Celite, eluting with EtOAc, followed by concentration *in vacuo*. Compound **249** was isolated as a white solid (0.007 g). HPLC: 90 at 3.520 min (retention time) (YMC S5 ODS column 4.6 x 50 mm, 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 476.13 $[M+H]^+$.

Example 250

(3aα,4β,7β,7aα)-4-[4-[2-[(6-Chloro-1,2-benzisoxazol-3-yl)oxy]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, (250)

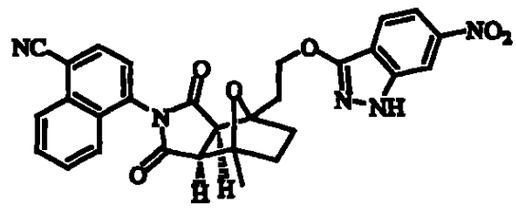


To a solution of PPh_3 (52 mg, 0.20 mmol) in 0.5 mL THF was added DBAD (46 mg, 0.20 mmol) as one solid portion. The resulting mixture was stirred for 10 min before 6-chloro-3-hydroxy-1,2-benzisoxazole (34 mg, 0.20 mmol) was added. Stirring was continued for 10 min before a solution of compound **223B** (50 mg, 0.13 mmol) in 0.5 mL THF was introduced via canula. The resulting mixture was stirred at ambient temperature for 24 h, concentrated *in vacuo* and purified by reverse phase preparative HPLC (YMC S5 ODS 20 x 100 mm column; eluting with 30-100% aqueous MeOH containing 0.1% TFA over 10 min at 20 mL/min) to yield a white solid. The obtained solids were dissolved in CH_2Cl_2, washed

with sat. $NaHCO_3$ solution, dried over Na_2SO_4 and concentrated *in vacuo* to yield 50 mg (71) of compound **250** as a colorless oil. HPLC: 3.89 min & 4.02 min (atropisomers, retention time) (YMC S5 ODS column 4.6 x 50 mm Ballistic, 10-90% aqueous methanol over 4 minutes containing 0.2 H_3PO_4, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 528.4 $[M+H]^+$.

Example 251

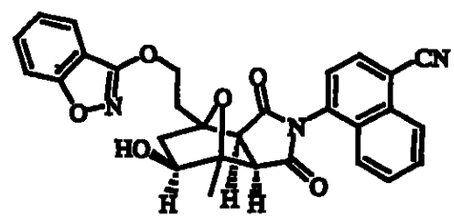
(3aα,4β,7β,7aα)-4-[Octahydro-4-methyl-7-[2-[(6-nitro-1H-indazol-3-yl)oxy]ethyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, (251)



To a solution of compound **223B** (50 mg, 0.13 mmol) in toluene (1 mL) was added ADDP (50 mg, 0.20 mmol), 6-nitro-3-indazolinone (36 mg, 0.20 mmol) and *n*-Bu_3P (50 μL, 0.2 mmol). The resulting mixture was heated at 80°C for 24 h, concentrated *in vacuo* and purified by a combination of reverse phase preparative HPLC (YMC S5 ODS 20 x 100 mm column; eluting with 30-100% aqueous MeOH containing 0.1% TFA over 10 min at 20 mL/min) and flash chromatography (silica gel, 25% acetone in $CHCl_3$) to give 17 mg (25%) of compound **251** as a yellow solid. HPLC: 3.60 min & 3.74 min (atropisomers, retention time) (YMC S5 ODS column 4.6 x 50 mm Ballistic, 10-90% aqueous methanol over 4 minutes containing 0.2% H_3PO_4, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 537.6 $[M+H]^+$.

Example 252

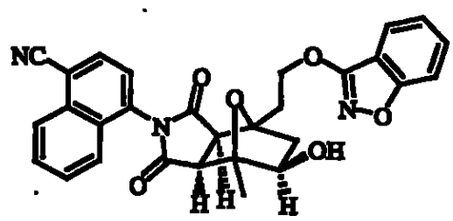
[3aS-(3aα,4β,5β,7β,7aα)]-4-[7-[2-(1,2-Benzisoxazol-3-yloxy)ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, (252)



PPh_3 (47 mg, 0.18 mmol), DBAD (41 mg, 0.18 mmol), 3-hydroxy-1,2-benzisoxazole (24 mg, 0.18 mmol) and compound 243DI (35 mg, 0.09 mmol) were reacted according to the procedure given for compound 250. Purification was achieved by reverse phase HPLC (YMC S5 ODS 20 x 100 mm column; eluting with 30-100% aqueous MeOH containing 0.1% TFA over 10 min at 20 mL/min) to yield a white solid. The obtained solids were dissolved in CH_2Cl_2, washed with sat. $NaHCO_3$ solution, dried over Na_2SO_4 and concentrated under reduced pressure to furnish 29 mg (64%) of compound 252 as a colorless oil. HPLC: 96% at 3.29 min (atropisomers, retention time) (YMC S5 ODS column 4.6 x 50 mm Ballistic, 0-100% aqueous methanol over 4 minutes containing 0.2% H_3PO_4, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 510.2 $[M+H]^+$.

Example 253

[3a*R*-(3aα,4β,5β,7β,7aα)]-4-[7-[2-(1,2-Benzisoxazol-3-yloxy)ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, (253)

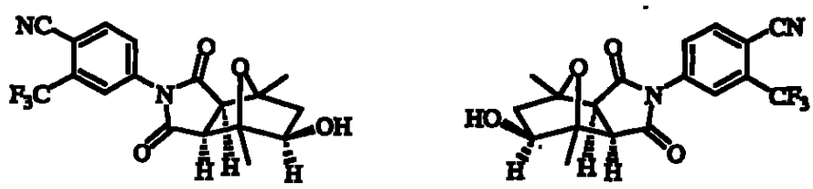


PPh_3 (47 mg, 0.18 mmol), DBAD (41 mg, 0.18 mmol), 3-hydroxy-1,2-benzisoxazole (24 mg, 0.18 mmol) and compound 243DII (35 mg, 0.09 mmol) were reacted according to the procedure given for compound 250. Purification was achieved by reverse phase HPLC (YMC S5 ODS 20 x 100 mm column; eluting with 30-100% aqueous MeOH containing 0.1% TFA

over 10 min at 20 mL/min) to yield a white solid. The obtained solids were dissolved in CH_2Cl_2, washed with sat. $NaHCO_3$ solution, dried over Na_2SO_4 and concentrated under reduced pressure to furnish 23 mg (51) of compound **253** as a colorless oil. HPLC: 95% at 3.29 min (atropisomers, retention time) (YMC S5 ODS column 4.6 x 50 mm Ballistic, 0-100% aqueous methanol over 4 minutes containing 0.2% H_3PO_4, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 510.4 $[M+H]^+$.

Example 254

[3aR-(3aα,4β,5β,7β,7aα)]-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile & [3aS-(3aα,4β,5β,7β,7aα)]-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile, (254i & 254ii)

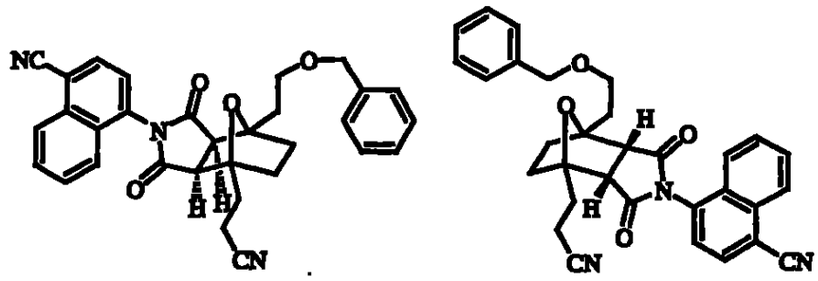


Racemic compound **221B** was separated into its enantiomers by normal phase preparative chiral HPLC (CHIRALPAK AD 5 x 50 cm column; eluting with 20% MeOH/EtOH (1:1) in heptane (isocratic) at 50 mL/min) to give the faster eluting compound **254i** (Chiral HPLC: 10.02 min; CHIRALPAK AD 4.6 x 250 mm column; eluting with 20% MeOH/EtOH (1:1) in heptane at 1 mL/min) and the slower eluting **254ii** (Chiral HPLC: 14.74 min; CHIRALPAK AD 4.6 x 250 mm column; eluting with 20% MeOH/EtOH (1:1) in heptane at 1 mL/min). (Names of title compounds based on absolute stereochemistry determination).

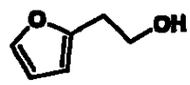
Example 255

(3aα,4β,7β,7aα)-2-(4-Cyano-1-naphthalenyl)octahydro-1,3-dioxo-7-[2-(phenylmethoxy)ethyl]-4,7-epoxy-4H-isoindole-4-propanenitrile

& (8aα,4α,7α,7aα)-2-(4-Cyano-1-naphthalenyl)octahydro-1,3-dioxo-7-[2-(phenylmethoxy)ethyl]-4,7-epoxy-4H-isoindole-4-propanenitrile, (255Hi & 255Hii)

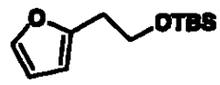


A. 2-(2-Hydroxyethyl)furan (255A)



2-(2-Hydroxyethyl)furan was made in accordance with the following reference: Harmata, M, et al. *J. Org. Chem.* 60, 5077-5092 (1995). *n*-BuLi (2.5 M in hexane, 44 mL, 110 mmol) was added to a solution of furan (8 mL, 110 mmol) in 100 mL of THF at –78°C. The solution was stirred at 0°C for 4 h and then ethylene oxide (7.5 mL) was added at –78°C. The reaction mixture was stirred at –15°C for 1 h and then overnight at rt. The reaction was quenched with sat. NH_4Cl and extracted with ether (3X). The combined extracts were washed with water (1X) and brine (1X). The ether solution was dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with 40% EtOAc/60% hexane gave 5.4 g (48.2 mmol, 43.8%) of compound 255A as a light brown oil.

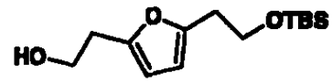
B. 2-[2-[[(1,1-Dimethlethyl)dimethylsilyl]oxy]ethyl]furan (255B)



Imidazole (3.65 g, 53.6 mmol) and TBSCl (6.47 g, 42.9 mmol) were added to the solution of compound 255A (4.00 g, 35.7 mmol) in 50 mL of DMF. The mixture was stirred at rt for 2 h and then the reaction mixture was poured into ether. The ether solution was washed with water (1X), 1 N HCl (1X), water (1X) and brine (1X). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure.

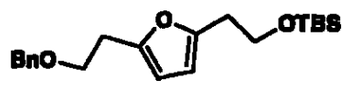
Purification by flash chromatography on silica gel eluting with 30% CH_2Cl_2/70% hexane gave 7.4 g (32.7 mmol, 91.7%) of 255B as a colorless oil.

C. 2-[2-[[(1,1-Dimethlethyl)dimethylsilyl]oxy]ethyl]-5-(2-hydroxyethyl)furan (255C)



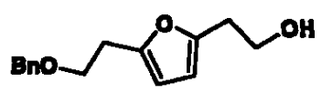
t-BuLi (1.2 M in pentane, 10 mL, 16.99 mmol) was added to a stirred solution of 255B (3.49 g, 15.44 mmol) in 13 mL of THF at –78°C dropwise. The mixture was stirred for an additional 4 h at 0°C. Ethylene oxide (1.05 mL) was added at –78°C to the reaction solution. The mixture was warmed to rt and stirred overnight. Aqueous sat. NH_4Cl was added and most of the THF was removed under reduced pressure. The mixture was extracted with ether (3X) and the combined organic layers were washed with water (1X) and brine (1X) and dried over Na_2SO_4. Purification by flash chromatography on silica gel eluting with 5% EtOAc/95% CH_2Cl_2 gave 2.8 g (10.4 mmol, 67%) of compound 255C as a yellow oil.

D. 2-[2-[[(1,1-Dimethlethyl)dimethylsilyl]oxy]ethyl]-5-[2-(phenylmethoxy)ethyl]furan (255D)



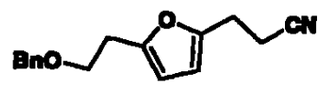
The alcohol 255C (1.00 g, 3.7 mmol) in 12 mL of THF was treated with 60% NaH (177.8 mg, 4.44 mmol), benzyl bromide (0.53 mL, 4.44 mmol) and tetrabutylammonium iodide (50 mg, 5%) for 3 h at rt. Water was added and the mixture was extracted with EtOAc (3X). The combined extracts were washed with water (1X) and brine (1X) and dried over Na_2SO_4. Purification by flash chromatography on silica gel eluting with 20% hexane/80% CH_2Cl_2 gave 1.10 g (3.05 mmol, 82.6%) of compound 255D as a yellow oil.

E. 2-(2-Hydroxyethyl)-5-[2-(phenylmethoxy)ethyl]furan (255E)



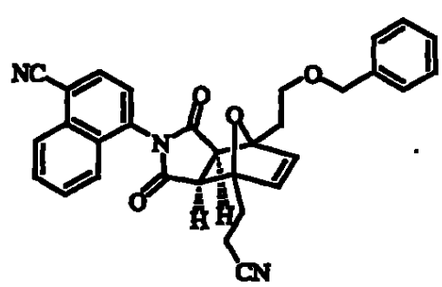
Tetrabutylammonium fluoride (1.0M in THF, 3.06 mL, 3.06 mmol) was added to the solution of compound **255D** (1.1 g, 3.06 mmol) in 10 mL of THF at 0°C. The reaction mixture was stirred at rt for 10 minutes, quenched by sat. NH_4Cl and extracted with ether (3X). The combined extracts were dried over Na_2SO_4. Purification by flash chromatography on silica gel eluting with 10% EtOAc/90% CH_2Cl_2 gave 750 mg (3.05 mmol, 99.6%) of compound **255E** as a light yellow oil.

F. 5-[2-(Phenylmethoxy)ethyl]furan-2-propanenitrile (255F)



DEAD (1.285 mL, 8.17 mmol) was added to a stirred solution of Ph_3P (2.14 g, 8.17 mmol) in 12 mL of dry THF at 0°C. The solution was stirred for 30 min at rt and compound **255E** (670 mg, 2.72 mmol) was added. The reaction was stirred for 15 min and acetone cyanohydrin (0.745 mL, 8.17 mmol) was added at –15°C. The reaction was stirred for 30 min at –15°C, then at rt overnight. The mixture was then concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with 100% CH_2Cl_2 gave 180 mg (0.705 mmol, 26%) of compound **255F** as a colorless oil.

G. (3aα,4β,7β,7aα)-2-(4-Cyano-1-naphthalenyl)-1,2,3,3a,7,7a-hexahydro-1,3-dioxo-7-[2-(phenylmethoxy)ethyl]-4,7-epoxy-4H-isoindole-4-propanenitrile (255G)



A solution of compound **255F** (180 mg, 0.706 mmol) and 4-(2,5-dihydro-2,5-dioxo-1H-1-yl)-1-naphthalenecarbonitrile (268 mg, 1.06 mmol) in CH_2Cl_2 (3 mL) was stirred at rt for 3 days. The reaction mixture was concentrated under reduced pressure. Purification by flash

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chromatography on silica gel eluting with 5% EtOAc/CH_2Cl_2 gave 318 mg (0.63 mmol, 89.6) of compound **255G** as a light gray solid which was used directly in the next step.

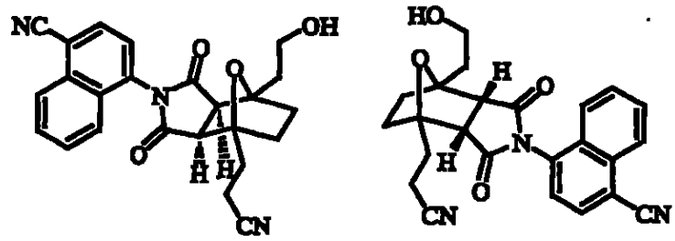
H. (3aα,4β,7β,7aα)-2-(4-Cyano-1-naphthalenyl)octahydro-1,3-dioxo-7-[2-(phenylmethoxy)ethyl]-4,7-epoxy-4H-isoindole-4-propanenitrile & (3aα,4α,7α,7aα)-2-(4-Cyano-1-naphthalenyl)octahydro-1,3-dioxo-7-[2-(phenylmethoxy)ethyl]-4,7-epoxy-4H-isoindole-4-propanenitrile (255Hi & 255Hii)

A mixture of compound **255G** (318 mg, 0.63 mmol) and 10% Pd/C (64 mg) in EtOH (10 mL) and EtOAc (5 mL) was stirred under a hydrogen atmosphere at rt overnight. The reaction mixture was filtered through Celite and concentrated under reduced pressure to give 320 mg of crude compounds **255Hi** & **255Hii**. Purification of 25 mg of this crude product by flash chromatography on silica gel eluting with 55% EtOAc/hexane gave 6.5 mg (0.013 mmol, 26% (based on 25 mg)) of compound **255Hi** & 8.1 mg (0.016 mmol, 32.4% (based on 25 mg)) of compound **255Hii**. Compound **255Hi**: HPLC conditions: 98% at 3.57 min (retention time) (YMC S5 ODS 4.6 x 50 mm, 10%-90% aqueous methanol over 4 minute gradient with 0.2% H_3PO_4, detecting at 220 nm, MS (ES): m/z 506.15 $[M+H]^+$. Compound **255Hii**: HPLC conditions: 98% at 3.51 min (retention time) (YMC S5 ODS 4.6 x 50 mm, 10%-90% aqueous methanol over 4 minute gradient with 0.2% H_3PO_4, detecting at 220 nm). MS (ES): m/z 506.15 $[M+H]^+$.

Example 256

(3aα,4β,7β,7aα)-2-(4-Cyano-1-naphthalenyl)octahydro-7-(2-hydroxyethyl)-1,3-dioxo-4,7-epoxy-4H-isoindole-4-propanenitrile &

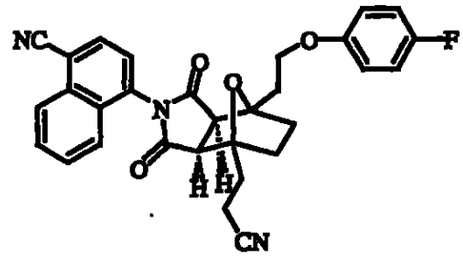
(3aα,4α,7α,7aα)-2-(4-Cyano-1-naphthalenyl)octahydro-7-(2-hydroxyethyl)-1,3-dioxo-4,7-epoxy-4H-isoindole-4-propanenitrile, (256i & 256ii)



A mixture of compounds 255Hi & 255Hii (200 mg, 0.396 mmol) and $PdCl_2$ (8.4 mg, cat.) in EtOH (1 mL) and EtOAc (3 mL) was stirred under a hydrogen atmosphere (30 psi) at rt overnight. The reaction mixture was filtered through Celite and concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with 5 MeOH/CH_2Cl_2 followed by a second column eluting with 100% EtOAc gave 28.9 mg (0.0696 mmol, 17.6%) of compound 256ii and 26.5 mg (0.0639 mmol, 16.1%) of compound 256i. Compound 256ii: HPLC conditions: 90 at 2.44 min (retention time) (YMC S5 ODS 4.6 x 50 mm, 10%-90 aqueous methanol over 4 minute gradient with 0.2% H_3PO_4, detecting at 220 nm.). MS (ES): m/z 416.11 $[M+H]^+$. Compound 256i: HPLC conditions: 99% at 2.47 min (retention time) (YMC S5 ODS 4.6 x 50 mm, 10%-90% aqueous methanol over 4 minute gradient with 0.2% H_3PO_4, detecting at 220 nm). MS (ES): m/z 416.11 $[M+H]^+$.

Example 257

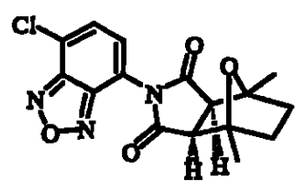
(3aα,4β,7β,7aα)-2-(4-Cyano-1-naphthalenyl)-7-[2-(4-fluorophenoxy)ethyl]octahydro-1,3-dioxo-4,7-epoxy-4H-isoindole-4-propanenitrile, (257)



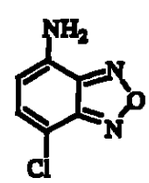
DBAD (15 mg, 0.065 mmol) was added to a solution of PPh_3 (17 mg, 0.065 mmol) in THF (0.3 mL). After stirring for 10 min, 4-fluorophenol (7.33 mg, 0.065 mmol) was added and the reaction mixture was stirred for a further 5 min. Compound 256l (18.1 mg, 0.044 mmol) was added and the mixture was stirred at rt for 3 h. The reaction was concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with 60% EtOAc/30% hexane gave 5.9 mg (0.0116 mmol, 26.34%) of compound 257. HPLC conditions: 98% at 3.59 min (retention time) (YMC S5 ODS 4.6 x 50 mm, 10%-90% aqueous methanol over 4 minute gradient with 0.2% H_3PO_4, detecting at 220 nm). MS (ES): m/z 510.14 $[M+H]^+$.

Example 258

(3aα,4β,7β,7aα)-2-(7-Chloro-2,1,3-benzoxadiazol-4-yl)hexahydro-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione. (258)



A. 4-Amino-7-chloro-2,1,3-benzoxadiazole (258A)



A solution of 1.0 g (5.02 mmol) of 4-chloro-7-nitrobenzofurazan in 20 mL AcOH, 10 mL EtOAc and 2 mL H_2O was heated at 50°C and treated with iron powder (1.4 g, 251 mmol). The mixture was heated at 80°C for

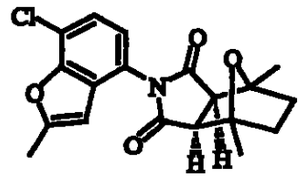
30 min and then allowed to cool to rt. The mixture was filtered through Celite eluting with EtOAc. The filtrate was washed with sat. aq. $NaHCO_3$, dried over $MgSO_4$, and concentrated under reduced pressure to give compound **258A** (0.80 g, 94%) as a red solid.

B. (3aα,4β,7β,7aα)-2-(7-Chloro-2,1,3-benzoxadiazol-4-yl)hexahydro-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione, (258B)

Compound **258A** (42 mg, 0.25 mmol) was reacted in a sealed tube with compound **20A** (73.5 mg, 0.375 mmol), $MgSO_4$ (75 mg, 0.625 mmol) and Et_3N (170 μL, 1.25 mmol) in 250 μL toluene according to the above procedure described in example **208C** to give after purification by reverse phase preparative HPLC (YMC S5 ODS 20 x 100 mm eluting with 30-100% aqueous methanol containing 0.1% TFA over 12 min, 20 mL/min) 23 mg (26%) of compound **258B** as a yellow solid. HPLC: 97.6% at 2.87 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol containing 0.2% phosphoric acid over 4 minutes , 4 mL/min, monitoring at 220 nm). MS (DCI): m/z 347.9 $[M]^+$.

Example 259

(3aα,4β,7β,7aα)-2-(7-Chloro-2-methyl-4-benzofuranyl)hexahydro-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione, (259)

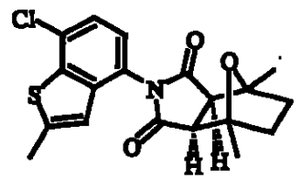


7-Chloro-2-methyl-4-benzofuranamine (38 mg, 0.25 mmol, prepared in accordance with the procedure described by Enomoto and Takemura in EP 0476697 A1) was reacted in a sealed tube with compound **20A** (73.5 mg, 0.375 mmol), $MgSO_4$ (75 mg, 0.625 mmol) and Et_3N (170 μL, 1.25 mmol) in 250 μL toluene according to the procedure described in example

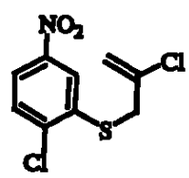
208C to give, after purification by reverse phase preparative HPLC (YMC S5 ODS 20 x 100 mm eluting with 30-100 aqueous methanol containing 0.1% TFA over 12 min, 20 mL/min), 42 mg (47%) of compound **259** as a white solid. HPLC: 98% at 3.45 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (DCI): m/z 359.9 $[M]^+$.

Example 260

(3aα,4β,7β,7aα)-2-(7-Chloro-2-methylbenzo[b]thiophen-4-yl)hexahydro-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione, (260)

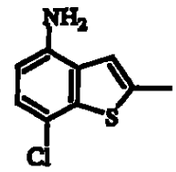


A. 1-Chloro-2-(2-chloro-allylsulfanyl)-4-nitro-benzene (260A)



A solution of 2-chloro-5-nitro-benzenethiol (1.0 g, 5.27 mmol, prepared in accordance with the procedure described by Still et al. *Synth. Comm.* 13, 1181 (1983)) in 15 mL DMF was treated with 2,3-dichloropropene (693 μL, 7.52 mmol) and K_2CO_3 (433 mg, 3.13 mmol). The mixture was heated at 80°C for 2 h and then allowed to cool to rt. EtOAc (200 mL) and H_2O (100 mL) were added. The organic phase was washed with H_2O (2 x 250 mL), saturated aqueous NaCl (100 mL), dried over $MgSO_4$, and concentrated *in vacuo*. The crude material was purified by flash column chromatography on silica gel eluting with 20% EtOAc in hexanes to give compound **260A** (1.09 g, 89%) as an orange oil.

B. 4-Amino-7-chloro-2-methylbenzo[b]thiophene (260B)



A solution of 1.09 g (4.67 mmol) of compound **260A** in 20 mL AcOH with 10 mL EtOAc and 2 mL H_2O was heated to 80°C and treated with iron powder (1.3 g, 23.4 mmol). The mixture was heated at 80°C for 40 min and then allowed to cool to rt. The mixture was filtered through Celite eluting with EtOAc. The filtrate was washed with sat. aq. $NaHCO_3$, dried over $MgSO_4$, and concentrated *in vacuo*. *N,N*-diethylaniline (10 mL) was added, and the reaction was heated at 215°C for 6 h. After cooling to rt, 1 N aqueous HCl (20 mL) was added, and the reaction was stirred at room temperature for 2 h. The mixture was extracted with EtOAc (3 x 30 mL). The organic phase was washed with saturated aqueous $NaHCO_3$, dried over $MgSO_4$, and concentrated *in vacuo*. The crude material was purified by flash column chromatography on silica gel eluting with 25% EtOAc in hexanes to give compound **260B** (320 mg, 35%) as a beige solid.

C. (3aα,4β,7β,7aα)-2-(7-Chloro-2-methylbenzo[b]thiophen-4-yl)hexahydro-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione, (260C)

Compound **260B** (49 mg, 0.25 mmol) was reacted in a sealed tube with compound **20A** (73.5 mg, 0.38 mmol), $MgSO_4$ (75 mg, 0.63 mmol) and Et_3N (170 μL, 1.25 mmol) in 250 μL toluene according to the procedure described in example **208C** to give, after purification by reverse phase preparative HPLC (YMC S5 ODS 20 x 100 mm eluting with 30-100% aqueous methanol over 12 min containing 0.1% TFA, 20 mL/min), 28 mg

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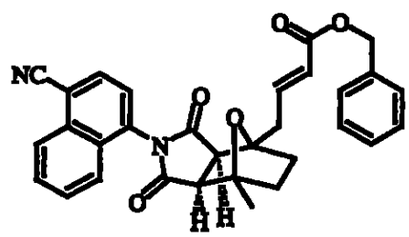
(30%) of compound 260C as a pale yellow solid. HPLC: 96 at 3.18 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90 aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (DCI): m/z 376.0 $[M]^+$.

Example 261

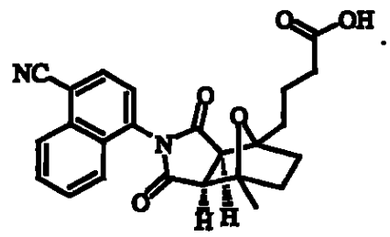
[3aα,4β(E),7β,7aα]-4-[2-(4-Cyano-1-naphthalenyl)octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindol-4-yl]-2-butenoic acid, phenylmethyl ester, (261)



Compound 247 (0.500 g, 1.34 mmol) was dissolved in THF (20 mL) and benzyl(triphenylphosphoranylidene) (0.55 g, 1.34 mmol) was added. The reaction mixture was stirred at 67°C for 2 h and then concentrated under reduced pressure. Purification by flash chromatography on SiO_2 eluting with 5% acetone/95% $CHCl_3$ gave 0.65 g of compound 261 as a yellow solid. HPLC: 99% at 3.717 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 507.1 $[M+H]^+$.

Example 262

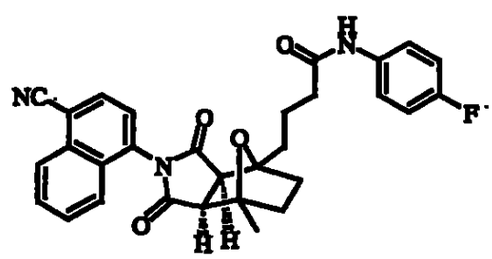
(3aα,4β,7β,7aα)-2-(4-Cyano-1-naphthalenyl)octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindole-4-butanoic acid, (262)



Compound **261** (0.60 g, 1.19 mmol) was dissolved in EtOH/EtOAc (5mL/5mL) and 10% Pd/C (0.30 g) was added. Hydrogen was then introduced via a balloon. After 8 h the reaction was filtered through Celite and then concentrated under reduced pressure to give compound **262** (0.47 g) as a white solid. HPLC: 98% at 2.81 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 419.1 $[M+H]^+$.

Example 263

(3aα,4β,7β,7aα)-2-(4-Cyano-1-naphthalenyl)-*N*-(4-fluorophenyl)octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindole-4-butanamide (263)



Compound **262** (0.030 g, 0.072 mmol) was dissolved in CH_3CN (1 mL). DCC (0.014 g, 0.072 mmol) and HOAc (0.0098 g, 0.072 mmol) were then added, followed by 4-flouroaniline (0.007 mL, 0.072 mmol). The reaction mixture was stirred under argon for 14 h and the crude material was dissolved in MeOH, purified by reverse phase preparative HPLC (YMC VP-ODS column, 20 x 100 mm, eluting with 20% B to 100% B in 15 minutes and hold @ 100%B for 10 minutes). Compound **263** (0.020 g) was isolated as white solid. HPLC: 100% at 3.217 min (retention time) (YMC

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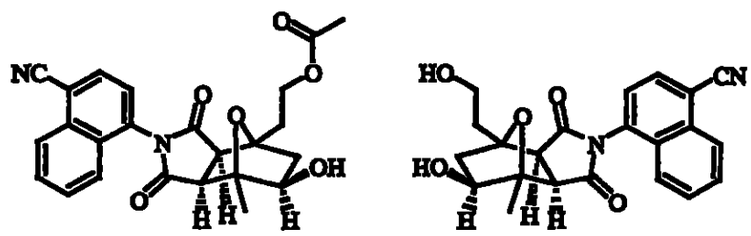
S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 512.1 $[M+H]^+$.

Example 264

[3aS-(3aα,4β,5β,7β,7aα)]-4-[7-[2-(Acetyloxy)ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile & [3aR-(3aα,4β,5β,7β,7aα)]-4-[Octahydro-5-hydroxy-7-(2-hydroxyethyl)-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, (264 & 243Dii)



A racemic mixture of compounds **243Di & 243Dii** (1.90 gram) were dissolved in 100 mL of anhydrous THF in a 2 L flask. Anhydrous *tert*-butyl-methyl ether (900 mL) and vinyl acetate (40 mL) were transferred into the flask with stirring and lipase (20 g, typeII, crude, from porcine pancreas; Sigma, Cat# L3126) was added. The reaction mixture was stirred for 21 hr at rt at which point an additional 5 grams of the lipase and 20 mL of vinyl acetate were added. The reaction was stirred at rt for an additional 19 h, stored at 4°C without stirring for 36 h and then stirred at rt for another 22 h (until the desired % ee was apparent by chiral HPLC). To monitor the reaction, 200 uL of the mixture was withdrawn and centrifuged. The supernatant (100 uL) was dried under nitrogen and the resulting residue was dissolved in 100 uL of EtOH and subjected to HPLC analysis:

1) Reverse phase HPLC: Column, YMC-ODS AQ 150x4.6; flow rate, 1.2 mL/min; sample size, 10 uL

solvent A,: 1 mM HCl in water; solvent B, MeCN; monitored at 300 nm

Gradient:

Time(min)	0	8	8.5	9.5	10	12
B%	30	60	85	85	30	30

2) Chiral-HPLC: Column, CHIRALCEL OJ 4.6 x 250 mm
mobile phase, hexanes/MeOH/EtOH (8:1:1)
flow rate, 1 mL/min; sample size, 20 uL
monitored at both 220 and 300 nm
performed at 25°C & 40°C.
(for ee% determination of reaction mixture)

The enzyme was removed by filtration and filtrate was concentrated under reduced pressure. The resulting mixture was dissolved in $CHCl_3$ and adsorbed onto silica gel (63-200 microns). These solids were applied to a VLC funnel (3 cm I.D., VLC is vacuum liquid chromatography using glass funnels having 24/40 joints at the bottom) containing a 5 cm bed height of silica gel (25-40 microns) and a step gradient was carried out. The gradient was 100% $CHCl_3$ in the first 3 fractions, followed by $CHCl_3$-1% MeOH (3 fractions), $CHCl_3$-2% MeOH (3 fractions), $CHCl_3$-3% MeOH (3 fractions), $CHCl_3$-4% MeOH (3 fractions), and finally with $CHCl_3$-5% MeOH (3 fractions). The volume of the fractions was 100 mL until reaching $CHCl_3$-3% MeOH and from that point on it was 200 mL. Compound **264** elutes in the last two fractions of 100% $CHCl_3$ and until the first fraction of $CHCl_3$-2% MeOH. Compound **243Dii** elutes starting with the second fraction of $CHCl_3$-2% MeOH, and continues to the first fraction of $CHCl_3$-5% MeOH. The crude compound **243Dii** contained a small amount of a colored impurity which was removed by a Sephadex column [LH-20 swollen in $CHCl_3$-MeOH (2:1), column (2.5 cm I.D. & 90 cm long) to yield 632 mg of compound **243Dii**. Compound **264**: HPLC conditions: 98% at 7.2 min (retention time)

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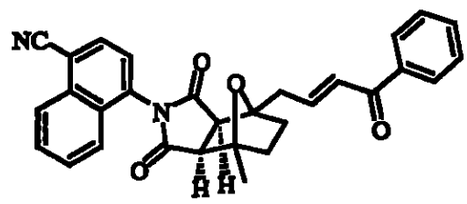
(method 1), chiral HPLC conditions: 29.0 min 25°C (method 2). Compound **243Dii**: HPLC conditions: 98% at 4.6 min (retention time) (method 1), chiral HPLC conditions: 96% ee at 25.7 min (retention time) (@ 25°C) & 19.8 min (retention time) (@ 40°C) (method 2).

Example 265

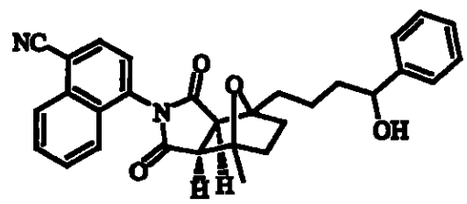
(3aα,4β,7β,7aα(E))-4-[Octahydro-4-methyl-1,3-dioxo-7-(4-oxo-4-phenyl-2-butenyl)-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, (265)



The compound **247** (0.050 g, 0.134 mmol) was dissolved in THF (1.5 mL) and (phenacylidene)triphenylphosphorane (0.051 g, 0.134 mmol) was added. The reaction mixture was stirred at 67°C for 24 h and then cooled to 23°C and concentrated *in vacuo*. The crude material was then purified by reverse phase preparative HPLC. (YMC VP-ODS column, 20 x 100 mm, eluting with 20% B to 100%B in 15 minutes and hold @ 100%B for 10 minutes.) to give compound **265** (0.040 g) as white solid. HPLC: 100% at 3.503 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 477.1 $[M+H]^+$.

Example 266

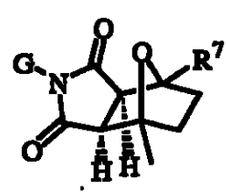
(3aα,4β,7β,7aα(E))-4-[Octahydro-4-methyl-1,3-dioxo-7-(4-hydroxy-4-phenyl-2-butyl)-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, (266)



Compound **265** (0.010 g, 0.021 mmol) was dissolved in EtOH (2.0 mL) and Pd/C (10% Pd, 0.005 g) was added. Hydrogen was then introduced via a balloon and the reaction was stirred at 25°C for 3 h. The reaction was then filtered through Celite rinsing with EtOAc and concentrated *in vacuo* to give compound **266** as a tan solid (0.009 g). No purification was necessary. HPLC: 100% at 3.38 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 503.2 $[M+Na]^+$. (Where this reaction was run for 1 hour, the resulting product was compound **455**.)

Examples 267 to 378

Additional compounds of the present invention were prepared by procedures analogous to those described above. The compounds of Examples 267 to 378 have the following structure (L is a bond):



where G, R^7, the compound name, retention time, molecular mass, and the procedure employed, are set forth in **Table 5**. The absolute

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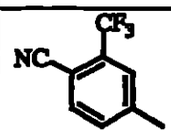
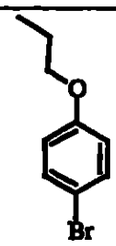
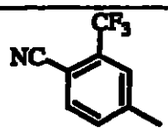
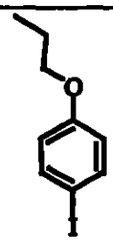
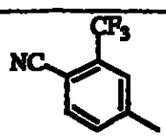
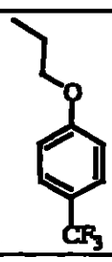
configuration for the following compounds was not determined. For simplicity in nomenclature, compound **238i** is designated herein as having an "R" configuration and compound **238ii** as having an "S" configuration. Enantiomerically pure products derived from compound **238i** are designated herein as having an "R" configuration and enantiomerically pure products derived from compound **238ii** are designated herein as having an "S" configuration.

The chromatography techniques used to determine the compound retention times of Table 5 are as follows: LCMS = YMC S5 ODS column, 4.6 X 50 mm eluting with 10-90% MeOH/H_2O over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm. LCMS* = YMC S5 ODS column, 4.6 X 50 mm eluting with 10-90% MeOH/H_2O over 2 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm. LC = YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% MeOH/H_2O over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm. The molecular mass of the compounds listed in Table 5 were determined by MS (ES) by the formula m/z.

Table 5.

Ex. No	G	R^7	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
267			(3aα,4β,7β,7aα)-(4-[7-[2-(4-Bromophenoxy)ethyl]octahydro-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile..	3.97 LCMS 549.0 $[M+H]^+$	204, 35
268			(3aα,4β,7β,7aα)-4-[Octahydro-7-[2-(4-iodophenoxy)ethyl]-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile.	4.09 LCMS 597.0 $[M+H]^+$	204, 35
269			(3aα,4β,7β,7aα)-4-[Octahydro-4-methyl-1,3-dioxo-7-[2-[4-	3.95 LC	204, 35

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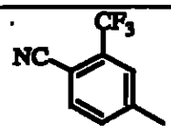
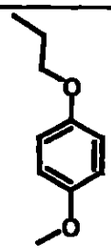
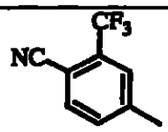
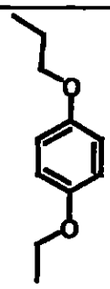
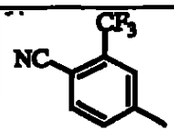
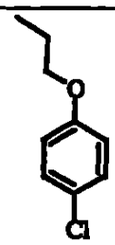
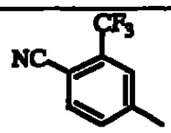
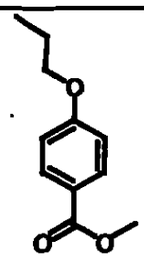
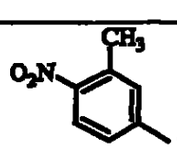
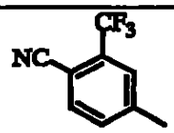
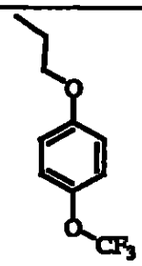
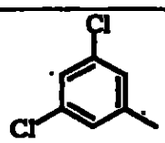
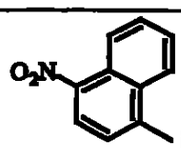
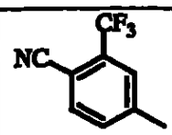
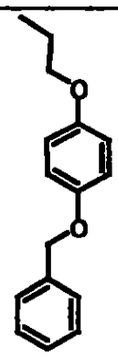
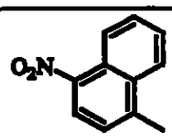
Ex. No	G	R^7	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
			(trifluoromethyl)phenoxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile.		
270			(3aα,4β,7β,7aα)-4-[Octahydro-7-[2-(4-methoxyphenoxy)ethyl]-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile.	3.66 LC	204, 35
271			(3aα,4β,7β,7aα)-4-[7-[2-(4-Ethoxyphenoxy)ethyl]octahydro-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-	3.81 LC	204, 35

Ex. No	G	R^7	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
			(trifluoromethyl)benzonitrile.		
272			(3aα,4β,7β,7aα)-4-[7-[2-(4-Chlorophenoxy)ethyl]octahydro-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile.	3.97 LCMS 522.2 $[M+H]^+$	204, 35
273			(3aα,4β,7β,7aα)-4-[2-[2-[4-Cyano-3-(trifluoromethyl)phenyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindol-4-yl]ethoxy]benzoic acid, methyl ester.	3.77 LCMS 529.12 $[M+H]^+$	204, 35
274			(3aα,4β,7β,7aα)-Hexahydro-4-(2-hydroxyethyl)	2.44 LC	204, 35

Ex. No	G	R'	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
			-7-methyl-2-(3-methyl-4-nitrophenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione.		
275			(3aα,4β,7β,7aα)-4-[Octahydro-4-methyl-1,3-dioxo-7-[2-[4-(trifluoromethoxy)phenoxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile.	3.97 LC	204, 35
276		CH_3	(3aα,4β,7β,7aα)-2-(3,5-Dichlorophenyl)hexahydro-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione.	3.31 LCMS 341.2 $[M+H]^+$	20
277		CH_3	(3aα,4β,7β,7aα)-Hexahydro-4,7-dimethyl-2-(4-nitro-1-	3.04 LCMS	20

Ex. No	G	R^7	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
			naphthalenyl) -4,7-epoxy- 1H-isoindole- 1,3(2H)-dione.		
278			(3aα,4β,7β,7a α)-4- [Octahydro-4- methyl-1,3- dioxo-7-[2-[4- (phenylmetho xy)phenoxy]et hyl]-4,7- epoxy-2H- isoindol-2-yl]- 2- (trifluorometh yl)benzonitril e.	4.06 LC	204, 35
279			(3aα,4β,7β,7a α)- Hexahydro-4- (2- hydroxyethyl) -7-methyl-2- (4-nitro-1- naphthalenyl) -4,7-epoxy- 1H-isoindole- 1,3(2H)-dione.	2.607 & 2.743 rotational isomers LC	204, 35

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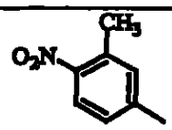
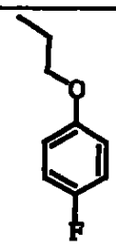
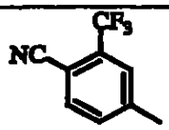
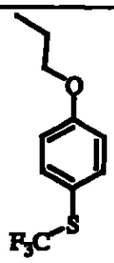
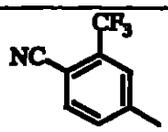
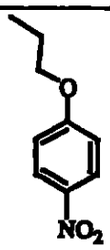
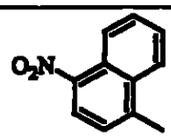
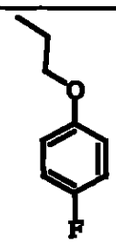
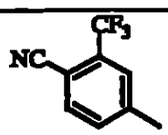
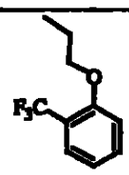
Ex. No	G	R^7	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
280			(3aα,4β,7β,7aα)-4-[2-(4-Fluorophenoxy)ethyl]hexahydro-7-methyl-2-(3-methyl-4-nitrophenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione.	3.68 LC	204, 35
281			(3aα,4β,7β,7aα)-4-[Octahydro-4-methyl-1,3-dioxo-7-[2-[4-[(trifluoromethyl)thio]phenoxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile.	4.11 LC	204, 35
282			(3aα,4β,7β,7aα)-4-[Octahydro-4-methyl-7-[2-(4-nitrophenoxy)ethyl]-1,3-dioxo-4,7-	3.68 LC	204, 35

Ex. No	G	R^7	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
			epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile.		
283			(3aα,4β,7β,7aα)-4-[2-(4-Fluorophenoxy)ethyl]hexahydro-7-methyl-2-(4-nitro-1-naphthalenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione.	3.68 & 3.80 rotational isomers LC	204, 35
284			(3aα,4β,7β,7aα)-4-[Octahydro-7-methyl-1,3-dioxo-7-[2-[2-(trifluoromethyl)phenoxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile.	3.89 LC	204, 35

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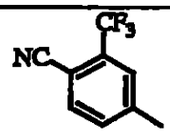
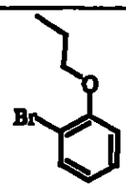
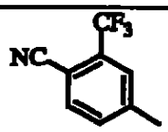
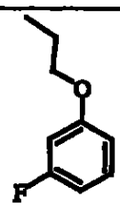
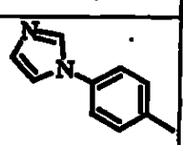
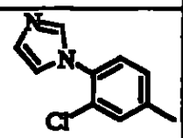
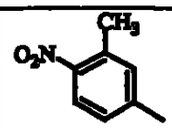
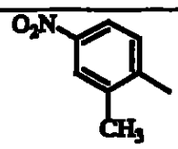
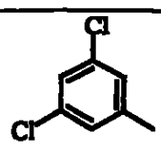
Ex. No	G	R^7	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
285			(3aα,4β,7β,7aα)-4-[4-[2-(2-Bromophenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile.	3.91 LC	204, 35
286			(3aα,4β,7β,7aα)-4-[4-[2-(3-Fluorophenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile.	3.78 LC	204, 35
287		H	(3aα,4β,7β,7aα)-Hexahydro-2-[4-(1H-imidazol-1-yl)phenyl]-4-methyl-4,7-epoxy-1H-isoindole-	1.16 LC	3

Ex. No	G	R'	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
			1,3(2H)-dione.		
288		H	(3aα,4β,7β,7aα)-2-[3-Chloro-4-(2-thiazolyl)phenyl]hexahydro-4-methyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione.	2.81 LC	3
289		CH_3	(3aα,4β,7β,7aα)-Hexahydro-4,7-dimethyl-2-(3-methyl-4-nitrophenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione.	2.74 LC	20
290		CH_3	(3aα,4β,7β,7aα)-Hexahydro-4,7-dimethyl-2-(2-methyl-4-nitrophenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione.	2.71 LC	20
291			(3aα,4β,7β,7aα)-2-(3,5-Dichlorophenyl)hexahydro-4-(2-	2.98 LC	204

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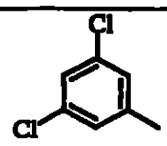
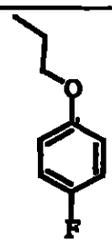
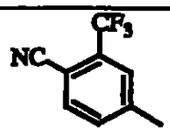
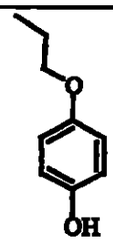
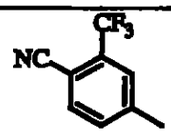
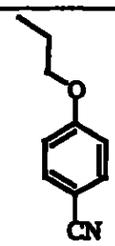
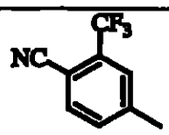
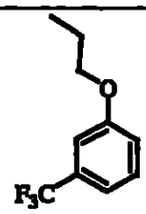
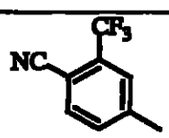
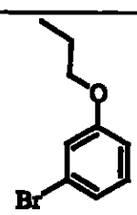
Ex. No	G	R^7	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
			hydroxyethyl)-7-methyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione.		
292			(3aα,4β,7β,7aα)-2-(3,5-Dichlorophenyl)-4-[2-(4-fluorophenoxy)ethyl]hexahydro-7-methyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione.	4.03 LC	204, 35
293			(3aα,4β,7β,7aα)-4-[Octahydro-4-[2-(4-hydroxyphenoxy)ethyl]-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile.	3.25 LC	204, 35

Ex. No	G	R^7	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
294			(3aα,4β,7β,7aα)-4-[4-[2-(4-Cyanophenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile.	3.51 LC	204, 35
295			(3aα,4β,7β,7aα)-4-[Octahydro-4-methyl-1,3-dioxo-7-[2-[3-(trifluoromethyl)phenoxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile.	3.85 LC	204, 35
296			(3aα,4β,7β,7aα)-4-[4-[2-(3-Bromophenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-	3.84 LC	204, 35

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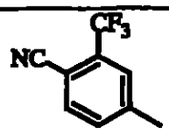
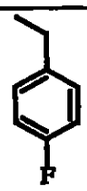
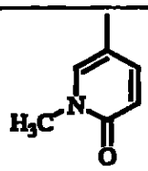
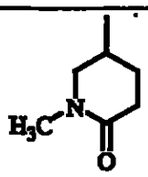
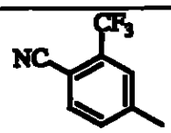
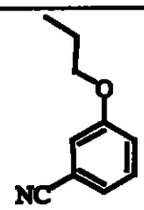
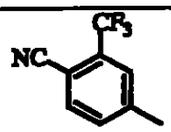
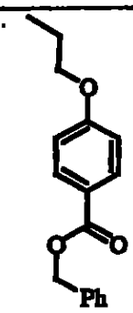
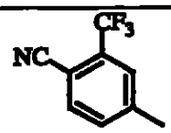
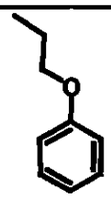
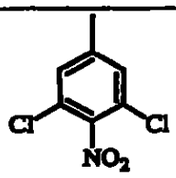
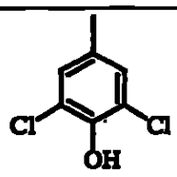
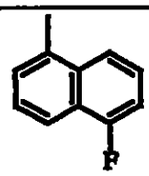
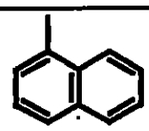
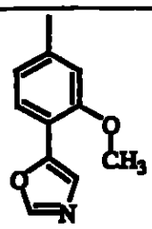
Ex. No	G	R^7	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
			isoindol-2-yl]-2-(trifluoromethyl)benzonitrile.		
297			(3aα,4β,7β,7aα)-4-[4-[(4-Fluorophenyl)methyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile.	3.73 LC	205
298		CH_3	(3aα,4β,7β,7aα)-2-(1,6-Dihydro-1-methyl-6-oxo-3-pyridinyl)hexahydro-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione.	1.61 LC	20
299		CH_3	(3aα,4β,7β,7aα)-Hexahydro-4,7-dimethyl-	1.73 LC	20

Ex. No	G	R^7	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
			2-(1-methyl-6-oxo-3-piperidinyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione.		
300			(3aα,4β,7β,7aα)-4-[4-[2-(3-Cyanophenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile.	3.46 LC	204, 35
301			(3aα,4β,7β,7aα)-4-[2-[4-Cyano-3-(trifluoromethyl)phenyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindol-4-yl]ethoxy]benzoic acid, phenylmethyl ester.	4.01 LC	204, 35

Ex. No	G	R^7	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
302			(3aα,4β,7β,7aα)-4-[Octahydro-4-methyl-1,3-dioxo-7-(2-phenoxyethyl)-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile.	3.57 LC	204, 35
303		CH_3	(3aα,4β,7β,7aα)-2-(3,5-Dichloro-4-nitrophenyl)hexahydro-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione.	3.40 LC	20
304		CH_3	(3aα,4β,7β,7aα)-2-(3,5-Dichloro-4-hydroxyphenyl)hexahydro-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione.	2.58 LC	20

Ex. No	G	R^7	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
305		CH_3	(3aα,4β,7β,7aα)-2-(5-Fluoro-1-naphthalenyl) hexahydro-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione.	2.96 & 3.06 rotational isomers LC	20
306		CH_3	(3aα,4β,7β,7aα)-Hexahydro-4,7-dimethyl-2-(1-naphthalenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione.	2.60 & 2.73 rotational isomers LC	20
307		CH_3	(3aα,4β,7β,7aα)-Hexahydro-2-[3-methoxy-4-(5-oxazolyl)phenyl]-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione.	2.62 LC	20

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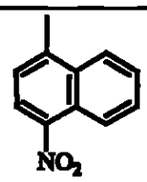
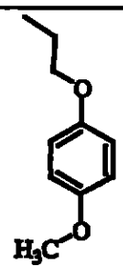
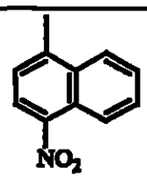
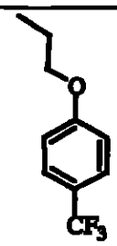
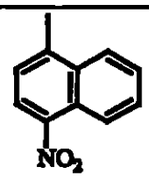
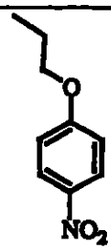
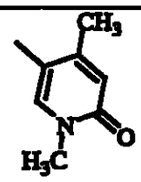
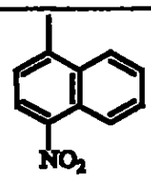
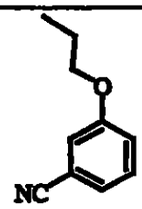
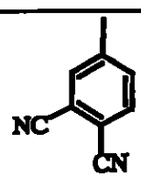
Ex. No	G	R^7	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
308			(3aα,4β,7β,7aα)-Hexahydro-4-[2-(4-methoxyphenoxy)ethyl]-7-methyl-2-(4-nitro-1-naphthalenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione.	3.42 & 3.55 rotational isomers LC	204, 35
309			(3aα,4β,7β,7aα)-Hexahydro-4-methyl-2-(4-nitro-1-naphthalenyl)-7-[2-[4-(trifluoromethyl)phenoxy]ethyl]-4,7-epoxy-1H-isoindole-1,3(2H)-dione.	3.81 & 3.93 rotational isomers LC	204, 35
310			(3aα,4β,7β,7aα)-Hexahydro-4-methyl-2-(4-nitro-1-naphthalenyl)-7-[2-(4-nitrophenoxy)	3.48 & 3.61 rotational isomers LC	204, 35

Ex. No	G	R'	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
			ethyl]-4,7-epoxy-1H-isoindole-1,3(2H)-dione.		
311		CH_3	(3aα,4β,7β,7aα)-2-(1,6-Dihydro-1,4-dimethyl-6-oxo-3-pyridinyl)hexahydro-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione.	1.89 LC	20
312			(3aα,4β,7β,7aα)-4-[Octahydro-7-methyl-2-(4-nitro-1-naphthalenyl)-1,3-dioxo-4,7-epoxy-4H-isoindol-4-yl]ethoxy]benzonitrile.	3.63 LC	204, 35
313		CH_3	(3aα,4β,7β,7aα)-4-(Octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-	2.38 LC	20

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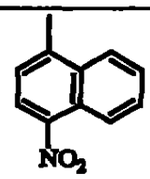
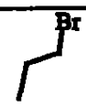
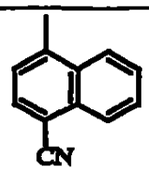
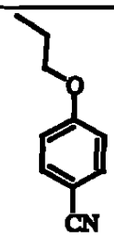
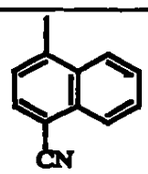
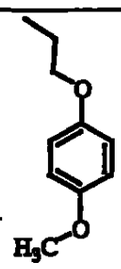
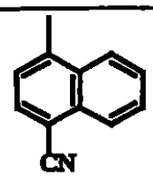
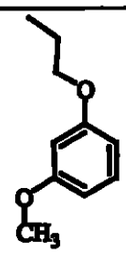
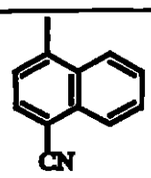
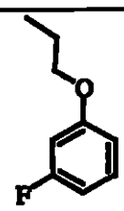
Ex. No	G	R^7	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
			1,2-benzenedicarbonitrile.		
314			(3aα,4β,7β,7aα)-4-(2-Bromoethyl)hexahydro-7-methyl-2-(4-nitro-1-naphthalenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione.	3.52 LC	36
315			(3aα,4β,7β,7aα)-4-[4-[2-(4-Cyanophenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.19 & 3.35 rotational isomers LC	223, 35
316			(3aα,4β,7β,7aα)-4-[Octahydro-4-[2-(4-methoxyphenoxy)ethyl]-7-methyl-1,3-dioxo-4,7-epoxy-2H-	3.34 & 3.50 rotational isomers LC	223, 35

Ex. No	G	R^7	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
			iscindol-2-yl]-1-naphthalenecarbonitrile.		
317			(3aα,4β,7β,7aα)-4-[Octahydro-4-[2-(3-methoxyphenoxy)ethyl]-7-methyl-1,3-dioxo-4,7-epoxy-2H-iscindol-2-yl]-1-naphthalenecarbonitrile.	3.34 & 3.50 rotational isomers LC	223, 35
318			(3aα,4β,7β,7aα)-4-[4-[2-(3-Fluorophenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-iscindol-2-yl]-1-naphthalenecarbonitrile.	3.46 & 3.61 rotational isomers LC	223, 35

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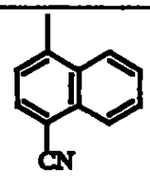
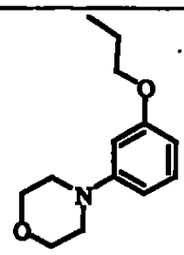
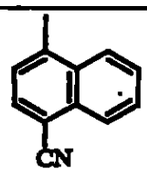
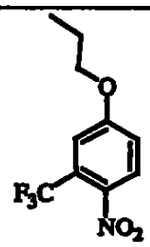
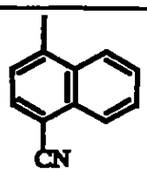
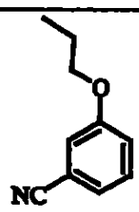
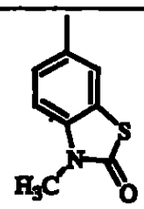
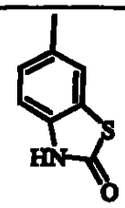
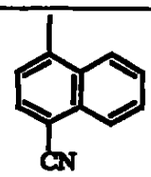
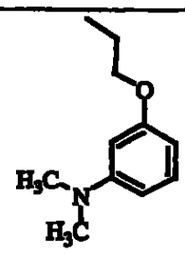
Ex. No	G	R^7	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
319			(3aα,4β,7β,7aα)-4-[Octahydro-4-methyl-7-[2-[3-(4-morpholinyl)phenoxy]ethyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.01 & 3.18 rotational isomers LC	223, 35
320			(3aα,4β,7β,7aα)-4-[Octahydro-4-methyl-7-[2-[4-nitro-3-(trifloucromethyl)phenoxy]ethyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.70 & 3.83 rotational isomers LC	223, 35
321			(3aα,4β,7β,7aα)-4-[4-[2-(3-Cyanophenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-	3.39 & 3.55 rotational isomers LC	223, 35

Ex. No	G	R'	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
			epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.		
322		CH_3	(3aα,4β,7β,7aα)-2-(2,3-Dihydro-3-methyl-2-oxo-6-benzothiazolyl)hexahydro-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione.	2.34 LC	20
323		CH_3	(3aα,4β,7β,7aα)-2-(2,3-Dihydro-2-oxo-6-benzothiazolyl)hexahydro-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione.	2.16 LC	20
324			(3aα,4β,7β,7aα)-4-[4-[2-[3-(Dimethylamino)phenoxy]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-	2.63 & 2.79 rotational isomers LC	223, 35

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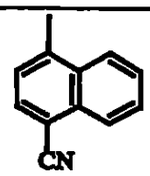
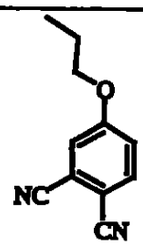
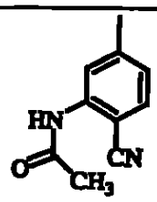
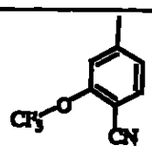
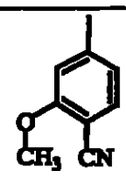
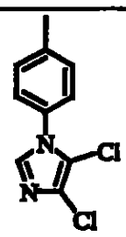
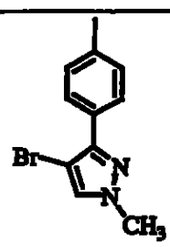
Ex. No	G	R^7	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
			epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.		
325			(3aα,4β,7β,7aα)-4-[2-[4-Cyano-3-(trifluoromethyl)phenyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindol-4-yl]ethoxy]-1,2-benzenedicarbonitrile.	3.42 LC	223, 35
326		CH_3	(3aα,4β,7β,7aα)-*N*-[2-Cyano-5-(octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)phenyl]acetamide.	1.94 LC	20
327		CH_3	(3aα,4β,7β,7aα)-4-(Octahydro-4,7-dimethyl-	3.52 LC	20

Ex. No	G	R^7	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
			1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethoxy)benzonitrile.		
328		CH_3	(3aα,4β,7β,7aα)-2-Methoxy-4-(octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)benzonitrile.	2.47 LC	20
329		CH_3	(3aα,4β,7β,7aα)-2-[4-(4,5-Dichloro-1H-imidazol-1-yl)phenyl]hexahydro-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione.	3.09 LC	20
330		CH_3	(3aα,4β,7β,7aα)-2-[4-(4-Bromo-1-methyl-1H-pyrazol-3-yl)phenyl]hexahydro-4,7-	3.04 LC	20

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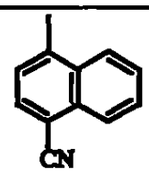
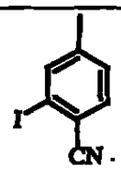
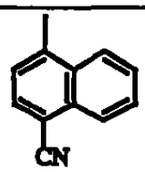
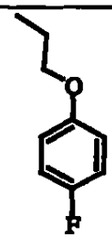
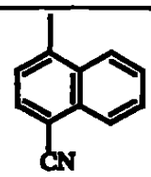
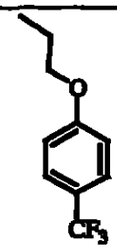
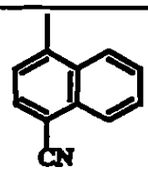
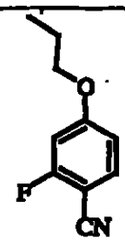
Ex. No	G	R^7	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
			dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione.		
331			(3aα,4β,7β,7aα)-4-[Octahydro-4-(2-hydroxyethyl)-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	2.44 & 2.60 rotational isomers LC	223
332		CH_3	(3aα,4β,7β,7aα)-2-Iodo-4-(Octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)benzonitrile.	2.78 LC	20
333			(3aα,4β,7β,7aα)-4-[4-[2-(4-Fluorophenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-	3.39 & 3.53 rotational isomers LC	223, 35

Ex. No	G	R'	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
			1-naphthalenecarbonitrile.		
334			(3aα,4β,7β,7aα)-4-[Octahydro-4-methyl-1,3-dioxo-7-[2-[4-(trifluoromethyl)phenoxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.66 & 3.78 rotational isomers LC	223, 35
335			(3aα,4β,7β,7aα)-4-[4-[2-(4-Cyano-3-fluorophenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.26 & 3.41 rotational isomers LC	223, 35

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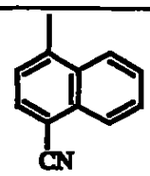
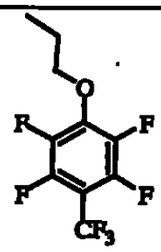
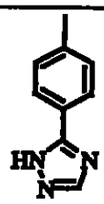
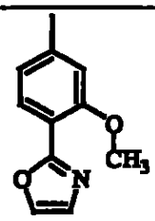
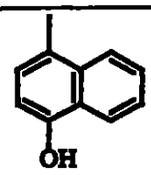
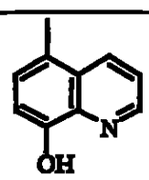
Ex. No	G	R'	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
336			(3aα,4β,7β,7aα)-4-[Octahydro-4-methyl-1,3-dioxo-7-[2-[2,3,5,6-tetrafluoro-4-(trifluoromethyl)phenoxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.94 & 4.01 rotational isomers LC	228, 35
337		CH_3	(3aα,4β,7β,7aα)-Hexahydro-4,7-dimethyl-2-[4-(1H-1,2,4-triazol-3-yl)phenyl]-4,7-epoxy-1H-isoindole-1,3(2H)-dione.	2.06 LC	20
338		CH_3	(3aα,4β,7β,7aα)-2-[4-(4,5-Dihydro-5-oxo-1,2,4-oxadiazol-3-yl)phenyl]hexahydro-4,7-dimethyl-4,7-	2.42 LC	20

Ex. No	G	R^7	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
			epoxy-1H-isoindole-1,3(2H)-dione.		
339		CH_3	(3aα,4β,7β,7aα)-Hexahydro-2-[3-methoxy-4-(2-oxazolyl)phenyl]-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione.	2.51 LC	20
340		CH_3	(3aα,4β,7β,7aα)-Hexahydro-2-(4-hydroxy-1-naphthalenyl)-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione.	2.30 LC	20
341		CH_3	(3aα,4β,7β,7aα)-Hexahydro-2-(8-hydroxy-5-quinolinyl)-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione, trifluoroaceta	1.49 LC	20

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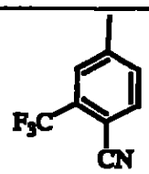
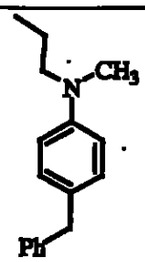
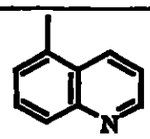
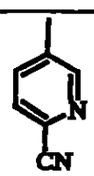
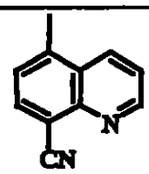
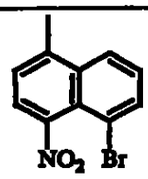
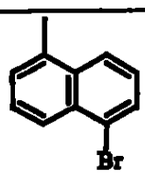
Ex. No	G	R^7	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
			te (1:1).		
342			(3aα,4β,7β,7aα)-4-[Octahydro-4-methyl-1,3-dioxo-7-[2-[methyl(phenylmethyl)amino]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile.	2.42 LC	204, 35
343		CH_3	(3aα,4β,7β,7aα)-Hexahydro-4,7-dimethyl-2-(5-quinolinyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione.	1.69 LC	20
344		CH_3	(3aα,4β,7β,7aα)-5-(Octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-pyridinecarbo	2.18 LC	20

Ex. No	G	R^7	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
			nitrile.		
345		CH_3	(3aα,4β,7β,7aα)-5-(Octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-8-quinolinecarbonitrile.	2.31 LC	20
346		CH_3	(3aα,4β,7β,7aα)-2-(5-Bromo-4-nitro-1-naphthalenyl) hexahydro-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione.	3.10 & 3.29 rotational isomers LC	20
347		CH_3	(3aα,4β,7β,7aα)-2-(5-Bromo-1-naphthalenyl) hexahydro-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione.	3.28 & 3.40 rotational isomers LC	20

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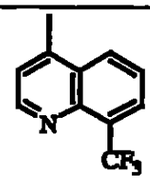
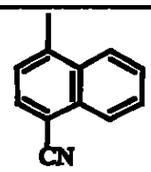
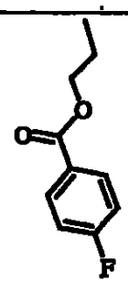
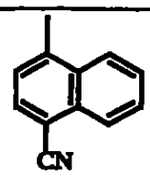
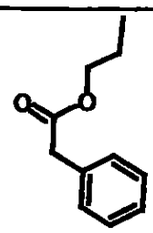
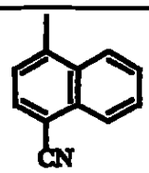
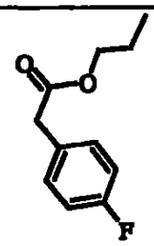
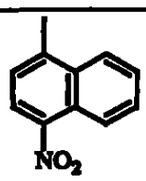
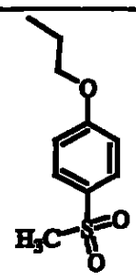
Ex. No	G	R^7	Compound Name	Retention Time Min/ Molecular Mass	Procedure of Ex.
348		CH_3	(3aα,4β,7β,7aα)-Hexahydro-4,7-dimethyl-2-[8-(trifluoromethyl)-4-quinolinyl]-4,7-epoxy-1H-isoindole-1,3(2H)-dione.	3.08 LC	20
349			4-Fluorobenzoic acid, 2-[(3aα,4β,7β,7aα)-2-(4-cyano-1-naphthalenyl) octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindol-4-y]ethyl ester.	3.64 & 3.77 rotational isomers LC	223
350			Benzeneacetic acid, 2-[(3aα,4β,7β,7aα)-2-(4-cyano-1-naphthalenyl) octahydro-7-methyl-1,3-dioxo-4,7-	3.53 & 3.67 rotational isomers LC	223

Ex. No	G	R'	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
			epoxy-4H-isoindol-4-y]ethyl ester.		
351			4-Fluorobenzeneacetic acid, 2-[(3aα,4β,7β,7aα)-2-(4-cyano-1-naphthalenyl)octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindol-4-y]ethyl ester.	3.53 & 3.66 rotational isomers LC	223
352			(3aα,4β,7β,7aα)-Hexahydro-4-methyl-7-[2-[4-(methylsulfonyl)phenoxy]ethyl]-2-(4-nitro-1-naphthalenyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione.	3.31 LC	204, 35

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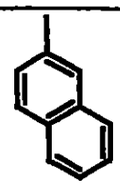
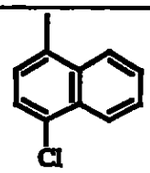
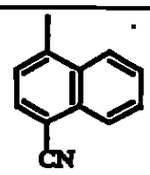
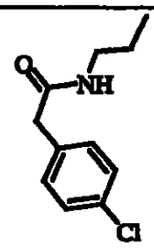
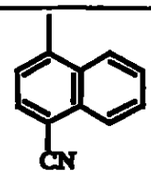
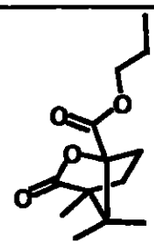
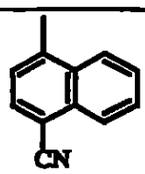
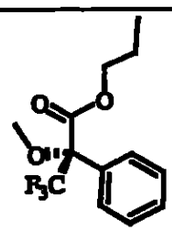
Ex. No	G	R^7	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
353		CH_3	(3aα,4β,7β,7aα)-Hexahydro-2-(2-naphthalenyl)-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione.	2.94 LC	20
354		CH_3	(3aα,4β,7β,7aα)-2-(4-Chloro-1-naphthalenyl) hexahydro-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione.	3.22 & 3.34 rotational isomers LC	20
355			(3aα,4β,7β,7aα)-*N*-[(4-Chlorophenyl) methyl]-2-(4-cyano-1-naphthalenyl) octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindole-4-acetamide.	3.52 LC	237

Ex. No	G	R^7	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
356			4,7,7-Trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carboxylic acid, 2-[(3aα,4β,7β,7aα)-2-(4-cyano-1-naphthalenyl) octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindol-4-y]ethyl ester.	3.45 LC	223
357			(αS)- α-Methoxy-α-(trifluoromethyl)benzeneacetic acid, 2-[(3aα,4β,7β,7aα)-2-(4-cyano-1-naphthalenyl) octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindol-4-y]ethyl ester.	3.91 LC	223

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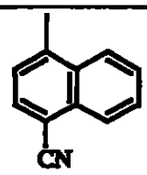
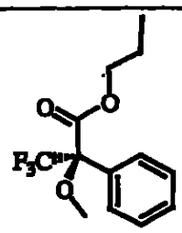
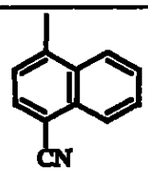
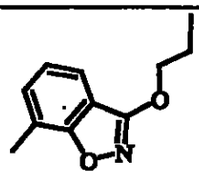
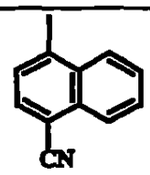
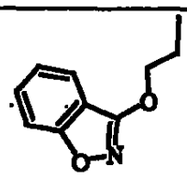
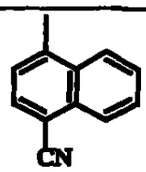
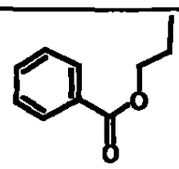
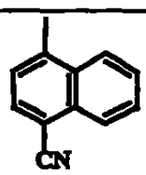
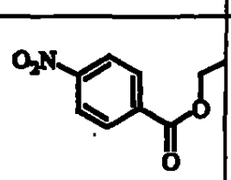
Ex. No	G	R^7	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
358			(αR)- α-Methoxy-α-(trifluoromethyl)benzeneacetic acid, 2-[(3aα,4β,7β,7aα)-2-(4-cyano-1-naphthalenyl) octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindol-4-y]ethyl ester.	2.00 LC	223
359			(3aα,4β,7β,7aα)-4-[Octahydro-4-methyl-7-[2-[(7-methyl-1,2-benzisoxazol-3-yl)oxy]ethyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.79 & 3.92 LC Rotationale isomers	250

Ex. No	G	R^7	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
360			(3aα,4β,7β,7aα)-4-[4-[2-(1,2-Benzisoxazol-3-yloxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.55 & 3.70 LC Rotationale Isomers	250
361			(3aα,4β,7β,7aα)-4-[2-(Benzoyloxy)ethyl]-2-(4-cyano-1-naphthalenyl)hexahydro-7-methyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione.	3.51 & 3.66 LC Rotationale isomers	223
362			(3aα,4β,7β,7aα)-2-(4-Cyano-1-naphthalenyl)-4-[2-[(4-nitrobenzoyl)oxy]ethyl]hexahydro-7-	3.52 & 3.67 LC Rotationale Isomers	223

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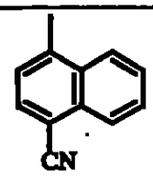
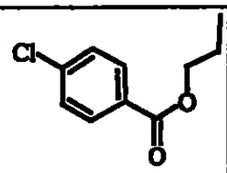
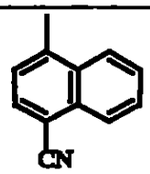
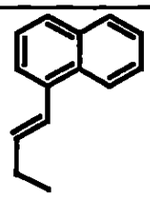
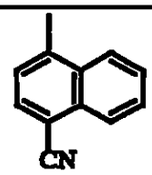
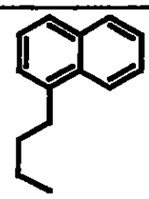
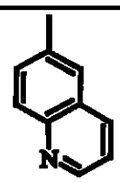
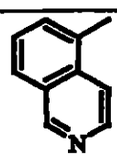
Ex. No	G	R^7	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
			methyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione.		
363			4-Chlorobenzoic acid, 2-[(3aα,4β,7β,7aα)-2-(4-cyano-1-naphthalenyl) octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindol-4-y]ethyl ester.	3.79 LC	223
364			[3aα,4β,7β,7aα(E)]-4-[Octahydro-4-methyl-7-[3-(1-naphthalenyl)-2-propenyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	4.14 LC 499.13 $[M+H]^+$	248

Ex. No	G	R'	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
365			(3aα,4β,7β,7aα)-4-[Octahydro-4-methyl-7-[3-(1-naphthalenyl)propyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	4.14 LC 501.14 $[M+H]^+$	248, 249
366		CH_3	(3aα,4β,7β,7aα)-Hexahydro-4,7-dimethyl-2-(2-methyl-6-quinolinyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione.	1.25 LC 337.0 $[M+H]^+$	20
367		CH_3	(3aα,4β,7β,7aα)-Hexahydro-2-(5-isoquinolinyl)-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione.	1.06 & 1.29 LC Rotationale Isomers 323.0 $[M+H]^+$	20

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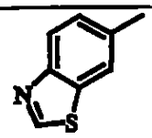
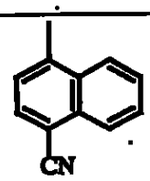
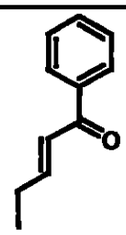
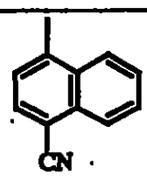
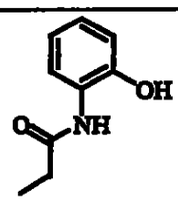
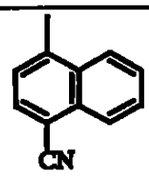
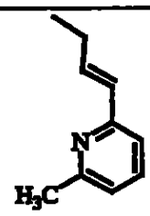
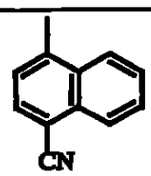
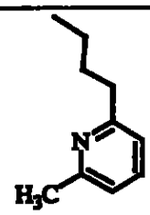
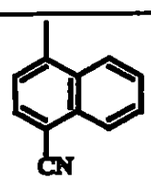
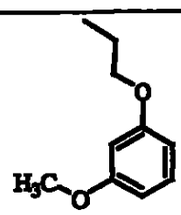
Ex. No	G	R^7	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
368		CH_3	(3aα,4β,7β,7aα)-2-(6-Benzothiazolyl)hexahydro-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione.	2.15 LC 329.0 $[M+H]^+$	20
369			[3aα,4β,7β,7aα(E)]-4-[Octahydro-4-methyl-1,3-dioxo-7-(4-oxo-4-phenyl-2-butenyl)-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.50 LC 477.1 $[M+H]^+$	265
370			(3aα,4β,7β,7aα)-2-(4-Cyano-1-naphthalenyl)octahydro-*N*-(2-hydroxyphenyl)-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindole-4-acetamide.	3.07 LC 482.14 $[M+H]^+$	236

Ex. No	G	R'	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
371			[3aα,4β(E),7β,7aα]-4-[Octahydro-4-methyl-7-[3-(6-methyl-2-pyridinyl)-2-propenyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	2.28 LC 464.19 $[M+H]^+$	248
372			(3aα,4β,7β,7aα)-4-[Octahydro-4-methyl-7-[3-(6-methyl-2-pyridinyl)propyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	2.19 LC 466.32 $[M+H]^+$	248, 249
373			[3aR-(3aα,4β,7β,7aα)]-4-[Octahydro-4-[2-(3-methoxyphenoxy)ethyl]-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-	3.73 LC 483.65 $[M+H]^+$	238, 239

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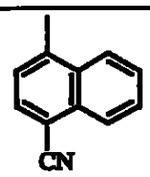
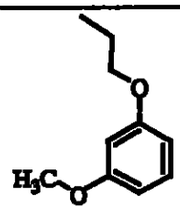
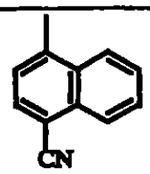
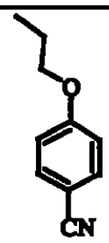
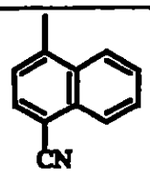
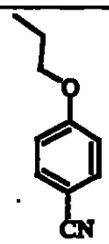
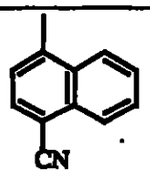
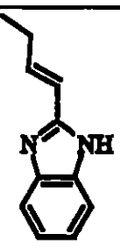
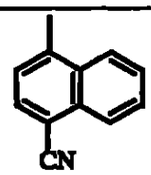
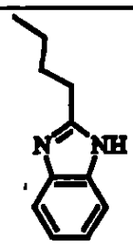
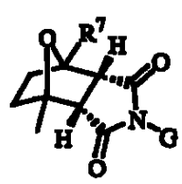
Ex. No	G	R^7	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
			naphthalenecarbonitrile.		
374			[3aS-(3aα,4β,7β,7aα)]-4-[Octahydro-4-[2-(3-methoxyphenoxy)ethyl]-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.73 LC	238ii, 239ii
375			[3a*R*-(3aα,4β,7β,7aα)]-4-[4-[2-(4-Cyanophenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.33 & 3.49 LC Rotationals Isomers	238i, 239i
376			[3aS-(3aα,4β,7β,7aα)]-4-[4-[2-(4-Cyanophenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.73 LC 483.65 $[M+H]^+$	238ii, 239ii
377			[3aα,4β(E),7β,7aα]-4-[4-[3-(1H-Benzimidazol-2-yl)-2-propenyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-	2.48 LC 489.26 $[M+H]^+$	248

Ex. No	G	R^7	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
			iscindol-2-yl]-1-naphthalenecarbonitrile		
378			(3aα,4β,7β,7aα)-4-[4-[3-(1H-Benzimidazol-2-yl)propyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-iscindol-2-yl]-1-naphthalenecarbonitrile	2.37 LC 491.26 $[M+H]^+$	249

Examples 379 to 381

Additional compounds of the present invention were prepared by procedures analogous to those described above. The compounds of Examples 379 to 381 have the following structure (L is a bond):

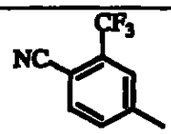
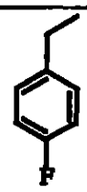
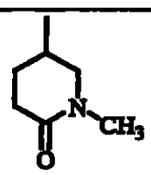
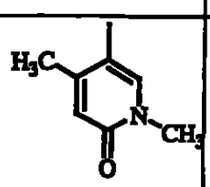


where G, R^7, the compound name, retention time, molecular mass, and the procedure employed, are set forth in Table 6. The chromatography techniques used to determine the compound retention times of Table 6 are as follows: LCMS = YMC S5 ODS column, 4.6 X 50 mm eluting with 10-90% MeOH/H_2O over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm. LCMS* = YMC S5 ODS column, 4.6 X 50 mm eluting with 10-90% MeOH/H_2O over 2 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm. LC = YMC S5 ODS column 4.6 x 50 mm eluting

with 10-90% MeOH/H_2O over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm.

The molecular mass of the compounds listed in Table 6 were determined by MS (ES) by the formula m/z.

Table 6

Ex. No	G	R^7	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
379			(3aα,4α,7α,7aα)-4-[4-[(4-Fluorophenyl)methyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl) benzonitrile.	3.75 LC	205
380		CH_3	(3aα,4α,7α,7aα)-Hexahydro-4,7-dimethyl-2-(1-methyl-6-oxo-3-piperidinyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione.	1.88 LC	27
381		CH_3	(3aα,4α,7α,7aα)-2-(1,6-Dihydro-1,4-dimethyl-6-	1.91 LC	27

Ex. No	G	R^7	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
			oxo-3-pyridinyl)hexahydro-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione.		

Examples 382 to 383

Additional compounds of the present invention were prepared by procedures analogous to those described above. The compounds of Examples 382 to 383 have the structure, compound name, retention time, molecular mass, and were prepared by the procedure employed, set forth in the following Table 7. The chromatography techniques used to determine the compound retention times of Table 7 are as follows: LCMS = YMC S5 ODS column, 4.6 X 50 mm eluting with 10-90% MeOH/H_2O over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm. LCMS* = YMC S5 ODS column, 4.6 X 50 mm eluting with 10-90% MeOH/H_2O over 2 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm. LC = YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% MeOH/H_2O over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm. The molecular mass of the compounds listed in Table 7 were determined by MS (ES) by the formula m/z.

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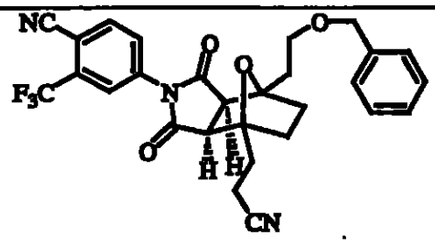
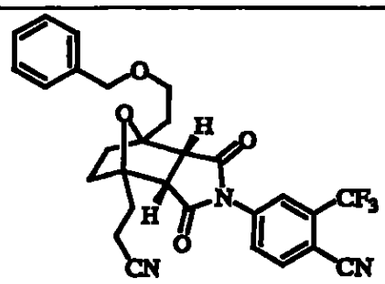
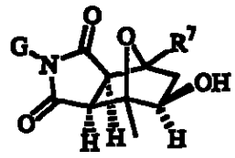
Table 7

Ex. No.	Structure	Compound Name	Retention Time Min.	Procedure of Example
382		(3aα,4β,7β,7aα)-2-[4-Cyano-3-(trifluoromethyl) phenyl]octahydro-1,3-dioxo-7-[2-(phenylmethoxy) ethyl]-4,7-epoxy-4H-isoindole-4-propanenitrile.	3.63 LC	255
383		(3aα,4β,7β,7aα)-2-[4-Cyano-3-(trifluoromethyl) phenyl]octahydro-1,3-dioxo-7-[2-(phenylmethoxy) ethyl]-4,7-epoxy-4H-isoindole-4-propanenitrile	3.64 LC	255

Examples 384 to 418

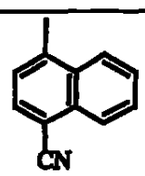
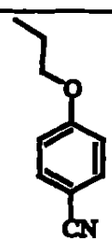
Additional compounds of the present invention were prepared by procedures analogous to those described above. The compounds of Examples 384 to 418 have the following structure (L is a bond):



where G, R^7, the compound name, retention time, molecular mass, and the procedure employed, are set forth in Table 8. The absolute configuration for the following compounds was not determined. For simplicity in nomenclature, compound **243Di** is designated herein as having an "S" configuration and compound **243Dii** as having an "R" configuration. Enantiomerically pure products derived from compound **243Di** are designated herein as having an "S" configuration and enantiomerically pure products derived from compound **243Dii** are designated herein as having an "R" configuration.

The chromatography techniques used to determine the compound retention times of Table 8 are as follows: LCMS = YMC S5 ODS column, 4.6 X 50 mm eluting with 10-90% MeOH/H_2O over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm. LCMS* = YMC S5 ODS column, 4.6 X 50 mm eluting with 10-90% MeOH/H_2O over 2 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm. LC = YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% MeOH/H_2O over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm. The molecular mass of the compounds listed in Table 8 were determined by MS (ES) by the formula m/z.

Table 8

Ex. No	G	R^7	Compound Name	Retention Time Min/ Molecular Mass	Procedure of Ex.
384			(3aα,4β,7β,7aα) -4-[7-[2-(4-Cyanophenoxy) ethyl]octahydro -5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-	3.18 LC 494.40 $[M+H]^+$	227, 228, 229

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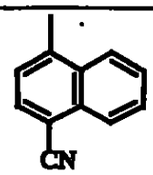
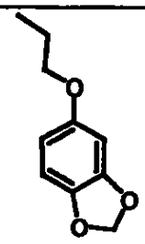
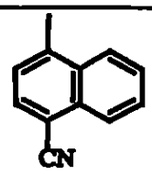
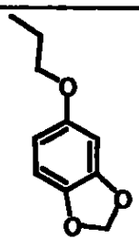
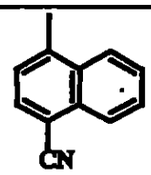
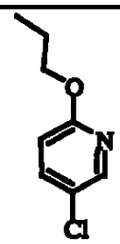
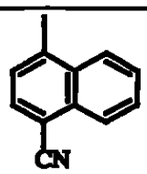
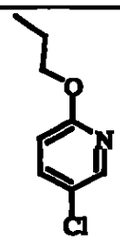
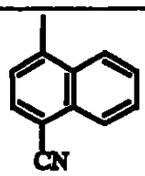
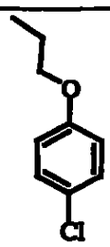
Ex. No	G	R^7	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
			yl]-1-naphthalenecarbonitrile.		
385			[3aS-(3aα,4β,7β,7aα)]-4-[7-[2-(1,3-Benzodioxol-5-yloxy)ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.19 LC 571.3 [M-H+OAc]⁻	243Di, 244i
386			[3aR-(3aα,4β,7β,7aα)]-4-[7-[2-(1,3-Benzodioxol-5-yloxy)ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.22 LC 571.2 [M-H+OAc]⁻	234Dii, 244ii

Ex. No	G	R^7	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
387			[3aS-(3aα,4β,7β,7aα)]-4-[7-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.37 LC 562.2 [M-H+OAc]⁻	243Di, 244i
388			[3a*R*-(3aα,4β,7β,7aα)]-4-[7-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.37 LC 504.0 $[M+H]^+$	243Dii, 244ii
389			[3aS-(3aα,4β,7β,7aα)]-4-[7-[2-(4-Chlorophenoxy)ethyl]octahydro-5-hydroxy-4-methyl-1,3-	3.51 LC 503.08 $[M+H]^+$	243Di, 244i

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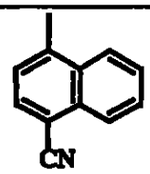
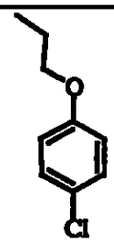
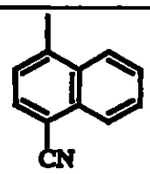
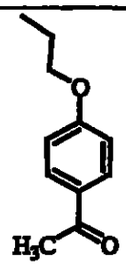
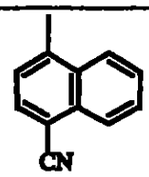
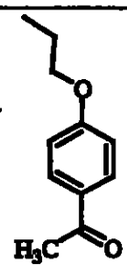
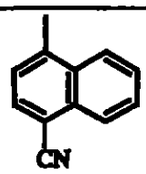
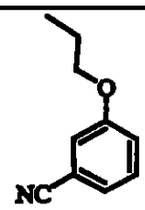
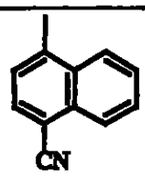
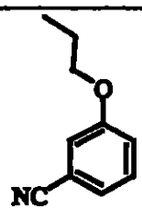
Ex. No	G	R^7	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
			dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.		
390			[3a*R*-(3aα,4β,7β,7aα)]-4-[7-[2-(4-Chlorophenoxy)ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.51 LC 503.08 $[M+H]^+$	243Dii, 244ii
391			[3aS-(3aα,4β,7β,7aα)]-4-[7-[2-(4-Acetylphenoxy)ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.05 LC 511.13 $[M+H]^+$	243Di, 244i

Ex. No	G	R^7	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
392			[3a*R*-(3aα,4β,7β,7aα)]-4-[7-[2-(4-Acetylphenoxy)ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.05 LC 503.13 $[M+H]^+$	243Dii, 244ii
393			[3aS-(3aα,4β,7β,7aα)]-4-[7-[2-(3-Cyanophenoxy)ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.09 LC 494.13 $[M+H]^+$	243Di, 244i
394			[3a*R*-(3aα,4β,7β,7aα)]-4-[7-[2-(3-Cyanophenoxy)ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-	3.09 LC 494.13 $[M+H]^+$	243Dii, 244ii

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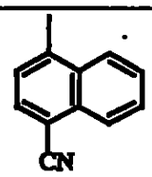
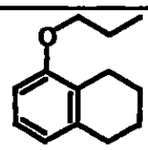
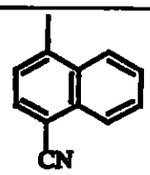
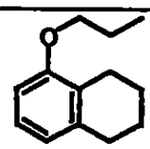
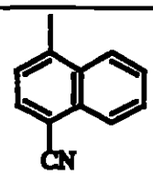
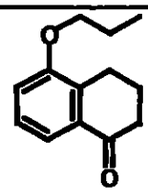
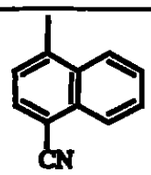
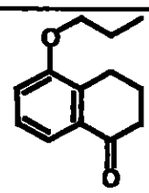
Ex. No	G	R'	Compound Name	Retention Time Min/ Molecular Mass	Procedure of Ex.
			yl]-1-naphthalenecarbonitrile.		
395			[3aS-(3aα,4β,7β,7aα)]-4-[Octahydro-5-hydroxy-4-methyl-1,3-dioxo-7-[2-[(5,6,7,8-tetrahydro-1-naphthalenyl)oxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.85 LC 523.17 $[M+H]^+$	243Di, 244i
396			[3a*R*-(3aα,4β,7β,7aα)]-4-[Octahydro-5-hydroxy-4-methyl-1,3-dioxo-7-[2-[(5,6,7,8-tetrahydro-1-naphthalenyl)oxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.85 LC 523.17 $[M+H]^+$	243Dii, 244ii

Ex. No	G	R^7	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
397			[3aS-(3aα,4β,7β,7aα)]-4-[Octahydro-5-hydroxy-4-methyl-1,3-dioxo-7-[2-[(5,6,7,8-tetrahydro-5-oxo-1-naphthalenyl)oxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.29 LC 537.13 $[M+H]^+$	243Di, 244i
398			[3a*R*-(3aα,4β,7β,7aα)]-4-[Octahydro-5-hydroxy-4-methyl-1,3-dioxo-7-[2-[(5,6,7,8-tetrahydro-5-oxo-1-naphthalenyl)oxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.29 LC 537.13 $[M+H]^+$	243Dii, 244ii

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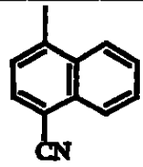
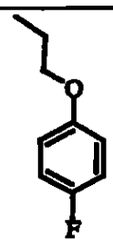
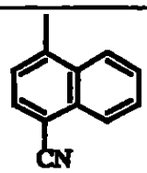
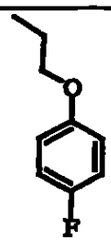
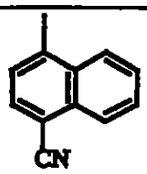
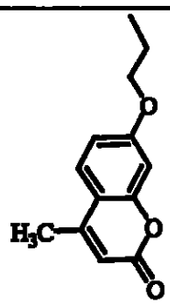
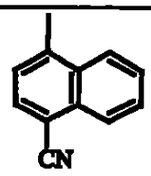
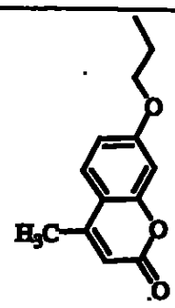
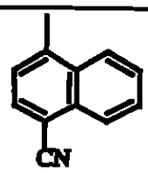
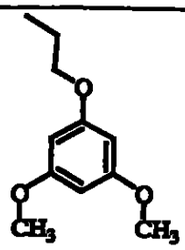
Ex. No	G	R^7	Compound Name	Retention Time Min/ Molecular Mass	Procedure of Ex.
399			[3aS-(3aα,4β,7β,7aα)]-4-[7-[2-(4-Fluorophenoxy)ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.28 LC 487.11 $[M+H]^+$	243Di, 244i
400			[3a*R*-(3aα,4β,7β,7aα)]-4-[7-[2-(4-Fluorophenoxy)ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.27 LC 487.11 $[M+H]^+$	243Dii, 244ii
401			[3aS-(3aα,4β,7β,7aα)]-4-[Octahydro-5-hydroxy-4-methyl-7-[2-[(4-methyl-2-oxo-2H-1-benzopyran-7-yl)oxy]ethyl]-	3.15 LC 551.15 $[M+H]^+$	243Di, 244i

Ex. No	G	R'	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
			1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.		
402			[3a*R*-(3aα,4β,7β,7aα)]-4-[Octahydro-5-hydroxy-4-methyl-7-[2-[(4-methyl-2-oxo-2H-1-benzopyran-7-yl)oxy]ethyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.16 LC 551.10 $[M+H]^+$	243Dii, 244ii
403			[3aS-(3aα,4β,7β,7aα)]-4-[7-[2-(3,5-Dimethoxyphenoxy)ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.28 LC 529.19 $[M+H]^+$	243Di, 244i

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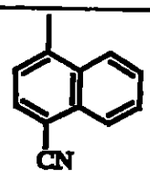
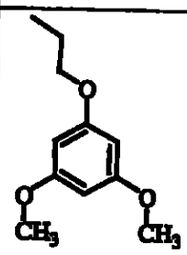
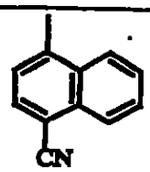
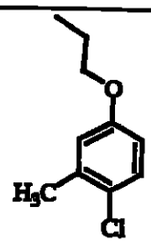
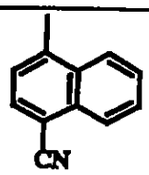
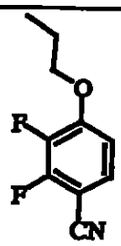
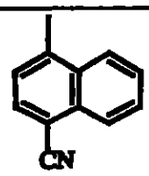
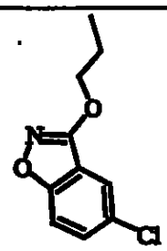
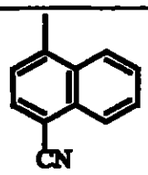
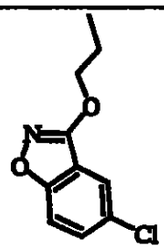
Ex. No	G	R^7	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
404			[3a*R*-(3aα,4β,7β,7aα)]-4-[7-[2-(3,5-Dimethoxyphenoxy)ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.26 LC 529.12 $[M+H]^+$	243Dii, 244ii
405			[3a*R*-(3aα,4β,7β,7aα)]-]-4-[7-[2-(4-Chloro-3-methylphenoxy)ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.68 LC 517.33 $[M+H]^+$	243Dii, 244ii
406			[3a*R*-(3aα,4β,7β,7aα)]-4-[7-[2-(4-Cyano-2,3-difluorophenoxy)ethyl]octahydro-5-hydroxy-4-methyl-1,3-	3.23 LC 530.13 $[M+H]^+$	243Dii, 244ii

Ex. No	G	R^7	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
			dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.		
407			[3aS-(3aα,4β,7β,7aα)]-4-[7-[2-[(5-Chloro-1,2-benzisoxazol-3-yl)oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.59 LC 602.1 [M-H+OAc]⁻	243Di, 252
408			[3a*R*-(3aα,4β,7β,7aα)]-4-[7-[2-[(5-Chloro-1,2-benzisoxazol-3-yl)oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	3.57 LC 602.0 [M-H+OAc]⁻	243Dii, 253

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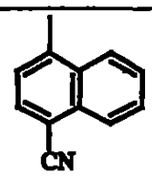
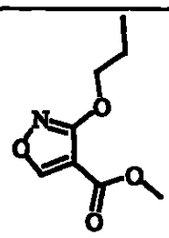
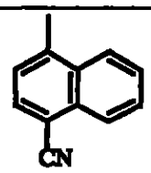
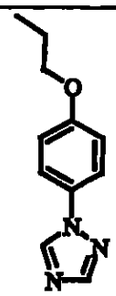
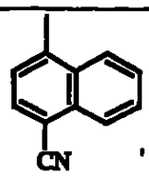
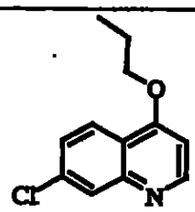
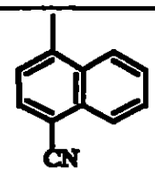
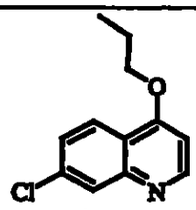
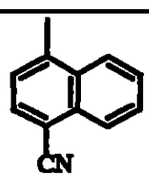
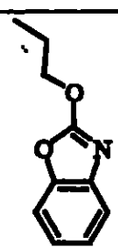
Ex. No	G	R'	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
409			[3a*R*-(3aα,4β,7β,7aα)]-3-[2-[2-(4-Cyano-1-naphthalenyl)octahydro-6-hydroxy-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindol-4-yl]ethoxy]-5-isoxazolecarboxylic acid, methyl ester.	2.90 LC 518.27 $[M+H]^+$	243Dii, 253
410			[3a*R*-(3aα,4β,7β,7aα)]-4-[Octahydro-5-hydroxy-4-methyl-1,3-dioxo-7-[2-[4-(1H-1,2,4-triazol-1-yl)phenoxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile.	2.93 LC 536.30 $[M+H]^+$	243Dii, 244ii
411			[3aS-(3aα,4β,7β,7aα)]-4-[7-[2-[(7-Chloro-4-quinolinyl)oxy]ethyl]octahydro-	2.52 LC 554.13 $[M+H]^+$	243Di, 244i

Ex. No	G	R^7	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
			5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, trifluoroacetate (1:1).		
412			[3a*R*-(3aα,4β,7β,7aα)]-4-[7-[2-[(7-Chloro-4-quinolinyl)oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, trifluoroacetate (1:1).	2.53 LC 554.27 $[M+H]^+$	243Dii, 244ii
413			[3a*R*-(3α,4β,5β,7β,7aα)]-4-[7-[2-(2-Benzoxazolyloxy)ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-	3.13 LC 568.1 $[M-H+OAc]^-$	243Dii, 244ii

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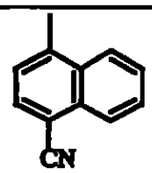
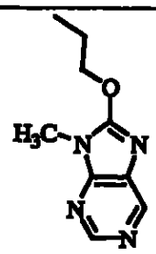
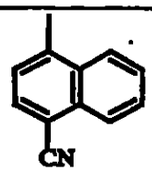
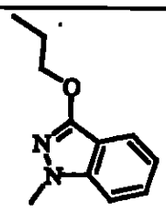
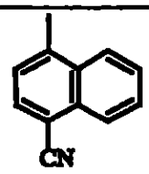
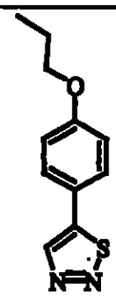
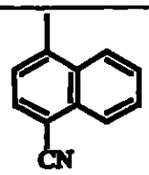
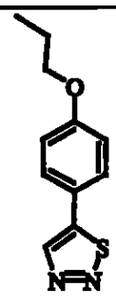
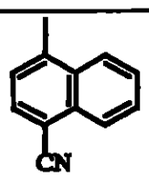
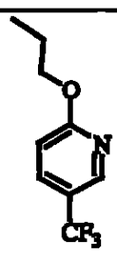
Ex. No	G	R^7	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
			yl]-1-naphthalenecarbonitrile		
414			[3a*R*-(3α,4β,5β,7β,7aα)]-4-[Octahydro-5-hydroxy-4-methyl-7-[2-[(9-methyl-9H-purin-8-yl)oxy]ethyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	2.34 LC 525.2 $[M+H]^+$	243Dii, 244ii
415			[3a*R*-(3α,4β,5β,7β,7aα)]-4-[Octahydro-5-hydroxy-4-methyl-7-[2-[(1-methyl-1H-indazol-3-yl)oxy]ethyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.33 LC	251,253

Ex. No	G	R^7	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
416			[3aS-(3α,4β,5β,7β,7aα)]-4-[Octahydro-5-hydroxy-4-methyl-7-[2-[4-(1,2,3-thiadiazol-5-yl)phenoxy]ethyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.17 LC 553.10 $[M+H]^+$	243Dii, 244ii
417			[3a*R*-(3α,4β,5β,7β,7aα)]-4-[Octahydro-5-hydroxy-4-methyl-7-[2-[4-(1,2,3-thiadiazol-5-yl)phenoxy]ethyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.20 LC 553.25 $[M+H]^+$	243Dii, 244ii
418			[3aS-(3α,4β,5β,7β,7aα)]-4-[Octahydro-5-hydroxy-4-methyl-1,3-dioxo-7-[2-[[5-(trifluoromethyl)-2-pyridinyl]oxy]ethyl]-4,7-epoxy-2H-isoindol-2-	3.45 LC 538.23 $[M+H]^+$	243Dii, 244ii

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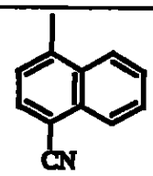
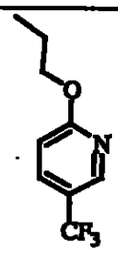
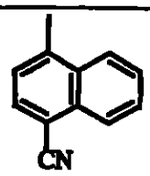
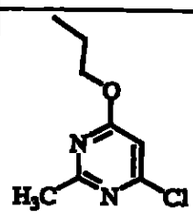
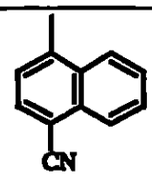
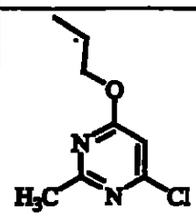
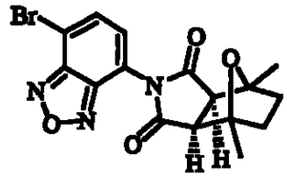
Ex. No	G	R^7	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
			yl]-1-naphthalenecarbonitrile		
419			[3a*R*-(3α,4β,5β,7β,7aα)]-4-[Octahydro-5-hydroxy-4-methyl-1,3-dioxo-7-[2-[[5-(trifluoromethyl)-2-pyridinyl]oxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.45 LC 538.23 $[M+H]^+$	243Dii, 244ii
420			[3aS-(3α,4β,5β,7β,7aα)]-4-[7-[2-[(6-Chloro-2-methyl-4-pyrimidinyl)oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.02 LC	243Dii, 244ii

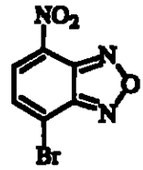
Ex. No	G	R^7	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
421			[3a*R*-(3α,4β,5β,7β,7aα)]-4-[7-[2-[(6-Chloro-2-methyl-4-pyrimidinyl)oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.02 LC	243Dii, 244ii

Example 422

(3aα,4β,7β,7aα)-2-(7-Bromo-2,1,3-benzoxadiazol-4-yl)hexahydro-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione (422C)



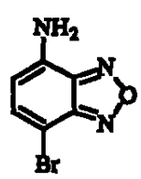
A. 4-Bromo-7-nitrobenzofurazan (422A)



To a solution of 2,6-dibromoaniline (1.0 g, 4.0 mmol) in $CHCl_3$ (8 mL) was added a suspension of *m*CPBA (70% by HPLC, 1.4 g, 8.0 mmol)

in $CHCl_3$ (8 mL) and the resulting mixture was stirred for 24 h at rt. The reaction mixture was diluted with $CHCl_3$ and washed successively with 2% $Na_2S_2O_3$ solution, 5% Na_2CO_3 solution and brine. The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to leave a solid, which was suspended, into DMSO (15 mL). To this suspension was added a solution of NaN_3 (272 mg, 4.19 mmol) in DMSO (15 mL) at rt. The resulting mixture was stirred at rt until most of the nitrogen had evolved and was then quickly heated to 120°C for 3 min. The reaction mixture was cooled and poured onto crushed ice (100 g). After standing for 1 h the precipitates were filtered off, dried in *vacuo* and redissolved in conc. H_2SO_4 (5 mL). To this solution was added a solution of $NaNO_2$ (400 mg, 4.7 mmol) in 50% H_2SO_4 (1.6 mL) and the temperature was maintained at 60°C. After the addition was complete, the mixture was heated at 85°C for 30 min, cooled to rt and poured onto crushed ice (40 g). EtOAc was added, the layers were separated and the aqueous layer was extracted with EtOAc. The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to leave a solid which was purified by flash chromatography (silica gel, EtOAc (20%) in hexanes) affording compound **422A** (785 mg, 81%) as a tan solid.

B. 4-Bromo-7-aminobenzofurazan (422B)



A solution of compound **422A** (563 mg, 2.31 mmol) in AcOH (5 mL) was heated to 70°C and Fe^0 powder (258 mg, 4.62 mmol) was added in one portion. The resulting dark reaction mixture was stirred for 15 min, cooled to rt and concentrated under reduced pressure. The residue was taken up in EtOAc and the resulting solution was washed with sat.

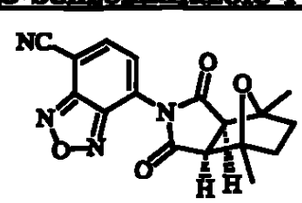
Na_2CO_3 solution. The organic layer was dried over Na_2SO_4, concentrated *in vacuo* and purified by flash chromatography on silica gel eluting with 10-60% EtOAc in hexanes to give 470 mg (95%) of compound **422B** as a red solid.

C. (3aα,4β,7β,7aα)-2-(7-Bromo-2,1,3-benzoxadiazol-4-yl)hexahydro-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione (422C)

A mixture of compound **422B** (43 mg, 0.20 mmol), compound **20A** (45 mg, 0.23 mmol), $MgSO_4$ (60 mg, 0.50 mmol), Et_3N (139 μL, 1.0 mmol) and 1,2-dimethoxyethane (300 μL) were placed in a sealed tube and heated at 135°C for 14 h. After cooling to rt the mixture was filtered through Celite eluting with MeOH to yield a dark solid which was purified by flash chromatography on silica gel eluting with 5-40% EtOAc in hexanes to give 42 mg (54%) of compound **422C** as a yellow solid. HPLC: 99% at 2.96 min (retention time) (YMC S5 ODS column 4.6 x 50 mm Ballistic, 10-90% aqueous methanol over 4 minutes containing 0.2% H_3PO_4, 4 mL/min, monitoring at 220 nm). ^{1}H NMR (acetone-d_6, 400 MHz): δ = 8.00 (d, J = 7.5 Hz, 1H), 7.45 (d, J = 7.5 Hz, 1H), 3.31 (s, 2H), 1.98-1.93 (m, 2H), 1.74-1.69 (m, 2H), 1.57 (s, 6H).

Example 423

(3aα,4β,7β,7aα)-7-[Octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2,1,3-benzoxadiazole-4-carbonitrile (423)



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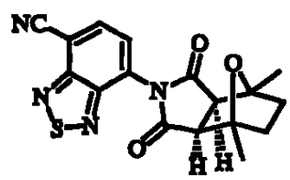
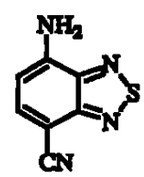
To a solution of compound 422C (42 mg, 0.11 mmol) in DMA (1 mL) was added CuCN (20 mg, 0.22 mmol) and the resulting mixture was heated at 150°C for 5 h. The mixture was allowed to cool to rt and partitioned between EtOAc and aqueous NaCN solution (5 g/50 mL). The layers were separated and the aqueous layer was extracted once with EtOAc. The combined organic phases were dried over Na_2SO_4, concentrated *in vacuo* and purified by flash chromatography on silica gel eluting with 20-70% EtOAc in hexanes to give 13 mg (35%) of compound 423 as a yellow oil. HPLC: 99% at 2.66 min (retention time) (YMC S5 ODS column 4.6 x 50 mm Ballistic, 10-90% aqueous methanol over 4 minutes containing 0.2% H_3PO_4, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 396.9 $[M-H+OAc]^-$.

Example 424

(3aα,4β,7β,7aα)-7-[Octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2,1,3-benzothiadiazole-4-carbonitrile (424B)



A. 4-Cyano-7-amino-benzothiadiazole (424A)



A solution of 2-cyano-5-nitrophenylenediamine (78 mg, 0.44 mmol, prepared as described in WO 0076501) in $SOCl_2$ (2 mL) was heated to reflux for 3 h. The resulting mixture was allowed to cool to rt and was then poured into ice/water. CH_2Cl_2 was added, the layers were separated and the aqueous layer was extracted twice with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography on silica gel eluting with 50% EtOAc in hexanes

to give 4-cyano-7-nitrobenzothiadiazole. This material was dissolved in AcOH (2 mL) containing EtOAc (1 mL) and H_2O (0.2 mL) and heated to 70°C. At this temperature Fe^0 powder (78 mg, 1.41 mmol) was added in one solid portion and the dark mixture was stirred for 20 min and then cooled to rt. The reaction mixture was filtered through Celite eluting with EtOAc, washed with sat. Na_2CO_3 solution, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by flash chromatography on silica gel eluting with 20-70% EtOAc in hexanes to yield 47 mg (67%) of compound **424A** as a brown solid.

B. (3aα,4β,7β,7aα)-7-[Octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2,1,3-benzothiadiazole-4-carbonitrile (424B)

A mixture of compound **424A** (35 mg, 0.20 mmol), compound **20A** (45 mg, 0.23 mmol), $MgSO_4$ (60 mg, 0.50 mmol), Et_3N (139 μL, 1.0 mmol) and DME (200 μL) was placed in a sealed tube and heated at 135°C for 14 h. After cooling to rt the mixture was filtered through Celite eluting with MeOH to yield a dark solid which was purified by a combination of flash chromatography on silica gel eluting with 10-50% EtOAc in hexanes reverse phase preparative HPLC (YMC S5 ODS 20 x 100 mm eluting with 27-100% aqueous methanol over 10 min containing 0.1% TFA, 20 mL/min) to give 36 mg (51%) of compound **424B** as a yellow solid. HPLC: 98% at 2.45 min (retention time) (YMC S5 ODS column 4.6 x 50 mm Ballistic, 10-90% aqueous methanol over 4 minutes containing 0.2% H_3PO_4, 4 mL/min, monitoring at 220 nm). MS (DCI): m/z 355.0 $[M+H]^+$.

Example 425

(3aα,4β,7β,7aα)-*N*-[2-[2-(4-Cyano-1-naphthalenyl)octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindol-4-yl]ethyl]-4-fluoro-*N*-methylbenzamide (425B)

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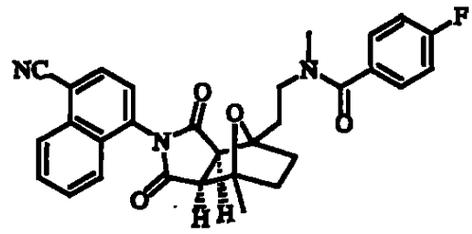
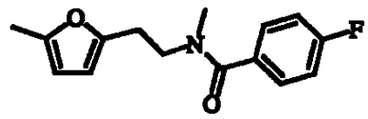


A. 4-Fluoro-*N*-methyl-*N*-[2-(5-methyl-furan-2-yl)-ethyl]-benzamide (425A)



NaH (60% dispersion in oil, 65 mg, 1.63 mmol) was added portionwise to a solution of 4-fluoro-*N*-[2-(5-methyl-2-furanyl)ethyl]benzamide (269 mg, 1.09 mmol, 237A) in THF (5 mL). After gas evolution ceased, iodomethane (0.14 mL, 2.18 mmol) was added drop-wise. Once HPLC analysis showed the reaction to be 50% complete, the mixture was concentrated under reduced pressure and resubjected to the above conditions. After all the starting material was consumed, H_2O was added and the resulting mixture was extracted with EtOAc (2 X 5 mL). The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with 20% acetone/$CHCl_3$ gave 238 mg (84%) of compound 425A. HPLC: 98% at 2.94 min (retention time) (Phenomenex-prime S5-C18 column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z [M+H] = 262.38.

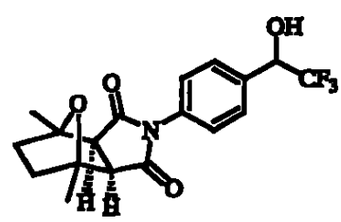
B. (3aα,4β,7β,7aα)-*N*-[2-[2-(4-Cyano-1-naphthalenyl)octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindol-4-yl]ethyl]-4-fluoro-*N*-methylbenzamide (425B)

A solution of compound 425A (183 mg, 0.75 mmol) and 4-(2,5-dihydro-2,5-dioxo-1H-1-yl)-1-naphthalenecarbonitrile (174 mg, 0.75 mmol) in benzene (1 mL) was heated at 60°C for 15 hr. The reaction mixture was concentrated under reduced pressure to give 357 mg crude intermediate. The crude intermediate (156 mg) was

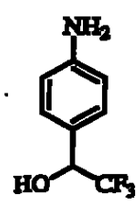
dissolved in EtOAc (6 mL) and 10% Pd/C (16 mg) was added and the mixture was stirred under a hydrogen balloon overnight. The reaction mixture was filtered through a pad of Celite and concentrated under reduced pressure. Purification by reverse phase preparative HPLC (YMC S5 ODS 20 X 100 mm, 20-100% aqueous methanol over 15 minutes containing 0.1% TFA, 20 mL/min, monitoring at 220 nm) gave 160.3 mg (72%) of compound 425B as an off-white solid. HPLC: 99% at 3.23 min (retention time) (Phenomenex-prime S5-C18 column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z [M+H] = 512.19.

Example 426

(3aα,4β,7β,7aα)-Hexahydro-4,7-dimethyl-2-[4-(2,2,2-trifluoro-1-hydroxyethyl)phenyl]-4,7-epoxy-1H-isoindole-1,3(2H)-dione (426B)



A. 1-(4-Amino-phenyl)-2,2,2-trifluoro-ethanol (426A)



Compound 426A was made according to the procedure described in Stewart, R. et al. *Can. J. Chem.* 58, 2491-2496 (1980). $NaBH_4$ (47 mg, 1.235 mmol) was added to a solution of p-aminotrifluoroacetophenone (155.7 mg, 0.823 mmol, synthesized as described by Klabunde, K. J. *et al. J. Org. Chem.* 35, 1711-1712 (1970)) in isopropanol (3 mL) at rt. After 30 min the reaction was quenched with phosphate buffer (pH 7.2), diluted with H_2O and extracted with EtOAc (2 X 10 mL).

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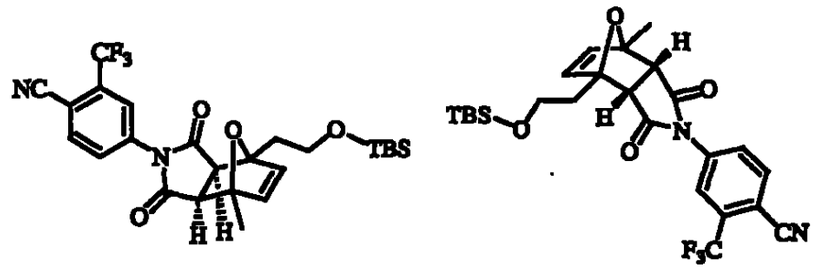
The combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure to give 154 mg (98%) of compound **426A** as a tan solid. The material was used directly in the next step without purification. HPLC: 99% at 0.42 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z [M+H] = 192.13.

B. (3aα,4β,7β,7aα)-Hexahydro-4,7-dimethyl-2-[4-(2,2,2-trifluoro-1-hydroxyethyl)phenyl]-4,7-epoxy-1H-isoindole-1,3(2H)-dione (426B)

A mixture of compound **426A** (75.3 mg, 0.394), compound **20A** (51.5 mg, 0.262 mmol), triethylamine (0.15 mL) and $MgSO_4$ (50 mg) in toluene (1 mL) was heated in a sealed tube to 135°C for 15 hr. The mixture was filtered and concentrated under reduced pressure. Purification by reverse phase preparative HPLC (YMC S5 ODS 20 X 100 mm, 20-100% aqueous methanol over 15 minutes containing 0.1% TFA, 20 mL/min, monitoring at 220 nm) gave 63.1 mg (65%) of compound **426B** as a white solid. HPLC: 98% at 2.49 min (retention time) (Phenomenex-prime S5-C18 column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z [M+H] = 370.16.

Example 427

(3aα,4β,7β,7aα)-4-[4-[2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]-1,3,3a,4,7,7a-hexahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile & (3aα,4α,7α,7aα)-4-[4-[2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]-1,3,3a,4,7,7a-hexahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile (427i & 427ii)



Compound **204A** (2.00 g, 8.50 mmol) and 4-(2,5-dihydro-2,5-dioxo-1H-pyrrol-1-yl)-2-trifluoromethylbenzonitrile (1.50 g, 5.60 mmol) were mixed in benzene (5.0 mL) and heated at 60°C for 14 h, then cooled to 25°C. The solvent was removed at 40°C under vacuum for 1 h to give the crude material which was purified by flash chromatography on SiO_2 eluting with 0.5% EtOAc/CH_2Cl_2 to give 2.0 g of compound **427i** and 1.3 g of compound **427ii**, both as light brown solids. Compound **427i**: HPLC: 95% at 4.200 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 507.1 $[M+H]^+$. Compound **427ii**: HPLC: 95% at 4.20 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 507.1 $[M+H]^+$.

Example 428

[3a*R*-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile & [3a*S*-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile (428i & 428ii)

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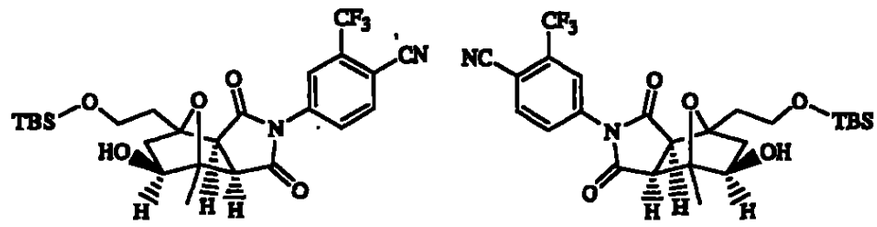


Compound **427i** (1.40 g, 2.77 mmol) and $RhCl(PPh_3)_3$ (0.128 g, 0.14 mmol) were mixed in a flask. The flask was then evacuated and filled with argon three times, followed by the syringe addition of THF (3.0 mL). Once all particulates were dissolved, catecholborane (0.59 mL, 5.54 mmol) was added dropwise. The reaction mixture was stirred at 25°C under argon for 30 min, then cooled to 0 °C. Phosphate buffer (pH 7, 20 mL) was added, followed by EtOH (10 mL), 30% H_2O_2/H_2O (2 mL). The reaction mixture was stirred at 0°C for 3 h, then extracted with dichloromethane (3 x 25 mL). The combined organic layers were washed with 1 N NaOH (25 mL), 10% Na_2SO_3 (25 mL) and brine (25 mL). The crude material was then concentrated *in vacuo* and purified by flash chromatography on SiO_2 eluting with 2% $EtOAc/CH_2Cl_2$ to 10% $EtOAc/CH_2Cl_2$ to give 0.63 g of a racemic mixture of compounds **428i** & **428ii** as a light yellow solid. HPLC: 99% at 3.867 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 525.1 [M+H]

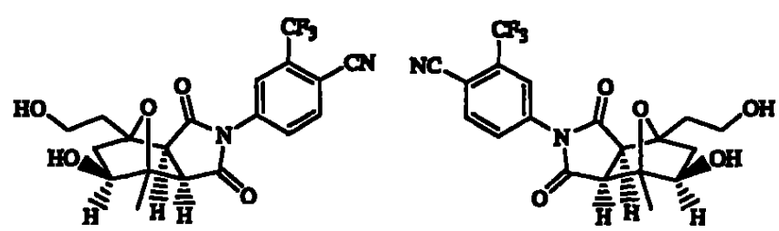
The racemic mixture of compounds **428i** & **428ii** was separated by normal phase preparative chiral HPLC using a Chiracel OD column (5 cm x 50 cm), eluting with 13% solvent B (EtOH) in solvent A (hexanes), flow rate: 50 mL/min. Compound **428i** eluted from 34 min to 38 min and compound **428ii** eluted from 44 min to 49 min. Enantiomeric excess was determined by chiral HPLC. Compound **428i**: >99% ee (12.576 min (retention time) (Chiralcel OJ column 4.6 x 250 mm eluting with isocratic 85% heptane / 15% MeOH/ethanol (1:1), 1 mL/min, monitoring at 220 nm,

40°C). Compound 428ii: 99% ee (18.133 min (retention time) (Chiralcel OJ column 4.6 x 250 mm eluting with isocratic 85% heptane / 15% MeOH/ethanol (1:1), 1 mL/min, monitoring at 220 nm, 40°C).

The absolute configurations for compounds 428i & 428ii were not established. For simplicity in nomenclature, compound 428i is designated herein as having an "R" configuration and compound 428ii as having an "S" configuration. Enantiomerically pure products derived from compound 428i are designated herein as having a "R" configuration and enantiomerically pure products derived from compound 428ii are designated herein as having an "S" configuration.

Example 429

[3a*R*-(3aα,4β,5β,7β,7aα)]-4-[Octahydro-5-hydroxy-7-(2-hydroxyethyl)-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile & [3a*S*-(3aα,4β,5β,7β,7aα)]-4-[Octahydro-5-hydroxy-7-(2-hydroxyethyl)-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile (429i & 429ii)



Compound 428i (180 mg, 0.34 mmol) was dissolved in 2% HCl/EtOH (5.0 mL). After 30 min, saturated $NaHCO_3$ was added and the aqueous layer was extracted with dichloromethane (20 mL x 3), washed with brine and dried over Na_2SO_4 to give 135 mg of compound 429i as a white solid. HPLC: 99% at 2.257 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4

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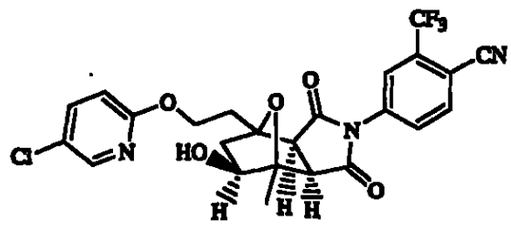
minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 411.1 $[M+H]^+$.

The above procedure was repeated with compound 428ii to yield the desired diol compound 429ii in similar yield.

Example 430

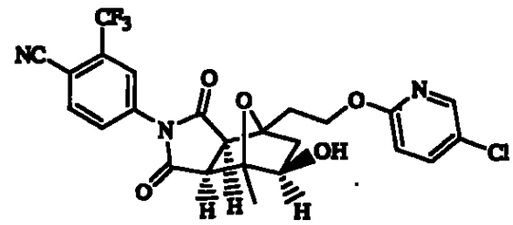
[3a*R*-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile (430)



Triphenylphosphine (0.026 g, 0.098 mmol) and DBAD (0.028 g, 0.098 mmol) were mixed in THF (0.5 mL). After allowing the previous mixture to react for 15 min, 2-hydroxy-6-chloropyridine (0.016 g, 0.100 mmol) was added, the mixture was allowed to stir for 10 min and compound 429i (0.020 g, 0.049 mmol) was added. The reaction mixture was stirred at 25°C for 2 h and then the crude material was purified by preparative TLC, eluting with 10% acetone/$CHCl_3$ to give 0.014 g of compound 430 as a light brown solid. HPLC: 100% at 3.370 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90 aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 522.08 $[M+H]^+$.

Example 431

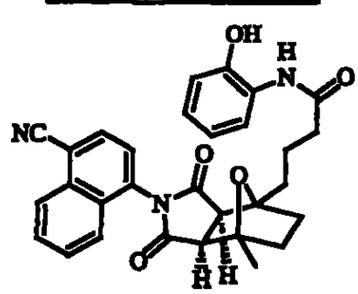
[3aS-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile (431)



Triphenylphosphine (0.026 g, 0.098 mmol) and DBAD (0.023 g, 0.098 mmol) were mixed in THF (0.5 mL). After allowing the previous mixture to react for 15 min, 2-hydroxy-6-chloropyridine (0.016 g, 0.100 mmol) was added, the mixture was allowed to stir for 10 min and compound **429ii** (0.020 g, 0.049 mmol) was added. The reaction mixture was stirred at 25°C for 2 h and then the crude material was purified by preparative TLC, eluting with 10% acetone/$CHCl_3$ to give 0.015 g of compound **431** as a light brown solid. HPLC: 100% at 3.870 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90 aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 522.08 $[M+H]^+$.

Example 432

(3aα,4β,7β,7aα)-2-(4-Cyano-1-naphthalenyl)octahydro-*N*-(2-hydroxyphenyl)-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindole-4-butanamide (432)



Compound **262** (0.100 g, 0.239 mmol) was dissolved in DMF (anhydrous, 1.5 mL), BOP (0.211 g, 0.478 mmol) was added followed by 2-aminophenol (0.052 g, 0.478 mmol) and *N*-methyl morpholine (0.052 mL,

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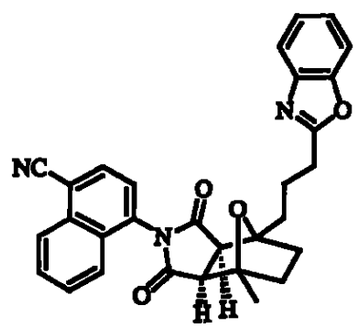
0.478 mmol). The reaction mixture was stirred at 25°C under argon for 3 h, then the crude material was purified by reverse phase preparative HPLC (YMC S5 ODS 20 X 100 mm, 20-100% aqueous methanol over 15 minutes containing 0.1% TFA, 20 mL/min, monitoring at 220 nm) to give 0.060 g of compound **432** as a light brown solid. HPLC: 100% at 3.037 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90 aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 510.34 $[M+H]^+$.

Example 433

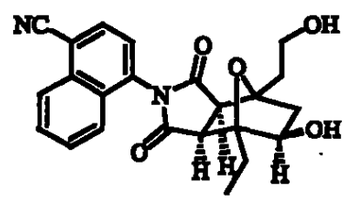
(3aα,4β,7β,7aα)-4-[4-[3-(2-Benzoxazolyl)propyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (433)



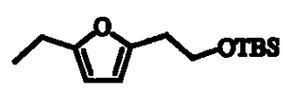
Triphenylphosphine (0.031 g, 0.118 mmol) and DBAD (0.027 g, 0.118 mmol) were mixed in THF (0.5 mL). After allowing the previous mixture to react for 15 min, compound **432** (0.030 g, 0.059 mmol) was added. The reaction mixture was stirred at 25°C for 2 h and then the crude material was purified by reverse phase preparative HPLC (YMC S5 ODS 20 X 100 mm, 20-100% aqueous methanol over 15 minutes containing 0.1% TFA, 20 mL/min, monitoring at 220 nm) to give 0.018 g of compound **433** as a light brown solid. HPLC: 100% at 3.357 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 492.37 $[M+H]^+$.

Example 434

(3aα,4β,5β,7β,7aα)-4-[4-Ethyloctahydro-5-hydroxy-7-(2-hydroxyethyl)-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (434C)

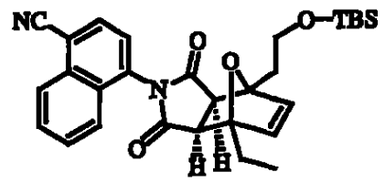


A. tert-Butyl-[2-(5-ethyl-furan-2-yl)-ethoxy]-dimethyl-silane (434A)



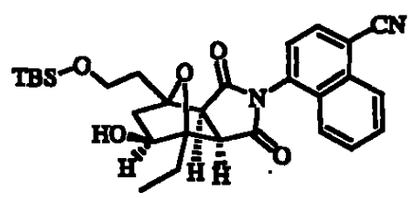
Imidazole (255 mg, 3.75 mmol) and TBSCl (414 mg, 2.75 mmol) were added to the solution of 245A (350 mg, 2.5 mmol) in DMF (4 mL). The mixture was stirred at rt for 15 hr and then 100 mg (0.66 mmol) of additional TBSCl was added to drive the reaction to completion. After stirring for an additional hour, the reaction mixture was diluted with diethylether (100 mL) and washed with water (20 mL), 1 N HCl (20 mL), water (20 mL) and brine (20 mL). The organic layer was dried over Na_2SO_4 and concentrated under reduced pressure to give 509 mg of compound 434A (80.3%) as a yellow oil.

B. (3aα,4β,7β,7aα)-4-[4-[2-[[(1,1-Dimethylethyl)-dimethylsilyl]oxy]ethyl]-4-ethyl-1,3,3a,4,7,7a-hexahydro-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (434B)



A solution of compound **434A** (509 mg, 2.00 mmol) and 4-(2,5-dihydro-2,5-dioxo-1H-1-yl)-1-naphthalenecarbonitrile (498 mg, 2.00 mmol) in benzene (2 mL) was heated at 60°C for 18 h. The reaction mixture was concentrated under reduced pressure to give 992 mg (99%) of crude compound **434B**, which was used directly in the next step without further purification.

C. (3aα,4β,5β,7β,7aα)-4-[7-[2-[[(1,1-Dimethylethyl)-dimethylsilyl]oxy]ethyl]-4-ethyloctahydro-5-hydroxy-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (434C)



A mixture of compound **434B** (992 mg, 1.98 mmol) and $RhCl_3(PPh_3)_3$ (183 mg, 0.198 mmol) was evacuated and filled with argon (3X). THF (20 mL) was added and once all particulates had dissolved, catecholborane (0.42 mL, 3.96 mmol) was slowly added dropwise. When the formation of product ceased, as was determined by HPLC, the reaction mixture was cooled to 0°C and quenched with phosphate buffer (34 mL, pH 7.2) followed by the addition of EtOH (19 mL) and 30% H_2O_2 (2.9 mL). After 2 h, additional phosphate buffer (6.8 mL, pH 7.2), EtOH (3.8 mL) and H_2O_2 (0.6 mL) were added. The reaction mixture was stirred at rt for 3 h. Once

the boronate intermediate was consumed, the mixture was extracted with CH_2Cl_2 (300 mL) and the combined organic layers were washed with 1 N NaOH, 10% aq. $NaHSO_3$ and brine and then dried over Na_2SO_4. Purification by flash chromatography on silica gel eluting with 10% MeOH/CH_2Cl_2 gave 75 mg (9.3%) of compound 434C as a gray solid. HPLC conditions: 97% at 2.43 min (retention time) (Phenomenex-prime S5-C18 column 4.6 x 50 mm, 10%-90% aqueous methanol over 4 minute gradient with 0.2% H_3PO_4, detecting at 220 nm). MS (ES): m/z 407.18 $[M+H]^+$.

D. (3aα,4β,5β,7β,7aα)-4-[4-Ethyloctahydro-5-hydroxy-7-(2-hydroxyethyl)-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (434D)

Compound 434C (24 mg, 0.046 mmol) was dissolved in 2% conc. HCl/EtOH (0.8 mL) and the mixture was stirred at rt for 20 min. Cold sat. $NaHCO_3$ was added to the mixture until the solution was basic (pH 8). The reaction was extracted with EtOAc (3 x 2 mL) and the combined organic layers were washed with brine (2 x 5 mL) and dried over anhydrous sodium sulfate. Concentration *in vacuo* gave 14 mg (75%) of compound 434D as a white solid. HPLC: 95% at 2.40 min (retention time) (YMC S5 ODS 4.6 x 50 mm, 10%-90% aqueous methanol over 4 minute gradient with 0.2% H_3PO_4, monitoring at 220 nm).

Example 435

(3aα,4β,5β,7β,7aα)-4-[7-[2-(4-Cyanophenoxy)ethyl]-4-ethyloctahydro-5-hydroxy-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (435)

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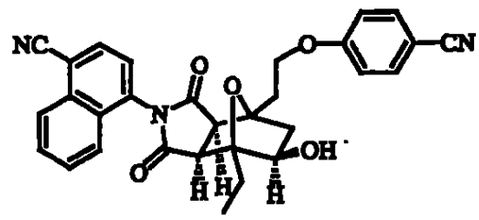
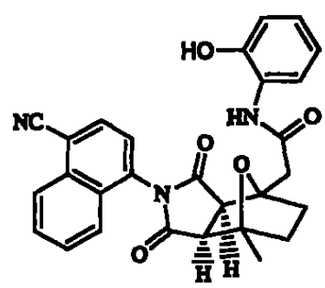


DBAD (39.6 mg, 0.172 mmol) was added to a solution of PPh_3 (45.1 mg, 0.172 mmol) in THF (0.8 mL). After stirring for 10 min, 4-cyanophenol (20.5 mg, 0.172 mmol) was added and the reaction mixture was stirred for an additional 5 min. Compound 434C (25.0 mg, 0.062 mmol) was added and the mixture was stirred at rt for 2 h. The reaction was concentrated under reduced pressure. Purification by Prep TLC eluting with 10% acetone/$CHCl_3$ gave 18.1 mg (0.036 mmol, 57.6%) of compound 435. HPLC conditions: 96% at 3.15 min (retention time) (YMC S5 ODS 4.6 X 50 mm, 10%-90% aqueous methanol over 4 minute gradient with 0.2% H_3PO_4, detecting at 220 nm). MS (ES): m/z 508.14 $[M+H]^+$.

Example 436

(3aα,4β,7β,7aα)-2-(4-Cyano-1-naphthyalenyl)octahydro-*N*-(2-hydroxyphenyl)-7-methyl-1,3-dioxo-4,7-expoxy-4H-isoindole-4-ethanamide (436)

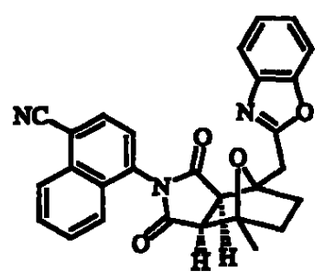


Compound 234B (0.100 g, 0.256 mmol) was dissolved in DMF (anhydrous, 1.5 mL), BOP (0.225 g, 0.51 mmol) was added followed by 2-aminophenol (0.056 g, 0.51 mmol) and *N*-methyl morpholine (0.056 mL, 0.51 mmol). The reaction mixture was stirred at 25°C under argon for 3 h,

then the crude material was purified by reverse phase preparative HPLC (YMC S5 ODS 20 X 100 mm, 20-100% aqueous methanol over 15 minutes containing 0.1% TFA, 20 mL/min, monitoring at 220 nm) to give 0.078 g of compound **436** as a light brown solid. HPLC: 100% at 3.037 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 482.34 $[M+H]^+$.

Example 437

(3aα,4β,7β,7aα)-4-[4-(2-Benzoxazolylmethyl)octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (437)



Triphenylphosphine (0.082 g, 0.312 mmol) and DBAD (0.072 g, 0.312 mmol) were mixed in THF (0.5 mL). After allowing the previous mixture to react for 15 min, compound **436** (0.075 g, 0.156 mmol) was added. The reaction mixture was stirred at 25°C for 2 h and then the crude material was purified by reverse phase preparative HPLC (YMC S5 ODS 20 X 100 mm, 20-100% aqueous methanol over 15 minutes containing 0.1% TFA, 20 mL/min, monitoring at 220 nm) to give 0.052 g of compound **437** as a light brown solid. HPLC: 100% at 3.443 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 464.18 $[M+H]^+$.

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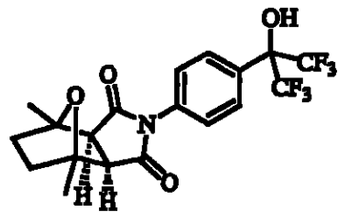
Example 438

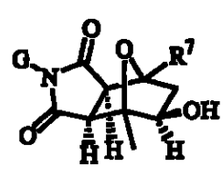
(3aα,4β,7β,7aα)-Hexahydro-4,7-dimethyl-2-[4-[2,2,2-trifluoro-1-hydroxy-1-(trifluoromethyl)ethyl]phenyl]-4,7-epoxy-1H-isoindole-1,3(2H)-dione (438)



A mixture of 2-(4'-aminophenyl)-1,1,1,3,3,3-hexafluoro-2-propanol (95.7 mg, 0.369), compound 20A (48.3 mg, 0.246 mmol), triethylamine (0.15 mL) and $MgSO_4$ (50 mg) in toluene (1 mL) was heated in a sealed tube to 135°C overnight. The mixture was filtered and concentrated under reduced pressure. Purification by reverse phase preparative HPLC (YMC S5 ODS 20 X 100 mm, 20-100% aqueous methanol over 15 minutes containing 0.1% TFA, 20 mL/min, monitoring at 220 nm) gave 44.0 mg (41%) of compound 438 as a white solid. HPLC: 99% at 3.10 min (retention time) (Phenomenex-prime S5-C18 column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z [M+H] = 438.14.

Examples 439 to 454

Additional compounds of the present invention were prepared by procedures analogous to those described above. The compounds of Examples 439 to 454 have the following structure (L is a bond):



where G, R^7, the compound name, retention time, molecular mass, and the procedure employed, are set forth in Table 9. The absolute configuration

for the following compounds was not determined. For simplicity in nomenclature, compound **243Di** is designated herein as having an "S" configuration and compound **243Dii** as having an "R" configuration. Enantiomerically pure products derived from compound **243Di** are designated herein as having an "S" configuration and enantiomerically pure products derived from compound **243Dii** are designated herein as having an "R" configuration. Similarly, compound 428i is designated herein as having an "S" configuration and compound 428ii as having an "R" configuration. Enantiomerically pure products derived from compound 428i are designated herein as having an "S" configuration and enantiomerically pure products derived from compound 428ii are designated herein as having an "R" configuration.

The chromatography techniques used to determine the compound retention times of Table 9 are as follows: LCMS = YMC S5 ODS column, 4.6 X 50 mm eluting with 10-90% MeOH/H_2O over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm. LCMS* = YMC S5 ODS column, 4.6 X 50 mm eluting with 10-90% MeOH/H_2O over 2 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm. LC = YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% MeOH/H_2O over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm. The molecular mass of the compounds listed in Table 9 were determined by MS (ES) by the formula m/z.

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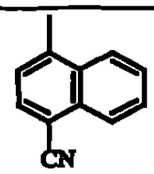
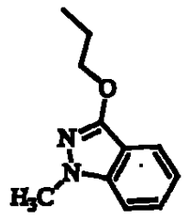
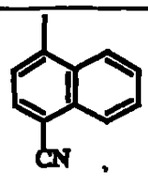
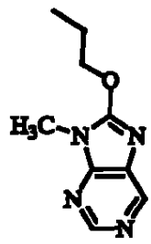
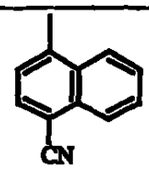
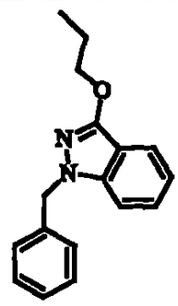
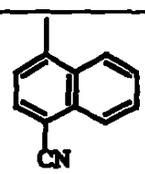
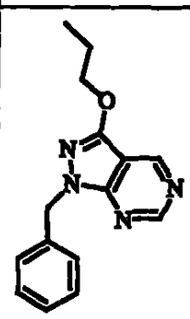
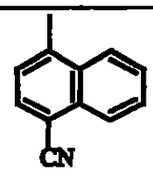
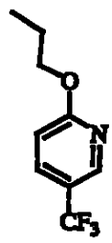
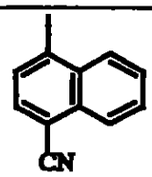
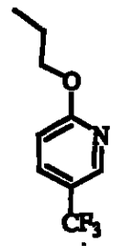
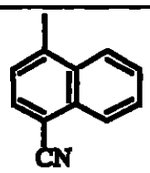
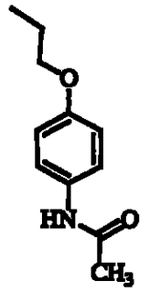
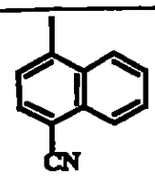
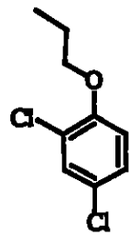
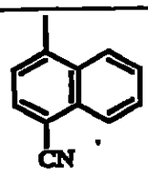
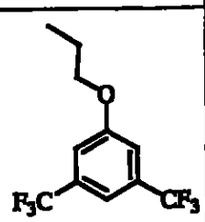
Table 9

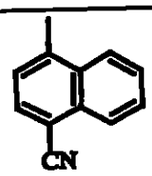
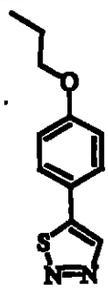
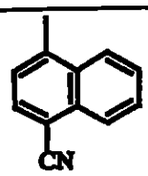
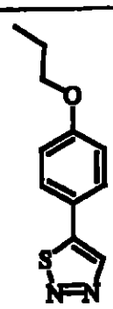
Ex. No	G	R^7	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
439			[3a*R*-(3aα,4β,5β,7β,7aα)]-4-[Octahydro-5-hydroxy-4-methyl-7-[2-[(1-methyl-1H-indazol-3-yl)oxy]ethyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.33 LC 523.3 $[M+H]^+$	251, 253
440			[3a*R*-(3aα,4β,5β,7β,7aα)]-4-[Octahydro-5-hydroxy-4-methyl-7-[2-[(9-methyl-9H-purin-8-yl)oxy]ethyl]-1,3-dioxo-4,7-epoxy-2H-	2.34 LC 525.2 $[M+H]^+$	251, 253

Ex. No	G	R^7	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
			isoindol-2-yl]-1-naphthalenecarbonitrile		
441			[3a*R*-(3aα,4β,5β,7β,7aα)]-4-[Octahydro-5-hydroxy-4-methyl-1,3-dioxo-7-[2-[[1-(phenylmethyl)-1H-indazol-3-yl]oxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.78 LC	251, 253
442			[3a*R*-(3aα,4β,5β,7β,7aα)]-4-[Octahydro-5-hydroxy-4-methyl-1,3-dioxo-7-[2-[[1-	3.37 LC	251, 253

Ex. No	G	R^7	Compound Name	Retention Time Min/ Molecular Mass	Procedure of Ex.
			(phenylmethyl)-1H-pyrazolo[3,4-d]pyrimidin-3-yl]oxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile		
443			[3aS-(3aα,4β,5β,7β,7aα)]-4-[Octahydro-5-hydroxy-4-methyl-1,3-dioxo-7-[2-[[5-(trifluoromethyl)-2-pyridinyl]oxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.45 LC 538.23 $[M+H]^+$	243Di, 244i

Ex. No	G	R^7	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
444			[3a*R*-(3aα,4β,5β,7β,7aα)]-4-[Octahydro-5-hydroxy-4-methyl-1,3-dioxo-7-[2-[[5-(trifluoromethyl)-2-pyridinyl]oxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.46 LC 538.24 $[M+H]^+$	243Dii, 244ii
445			[3a*R*-(3aα,4β,5β,7β,7aα)]-*N*-[4-[2-[2-(4-Cyano-1-naphthalenyl)octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-7H-isoindol-7-	2.747 LC 526.28 $[M+H]^+$	243Dii, 244ii

Ex. No	G	R'	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
			yl]ethoxy]phenyl]acetamide		
446			[3a*R*-(3aα,4β,5β,7β,7aα)]-4-[7-[2-(2,4-Dichlorophenoxy)ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.71 LC 537.17 $[M+H]^+$	243Dii, 244ii
447			[3a*R*-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[3,5-Bis(trifluoromethyl)phenoxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-	3.89 LC 605.25 $[M+H]^+$	243Dii, 244ii

Ex. No	G	R'	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
			epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile		
448			[3aS-(3aα,4β,5β,7β,7aα)]-4-[Octahydro-5-hydroxy-4-methyl-1,3-dioxo-7-[2-[4-(1,2,3-thiadiazol-5-yl)phenoxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.14 LC 553.1 $[M+H]^+$	243Di, 244i
449			[3a*R*-(3aα,4β,5β,7β,7aα)]-4-[Octahydro-5-hydroxy-4-methyl-1,3-	3.15 LC 553.23 $[M+H]^+$	243Dii, 244ii

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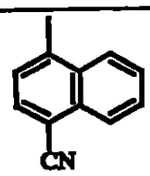
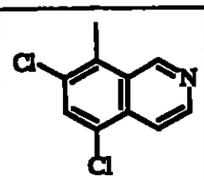
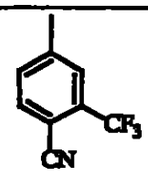
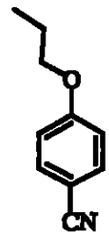
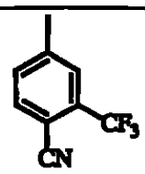
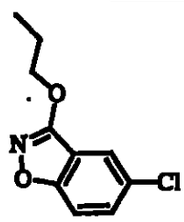
Ex. No	G	R^7	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
			dioxo-7-[2-[4-(1,2,3-thiadiazol-5-yl)phenoxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile		
450			[3a*R*-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[(5,7-Dichloro-8-quinolinyl)oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, trifluoroacetate (1:1)	3.70 LC 588.26 $[M+H]^+$	243Dii, 244ii

Ex. No	G	R^7	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
451			[3aS-(3aα,4β,5β,7β,7aα)]-4-[7-[2-(4-Cyanophenoxy)ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile	3.087 LC 512.13 $[M+H]^+$	431
452			[3aS-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[(5-Chloro-1,2-benzisoxazol-3-yl)oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-	3.563 LC 562.08 $[M+H]^+$	431

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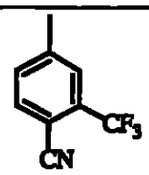
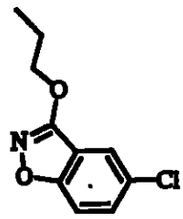
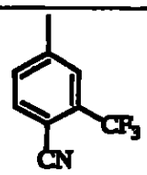
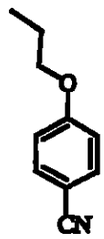
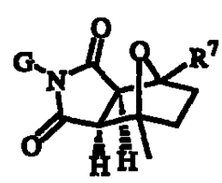
Ex. No	G	R^7	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
			isoindol-2-yl]-2-(trifluoromethyl)benzonitrile		
453			[3a*R*-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[(5-Chloro-1,2-benzisoxazol-3-yl)oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile	3.57 LC 562.08 $[M+H]^+$	430
454			[3a*R*-(3aα,4β,5β,7β,7aα)]-4-[7-[2-(4-Cyanophenoxy)ethyl]octahydro-5-	3.087 LC 512.08 $[M+H]^+$	430

Ex. No	G	R^7	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
			hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile		

Examples 455 to 457

Additional compounds of the present invention were prepared by procedures analogous to those described above. The compounds of Examples 455 to 457 have the following structure (L is a bond):



where G, R^7, the compound name, retention time, molecular mass, and the procedure employed, are set forth in Table 10. The absolute configuration for the following compounds was not determined. For simplicity in nomenclature, compound 238i is designated herein as having an "R" configuration and compound 238ii as having an "S" configuration. Enantiomerically pure products derived from compound 238i are designated herein as having an "R" configuration and enantiomerically pure products derived from compound 238ii are designated herein as having an "S" configuration.

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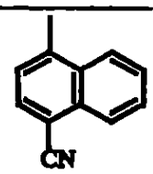
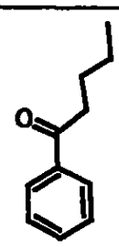
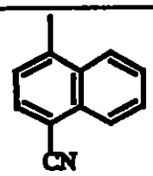
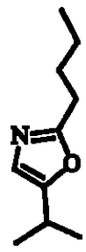
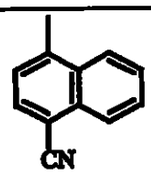
The chromatography techniques used to determine the compound retention times of Table 10 are as follows: LCMS = YMC S5 ODS column, 4.6 X 50 mm eluting with 10-90% MeOH/H_2O over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm. LCMS* = YMC S5 ODS column, 4.6 X 50 mm eluting with 10-90% MeOH/H_2O over 2 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm. LC = YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% MeOH/H_2O over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm. The molecular mass of the compounds listed in Table 10 were determined by MS (ES) by the formula m/z.

Table 10

Ex. No	G	R^7	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
455			(3aα,4β,5β,7β,7aα)-4-[Octahydro-4-methyl-1,3-dioxo-7-(4-oxo-4-phenylbutyl)-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.53 LC 479.35 $[M+H]^+$	265, 266

Ex. No	G	R'	Compound Name	Retention Time Min./ Molecular Mass	Procedure of Ex.
456			(3aα,4β,5β,7β,7aα)-4-[Octahydro-4-methyl-7-[3-[5-(1-methylethyl)-2-oxazolyl]propyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.547 LC 484.28 $[M+H]^+$	248, 249
457			[3aα,4β,5β,7β,7aα(E)]-4-[Octahydro-4-methyl-7-[3-[5-(1-methylethyl)-2-oxazolyl]-2-propenyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenec	3.66 LC 482.28 $[M+H]^+$	248, 249

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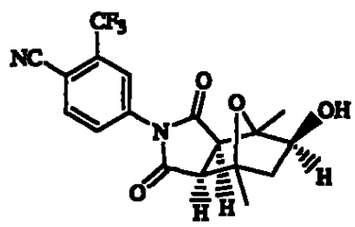
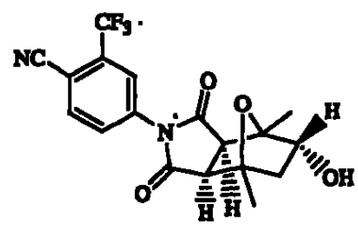
Ex. No	G	R^7	Compound Name	Retention Time Min/ Molecular Mass	Procedure of Ex.
			arbonitrile		

Example 458

(3aα,4β,5β,7β,7aα)-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile & (3aα,4β,5α,7β,7aα)-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (221B & 222D)





Compound 20B was converted to compounds 221B and 222D (also synthesized as compounds 221B and 222D) by biotransformation.

Compound 20B was hydroxylated by *Amycolatopsis orientalis* (ATCC 43491). A 1 mL culture from a frozen vial was used to inoculate 100 mL medium in a 500 mL portion Erlenmeyer flask and the flask was incubated at 28°C, at 200 rpm for 3 days. A 10 mL portion of this culture was used to inoculate 100 mL medium in a 500 mL Erlenmeyer flask and the flask was incubated at 28°C, at 200 rpm for 1 day. 10 mL portions of the 1-day culture were distributed to each of three 50 mL flasks. Compound 20B (3 mg in 0.1 mL methanol) was added to each culture and the incubations were continued for 3 days. The culture broth in each flask was extracted with 20 mL ethyl acetate, and the pooled ethyl acetate extracts were evaporated to dryness at 40°C under a nitrogen stream. The residue was dissolved in 1.2 mL methanol and analyzed by HPLC, LC/MS and LC/NMR. The solution contained 2.5 mg of remaining Compound 20B, 1.6 mg of compound 221B, and 1.3 mg of compound 222D. MS and NMR analyses were in agreement with the structures shown above.

Medium: 0.5% toasted nutrisoy, 2% glucose, 0.5% yeast extract, 0.5% K_2HPO_4, 0.5% NaCl, adjusted to pH 7 with HCl (R. V. Smith and J. P. Rosazza, Arch. Biochem. Biophys., 161, 551-558 (1974)

HPLC Analysis

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Column: Phenomenex Luna C18, 150x2 mm, 5μ

mobile phase: solvent A: 95% 20 mM ammonium acetate pH 5.1, 5% acetonitrile

solvent B: 95% acetonitrile, 5% 20 mM ammonium acetate pH 5.1

linear gradient going from 100% solvent A to 5% solvent A in 25 minutes followed by equilibration at 100% solvent A for 8 minutes.

temperature: 40 °C

detection: 250 nm

injection volume: 1 μL

retention times: compound **20B**, 20.8 min; compound **221B**, 16.5 min; compound **222D**, 17.8 min

<u>HPLC Conditions</u>

Chiral HPLC conditions were employed for the separation of enantiomers and achiral HPLC conditions were employed for the separation of diastereomers of the hydroxylated analogs of compound **20B** (i.e., compounds **221B** and **222D** and compounds **254i** and **254ii**)

Two methods were used under chiral HPLC conditions, reverse phase (RP) for chiral analysis of biotransformation products in biological samples and normal phase (NP) for non-biological samples.

Chiral RP-HPLC Condition

Column:	CHIRALPAK AD-R	
	4.6 x 250 mm, 10 μ	
Temperature:	40°C	
Injection Volume:	5 or 20 μL	
Mobile Phase:	A:	MeCN
	B:	H_2O
	Isocratic, 30% of A, 18 min.	
Flow Rate:	1 mL/min.	
UV Detection:	242 nm	

Chiral NP-HPLC Condition

Column:	CHIRALPAK AD	
	4.6 x 250 mm, 10 μ	
Temperature:	25°C	
Injection Volume:	5 or 20 μL	
Mobile Phase:	A:	Heptane
	B:	MeOH/Ethanol (1:1)
	Isocratic, 80% of A, 20 min.	
Flow Rate:	1 mL/min.	
UV Detection:	242 nm	

Under these conditions compounds 254I and 254II had retention times of 8.5 minutes and 9.85 minutes, respectively.

Reverse phase HPLC was employed for the separation of the diastereomeric compounds 221B and 222D:

Mobile Phase:

Solvent A: 95% 20 mM ammonium acetate pH 5.1, 5% acetonitrile
Solvent B: 95% acetonitrile, 5% 20 mM ammonium acetate pH 5.1

Gradient:

Linear gradient going from 100% solvent A to 5% solvent A in 25 minutes followed by equilibration at 100% solvent A for 8 minutes. Total run time of 36 minutes.

Flow Rate:

0.2 mL/min

Column:

Phenomenex Luna 5 micron C_{18} 150X2.0 mm id

Detection:

UV detection at 242 nm

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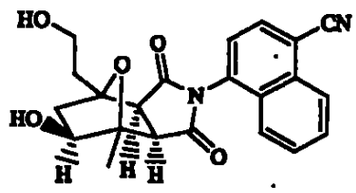
Under these conditions, compounds 221B and 222D had retention times of 18.983 min and 20.362 min, respectively.

Example 459

(3aα,4β,5β,7β,7aα)-4-[Octahydro-5-hydroxy-7-(2-hydroxyethyl)-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (459)



Compounds 223A and 331 were converted to compound 459 by biotransformation.

Microbial hydroxylation of compound 223A

1. Reaction

To a 500 mL flask containing 100 mL of the transformation medium was added one frozen vial (approximately 2 mL) of *Streptomyces griseus* ATCC 10137. The transformation medium was prepared as follows: to a 2 L plastic beaker was added 20 g of dextrose, 5.0 g of yeast extract, 5.0 g of soybean meal, 5.0 g of sodium chloride, 5.0 g of potassium phosphate (diabasic) and 1 L of deionized water, and the mixture was stirred at room temperature for 3 to 30 min. The pH of the mixture was then adjusted to 7.0 with 1 N HCl or 1 N NaOH. The resulting mixture was dispensed into 500 mL flasks (100 mL per flask). The flasks were covered with Bio/Wrap and autoclaved at 121°C for 15 min. and cooled down to room temperature before use.

The culture was incubated at 28°C and at 250 rpm for 24 hours. Ten mL of the resulting culture was transferred to a 50 mL flask, to which 1 mg of compound 223A in 0.2 mL ethanol was added. The flask was incubated at 28°C and 250 rpm for 24 hours, and the reaction culture was extracted with EtOAc (10 mL). The EtOAc

extract was dried under N_2 and the residue was dissolved in 1 mL of MeOH (reaction extract).

2. Product analysis

HPLC:

10 µL of the reaction extract was injected into HPLC column (YMC ODS-AQ C-18 column, 150 x 6.0 mm i.d.). The column was eluted with 1 mM HCl in water/CH_3CN at 1.2 mL/min flow rate: 30 to 60% CH_3CN over 8 min, 60 to 85% CH_3CN over 0.5 min, 85% CH_3CN for 1 min, 85 to 30% CH_3CN over 0.5 min. The eluents were monitored at 300 nm. Two major peaks with about a 1 to 1 area ratio were observed, which had the same UV spectra as those of compounds 459 and 331, and had retention times of 4.55 min and 7.23 min, respectively, matching the retention times of authentic samples of compound 459 (4.53 min) and compound 331 (7.2 min).

LC/MS

The reaction extract: two major UV peaks.

Peak 1, Tr 4.68 min: 391 $[M+H]^+$, 343, 319, 303, 289

Peak 2, Tr 5.35 min: 375 $[M+H]^+$, 345

Authentic samples

Compound 459, Tr 4.82 min: 391 $[M+H]^+$, 343, 319, 289

Compound 331, Tr 5.48 min: 375 $[M+H]^+$, 345

Microbial hydroxylation of Compound 331

To a 500 mL flask containing 100 mL of the transformation medium was added one frozen vial (approximately 2 mL) of *Streptomyces griseus* ATCC 10137. The transformation medium was prepared as follows: to a 2 L plastic beaker was added 20 g of dextrose, 5.0 g of yeast extract, 5.0 g of

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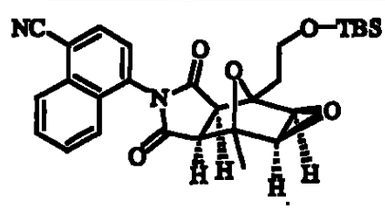
soybean meal, 5.0 g of sodium chloride, 5.0 g of potassium phosphate (dibasic) and one L of deionized water, and the mixture was stirred at room temperature for 3 to 30 min. The pH of the mixture was then adjusted to 7.0 with 1 N HCl or 1 N NaOH. The resulting mixture was dispensed into 500 mL flasks (100 mL per flask). The flasks were covered with Bio/Wrap and autoclaved at 121°C for 15 min. and cooled down to room temperature before use.

The culture was incubated at 28°C and 250 rpm for 3 days. One mL of the resulting culture was added to a 500 mL flask containing 100 mL of the transformation medium and the flask was incubated at 28°C and 250 rpm for 24 hours. Ten mL of the resulting culture was transferred to a 50 mL flask, to which 1 mg of compound 331 in 0.2 mL ethanol was added. The flask was incubated at 28°C and 250 rpm for 23 hours. HPLC analysis showed that the peak area ratio of compound 459 to compound 331 in the reaction culture was about 1.1/1.

Example 460

(1aα,2β,2aα,5aα,6β,6aα)-4-[2-[2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]octahydro-6-methyl-3,5-dioxo-2,6-epoxy-4H-oxireno[f]isoindol-4-yl]-1-naphthalenecarbonitrile (460)

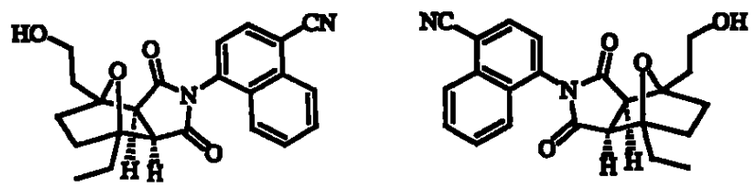


Compound 231A (2.00 g, 4.10 mmol) was dissolved in dicholomethane (40 mL) and cooled to 0°C. mCPBA (2.36 g, 8.20 mmol) was added. The reaction mixture was then warmed up to room temperature and stirred under argon for 18 hours, followed by the addition of 10% Na_2SO_3 (25 mL) and saturated $NaHCO_3$ (25 mL). After stirring for 20 minutes, the organic layer was separated and the aqueous layer was extracted with dicholomethane (3 x 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated under reduced pressure

to give 2.0 g compound 460 as light yellow solid. HPLC: 99% at 4.00 min (retention time) (Phenomenex-prime S5-C18 column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z [M+H] = 505.19

Example 461

[3a*R*-(3aα,4β,7β,7aα)]-4-[4-Ethyloctahydro-7-(2-hydroxyethyl)-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile & [3a*S*-(3aα,4β,7β,7aα)]-4-[4-Ethyloctahydro-7-(2-hydroxyethyl)-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (461i & 461ii)



The racemic mixture of compounds 245C was separated by normal phase preparative chiral HPLC using a Chiracel AD column (5 cm x 50 cm), eluting with 20% solvent B (50% MeOH/EtOH) in solvent A (Heptane), flow rate: 50 mL/min. Compound 461i eluted from 80 min to 100 min and compound 461ii eluted from 125 min to 150 min.

The absolute conformation for compounds 461i and 461ii was not determined. For simplicity in nomenclature, compound 461i is designated herein as having an "R" configuration and compound 461ii as having an "S" configuration. Enantiomerically pure products derived from compound 461i are designated herein as having an "R" configuration and enantiomerically pure products derived from compound 461ii are designated herein as having an "S" configuration.

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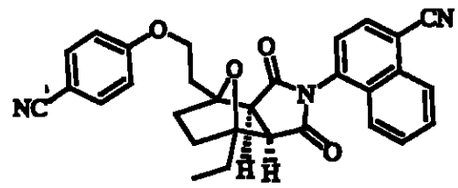
Example 462

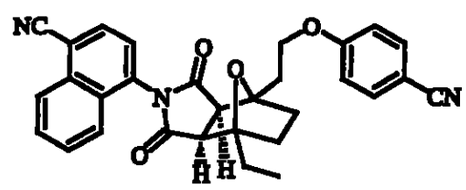
[3aR-(3aα,4β,7β,7aα)]-4-[4-[2-(4-Cyanophenoxy)ethyl]-7-ethyloctahydro-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (462)



DBAD (29.5 mg, 0.128 mmol) was added to a solution of PPh_3 (33.6 mg, 0.128 mmol) in THF (0.5 mL). After stirring for 10 min, 4-cyanophenol (15.2 mg, 0.128 mmol) was added and the reaction mixture was stirred for an additional 5 min. Compound 461i (18.3 mg, 0.047 mmol) was added and the mixture was stirred at rt for 2 h. The reaction was concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with 40% EtOAc/hexane gave 16.9 mg (0.034 mmol, 73.2%) of compound 462. HPLC conditions: 98% at 3.64 min (retention time) (YMC S5 ODS 4.6 X 50 mm, 10%-90% aqueous methanol over 4 minute gradient with 0.2% H_3PO_4, detecting at 220 nm). MS (ES): m/z 492.23 $[M+H]^+$.

Example 463

[3aS-(3aα,4β,7β,7aα)]-4-[4-[2-(4-Cyanophenoxy)ethyl]-7-ethyloctahydro-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (463)



DBAD (29.5 mg, 0.128 mmol) was added to a solution of PPh_3 (33.6 mg, 0.128 mmol) in THF (0.5 mL). After stirring for 10 min, 4-cyanophenol (15.2 mg, 0.128 mmol) was added and the reaction mixture

was stirred for an additional 5 min. Compound **461ii** (18.8 mg, 0.047 mmol) was added and the mixture was stirred at rt for 2 h. The reaction was concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with 40% EtOAc/hexane gave 18.1 mg (0.037 mmol, 78.4%) of compound **463**. HPLC conditions: 97% at 3.63 min (retention time) (YMC S5 ODS 4.6 X 50 mm, 10%-90% aqueous methanol over 4 minute gradient with 0.2% H_3PO_4, detecting at 220 nm). MS (ES): m/z 492.17 $[M+H]^+$.

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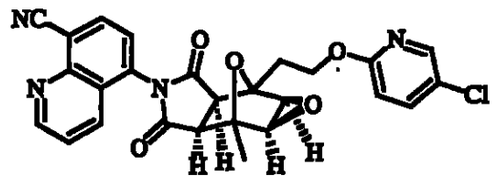
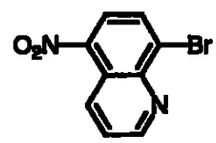
Example 464

(1aα,2β,2aα,5aα,6β,6aα)-5-[2-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]octahydro-6-methyl-3,5-dioxo-2,6-epoxy-4H-oxireno[f]isoindol-4-yl]-8-quinolinecarbonitrile (464H)

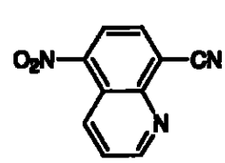


A. 8-Bromo-5-nitro-quinoline (464A)



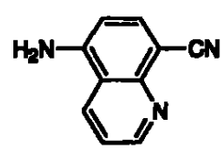
8-Bromoquinoline (25.00 g, 120.2 mmol) was dissolved in sulfuric acid (82.5 mL) at rt and then cooled to 0°C. HNO_3 (fuming, 32.5 mL) was then slowly added over a 10 minute period. The reaction was then warmed to rt and then to 65°C. After 48 h at 65°C, the reaction was cooled to rt and poured onto 500 g of ice. This solution was extracted with methylene chloride (5 x 200 mL). The organic layers were washed once with brine and dried over anhydrous sodium sulfate. Concentration gave the crude compound 464A as a light yellow solid (28.6 g, 94%). HPLC: 98% at 2.717 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm).

B. 5-Nitro-quinoline-8-carbonitrile (464B)



Compound **464A** (15.0 g, 59.3 mmol) was dissolved in DMF (120 mL) and zinc cyanide (4.20 g, 35.9 mmol) was added. Bis(diphenylphosphino)ferrocene (3.00 g, 5.40 mmol) and tris(benzylidineacetone)dipalladium (3.00 g, 3.30 mmol) were then added and the reaction was heated to 100°C for 1.5 h. The reaction was cooled to 22°C and then poured into concentrated ammonium hydroxide (900 mL) resulting in an orange precipitate which was filtered and rinsed with cold water (1 L). The resulting precipitate was dissolved in methylene chloride, washed with brine (1 x 300 mL) and then dried over anhydrous sodium sulfate. Concentration *in vacuo* gave the crude material as an orange solid which was purified by flash chromatography on silica gel eluting with methylene chloride to give 6.01 g (51%) of compound **464B** as a yellow solid. HPLC: 99% at 1.900 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm).

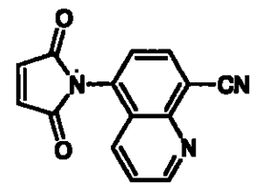
C. 5-Amino-quinoline-8-carbonitrile (464C)



Compound **464B** (6.00 g, 30.1 mmol) was dissolved in THF (150 mL) at reflux with mechanical stirring. EtOH (150 mL) was then added followed by aqueous ammonium chloride (2.4 g/225 mL water). The mixture was heated at 70°C and then iron powder (325 mesh, 6.75 g, 120 mmol) was added with vigorous mechanical stirring. After 1 h, the reaction was cooled to 22°C and filtered through Celite rinsing with methylene chloride. The filtrate was then concentrated to ~250 mL and the pH was adjusted to 10 by addition of 1N NaOH. The solution was then extracted with ethyl acetate (5 x 150 mL). The combined organic layers were washed once with brine (250 mL) and then dried over anhydrous magnesium sulfate. Concentration *in vacuo* gave 5.09 g (100%) of compound **464C** as a yellow solid. HPLC: 99 at 1.143 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90

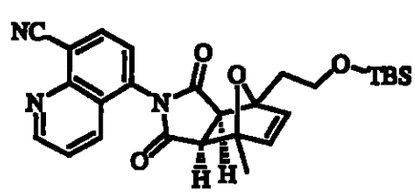
aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 170.16 $[M+H]^+$.

D. 5-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-quinoline-8-carbonitrile (464D)



Compound **464C** (7.00 g, 41.4 mmol) and maleic anhydride (6.00 g, 62.1 mmol) were combined in a sealed tube and THF (10 mL) was added. The reaction mixture was heated to 115°C for 15 min then cooled to room temperature, resulting in the precipitation of the intermediate acid amide. The solid was filtered and rinsed with cold THF to give 11.0 g of the acid as a yellow solid. To the above acid amide was added Ac_2O (25 mL) in a sealed tube and the mixture was heated at 100°C for 15 min then cooled to room temperature. The resulting solid was filtered and rinsed with cold diethyl ether to give 8.30 g (80%) of compound **464D** as a yellow solid. HPLC: 97% at 1.783 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm).

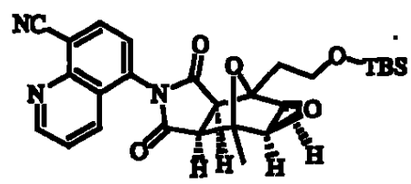
E. (3aα, 4β,7β,7aα)-5-[4-[2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]-1,3,3a,4,7,7a-hexahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile (464E)



Compound **464D** (6.00 g, 24.1 mmol) was dissolved in a mixture of benzene (80 mL) and acetone (20 mL) followed by addition of compound **204A** (14.46 g,

60.15 mmol). The mixture was heated at 80°C for 14 h and then cooled to 22°C. Concentration *in vacuo* at 40°C followed by addition of acetone (40 mL) and concentration again at 40°C. The resulting yellow oil was purified by flash column chromatography on silica gel eluting with 0 – 10% acetone in chloroform to give 9.98 g (85%) of compound **464E** as a yellow oil. Compound **464E** was shown to be a single isomer by NMR spectroscopy. HPLC: 97% at 3.853 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 490.35 $[M+H]^+$.

F. (1aα,2β,2aα,5aα,6β,6aα)-5-[2-[2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]octahydro-6-methyl-3,5-dioxo-2,6-epoxy-4H-oxireno[f]isoindol-4-yl]-8-quinolinecarbonitrile (464F)



To a solution of compound **464E** (0.050 g, 0.10 mmol) in dichloromethane (2 mL) was added *m*CPBA (60% mixture, 0.063 g, 0.22 mmol). The reaction mixture was stirred at room temperature for 16 h and then additional dichloromethane (20 mL), saturated $NaHCO_3$ (10 mL) and 10% Na_2SO_3 (10 mL) were added. The mixture was stirred vigorously for 40 min, the organic layer was then separated, washed once with brine, and dried over Na_2SO_4. Concentration *in vacuo* gave 48 mg (96%) of compound **464F** as a light yellow solid. HPLC: 98% at 3.783 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 506.25 $[M+H]^+$.

G. (1aα,2β,2aα,5aα,6β,6aα)-5-[Octahydro-2-(2-hydroxyethyl)-6-methyl-3,5-dioxo-2,6-epoxy-4H-oxireno[f]isoindol-4-yl]-8-quinolinecarbonitrile (464G)

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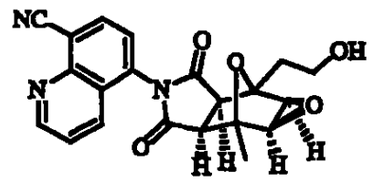


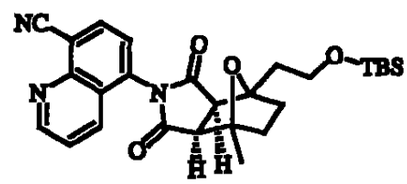
Compound 464F (1.30 g, 2.57 mmol) was dissolved in 2% conc. HCl/EtOH (50 mL). The reaction mixture was stirred at room temperature for 1 h and then saturated $NaHCO_3$ (50 mL) and dichloromethane (100 mL) were added. The organic layer was separated, washed once with brine and dried over Na_2SO_4. Concentration *in vacuo* gave 930 mg (93%) of compound 464G as a yellow solid. HPLC: 98% at 1.863 (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 392.20 $[M+H]^+$.

H. (1aα, 2β,2aα,5aα,6β,6aα)-5-[2-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]octahydro-6-methyl-3,5-dioxo-2,6-dioxo-2,6-epoxy-4H-oxireno[f]isoindol-4-yl]-8-quinolinecarbonitrile (464H)

Triphenylphosphine (25 mg, 0.096 mmol) and DBAD (22 mg, 0.096 mmol) were mixed in THF (0.5 mL) under argon. After 5 min, 5-chloro-2-pyridinol (13 mg, 0.096 mmol) was added. The reaction mixture was stirred at 22°C for another 10 min, then compound 464G (25 mg, 0.064 mmol) was added. The reaction mixture was stirred at 22°C under argon for 3 h, and then concentrated *in vacuo*. The crude material was purified by preparative TLC on silica gel eluting with 10% acetone in chloroform to give 11 mg (23%) of compound 464H as a white solid. HPLC: 100% at 3.177 (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 503.14 $[M+H]^+$.

Example 465

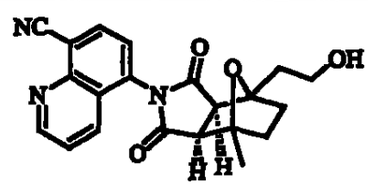
(3aα,4β,7β,7aα)-5-[4-[2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile (465)



Compound 464E (2.40 g, 4.91 mmol) was dissolved in ethyl acetate and Pd/C (10% Pd, 0.50 g) was added. Hydrogen was then introduced via a balloon. After 3 h, the reaction was purged with nitrogen and filtered through Celite, rinsing with ethyl acetate. Concentration *in vacuo* gave 2.39 g (99%) of compound 465 as a yellow oil. HPLC: 95% at 4.013 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 492.22 $[M+H]^+$.

Example 466

(3aα,4β,7β,7aα)-5-[Octahydro-4-(2-hydroxyethyl)-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile (466)



Compound 465 (1.40 g, 2.85 mmol) was dissolved in 2% conc. HCl/MeOH (20 mL) and stirred at 22°C for 3 h. The reaction was then concentrated to ~5 mL volume and quenched with a minimum amount of sat. aq. sodium bicarbonate. This solution was then extracted with methylene chloride (3 x 30 mL) and the combined organic layers were dried over anhydrous sodium sulfate. Concentration *in vacuo* gave 0.893 g (93%) of compound 466 as a yellow solid. This material was taken on without further purification. HPLC: 98% at 2.140 min (retention time) (YMC S5

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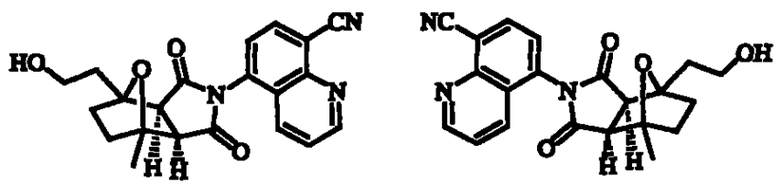
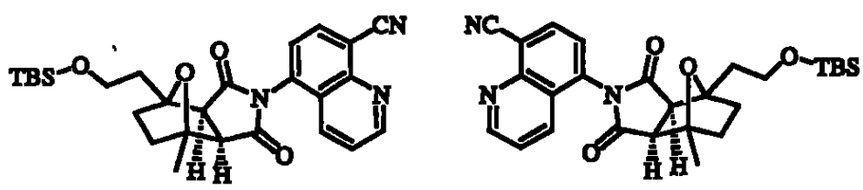
ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 378.25 $[M+H]^+$.

Example 467

[3a*R*-(3aα,4β,7β,7aα)]-5-[Octahydro-4-(2-hydroxyethyl)-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile (467Bi) & [3a*S*-(3aα,4β,7β,7aα)]-5-[Octahydro-4-(2-hydroxyethyl)-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile (467Bii)



A. **[3a*R*-(3aα,4β,7β,7aα)]-5-[4-[2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile (467Ai) & [3a*S*-(3aα,4β,7β,7aα)]-5-[4-[2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile (467Aii)**



Compounds 465 was separated into its individual antipodes by normal phase preparative chiral HPLC. A Chiralcel OD column (50 x 500 mm) was used with a flow rate of 50 mL/min (16% EtOH/hexanes) monitoring at 220 nm. The faster eluting antipode compound 467Ai had a retention time of 40.85 min (>99% ee) and

the slower antipode compound **467AII** had a retention time of 62.81 min (>99% ee). Both antipodes were isolated as white solids after separation. The absolute conformation for compounds **467AI** & **467AII** was not established. For simplicity in nomenclature, compound **467AI** is designated herein as having an "R" configuration and compound **467AII** as having an "S" configuration. Enantiomerically pure products derived from compound **467AI** are designated herein as having a "R" configuration and enantiomerically pure products derived from compound **467AII** are designated herein as having an "S" configuration.

B. [3a*R*-(3aα,4β,7β,7aα)]-5-[Octahydro-4-(2-hydroxyethyl)-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile (467BI) & [3a*S*-(3aα,4β,7β,7aα)]-5-[Octahydro-4-(2-hydroxyethyl)-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile (467BII)

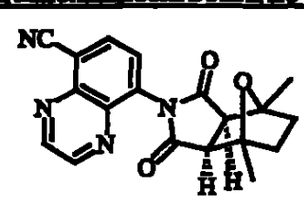
Both antipodes were deprotected as described in example **464G** to give the corresponding alcohols, compounds **467BI** and **467BII** as white solids:

Compound **467BI**: HPLC: 98% at 2.110 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 378.21 $[M+H]^+$.

Compound **467BII**: HPLC: 98% at 2.117 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 378.20 $[M+H]^+$.

Example 468

(3aα,4β,7β,7aα)-8-[Octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-5-quinoxalinecarbonitrile (468C)



A. 8-Nitro-quinoxaline-5-carbonitrile (468A)

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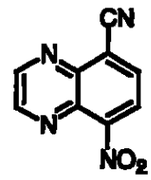
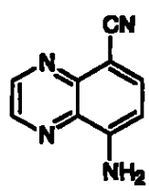


2,3-Diamino-4-nitro-benzonitrile (0.050 g, 0.28 mmol, as prepared in WO-98/32439) was added to solution of glyoxal (40% in water, 0.032 mL, 0.28 mmol) in acetic acid (0.75 mL) and stirred at 22°C for 3 h. The reaction was cooled to 0°C and water (2.0 mL) was added and the pH was adjusted to 9.0 by addition of ammonium hydroxide which caused the product to precipitate. The mixture was then filtered and rinsed with cold water. Drying *in vacuo* gave 0.039 g (70%) of compound **468A** as an orange solid. HPLC: 100% at 2.037 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm).

B. 8-Amino-quinoxaline-5-carbonitrile (468B)



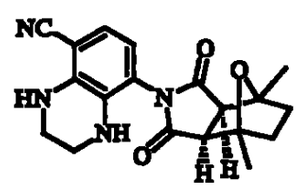
Compound **468A** (0.200 g, 1.00 mmol) was suspended in acetic acid (5.0 mL) and iron powder (325 mesh, 0.112 g, 2.00 mmol) was added. The reaction was then heated at 70°C for 20 min and then cooled to 22°C. The reaction was filtered through Celite, rinsing with ethyl acetate. The ethyl acetate rinse was collected and washed with sat. aq. K_2CO_3. The aqueous layer was extracted with ethyl acetate (3 x 20 mL) and the combined organic layers were dried over anhydrous magnesium sulfate. Concentration *in vacuo* gave 0.170 g (100%) of compound **468B** as a yellow solid. HPLC: 88% at 1.677 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 171.29 $[M+H]^+$.

C. (3aα,4β,7β,7aα)-8-[Octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-5-quinoxalinecarbonitrile (468C)

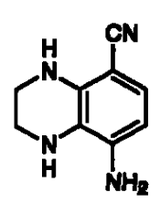
Compound 468B (0.060 g, 0.35 mmol) was suspended in toluene (1.0 mL) with magnesium sulfate (0.060 g) and compound 20A (0.104 g, 0.529 mmol). TEA (0.2 mL) was then added and the mixture was heated to 145°C in a sealed tube. After 16 h the reaction was cooled to 22°C and filtered through Celite, rinsing with acetone. The mixture was concentrated *in vacuo* and then purified by preparative TLC on silica gel eluting with 7% ethyl acetate/methylene chloride. This gave 0.018 g (15%) of compound 468C as a yellow solid. HPLC: 100% at 2.040 and 2.133 min (atropisomers, retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 349.33 $[M+H]^+$.

Example 469

(3aα,4β,7β,7aα)-1,2,3,4-Tetrahydro-8-(octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-5-quinoxalinecarbonitrile (469B)



A. 8-Amino-1,2,3,4-tetrahydro-quinoxaline-5-carbonitrile (469A)



Compound 468A (0.037 g, 0.18 mmol) was dissolved in a mixture of ethyl acetate (1.0 mL)/ethanol (1.0 mL) and 10% Pd/C (0.050 g) was added. Hydrogen was

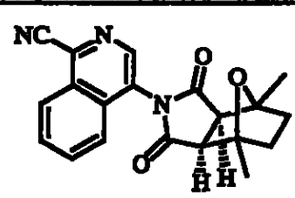
then introduced via a balloon. After 2 h, the reaction was purged with nitrogen and filtered through Celite, rinsing with ethyl acetate. Concentration *in vacuo* gave 0.029 g (90%) of compound **469A** as a red oil, which was taken on without further purification. HPLC: 97% at 3.217 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm).

B. (3aα,4β,7β,7aα)-1,2,3,4-Tetrahydro-8-(octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-5-quinoxalinecarbonitrile (469B)

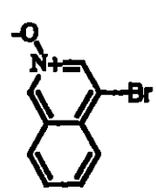
Compound **469A** (0.029 g, 0.17 mmol) was suspended in toluene (1.0 mL) with magnesium sulfate (0.030 g) and compound **20A** (0.050 g, 0.256 mmol). TEA (0.2 mL) was then added and the mixture was heated at 145°C in a sealed tube. After 48 h the reaction was cooled to 22°C and filtered through Celite, rinsing with acetone. The mixture was concentrated *in vacuo* and then purified by preparative TLC eluting with 20% acetone in chloroform. This gave 0.014 g (24%) of compound **469B** as a yellow solid. HPLC: 85% at 2.267 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 353.19 $[M+H]^+$.

Example 470

(3aα,4β,7β,7aα)-4-(Octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-1-isoquinolinecarbonitrile (470E)

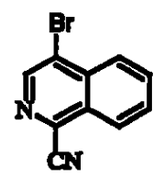


A. 4-Bromo-isoquinoline 2-oxide (470A)



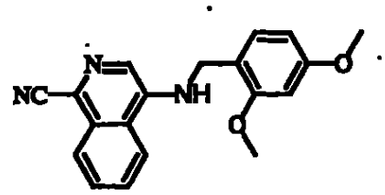
A solution of 4-bromoisoquinoline (4.16 g, 18.6 mmol) in 100 mL of chloroform was added dropwise over 1 h to a solution of 70% *m*CPBA (12.4 g, 50.3 mmol) in 100 mL of chloroform at room temperature. After stirring 18 h, the reaction mixture was washed with 1N NaOH (2 x 150 mL), dried over magnesium sulfate and concentrated *in vacuo* to afford 4.23 g (94%) of compound **470A** as an off-white solid. ^{1}H NMR-400 MHz ($CDCl_3$): δ 8.71 (s, 1H), 8.43 (s, 1H), 8.09 (d, 1H, J = 8 Hz), 7.70 (m, 3H).

B. 4-Bromo-isoquinoline-1-carbonitrile (470B)



1,8-Diazabicyclo[5.4.0]undec-7-ene (1.67 mL, 11.2 mmol) was added to a mixture of compound **470A** (1.12 g, 5.00 mmol) and cyanotrimethylsilane (0.75 mL, 5.5 mmol) in 35 mL of THF. The resulting homogeneous mixture was refluxed for 20 min. After concentrating *in vacuo*, the residue was purified by flash chromatography on a 5 x 15 cm silica gel column, eluting with 3:1 hexane:ethyl acetate to give 0.95 g (82%) of compound **470B** as a white powder. ^{1}H NMR (400 MHz, $CDCl_3$): δ 8.85 (s, 1H), 8.36 (d, 1H, J = 8.5 Hz), 8.28 (d, 1H, J = 8.5 Hz), 7.96 (t, 1H, J = 8.5 Hz), 7.89 (t, 1H, J = 8.5 Hz).

C. 4-(2,4-Dimethoxy-benzylamino)-isoquinoline-1-carbonitrile (470C)



A mixture of compound **470B** (699 mg, 3.00 mmol) and 2,4-dimethoxybenzylamine (4.8 mL, 30 mmol) in 15 mL of acetonitrile was refluxed for 16 h. After concentration *in vacuo*, the residue was purified on a 5 x 15 cm silica gel

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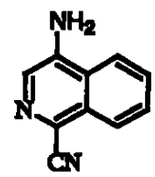
column, eluting with 3:2 hexane:ethyl acetate to afford 290 mg (30%) of **470C** as a light yellow solid. HPLC: 1.76 min (retention time) (Phenomenex C-18, 5 micron column, 4.6 x 30 mm, eluting with 10-90% aqueous methanol over 2 min containing 0.1% TFA, 4 mL/min, monitoring at 254 nm).

D. 4-Amino-isoquinoline-1-carbonitrile (470D)



Compound **470C** (50 mg, 0.16 mmol) was treated with trifluoroacetic acid (0.5 mL) for 1 h. The highly colored mixture was partitioned between ethyl acetate (30 mL) and 1N NaOH (30 mL). After washing with brine (15 mL), the organic layer was dried over magnesium sulfate and concentrated *in vacuo* to afford 24 mg (92) of compound **470D** as a yellow solid. HPLC: 99% at 1.09 min (retention time) (Phenomenex C-18, 5 micron column, 4.6 x 30 mm, eluting with 10-90% aqueous methanol over 2 min containing 0.1% TFA, 4 mL/min, monitoring at 254 nm). MS (ES^+): m/z 170.2 $[M+H]^+$.

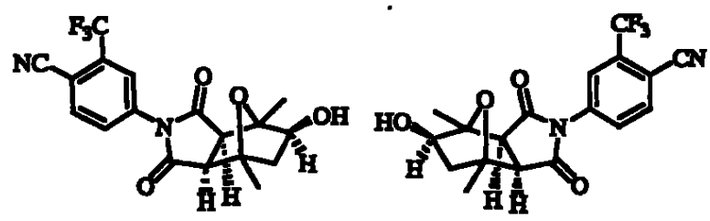
An alternative route to the synthesis of compound **470D** is as follows. A mixture of compound **470B** (1.17 g, 5.02 mmol), benzophenone imine (1.05 mL, 6.26 mmol), palladium acetate (25 mg, 0.11 mmol), *rac*-2,2'-bis(diphenylphosphino)-1,1' binaphthyl (100 mg, 0.161 mmol) and cesium carbonate (2.30 g, 7.06 mmol) in 20 mL of toluene was heated at 100°C for 20 h. The reaction mixture was diluted with ethyl ether (200 mL) and filtered through Celite. After concentrating the filtrate, the residue was dissolved in 120 mL of THF and treated with 40 mL of 1N HCl. After standing for 2 h at room temperature, the mixture was partitioned between ethyl acetate (150 mL) and 0.25 N NaOH (160 mL). After washing with brine (100 mL), the organic layer was dried over magnesium sulfate. The organic layer was filtered and ~ 50 g of celite was added to the filtrate. After concentration *in vacuo*, the powdery residue was purified by flash chromatography on a 5 x 15 cm silica gel column eluting with 1 L each of 1:1 ethyl acetate:hexane, 6:4 ethyl acetate:hexane and 8:2 ethyl acetate:hexane to give 450 mg (53%) of **470D** as a yellow powder.

E. (3aα,4β,7β,7aα)-4-(Octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-1-isoquinolinecarbonitrile (470E)

A mixture of compound **470D** (24 mg, 0.14 mmol), compound **20A** (55 mg, 0.28 mmol), triethylamine (0.1 mL), magnesium sulfate (100 mg), 2-methoxyethylether (0.5 mL) and DMF (0.1 mL) was heated in a sealed vessel to 250°C for a total of 2.5 h using a microwave heating device. After partitioning the reaction mixture between ethyl acetate (25 mL) and water (25 mL), the organic layer was dried over magnesium sulfate and concentrated *in vacuo*. Approximately half of the residue was purified by reverse phase preparative HPLC (YMC S5 ODS 20 x 50 mm, eluting with 10-100% aqueous methanol over 10 min containing 0.1% TFA, 20 mL/min). Concentration of the pure fraction afforded 6 mg (12%) of compound **470E** as a white powder. HPLC: 99% at 1.42 min (retention time) (Phenomenex C-18, 5 micron column, 4.6 x 30 mm, eluting with 10-90% aqueous methanol over 2 min containing 0.1% TFA, 4 mL/min, monitoring at 254 nm). MS (ES^+): m/z 348.23 $[M]^+$.

Example 471

[3aR-(3aα,4β,5β,7β,7aα)]-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (471Di) & [3aS-(3aα,4β,5β,7β,7aα)]-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (471Dii)



A. 4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-2-trifluoromethyl-benzonitrile (471A)

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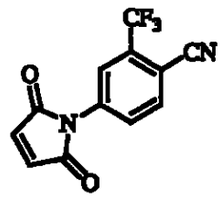
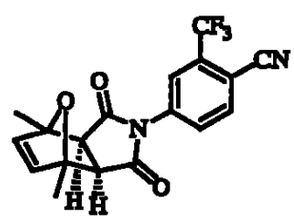


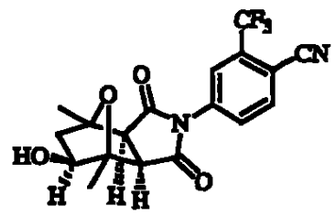
A mixture of 3-trifluoromethyl-4-cyano-aniline (24.0 g, 129 mmol) and maleic anhydride (14.0 g, 143 mmol) in 50 mL of acetic acid was heated at 115°C overnight. A precipitate was obtained during the heating period. The reaction was allowed to stand at rt for an additional overnight period. The solid was removed by filtration, the filter cake was washed with diethyl ether and dried to give 21 g (79 mmol, 61%) of compound **471A** as an off white solid. HPLC: 100% at 2.11 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm).

B. (3aα,4β,7β,7aα)-4-(1,3,3a,4,7,7a-Hexahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (471B)



A suspension of compound **471A** (13.0 g, 48.8 mmol) and 2,5-dimethylfuran (10.5 mL, 98.6 mmol) in 50 mL of toluene was heated at 60°C, under argon. A solution was obtained on initial heating and a precipitate was observed after approximately 1 h. Heating was continued overnight. After cooling to rt, the suspension was allowed to stand at 4°C overnight. The resulting solid was filtered and the filter cake was washed with cold toluene followed by air drying to give 13.2 g of pure compound **471B** as a white solid. The filtrate volume was reduced *in vacuo* by one half and the resulting solution was treated as above to yield an additional 2.8 g of pure compound **471B** (total 16.0 g, 90%). HPLC: 90% at 3.65 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm).

C. (3aα,4β,5β,7β,7aα)-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (471C)



A solution of compound 471B (25 g, 69 mmol) in 125 mL of THF, in a dry flask under nitrogen, was cooled to 10°C with an ice bath. To this solution was added neat borane-dimethylsulfide complex (13.0 mL, 138 mmol) dropwise over 10 min, while maintaining a reaction temperature of <15°C. The reaction mixture was stirred for 30 min at rt and then in an ice bath cooled to 10°C. To the cool solution was slowly added 480 mL of pH 7 phosphate buffer, which resulted in a strong exothermic reaction and vigorous gas evolution. The solution was maintained at <21°C throughout the addition by means of an ice bath. To the resulting solution was added 240 mL of ethanol and the resulting mixture was cooled to 5°C with an ice bath. To the cooled solution was added 50 mL of 30% hydrogen peroxide and the resulting mixture was stirred at 10-20°C for 1.5 h. The mixture was extracted with ethyl acetate (2 x 1 L) and the combined organic layers were washed with 10% sodium sulfite (1 x 500 mL) and brine (2 x 300 mL) and dried over $MgSO_4$. Concentration *in vacuo* afforded 29 g of crude product as a white solid. This material was subjected to flash chromatography on a 1.2 L column of silica gel equilibrated with 100% CH_2Cl_2. The material was applied to the column as a solution consisting of 100 mL EtOAc (warm) and 400 mL CH_2Cl_2. Initial elution with CH_2Cl_2 (3 L), followed by 25% EtOAc/75% CH_2Cl_2 (3 L) and finally 50% EtOAc/50% CH_2Cl_2 (6 L) gave 11.8 g (45%) of compound 471C which is a racemic mixture.

Alternatively compound 471C can be made by the following approach: A dry flask containing compound 471B (8.90 g, 24.6 mmol) and Wilkinson's catalyst (0.57 mg, 0.62 mmol) was degassed 4x with vacuum/argon. THF (40 mL) was added to the flask and the mixture was stirred until a clear brown solution was obtained. Catecholborane (49 mL, 49 mmol, 1 M in THF) was then added dropwise over 20

min and a slight exotherm was observed. Stirring was continued for 45 min followed by cooling of the reaction mixture with an ice bath. pH 7 phosphate buffer (175 mL) was slowly added, followed by the consecutive addition of ethanol (87 mL) and 30% hydrogen peroxide (18 mL). Stirring was continued with cooling and the reaction progress was monitored by HPLC for 4 h. The reaction was extracted with CH_2Cl_2 (3 x 250 mL). The combined extracts were washed with 1:1 1N NaOH:15% sodium sulfite (300 mL) and brine, dried over $MgSO_4$, and the solvent was removed *in vacuo* to afford 8.5 g of a tan solid. The crude product was subjected to flash chromatography on a 500 cm^3 silica gel column eluting with a gradient of 25-50% EtOAc/CH_2Cl_2 to give 6.00 g compound 471C (15.8 mmol, 64%) as a white solid. HPLC: 90% at 2.45 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 381.11 $[M+H]^+$.

D. [3aR-(3aα,4β,5β,7β,7aα)]-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (471DI) & [3aS-(3aα,4β,5β,7β,7aα)]-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (471DII)

The individual antipodes of compound 471C were separated by normal phase preparative chiral HPLC (CHIRALPAK AD, 5 x 50 cm column). A 2.5 g portion of 471C was dissolved into 25 mL of warm acetone and diluted to 50-75 mL with hexane for injection. Isocratic elution with 20% MeOH/EtOH (1:1) in heptane at 50 mL/min gave the faster eluting compound 471DI (Chiral HPLC: 10.02 min; CHIRALPAK AD 4.6 x 250 mm column; isocratic elution with 20% MeOH/EtOH (1:1) in heptane at 1 mL/min) and the slower eluting compound 471DII (Chiral HPLC: 14.74 min; CHIRALPAK AD 4.6 x 250 mm column; isocratic elution with 20% MeOH/EtOH (1:1) in heptane at 1 mL/min). Compounds 471DI & 471DII: HPLC: 90% at 2.45 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 381.11 $[M+H]^+$. The absolute

stereochemistry of compounds 471Di & 471Dii was determined by single crystal X-ray diffraction studies and is as described by the designated nomenclature.

The resulting HPLC purified fractions of compounds 471Di & 471Dii were further purified by crystallization using any one of the procedures described below.

1) From Ethyl Acetate

A 700 mg portion of compound 471Di, obtained after chiral chromatography as described above, was dissolved in ethyl acetate (10 mL) at rt. The solution was diluted with small portions of hexane (20 mL) until cloudiness was observed. The solution was allowed to stand overnight at rt. The resulting white solid was filtered and air dried to afford 430 mg of compound 471Di as a white powder. This sample was further dried at 60°C (3 h, 0.5 Torr), then at 70°C, (12 h, 0.5 Torr).

2) From Acetone

A 500 mg portion of compound 471Di, obtained after chiral chromatography as described above, was dissolved in a minimal amount of acetone (3 mL) and slowly diluted with hexane (1 mL). The clear colorless solution was allowed to stand overnight at rt. The resulting white solid was filtered and air dried to afford 440 mg of compound 471Di as a white powder. This sample was further dried at 60°C, (3 h, 0.5 Torr) then at 70°C, (12 h, 0.5 Torr).

3) From Methanol

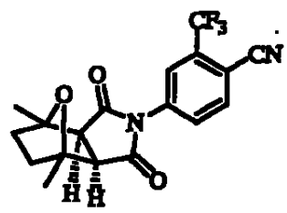
A 500 mg portion of compound 471Di, obtained after chiral chromatography as described above, was dissolved in 5 mL of hot (steam bath) methanol. The clear colorless solution was allowed to stand at rt for 2 h, then at 4°C overnight. The resulting solid was filtered, washed with minimal cold methanol and air dried for to afford 360 mg of compound 471Di as a white powder. This sample was further dried at 70°C, (12 h, 0.5 Torr).

4) From CH_2Cl_2

A 7.00 g portion of compound 471Di, obtained after chiral chromatography as described above, was dissolved in 75 mL of CH_2Cl_2 at rt. The clear and colorless solution was slowly diluted with hexane (48 mL) until crystallization was observed. The solution was allowed to stand at rt for 1 h, then at 4°C overnight. The resulting crystalline material was filtered and then washed with a minimal amount of cold 2:1 CH_2Cl_2:hexane. The large crystals were ground to a fine powder and dried at 50°C (12 h, 0.5 Torr) to yield 5.96 g of compound 471Di as a white powder

Example 472

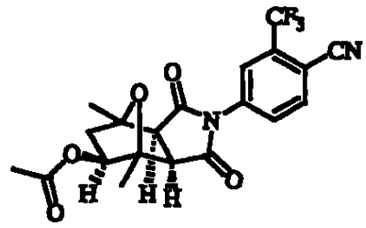
(3aα,4β,7β,7aα)-4-(Octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (472)



A solution of compound 471B (500 mg, 1.38 mmol) in ethyl acetate (10 mL), containing 10% Pd/C (25 mg, cat.) was stirred at rt under an atmosphere of hydrogen introduced via a balloon. After 2 h the reaction was filtered through Celite and the filter cake was washed with EtOAc. The clear, colorless filtrate was concentrated *in vacuo* to yield 501 mg (1.38 mmol, 100%) of compound 472 as a white solid. No further purification was required. HPLC: 99% at 3.04 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ESI): m/z 382.2 $[M+NH_4]^+$.

Example 473

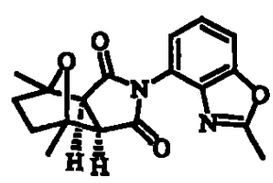
(3aα,4β,5β,7β,7aα)-4-[5-(Acetyloxy)octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile (473)



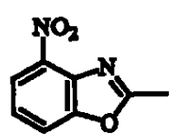
To a solution of compound 471C (1.50 g, 3.95 mmol) in 10 mL of pyridine, cooled to 0°C under argon, was added acetic anhydride (0.42 mL, 4.4 mmol) dropwise, followed by DMAP (5 mg, 0.04 mmol). Stirring was continued at rt for 4 h. The solution was concentrated *in vacuo* and the resulting residue was diluted with ethyl acetate, and washed consecutively with 1N HCl (2x), brine (2x), sat. $NaHCO_3$, and brine (2x). The organic layer was dried over $MgSO_4$ and concentrated *in vacuo*. The resulting solid was dried at 60°C (20 h, 0.5 Torr) to yield 1.55 g (3.67 mmol, 93%) of compound 473 as a white crystalline solid. HPLC: 99% at 2.10 min (retention time) (Phenomenex Luna C18 column, 2 x 30 mm, 0-100% aqueous acetonitrile over 3 min containing 10 mM NH_4OAc at 1 mL/min, monitoring at 220 nm). MS (ESI): m/z 421.4 $[M-H]^-$.

Example 474

(3aα,4β,7β,7aα)-Hexahydro-4,7-dimethyl-2-(2-methyl-4-benzoxazolyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione (474F)



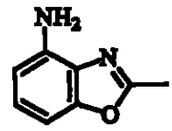
A. 2-Methyl-4-nitrobenzoxazole (474A)



To 2-amino-3-nitrophenol (6.17 g, 40.0 mmol) was added triethylorthoacetate (25.96 g, 160.0 mmol) and the mixture was heated at 100°C for 12 h to give a dark red solution. Cooling to room temperature produced a crystalline mass which was

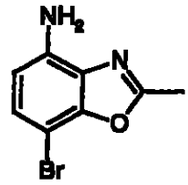
filtered and washed with hexane to give compound 474A (6.78 g, 95%) as light maroon needles. HPLC: 98.1% at 1.86 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 179.08 $[M+H]^+$.

B. 4-Amino-2-methylbenzoxazole (474B)



Compound 474A (6.78 g, 38.1 mmol) was dissolved in a 1:1 mixture of 10% acetic acid/ethyl acetate (100 mL total volume) and heated to 65°C. Iron powder (10.63 g, 190.2 mmol) was added portionwise. After stirring for 3 h, TLC indicated complete consumption of starting material. The cooled reaction mixture was filtered through a pad of Celite and the pad was washed with 50 mL of ethyl acetate. The organic layer was separated, washed with water (2 x 25 mL), brine (1 x 25 mL), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The crude material was purified by flash chromatography on silica gel eluting with 25% ether/CH_2Cl_2 to give 3.90 g (69%) of compound 474B as a light brown solid. HPLC: 95.8% at 2.43 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 149.11 $[M+H]^+$.

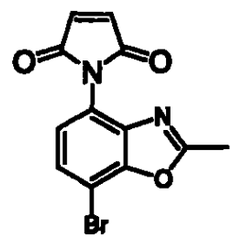
C. 4-Amino-7-bromo-2-methylbenzoxazole (474C)



Compound 474B (3.90 g, 26.3 mmol) was dissolved in DMF (45 mL) and cooled to ⁻5°C and *N*-bromosuccinimide (4.68 g, 26.3 mmol) was added in small portions and the reaction stirred for 5 h. The mixture was poured into 150 mL of ice water to give a cream colored solid which was filtered, washed with water, dissolved

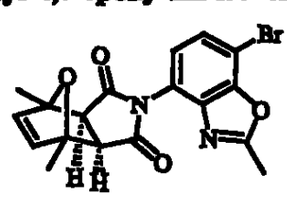
in CH_2Cl_2, dried over $MgSO_4$, filtered and concentrated *in vacuo*. Purification of the crude material by flash chromatography on silica gel eluting with 20% ether/CH_2Cl_2 gave compound 474C (3.36 g, 56%) as a beige solid. HPLC: 95.4% at 2.583 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 228.03 $[M+H]^+$.

D. 1-(7-Bromo-2-methyl-benzoxazol-4-yl)-pyrrole-2,5-dione (474D)



Compound 474C (1.40 g, 6.17 mmol) was dissolved in 20 mL of acetic acid, maleic anhydride (0.635 g, 6.47 mmol) was added and the reaction was heated at reflux under nitrogen for 5 h. The solvent was removed *in vacuo* and the crude product was purified by flash chromatography on silica gel eluting with 10% ether/CH_2Cl_2 to give compound 474D (1.73 g, 91%) as a pale yellow solid. HPLC: 93.6% at 1.36 min. (Phenomenex column, 30 x 4.6 mm, 10-90% aqueous methanol over 2 min containing 0.1% TFA, 5 mL/min, monitoring at 220 nm. MS (ES): m/z 308.02 $[M+H]^+$.

E. (3aα,4β,7β,7aα)-2-(7-Bromo-2-methyl-4-benzoxazolyl)-3a,4,7,7a-tetrahydro-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione (474E)



Compound 474D (0.307 g, 1.00 mmol) was dissolved in benzene (2 mL) and 2,5-dimethylfuran (0.154 g, 1.60 mmol) was added via syringe. The reaction mixture

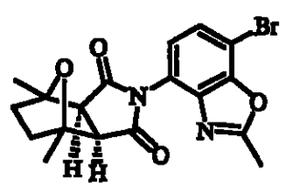
was heated to 60°C for 12 h. The cooled reaction mixture was concentrated *in vacuo* at 40°C to give compound **474E** as an off-white foam which was used directly in the next reaction without purification.

F. (3aα,4β,7β,7aα)-Hexahydro-4,7-dimethyl-2-(2-methyl-4-benzoxazolyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione (474F)

Compound **474E** (0.403 g, 1.00 mmol) was dissolved in EtOH/EtOAc (4 mL/4 mL) and 10% Pd/C (100 mg) was added. The reaction mixture was stirred at room temperature for 6 h under an atmosphere of H_2 supplied by a balloon and then filtered through Celite. Concentration of the filtrate *in vacuo* gave a brown solid. Purification by flash chromatography on silica gel eluting with 10% acetone/$CHCl_3$ (250 mL), 15% acetone/$CHCl_3$ (250 mL), and 20% acetone/$CHCl_3$ (250 mL) gave compound **474F** (0.089 g, 27%) as a white foam. HPLC: 91% at 2.28 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 328.34 $[M+H]^+$.

Example 475

(3aα,4β,7β,7aα)-2-(7-Bromo-2-methyl-4-benzoxazolyl)hexahydro-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione (475)

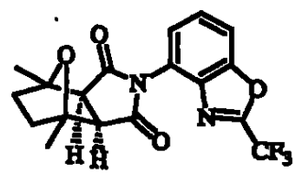


Compound **474E** (0.202 g, 0.501 mmol) was dissolved in 1/1 EtOAc/EtOH (10 mL) and 10% Pt/C (100 mg) was added. The reaction mixture was stirred at room temperature under an H_2 balloon for 6 h. The reaction was filtered through Celite and concentrated *in vacuo*. Purification by flash chromatography on silica gel eluting with 10% ether/CH_2Cl_2 gave 0.063 g (31%) of compound **475** as a colorless oil which solidified upon standing to give a white solid. HPLC: 92.5% at 2.83 min (retention

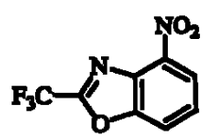
time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 406.21 $[M+H]^+$.

Example 476

(3aα,4β,7β,7aα)-Hexahydro-4,7-dimethyl-2-[2-(trifluoromethyl)-4-benzoxazolyl]-4,7-epoxy-1H-isoindole-1,3(2H)-dione (476D)

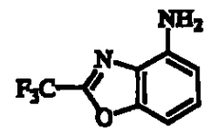


A. 4-Nitro-2-trifluoromethylbenzoxazole (476A)



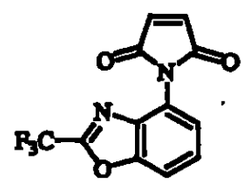
2-Amino-3-nitrophenol (10.00 g, 64.88 mmol) was added to 100 mL of vigorously stirring trifluoroacetic anhydride and the resulting mixture was stirred at room temperature for 12 h. The solvent was removed *in vacuo* to give a dark blue solid which was dissolved in 200 mL of CH_2Cl_2 and washed sequentially with 10% NaOH (2 x 100 mL), water (100 mL), brine (100 mL), and dried over $MgSO_4$. Filtration and concentration *in vacuo* gave compound 476A (10.78 g, 72%) as a brown solid. No further purification was required. HPLC: 92.9% at 2.43 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm).

B. 4-Amino-2-trifluoromethylbenzoxazole (476B)



Compound 476A (10.75 g, 46.30 mmol) was dissolved in 1:1 EtOAc/10% HOAc (250 mL) and heated to 65°C. Iron powder (12.93 g, 231.5 mmol) was added portionwise and the reaction was stirred for 6 h at 65°C. After cooling, the mixture was filtered through Celite rinsing with EtOAc. The organic layer was separated, washed with H_2O (3 x 100 mL), brine (100 mL), dried over $MgSO_4$, and concentrated *in vacuo* to give a brown oil. The crude material was purified by flash chromatography on silica gel eluting with 70/30 CH_2Cl_2/hexanes to give compound 476B (7.02 g, 75%) as a yellow crystalline solid. HPLC : 96.7% at 2.68 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm).

C. 1-(2-Trifluoromethyl-benzoxazol-4-yl)-pyrrole-2,5-dione (476C)



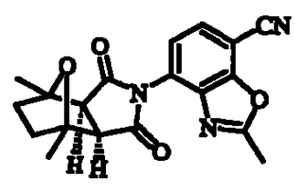
Compound 476B (0.500 g, 2.48 mmol) was dissolved in acetic acid (10 mL) and maleic anhydride (0.267 g, 2.72 mmol) was added. The mixture was heated at reflux for 3 h, cooled and the solvent removed *in vacuo* to give a tan solid. The crude product was purified by flash chromatography on silica gel eluting with 2% MeOH/CH_2Cl_2 to give compound 476C (0.40 g, 57%) as an off-white solid. HPLC: 89.7% at 2.38 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 283.21 $[M+H]^+$.

D. (3aα,4β,7β,7aα)-Hexahydro-4,7-dimethyl-2-[2-(trifluoromethyl)-4-benzoxazolyl]-4,7-epoxy-1H-isoindole-1,3(2H)-dione (476D)

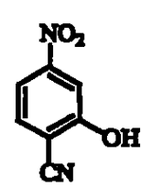
Compound 476C (0.24 g, 0.85 mmol) and 2,5-dimethylfuran (0.132 g, 1.37 mmol) were combined in 3 mL of benzene in a sealed tube and heated at 60°C for 12 h. The mixture was cooled and concentrated *in vacuo* to give a yellow oil which was dissolved in 1/1 EtOAc/EtOH (6 mL). 10% Pd/C (100 mg) was added and the mixture was stirred under an H_2 balloon for 3.5 h. The reaction was filtered through Celite and the solvent removed *in vacuo* to give the crude product as a pale yellow oil. Purification by flash chromatography on silica gel eluting with 2% Et_2O/CH_2Cl_2 gave 0.107 g (33%) of compound 476D as a white foam. HPLC: 96.5% at 2.80 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 381.17 $[M+H]^+$.

Example 477

(3aα,4β,7β,7aα)-2-Methyl-4-(octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-7-benzoxazolecarbonitrile (477E)



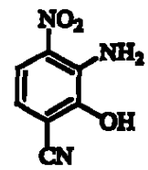
A. 2-Cyano-5-nitrophenol (477A)



3,4-Methylenedioxynitrobenzene (1.67 g, 10.0 mmol) was dissolved in 20 mL of HMPA and sodium cyanide (0.49 g, 10.0 mmol) was added. The reaction was heated to 150°C under nitrogen and three portions of sodium cyanide (0.245 g, 5.00 mmol, total) were added over 15 min. The reaction was maintained at 150°C for 45 min, cooled, and poured into 50 mL of H_2O followed by the addition of 50 mL of 5%

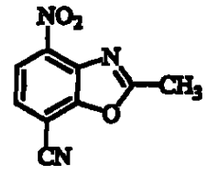
NaOH. The aqueous layer was extracted with ether (2 x 25 mL) and the organic layer was discarded. The basic aqueous layer was carefully acidified to pH 4 by addition of 10% HCl and extracted with ether (3 x 25 mL). The combined organic layers were washed with brine (25 mL), dried over sodium sulfate and concentrated *in vacuo*. Purification by flash chromatography on silica gel eluting with 5% $MeOH/CH_2Cl_2$ gave 1.05 g (64%) of compound 477A as a yellow-brown solid. HPLC: 91.6% at 1.03 min (retention time) (Phenomenex column, 30 x 4.6 mm, 10-90% aqueous methanol over 2 min containing 0.1% TFA, 5 mL/min, monitoring at 220 nm. MS (ES): m/z 165.23 $[M+H]^+$.

B. 2-Amino-4-cyano-3-hydroxynitrobenzene (477B)



Compound 477A (0.438 g, 2.67 mmol) was dissolved in 25 mL of DMSO and trimethylhydrazinium iodide (0.534 g, 2.67 mmol) was added. Sodium pentoxide (0.880 g, 8.01 mmol) was added under N_2 to give a deep red solution and stirring was continued overnight at rt. The reaction mixture was poured into 50 mL of 10% HCl and extracted with EtOAc (2 x 25 mL). The combined organic layers were washed with water (25 mL), brine (25 mL), dried over sodium sulfate and concentrated *in vacuo* to give compound 477B as an oily red solid which was used directly in the next reaction without further purification.

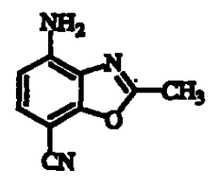
C. 7-Cyano-2-methyl-4-nitrobenzoxazole (477C)



Compound 477B (0.360 g, 2.01 mmol) and triethyl orthoacetate (1.30 g, 8.04 mmol) were combined and heated at reflux under nitrogen for 1 h. The solvent was

removed *in vacuo* and the resulting residue purified by flash chromatography eluting with 5% ether/CH_2Cl_2 to give 0.255 g (63%) of compound **477C** as a brown solid. HPLC: 98.4% at 1.80 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 204.28 $[M+H]^+$.

D. 4-Amino-7-cyano-2-methylbenzoxazole (477D)



Compound **477C** (0.156 g, 0.77 mmol) was dissolved in a 1:1 mixture of EtOAc/10% HOAc (20 mL) and heated to 65°C. Iron powder (325 mesh, 0.214 g, 3.83 mmol) was added and the reaction was stirred for 4 h. The cooled mixture was filtered through Celite and the resulting filtrate was washed with water (25 mL), brine (25 mL), dried over $MgSO_4$, and concentrated to give compound **477D** (0.118 g, 89%) as an orange solid. HPLC: 87% at 2.03 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 174.05 $[M+H]^+$.

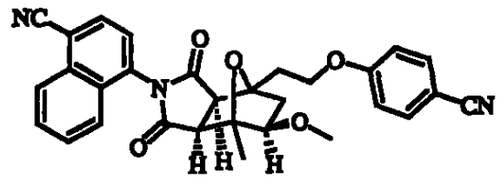
E. (3aα,4β,7β,7aα)-2-Methyl-4-(octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-7-benzoxazolecarbonitrile (477E)

Compound **477D** (0.060 g, 0.35 mmol) and compound **20A** (0.071 g, 0.37 mmol) were combined in a sealed tube with toluene (2 mL), triethylamine (0.24 mL, 1.7 mmol), and $MgSO_4$ (0.104 g, 0.866 mmol). The sealed tube was heated at 135°C for two days. The cooled reaction mixture was diluted with EtOAc, filtered, and concentrated *in vacuo* to give crude product as a brown oil. Purification by flash chromatography on silica gel eluting with 1/1 EtOAc/hexanes gave 0.014 g (12%) of compound **477E** as an off-white solid. HPLC: 96.5% at 2.27 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4

min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 352.23 $[M+H]^+$.

Example 478

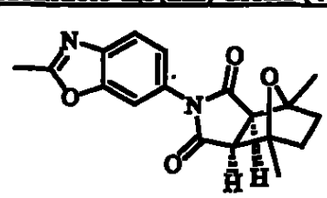
(3aα,4β,5β,7β,7aα)-4-[7-[2-(4-Cyanophenoxy)ethyl]octahydro-5-methoxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, slow eluting enantiomer (478)



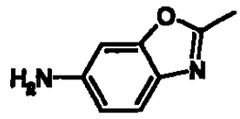
n-BuLi (0.050 mL, 1.6 M, 0.075 mmol) was added to a solution of compound 244li (33.7 mg, 0.0683 mmol) in THF (1.0 mL) at –78°C under argon. The reaction mixture was warmed to room temperature and methyl fluorosulfonate (0.010 mL, 0.12 mmol) was added dropwise. Once starting material was consumed, as was evident by HPLC, the reaction was quenched with H_2O and the resulting aqueous mixture was extracted with CH_2Cl_2 (3 x 5 mL). The combined organic layers were dried over $MgSO_4$ and concentrated under reduced pressure. Purification by reverse phase preparative HPLC [22.09 min (YMC S5 ODS column, 20 x 100 mm, 0-100% aqueous methanol over 25 min containing 0.1% TFA, 20 mL/min, monitoring at 220 nm)] gave 13.0 mg (38%) of compound 478 as a white solid. HPLC: 93% at 3.35 min (YMC S5 ODS column, 4.6 x 50 mm, 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 508.17 $[M+H]^+$.

Example 479

(3aα,4β,7β,7aα)-Hexahydro-4,7-dimethyl-2-(2-methyl-6-benzoxazolyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione (479B)



A. 2-Methyl-6-aminobenzoxazole (479A)



To a solution of 2-methyl-6-nitrobenzoxazole (100 mg, 0.560 mmol) in AcOH (2 mL) was added iron powder (325 mesh, 63.0 mg, 1.12 mmol) at 70°C in a single portion. After 15 min at 70°C additional iron powder (325 mesh, 63.0 mg, 1.12 mmol) was added and stirring was continued for 15 min. The mixture was cooled and concentrated under reduced pressure. The resulting residue was taken up into EtOAc and washed with sat. Na_2CO_3 followed by H_2O. The organic layer was dried over $MgSO_4$, concentrated under reduced pressure and purified by flash chromatography on silica gel eluting with a gradient of 0 to 25% EtOAc in CH_2Cl_2 to yield 69 mg (83%) of compound **479A** as a solid. HPLC: 97% at 0.24 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm Ballistic, 10-90% aqueous methanol over 4 min containing 0.2% H_3PO_4, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 149.2 $[M+H]^+$.

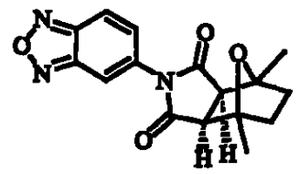
B. (3aα,4β,7β,7aα)-Hexahydro-4,7-dimethyl-2-(2-methyl-6-benzoxazolyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione (479B)

Compound **479A** (30 mg, 0.20 mmol), $MgSO_4$ (60 mg, 0.50 mmol), triethylamine (140 µL, 1.00 mmol) and compound **20A** (45 mg, 0.23 mmol) were taken up in 0.25 mL of toluene and placed in a sealed tube. The sealed tube was heated at 135°C for 14 h and the reaction was allowed to cool to rt. The mixture was filtered through a short pad of Celite, eluting with MeOH and the solvent was removed *in vacuo*. The residue was purified by flash chromatography on silica gel eluting with a gradient of 0 to 50% EtOAc in CH_2Cl_2 to give 49 mg (65%) of compound **479B** as a tan solid. HPLC: 98% at 2.30 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min

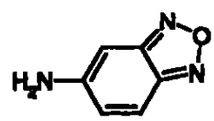
containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 326.9 $[M+H]^+$.

Example 480

(3aα,4β,7β,7aα)-2-(2,1,3-Benzoxadiazol-5-yl)hexahydro-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione (480B)



A. 5-Amino-2,1,3-benzoxadiazole (480A)



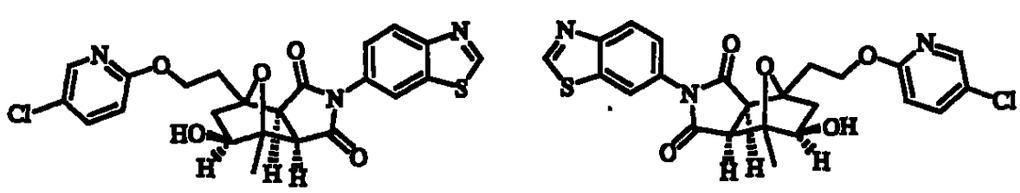
To a solution of 2,1,3-benzoxadiazole-5-carboxylic acid (102 mg, 0.621 mmol) in THF (3 mL) was added triethylamine (103 μL, 0.739 mmol) followed by DPPA (160 μL, 0.739 mmol) at room temperature. The mixture was stirred for 4 h, diluted with CH_2Cl_2 and washed with water. The organic layer was dried over $MgSO_4$, concentrated and purified by flash chromatography on silica gel with 0 to 50% EtOAc in CH_2Cl_2. The resulting material was dissolved in AcOH (2 mL) and water (0.7 mL) was added dropwise yielding a slightly cloudy solution which was heated at 105°C for 30 min. The mixture was cooled, made basic with sat. Na_2CO_3 solution and extracted several times with THF. The combined organic layers were dried over $MgSO_4$, concentrated and purified by flash chromatography on silica gel eluting with 0 to 15% MeOH in CH_2Cl_2 to give 34 mg (41%) of compound 480A as a yellow solid. HPLC: 100% at 1.27 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm Ballistic, 10-90% aqueous methanol over 4 min containing 0.2% H_3PO_4, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 136.0 $[M+H]^+$.

B. (3aα,4β,7β,7aα)-2-(2,1,3-Benzoxadiazol-5-yl)hexahydro-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione (480B)

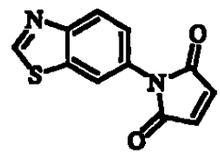
Compound **480A** (34 mg, 0.25 mmol), $MgSO_4$ (76 mg, 0.63 mmol), triethylamine (180 μL, 1.26 mmol) and compound **20A** (74 mg, 0.38 mmol) were dissolved in 0.25 mL of toluene and placed in a sealed tube. The sealed tube was heated at 135°C for 14 h. The cooled reaction mixture was filtered through a short pad of Celite, eluting with acetone and the solvent was removed *in vacuo*. The residue was purified by reverse phase preparative HPLC (YMC S5 ODS 20 x 100 mm, eluting with 30-100% aqueous methanol over 10 min containing 0.1% TFA, 20 mL/min). Concentration of the desired fractions afforded a residue which was partitioned between CH_2Cl_2 and sat. $NaHCO_3$ solution. The aqueous layer was extracted once with CH_2Cl_2 and the combined organic phases were dried over Na_2SO_4. Concentration under reduced pressure gave 42 mg (53%) of compound **480B** as a yellow solid. HPLC: 100% at 2.62 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). ^1H NMR (400 MHz, $CDCl_3$) δ = 7.91 (d, 1H), 7.90 (dd, 1H), 7.37 (dd, 1H), 3.09 (s, 2H), 1.85 (s, 4H), 1.67 (s, 6H).

Example 481

[3a*R*-(3aα,4β,5β,7β,7aα)]-2-(6-Benzothiazolyl)-7-[2-[(5-chloro-2-pyridinyl)oxy]ethyl]hexahydro-5-hydroxy-4-methyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione (481D) & [3a*S*-(3aα,4β,5β,7β,7aα)]-2-(6-Benzothiazolyl)-7-[2-[(5-chloro-2-pyridinyl)oxy]ethyl]hexahydro-5-hydroxy-4-methyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione (481E)

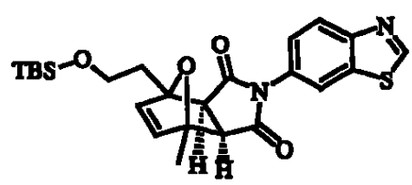


A. 1-Benzothiazol-6-yl-pyrrole-2,5-dione (481A)



A mixture of 5-aminobenzothiazole (2.00 g, 13.3 mmol) and maleic anhydride (1.96 g, 20.0 mmol) in AcOH (27 mL) was heated at 115°C for 20 h. The mixture was cooled and concentrated under reduced pressure. The residue was taken up in THF and washed with saturated Na_2CO_3. The aqueous layer was extracted several times with THF and the combined organic layers were dried over $MgSO_4$. Purification by flash chromatography on silica gel eluting with 0 to 50% EtOAc in CH_2Cl_2 gave 1.37 g (45%) of compound 481A as a pale yellow solid. HPLC: 100% at 2.62 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 231.0 $[M+H]^+$.

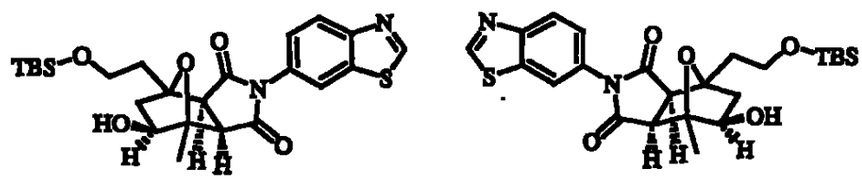
B. (3aα,4β,7β,7aα)-2-(6-Benzothiazolyl)-4-[2-[[(1,1-dimethylethyl)dimethylsilyl]oxy]ethyl]-3a,4,7,7a-tetrahydro-7-methyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione (481B)



A suspension of compound 481A (445 mg, 1.93 mmol) and compound 204A (929 mg, 3.87 mmol) in benzene (2 mL) was heated to 60°C and acetone was added until a clear solution was obtained. The resulting mixture was stirred at 60°C for 24 h and was then slowly concentrated *in vacuo*. The resulting residue was dissolved in acetone and slowly concentrated *in vacuo*. This process was repeated a total of three times. Purification by flash chromatography on silica gel eluting with 0 to 30% acetone in hexanes gave 820 mg (90%) of compound 481B as a white solid. HPLC:

100% at 2.62 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 471.3 $[M+H]^+$.

C. [3a*R*-(3aα,4β,5β,7β,7aα)]-2-(6-Benzothiazolyl)-7-[2-[[(1,1-dimethylethyl)dimethylsilyl]oxy]ethyl]hexahydro-5-hydroxy-4-methyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione (481Ci) & [3a*S*-(3aα,4β,5β,7β,7aα)]-2-(6-Benzothiazolyl)-7-[2-[[(1,1-dimethylethyl)dimethylsilyl]oxy]ethyl]hexahydro-5-hydroxy-4-methyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione (481Cii)



To a solution of compound **481B** (75 mg, 0.16 mmol) in THF (1 mL) was added Wilkinson's catalyst (32 mg, 0.030 mmol) and catecholborane (1.0 M in THF, 1.6 mL, 1.6 mmol) at room temperature under nitrogen. The resulting mixture was stirred for 2.5 h before it was cooled to 0°C. EtOH (5 mL), 3 N NaOH (2 mL) and H_2O_2 (30%, 1 mL) were added sequentially, and the mixture was stirred for 2 h at 0°C. The reaction was quenched by the addition of cold 10% Na_2SO_3 solution (excess) followed by water. The aqueous layer was extracted several times with CH_2Cl_2 and the combined organic layerss were dried over Na_2SO_4. Concentration under reduced pressure followed by purification by flash chromatography on silica gel eluting with 0 to 100% EtOAc in hexanes gave 13 mg (17%) of a racemic mixture of compounds **481Ci** & **481Cii** as a tan solid. HPLC: 96% at 3.58 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm Ballistic, 10-90% aqueous methanol over 4 min containing 0.2% H_3PO_4, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 489.3 $[M+H]^+$. The racemic mixture was separated into its individual enantiomers by normal phase preparative chiral HPLC (CHIRALPAK AD 5 x 50 cm column; eluting with 20% MeOH/EtOH (1:1) in heptane (isocratic) at 50 mL/min) to give the faster eluting enantiomer, compound **481Ci**: (Chiral HPLC: 9.40 min; CHIRALPAK AD 4.6 x 250 mm column; eluting with 20% MeOH/EtOH (1:1) in heptane at 1 mL/min)

and the slower eluting enantiomer, compound **481Cii**: (Chiral HPLC: 10.47 min; CHIRALPAK AD 4.6 x 250 mm column; eluting with 20% MeOH/EtOH (1:1) in heptane at 1 mL/min). The absolute conformation for compounds **481Ci** & **481Cii** was not established. For simplicity in nomenclature, compound **481Ci** is designated herein as having an "R" configuration and compound **481Cii** as having an "S" configuration. Enantiomerically pure products derived from compound **481Ci** are designated herein as having a "R" configuration and enantiomerically pure products derived from compound **481Cii** are designated herein as having an "S" configuration.

D. [3a*R*-(3aα,4β,5β,7β,7aα)]-2-(6-Benzothiazolyl)-7-[2-[(5-chloro-2-pyridinyl)oxy]ethyl]hexahydro-5-hydroxy-4-methyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione (481D)

Compound **481Ci** (84 mg, 0.17 mmol) was suspended into EtOH (2 mL) and conc. HCl (40 μL) was added at room temperature. The mixture was stirred for 15 min before several drops of sat. $NaHCO_3$ solution were added. Concentration under reduced pressure yielded a residue which was partitioned between CH_2Cl_2 and sat. $NaHCO_3$ solution. The aqueous layer was extracted several times with CH_2Cl_2 and finally with EtOAc. The combined organic phases were dried over Na_2SO_4, concentrated and purified by preparative TLC eluting with 50% acetone in $CHCl_3$. This procedure served to remove the TBS group from compound **481Ci**, yielding the free primary alcohol. A 12 mg (0.03 mmol) portion of the free alcohol of compound **481Ci** was reacted with 5-chloro-2-pyridinol (8 mg, 0.06 mmol), PPh_3 (17 mg, 0.060 mmol) and di-*tert*-butylazodicarboxylate (15 mg, 0.060 mmol) in THF (0.5 mL) according to the general procedure described in Example 244. The mixture was stirred for 24 h at room temperature, diluted with 1N NaOH and the aqueous layer was extracted several times with CH_2Cl_2. The combined organic layers were dried over Na_2SO_4, concentrated and purified by preparative TLC, eluting with 25% acetone in $CHCl_3$ to give 9 mg (58%) compound **481D** as a white solid. HPLC: 98% at 2.94 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm Ballistic, 10-90%

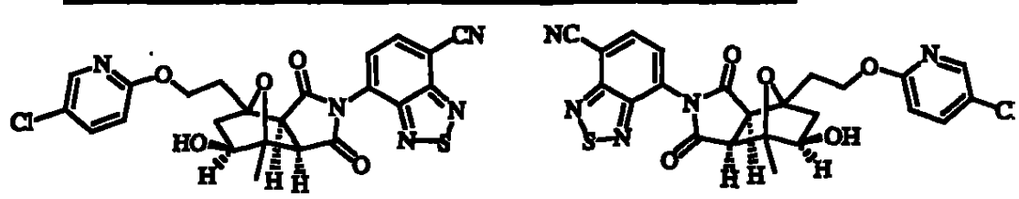
aqueous methanol over 4 min containing 0.2% H_3PO_4, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 486.2 $[M+H]^+$.

E. [3a*S*-(3aα,4β,5β,7β,7aα)]-2-(6-Benzothiazolyl)-7-[2-[(5-chloro-2-pyridinyl)oxy]ethyl]hexahydro-5-hydroxy-4-methyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione (481E)

As described in Example 481D, compound 481Cii (58 mg, 0.12 mmol) was treated with EtOH (2 mL) containing 12 N HCl (40 μL) to yield the free primary alcohol product of compound 481Cii. A 15 mg (0.040 mmol) of the free alcohol of compound 481Cii was reacted with 5-chloro-2-pyridinol (10 mg, 0.080 mmol), PPh_3 (21 mg, 0.080 mmol) and di-*tert*-butylazodicarboxylate (18 mg, 0.080 mmol) in THF (0.5 mL) in the manner described above and the resulting product was purified as described above to yield 8 mg (41%) of compound 481E as a white solid. HPLC: 99% at 2.93 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm Ballistic, 10-90% aqueous methanol over 4 min containing 0.2% H_3PO_4, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 486.2 $[M+H]^+$.

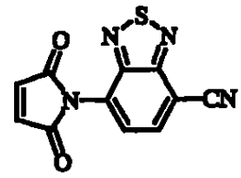
Example 482

[3a*R*-(3aα,4β,5β,7β,7aα)]-7-[7-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2,1,3-benzothiadiazole-4-carbonitrile (482F) & [3a*S*-(3aα,4β,5β,7β,7aα)]-7-[7-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2,1,3-benzothiadiazole-4-carbonitrile (482G)



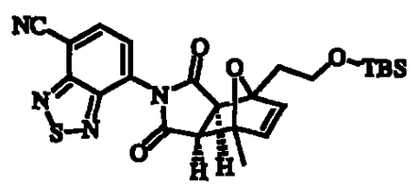
A. 7-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-benzo[1,2,5]thiadiazole-4-carbonitrile

(482A)



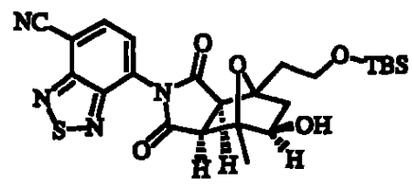
Maleic anhydride (667 mg, 6.80 mmol) was added to a solution of compound **424A** (600 mg, 3.41 mmol) in THF (9 mL). The mixture was heated at 110°C for 10 h. The reaction was concentrated under reduced pressure and acetic anhydride (1 mL) was added to the residue. The reaction mixture was heated at 75°C for 30 min and then cooled to rt. Purification by flash chromatography on silica gel eluting with 3% acetone/$CHCl_3$ gave 758 mg (2.96 mmol, 67%) of compound **482A**. HPLC: 97% at 1.98 min (retention time) (YMC S5 ODS 4.6 x 50 mm, 10%-90% aqueous methanol over 4 min gradient with 0.2% H_3PO_4, monitoring at 220 nm). MS (ES): m/z 257.01 $[M+H]^+$.

B. (3aα,4β,7β,7aα)-7-[4-[2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]-1,3,3a,4,7,7a-hexahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2,1,3-benzothiadiazole-4-carbonitrile (482B)



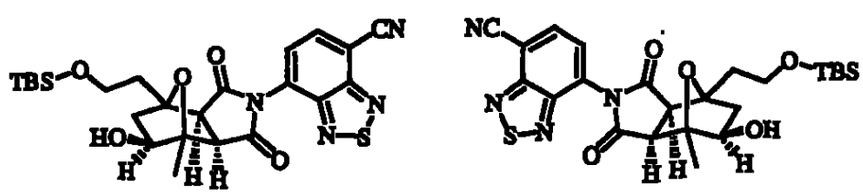
A solution of compound **482A** (758 mg, 2.96 mmol) and compound **204A** (711 mg, 2.96 mmol) in benzene (2 mL) and acetone (2 mL) was heated at 60°C for 6 h. The reaction mixture was concentrated *in vacuo* at 42°C for 40 min to give 1.5 g of crude compound **482B**, which was used directly in the next step without further purification.

C. (3aα,4β,5β,7β,7aα)-7-[7-[2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2,1,3-benzothiadiazole-4-carbonitrile (482C)



Borane-dimethylsulfide complex (0.66 mL, 6.96 mmol) was added to a solution of compound **482B** (1.15 g, 2.32 mmol) in THF (6 mL) at 0°C. After stirring at 0°C for 2 h, the reaction mixture was quenched with phosphate buffer (60 mL, pH 7.2) and then EtOH (35 mL), H_2O_2 (8 mL, 30% aq.) and THF (4 mL) were added. The reaction mixture was stirred at 0°C for 1 h and was then extracted with CH_2Cl_2 (4 x 100 mL). The combined organic layers were washed with 10% aq. Na_2SO_3 (1 x 160 mL) followed by brine (1 x 160 mL) and dried over Na_2SO_4. Purification by flash chromatography on silica gel eluting with 10% acetone/$CHCl_3$ gave 250 mg (0.486 mmol, 21%) of compound **482C** as an orange solid. HPLC: 85% at 3.70 min (retention time) (YMC S5 ODS 4.6 x 50 mm, 10%-90% aqueous methanol over 4 min gradient with 0.2% H_3PO_4, monitoring at 220 nm). MS (ES): m/z 515.27 $[M+H]^+$.

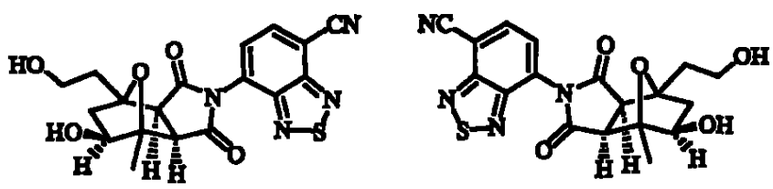
D. [3a*R*-(3aα,4β,5β,7β,7aα)]-7-[7-[2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2,1,3-benzothiadiazole-4-carbonitrile & [3a*S*-(3aα,4β,5β,7β,7aα)]-7-[7-[2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2,1,3-benzothiadiazole-4-carbonitrile (482DI & 482DII)



The racemic compounds **482C** was separated by normal phase preparative chiral HPLC using a Chiracel OD column (5 cm x 50 cm), eluting with 10% EtOH in hexane at 50 mL/min to give the faster eluting compound **482DI** (Chiral HPLC: 11.89 min; CHIRALCEL OD 4.6 x 250 mm column; isocratic elution with 12% EtOH in

hexane at 2 mL/min) and the slower eluting compound **482DII** (Chiral HPLC: 16.10 min; CHIRALCEL OD 4.6 x 250 mm column; isocratic elution with 12% EtOH in hexane at 2 mL/min). The absolute conformation for compounds **482DI** & **482DII** was not established. For simplicity in nomenclature, compound **482DI** is designated herein as having an "R" configuration and compound **482DII** as having an "S" configuration. Enantiomerically pure products derived from compound **482DI** are designated herein as having a "R" configuration and enantiomerically pure products derived from compound **482DII** are designated herein as having an "S" configuration.

E. [3a*R*-(3aα,4β,5β,7β,7aα)]-7-[Octahydro-5-hydroxy-7-(2-hydroxyethyl)-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2,1,3-benzothiadiazole-4-carbonitrile (482EI) & [3a*R*-(3aα,4β,5β,7β,7aα)]-7-[Octahydro-5-hydroxy-7-(2-hydroxyethyl)-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2,1,3-benzothiadiazole-4-carbonitrile (482EII)



Compound **482DI** (91 mg, 0.18 mmol) was dissolved in 2% 12 N HCl/EtOH (3.0 mL) and the mixture was stirred at rt for 20 min. Cold sat. $NaHCO_3$ was added to the mixture until it was basic (pH 8). The reaction was extracted with EtOAc. The organic layers were then washed with brine and dried over anhydrous sodium sulfate. Concentration *in vacuo* gave 73 mg (0.18 mmol, 100%) compound **482EI** as a yellow solid which was not purified further. HPLC: 95% at 1.73 min (retention time) (YMC S5 ODS 4.6 x 50 mm, 10%-90% aqueous methanol over 4 min gradient with 0.2% H_3PO_4, monitoring at 220 nm). MS (ES): m/z 401.13 $[M+H]^+$.

Compound **482DII** (90 mg, 0.17 mmol) was dissolved in 2% 12 N HCl/EtOH (3.0 mL) and the mixture was stirred at rt for 20 min. Cold sat. $NaHCO_3$ was added to the mixture until it was basic (pH 8). The reaction was extracted with EtOAc. The organic layers were then washed with brine and dried over anhydrous sodium sulfate. Concentration *in vacuo* gave 70 mg (0.17 mmol, 100%) compound **482EII** as an

orange solid which was not purified further. HPLC: 90% at 1.74 min (retention time) (YMC S5 ODS 4.6 x 50 mm, 10%-90% aqueous methanol over 4 min gradient with 0.2% H_3PO_4, monitoring at 220 nm). MS (ES): m/z 401.14 $[M+H]^+$.

F. [3a*R*-(3aα,4β,5β,7β,7aα)]-7-[7-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2,1,3-benzothiadiazole-4-carbonitrile (482F)

DBAD (21 mg, 0.090 mmol) was added to a solution of PPh_3 (24 mg, 0.090 mmol) in THF (0.4 mL). After stirring for 10 min, 5-chloro-2-pyridinol (12 mg, 0.090 mmol) was added and the reaction mixture was stirred for an additional 5 min. Compound 482Ei (18 mg, 0.045 mmol) was added and the mixture was stirred at rt for 1 h. The reaction was then concentrated under reduced pressure. Purification by preparative TLC eluting with 20% acetone/$CHCl_3$ gave 12 mg (0.023 mmol, 52) of compound 482F. HPLC: 98% at 3.15 min (retention time) (YMC S5 ODS 4.6 x 50 mm, 10%-90% aqueous methanol over 4 min gradient with 0.2% H_3PO_4, monitoring at 220 nm). MS (ES): m/z 512.11 $[M+H]^+$.

G. [3a*S*-(3aα,4β,5β,7β,7aα)]-7-[7-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2,1,3-benzothiadiazole-4-carbonitrile (482G)

DBAD (21 mg, 0.090 mmol) was added to a solution of PPh_3 (24 mg, 0.090 mmol) in THF (0.4 mL). After stirring for 10 min, 5-chloro-2-pyridinol (12 mg, 0.090 mmol) was added and the reaction mixture was stirred for an additional 5 min. Compound 482Eii (18 mg, 0.045 mmol) was added and the mixture was stirred at rt for 1 h. The reaction was then concentrated under reduced pressure. Purification by preparative TLC eluting with 20% acetone/$CHCl_3$ gave 11 mg (0.021 mmol, 47.0%) of compound 482G. HPLC: 98% at 3.15 min (retention time) (YMC S5 ODS 4.6 x 50 mm, 10%-90% aqueous methanol over 4 min gradient with 0.2% H_3PO_4, monitoring at 220 nm). MS (ES): m/z 512.15 $[M+H]^+$.

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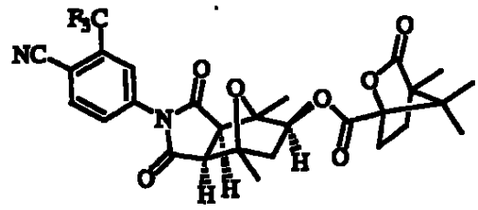
Example 483

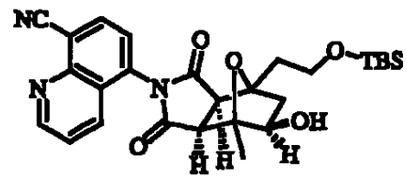
(1*S*,4*R*)-4,7,7-Trimethyl-3-oxo-2-oxabicyclo[2.2.1]heptane-1-carboxylic acid, [3a*S*-(3aα,4β,5β,7β,7aα)]-2-[4-cyano-3-(trifluoromethyl)phenyl]octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-1H-isoindol-5-yl ester (483)



To a solution of compound 471Di (25 mg, 0.066 mmol) in 0.25 mL of CH_2Cl_2 at rt and under argon, was added a solution of (1*S*)-(-)-camphanic acid (20 mg, 0.10 mmol) in 0.2 mL of CH_2Cl_2. A solution of DCC (20 mg, 0.10 mmol) in 0.25 mL of CH_2Cl_2 was then added followed by DMAP (4.0 mg, 0.034 mmol). A white precipitate was obtained immediately and stirring was continued overnight. The precipitate was removed by filtration and the filtrate was diluted with EtOAc. The resulting solution was washed with 1N HCl, brine, sat. $NaHCO_3$, and brine then dried over $MgSO_4$. Concentration *in vacuo* afforded a viscous oily residue. The crude material was subjected to flash chromatography on a 20 cm^3 column of silica gel eluting with 50% EtOAc in hexanes to 32 mg of a white solid. Recrystallization from CH_2Cl_2/hexane yielded 20 mg (86%) of compound 483 as large crystals. This material was subjected to X-ray crystal diffraction studies to elucidate the exact stereochemistry of compound 471Di as referenced to the known fixed stereochemistry of the (1*S*)-(-)-camphanic acid appendage. LCMS: 100% at 1.9 min (retention time) (Phenomenex Luna C18 column, 2 x 30 mm, 0-100% aqueous acetonitrile over 3 min containing 10 mM NH_4OAc at 1 mL/min, monitoring at 220 nm). MS (ESI): m/z 559.3 $[M-H]^-$.

Example 484

(3aα,4β,5β,7β,7aα)-5-[7-[2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile (484)



To a dry, 3-necked, 25 mL round-bottom was added $TiCl_2Cp_2$ (0.500 g, 2.01 mmol) and THF (4 mL) to give a deep red solution. Activated zinc dust (0.392 g, 6 mmol, prepared as described in Fieser and Fieser, Volume 1, p. 1276) was added and the suspension was stirred for 30 min during which time the color changed from brick-red to emerald-green. The unreacted zinc dust was allowed to settle. In a separate 3-necked, 25 mL round-bottom flask was added compound **464F** (0.202 g, 0.399 mmol), THF (1 mL) and 1,4-cyclohexadiene (0.380 mL, 4.02 mmol). The Ti(III) reagent (0.90 mL, 0.45 mmol) was added via an addition funnel with a cotton plug at the bottom rinsing with THF (1 mL). After 1 h, HPLC showed ~ 50% conversion and an additional 0.9 mL (0.45 mmol) of the titanium reagent was added. After 1 h, HPLC showed complete consumption of starting material. Saturated ammonium chloride (5 mL) was added, followed by 10 mL of EtOAc. The organic layer was separated, washed with brine (5 mL), dried over Na_2SO_4, and concentrated *in vacuo* to give the crude product as an orange semi-solid. The crude material was purified by flash chromatography on silica gel eluting with 50% CH_2Cl_2/48% EtOAc/2% MeOH to give 0.10 g (59%) of compound **484** as a light yellow foam. HPLC: 91% at 3.65 min (retention time) (YMC S5 ODS column, 4.6x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 508.27 $[M+H]^+$.

Example 485

[3a*R*-(3aα,4β,5β,7β,7aα)]-5-[7-[2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile (485I) & [3a*S*-(3aα,4β,5β,7β,7aα)]-5-[7-[2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile (485II)

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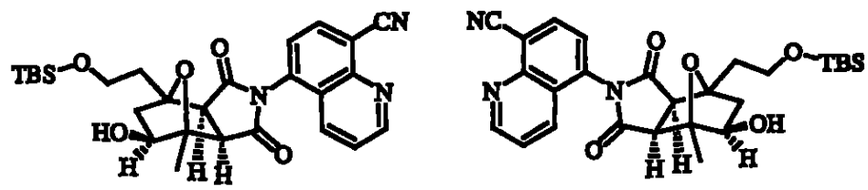
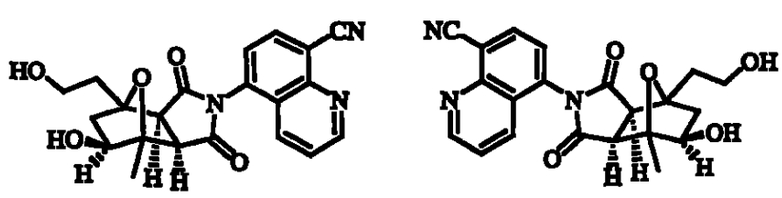


The racemic compound **484**, was separated into its individual antipodes by normal phase preparative chiral HPLC. A Chiralcel OD column (50 x 500 mm) was used with a flow rate of 50 mL/min (20% EtOH/hexanes) monitoring at 220 nm. The faster eluting antipode, compound **485i** had a retention time of 35.8 min and the slower antipode, compound **485ii** had a retention time of 49.7 min. Both antipodes were isolated as white solids after separation. Compound **485i**: HPLC: 100% at 4.980 min (retention time) (Chiracel OD column (5 x 50 mm), 2.0 mL/min, 20% EtOH/hexanes, monitoring at 220 nm), >99% ee. MS (ES): m/z 508.23 $[M+H]^+$. Compound **485ii**: HPLC: 98.6% at 7.357 min (retention time) (Chiracel OD column (5 x 50 mm), 2.0 mL/min, 20% EtOH/hexanes, monitoring at 220 nm), 97.2% ee. MS (ES): m/z 508.21 $[M+H]^+$. The absolute conformation for compounds **485i** & **485ii** was not established. For simplicity in nomenclature, compound **485i** is designated herein as having an "R" configuration and compound **485ii** as having an "S" configuration. Enantiomerically pure products derived from compound **485i** are designated herein as having a "R" configuration and enantiomerically pure products derived from compound **485ii** are designated herein as having an "S" configuration.

Example 486

[3a*R*-(3aα,4β,5β,7β,7aα)]-5-[Octahydro-5-hydroxy-7-(2-hydroxyethyl)-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile (486i) & [3a*S*-(3aα,4β,5β,7β,7aα)]-5-[Octahydro-5-hydroxy-7-(2-hydroxyethyl)-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile (486ii)



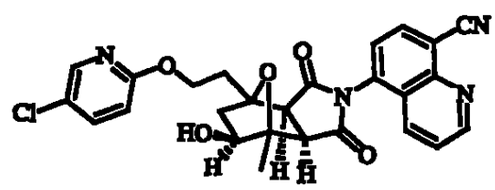
Compounds **485i** & **485ii** were converted to the free primary alcohol products as described in example **466** to give compounds **486i** and **486ii** as white solids.

Compound **486i**: HPLC: 98% at 1.650 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 394.21 $[M+H]^+$.

Compound **486ii**: HPLC: 98% at 1.663 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 394.20 $[M+H]^+$.

Example 487

[3a*R*-(3aα,4β,7β,7aα)]-5-[7-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile (487)



DBAD (0.088 g, 0.38 mmol) was added to a solution of triphenylphosphine (0.100 g, 0.382 mmol) in THF (1.0 mL) at 22°C and stirred for 10 min. 5-Chloro-2-pyridinol (0.049 g, 0.38 mmol) was added as a solid and stirring was continued for 10 min. The reaction mixture was added to compound **486i** (0.100 g, 0.250 mmol) in THF (1.0 mL). After stirring for 3 h, the reaction was concentrated *in vacuo* and purified by flash chromatography on silica gel eluting with 20-50% acetone/chloroform to give 0.080 g (63%) of compound **487** as a white solid. HPLC: 100% at 3.023 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 505.16 $[M+H]^+$.

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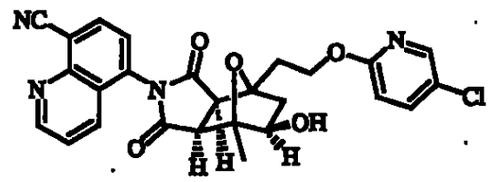
Example 488

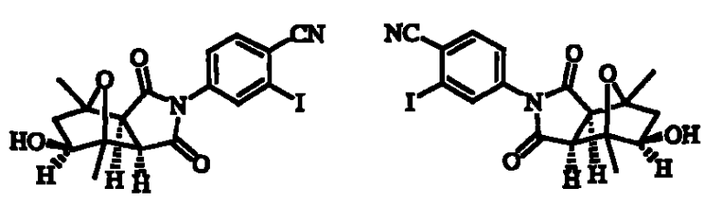
[3aS-(3aα,4β,7β,7aα)]-5-[7-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile (488)



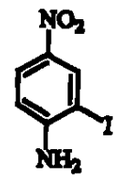
DBAD (0.088 g, 0.38 mmol) was added to a solution of triphenylphosphine (0.100 g, 0.382 mol) in THF (1.0 mL) at 22°C and stirred for 10 min. 5-Chloro-2-pyridinol (0.049 g, 0.38 mmol) was added as a solid and stirring was continued for 10 min. The reaction mixture was added to compound 486II (0.100 g, 0.250 mmol) in THF (1.0 mL). After stirring for 3 h, the reaction was concentrated *in vacuo* and purified by flash chromatography on silica gel eluting with 10-50 acetone/chloroform to give 0.080 g (63%) of compound 488 as a white solid. HPLC: 95% at 3.030 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 505.12 $[M+H]^+$.

Example 489

[3aR-(3aα,4β,5β,7β,7aα)]-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-iodobenzonitrile (489GI) & [3aS-(3aα,4β,5β,7β,7aα)]-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-iodobenzonitrile (489GII)

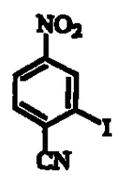


A. 2-Iodo-4-nitro-phenylamine (489A)



To a mixture of iodine (46.0 g, 0.180 mol) and silver sulfate (56.3 g, 0.180 mol) in anhydrous ethanol (500 mL) was added 4-nitroaniline (25.0 g, 0.180 mol) and the reaction mixture was stirred for 5 h at rt. The resulting yellow solution was filtered and concentrated *in vacuo*. The resulting residue was dissolved into 400 mL ethyl acetate, washed with 1N sodium hydroxide solution (2 x 250 mL), dried over sodium sulfate, filtered, and concentrated *in vacuo* to yield 45.5 (95%) of compound **489A**, as a yellow solid. HPLC: 98% at 2.837 min (retention time) (Shimadzu VP-ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.1% trifluoracetic acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 265.08 $[M+H]^+$.

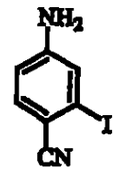
B. 2-Iodo-4-nitro-benzonitrile (489B)



Compound **489A** (10.0 g, 37.9 mmol) was dissolved in a mixture of 20 mL 12 N HCl/40 mL water and then cooled to 0°C. To this mixture was slowly added a solution of sodium nitrite (5.23 g, 75.8 mmol) in 10 mL water while maintaining the reaction temperature at 0°C. The reaction was stirred for 1 h at 0°C and then slowly added to a mechanically stirred solution of freshly prepared cuprous cyanide (3.0 g, 33 mmol, prepared as described in Vogel's Textbook of Practical Organic Chemistry, 5th edition , pg. 429) and potassium cyanide (6.30 g, 96.7 mmol) in water (50 mL) at 50°C. The reaction was stirred for 1 h at 50°C, cooled to 25°C and extracted with methylene chloride (2 x 200 mL). The organic portion was dried over sodium sulfate, filtered and concentrated *in vacuo*. The resulting residue was purified by chromatography on silica gel eluting with 4:1 hexane:ethyl acetate to yield 4.6 g (44%) of compound **489B** as an orange solid. HPLC: 98% at 2.647 min (retention

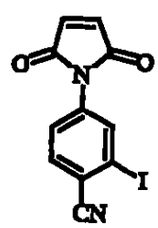
time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90 aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm).

C. 4-Amino-2-iodo-benzonitrile (489C)



A mixture of compound 489B (4.60 g, 16.8 mmol), tetrahydrofuran (75 mL), ethanol (100 mL), ammonium chloride solution (1.51 g, 28.3 mmol, dissolved in 100 mL of water), and iron (325 mesh, 4.21 g, 75.4 mmol) was mechanically stirred. The reaction mixture was heated to reflux for 3 h or until all starting material was consumed. The reaction mixture was cooled, filtered through Celite and concentrated *in vacuo*. The resulting residue was dissolved in ethyl acetate (200 mL) and washed with 1N sodium hydroxide (2 x 150 mL), dried over sodium sulfate, filtered and concentrated *in vacuo* to yield 3.97 g (97%) of compound 489C as a dark solid. HPLC: 95% at 1.877 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 245.13 $[M+H]^+$.

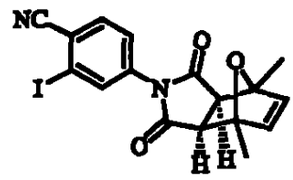
D. 4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-2-iodo-benzonitrile (489D)



Compound 489C (3.97 g, 16.3 mmol) and maleic anhydride (2.41 g, 24.4 mmol) were refluxed in glacial acetic acid (15 mL) for 5 h. The reaction was cooled to 25°C and then poured onto ice (100 mL). The resulting precipitate was isolated by filtration and washed with water (2 x 25 mL) and dried under vacuum to yield 4.78 g (90%) of compound 489D as a tan solid. HPLC: 82% at 2.68 min (retention time) C

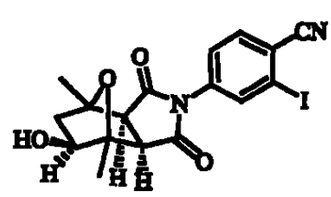
Shimadzu VP-ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.1% trifluoroacetic acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 325.04 $[M+H]^+$.

E. **(3aα,4β,7β,7aα)-4-(1,3,3a,4,7,7a-Hexahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-iodobenzonitrile (489E)**



A solution of compound **489D** (0.40 g, 1.2 mmol) in 2,5-dimethylfuran (2.0 g) was stirred at 75°C for 2 h. The reaction was decanted from any insoluble materials and the particulates were washed with diethyl ether. The combined decant and ether washes were combined and concentrated *in vacuo* while maintaining a temperature of <50°C. The resulting residue was triturated with hexanes to yield 0.56 g (94% based on purity) of compound **489E** as a tan solid. Due to the propensity of the product to undergo a retro-Diels-Alder reaction, no further purification was attempted. HPLC: 85% at 3.01 min (retention time) (Shimadzu VP-ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.1% trifluoroacetic acid acid, 4 mL/min, monitoring at 254 nm). MS (ES): m/z 421.05$[M+H]^+$.

F. **(3aα,4β,5β,7β,7aα)-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-iodobenzonitrile (489F)**



To a solution of compound **489E** (0.40 g, 0.95 mmol) in dry THF (5 mL) cooled to 0°C was added borane-dimethylsulfide complex (0.2 mL, 1.9 mmol, 10 M) and the reaction solution was allowed to warm to 25°C. After stirring for 30 min, the

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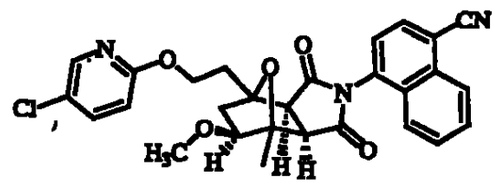
reaction was cooled to 0°C and pH 7 phosphate buffer (6.6 mL) was slowly added, followed by the addition of 30% hydrogen peroxide (0.7 mL). The reaction was stirred at 25°C for 1 h and then partitioned between ethyl acetate (100 mL) and water (100 mL). The organic portion was isolated, dried over sodium sulfate, filtered and concentrated *in vacuo*. The resulting residue was purified by silica gel eluting with 3:1 methylene chloride:ethyl acetate to yield 0.11 g (25%) of compound **489F** as a white solid. HPLC: 99% at 2.527 min (retention time) (Shimadzu VP-ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.1% trifluoroacetic acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 439.09 $[M+H]^+$.

G. [3a*R*-(3aα,4β,5β,7β,7aα)]-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-iodobenzonitrile (489Gi) & [3a*S*-(3aα,4β,5β,7β,7aα)]-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-iodobenzonitrile (489Gii)

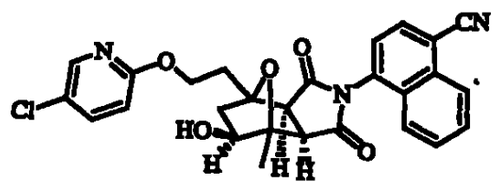
The racemic compounds **489F**, was separated into its individual antipodes by normal phase preparative chiral HPLC. A Chiralcel AD column (50 x 500 mm) was used with a flow rate of 50 mL/min (70% Isopropanol/hexanes) monitoring at 220 nm. The faster eluting antipode, compound **489Gi** had a retention time of 4.587 min and the slower eluting antipode, compound **489Gii** had a retention time of 6.496 min. Both antipodes were isolated as white solids after separation. The absolute conformation for compounds **489Gi** & **489Gii** was not established. For simplicity in nomenclature, compound **489Gi** is designated herein as having an "R" configuration and compound **489Gii** as having an "S" configuration.

Example 490

(3aα,4β,5β,7β,7aα)-4-[7-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]octahydro-5-methoxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (490B)



A. (3aα,4β,7β,7aα)-4-[7-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (490A)



A mixture of triphenylphosphine (166 mg, 0.633 mmol) and DBAD (146 mg, 0.633 mmol) was dissolved in THF (4 mL) under nitrogen and the yellow solution was stirred for 10 min. 5-Chloro-pyridin-2-ol (82 mg, 0.63 mmol) was added and the mixture was stirred for 5 min after which compound **242B** (165 mg, 0.327 mmol) was added. The mixture was stirred for 12 h and the solvent was removed under a stream of nitrogen. The resulting oil was adsorb onto silica gel (1 g) and purified by flash chromatography on a Jones Chromatography silica cartridge (5 g/25 mL) eluting with a gradient of 0-50% acetone in chloroform to give 79.4 mg (47%) of compound **490A** as a white foam. HPLC: 99% at 3.48 min (retention time) (Phenomenex ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 504.17 $[M+H]^+$.

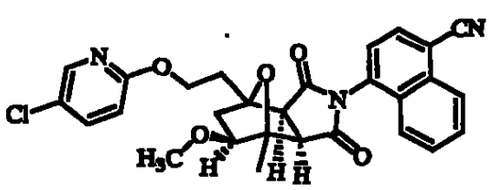
B. (3aα,4β,5β,7β,7aα)-4-[7-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]octahydro-5-methoxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (490B)

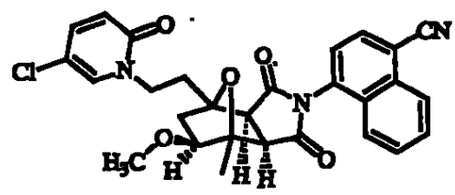
Compound **490A** (24 mg, 0.048 mmol) was dried into a 1 dram vial with a magnetic stir bar. Silver oxide (57 mg, 0.24 mmol), CH_3CN (500 μL) and iodomethane (20 μL, 0.32 mmol) were added under nitrogen and the mixture was put in a heated block (82°C) and stirred for 14 h. The mixture turned brown after 20 min

then green. The mixture was filtered through Celite and Florisil and was purified by reverse phase preparative HPLC (Shimadzu Shimpac VP ODS column, 20 x 50 mm, 0-100% aqueous methanol over 6 min containing 0.1% TFA, monitoring at 220 nm) to give 6.9 mg (28%) of compound 490B as a white foam. HPLC: 99% at 3.64 min, 3.76 min (atropisomers, retention time) (Phenomenex ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 518.19 $[M+H]^+$.

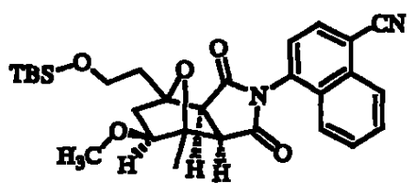
Example 491

[3a*R*-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]octahydro-5-methoxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, (491Ci) & [3a*R*-(3aα,4β,5β,7β,7aα)]-4-[7-[2-(5-Chloro-2-oxo-1(2H)-pyridinyl)ethyl]octahydro-5-methoxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (491Cii)





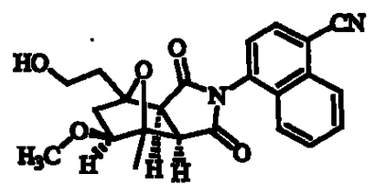
A. **(3aα,4β,5β,7β,7aα)-4-[7-[2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]octahydro-5-methoxy-4-methyl-1,3-dioxo-4,7-epoxy-2*H*-isoindol-2-yl]-1-naphthalenecarbonitrile (491A)**



Compound 243Cii (142 mg, 0.280 mmol) was dried into a 1 dram vial equipped with a magnetic stir-bar and a Teflon lined cap. Silver oxide (324 mg, 1.40 mmol), CH_3CN (3 mL) and iodomethane (90 μL, 1.4 mmol) were added under nitrogen and the mixture was put in a heated block (82°C). The reaction was stirred overnight, then filtered through Celite and concentrated *in vacuo*. The resulting residue was purified by flash chromatography on silica gel eluting with a gradient of

0-50% acetone in chloroform to yield 62.2 mg (43%) of compound **491A**. HPLC: 99% at 3.87 & 3.95 min (atropisomers, retention time) (Phenomenex ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 521.37 $[M+H]^+$.

B. 3aα,4β,5β,7β,7aα)-4-[Octahydro-7-(2-hydroxyethyl)-5-methoxy-4-methyl-1,3-dioxo-4,7-epoxy-2*H*-isoindol-2-yl]-1-naphthalenecarbonitrile (491B)



Compound **491A** (62.2 mg, 0.119 mmol) was dissolved in ethanol (2 mL) and 12 N hydrochloric acid (50 μL) was added and the mixture was stirred for 10 min. The solvent was removed *in vacuo* and the product was purified by flash chromatography on silica gel eluting with a gradient of 0-20% acetone in chloroform to yield 40.3 mg (83%) of compound **491B** as a white solid. HPLC: 96% at 2.30 & 2.45 min (atropisomers, retention time) (Phenomenex ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 407.22 $[M+H]^+$.

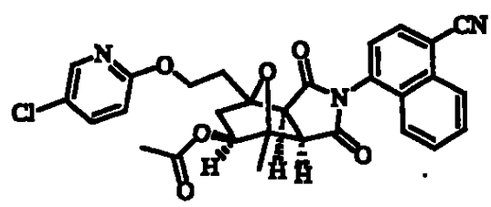
C. [3a*R*-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]octahydro-5-methoxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, slow eluting enantiomer (491Cl) & [3a*R*-(3aα,4β,5β,7β,7aα)]-4-[7-[2-(5-Chloro-2-oxo-1(2H)-pyridinyl)ethyl]octahydro-5-methoxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (491Cll)

Triphenylphosphine (40 mg, 0.15 mmol) and DBAD (35 mg, 0.15 mmol) were dissolved in THF under nitrogen and stirred 10 min. 5-Chloropyridin-2-ol (20 mg, 0.15 mmol) was added and the mixture was stirred for 5 min. Compound **491B** (40.3 mg, 0.0991 mmol) was added and the resulting mixture was stirred for 2.5 h. The solvent was concentrated *in vacuo* and the resulting residue was purified by

chromatography over Florisil (1.3 g) eluting with a gradient of 0-40% acetone in chloroform to give 140 mg of a mixture of 491Ci, 491Cii and DBAD. The oil was suspended in dichloromethane (3 mL) and trifluoroacetic acid (2 mL) was added. After 45 min, the solvent was removed *in vacuo* and the resulting oil was partitioned between saturated sodium bicarbonate (20 mL) and EtOAc (20 mL). The aqueous layer was extracted with EtOAc (2 x 20 mL) and the combined organic layers were dried over magnesium sulfate. Purification by reverse phase preparative HPLC (Shimadzu Shimpac VP ODS column, 20 x 50 mm, 0-100% aqueous methanol over 6 min containing 0.1% TFA, monitoring at 220 nm) gave 22 mg (44%) of compound 491Ci and 4.6 mg (9% yield) of compound 491Cii. Compound 491Ci: HPLC: 95% at 3.50 min (retention time) (Phenomenex ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 518.28 $[M+H]^+$. Compound 491Cii: HPLC: 85% at 2.94 & 3.07 min (atropisomers, retention time) (Phenomenex ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 518.27 $[M+H]^+$.

Example 492

[3a*R*-(3aα,4β,5β,7β,7aα)]-4-[5-(Acetyloxy)-7-[2-[(5-chloro-2-pyridinyl)oxy]ethyl]octahydro-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, slow eluting enantiomer (492)

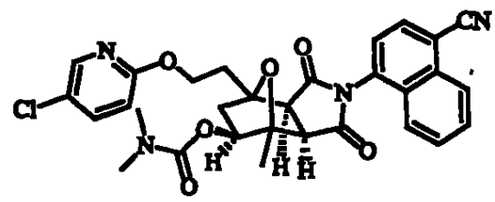


Acetyl chloride (25 μL, 0.35 mmol) was added to a solution of compound 490A (30 mg, 0.060 mmol) in pyridine (600 μL). The mixture was stirred overnight, diluted with hydrochloric acid (0.5 N, 10 mL), extracted with chloroform (3 x 7 mL). The organic layers were combined, washed with water (3 x 4 mL) and brine (4 mL), dried over magnesium sulfate and concentrated *in vacuo*. Purification by flash chromatography on silica gel eluting with a gradient of 0-50% acetone in chloroform gave 17 mg (53%) of compound 492. HPLC: 99% at 3.48 & 3.63 min (atropisomers,

retention time) (Phenomenex ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 546.15 $[M+H]^+$.

Example 493

Dimethylcarbamic acid, [3a*R*-(3aα,4β,5β,7β,7aα)]-7-[2-[(5-chloro-2-pyridinyl)oxy]ethyl]-2-(4-cyano-1-naphthalenyl)octahydro-4-methyl-1,3-dioxo-4,7-epoxy-1H-isoindol-5-yl ester, slow eluting enantiomer (493)



To a solution of compound 490A (30 mg, 0.060 mmol) in pyridine (300 µl) was added dimethylcarbamyl chloride (28 µl, 0.30 mmol) and the mixture was stirred at 25°C for 12 h. An additional portion of dimethylcarbamyl chloride (28 µL, 0.30 mmol) was added and the reaction was heated at 70°C for 12 h. A third portion of dimethylcarbamoyl chloride (28 µl, 0.30 mmol) as well as pyridine (300 µl) were added and the mixture was stirred at 100°C for 24 h. The solution was diluted with 0.5 N HCl (10 mL) and extracted with chloroform (3 x 7 mL). The organic layers were combined and washed with water (3 x 4 mL) and brine (4 mL), dried over magnesium sulfate and concentrated *in vacuo*. Purification by reverse phase preparative HPLC (Shimadzu Shimpac VP ODS column, 20 x 50 mm, 0-100% aqueous methanol over 6 min containing 0.1% TFA, monitoring at 220 nm) gave 15.7 mg (46%) of compound 493 as a white solid. HPLC: 99% at 3.52 min & 3.69 min (atropisomers, retention time) (Phenomenex ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 575.10 $[M+H]^+$.

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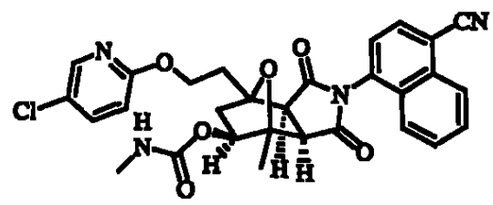
Example 494

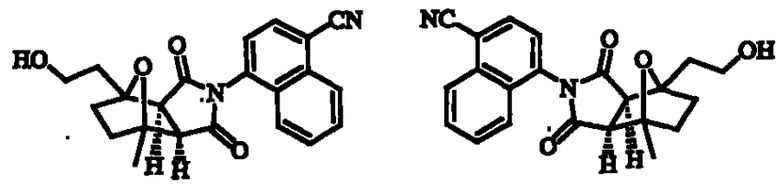
[3a*R*-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]octahydro-4-methyl-5-[[(methylamino)carbonyl]oxy]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, slow eluting enantiomer (494)



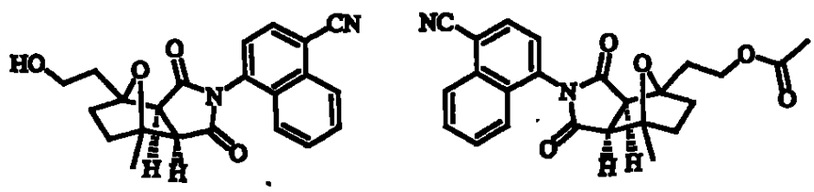
Methyl isocyanate (36 μL, 0.60 mmol) was added to a solution of compound **490A** (30 mg, 0.060 mmol) in dioxane (600 μL) and was heated at 80°C overnight. An additional portion of methyl isocyanate (36 μL, 0.60 mmol) was added and the mixture was heated at 100°C for 24 h. A third portion of methyl isocyanate (36 μL, 0.60 mmol) was added and the mixture was stirred at 100°C for 24 h. The solvent was removed *in vacuo* and the oil was purified by reverse phase preparative HPLC (Shimadzu Shimpac VP ODS column, 20 x 50 mm, 0-100% aqueous methanol over 6 min containing 0.1% TFA, monitoring at 220 nm) to give 20 mg (59%) of compound **494** as a clear glass. HPLC: 99% at 3.33 min & 3.42 min (atropisomers, retention time) (Phenomenex ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 561.08 $[M+H]^+$.

Example 495

[3a*R*(3aα,4β,5β,7β,7aα)]-4-[Octahydro-4-(2-hydroxyethyl)-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (495A) & [3a*S*(3aα,4β,5β,7β,7aα)]-4-[Octahydro-4-(2-hydroxyethyl)-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (495B)



A. [3a*S*-(3aα,4β,5β,7β,7aα)]-4-[Octahydro-4-(2-hydroxyethyl)-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (495AI) & (3aα,4β,5β,7β,7aα)-4-[2-(Acetyloxy)ethyl]-2-(4-cyano-1-naphthalenyl)hexahydro-7-methyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione (495AII)



Racemic compound 223B (10.26 g, 27.26 mmol) was dissolved in anhydrous THF (500 mL) in a 10 L bottle. *tert*-Butyl methyl ether (4.86 L), vinyl acetate (216 mL) and Lipase (108 g, [Sigma, Lipase type II, crude from Porcine pancreas, product No. L3126, Lot No. 021K1445]) were added. The reaction mixture was agitated for 24 h at rt and the reaction was monitored by HPLC using the following conditions: A 200 μL sample of the reaction mixture was filtered, dried under a stream of nitrogen and subjected to HPLC analysis (YMC ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). The reaction was stopped after 60% of the starting material was consumed. The enzyme was removed by filtration and the filtrate was concentrated *in vacuo*. The resulting residue was dissolved in $CHCl_3$ and absorbed onto silica gel. Purification by flash chromatography on silica gel eluting with a gradient of 1-5% MeOH in $CHCl_3$ gave 3.78 g (37%) of compound 495AI and 6.84 g (60%) of compound 495AII, both as white solids. Compound 495AI: HPLC: 99% at 3.47 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 377.09 $[M+H]^+$. Normal phase preparative chiral HPLC: 37.8 min (retention time) (chiralpak AD column, 4.6 x 250 mm, 10 micron, 40°C, isocratic elution with 8% EtOH/MeOH

(1:1) in heptane, monitoring at 220 nm), 99% ee. Compound 495Aii: HPLC: 99% at 2.92 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.1% TFA, 4 mL/min, monitoring at 220 nm).

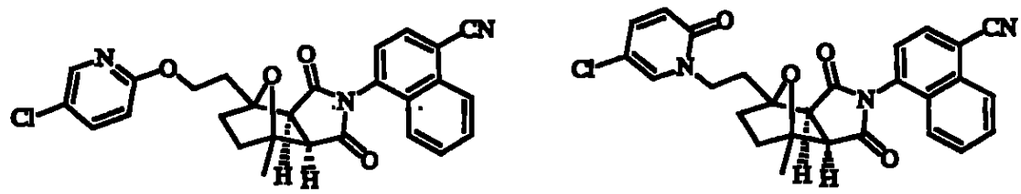
B. [3a*R*-(3aα,4β,5β,7β,7aα)]-4-[Octahydro-4-(2-hydroxyethyl)-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (495B)

Lipase (134 g, [Sigma, Lipase type II, crude from Porcine pancreas, product No. L3126, Lot No. 021K1445]) was added to 3.5 L of deionized water. The mixture was centrifuged to remove most of the suspended material. The pH of the supernatant was adjusted to 7.06 with 1N sodium hydroxide and a solution of compound 495Aii (8.04 g, 19.2 mmol) in TBME (1.5 L) was added. The pH was increased to 7.16 by addition of 1N sodium hydroxide. The reaction mixture was agitated at rt and was monitored by analytical HPLC as described in Example 495A. After 30 min, the reaction was filtered through Celite and the filtrate was extracted with ethyl acetate (4 x 1 L) until HPLC showed that all the alcohol has been removed. The organic fractions were combined, dried over magnesium sulfate, filtered and concentrated *in vacuo*. Purification by flash chromatography on silica gel (Jones, 50 g column) using a gradient of 0-70% acetone in chloroform followed by 5% MeOH in chloroform gave 2.44 g (33%) of compound 495B as a white solid. HPLC: 99% at 2.89 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 377.09 $[M+H]^+$. Normal phase preparative chiral HPLC: 11.1 min (retention time) (chiralpak AD column, 4.6 x 250 mm, 10 micron, 40°C, isocratic elution with 8% EtOH/MeOH (1:1) in heptane, monitoring at 220 nm), 95% ee.

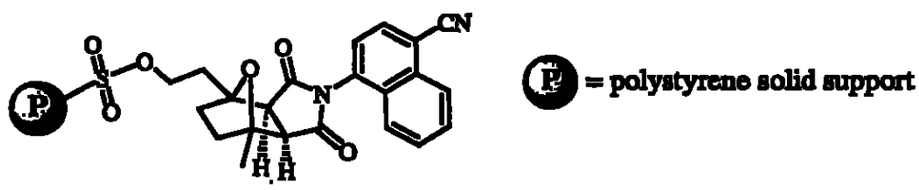
Example 496

[3a*R*-(3aα,4β,7β,7aα)]-4-[4-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (496Bi) & [3a*R*-(3aα,4β,7β,7aα)]-4-[4-[2-(5-Chloro-2-oxo-1(2H)-

pyridinyl)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (496Bii)



A. Preparation of solid Support (496A)



A mixture of anhydrous CH_2Cl_2 (10 mL) and pyridine (10 mL) was added under nitrogen to chlorosulfonylpolystyrene (Argonaut, 1.70 mmol/g, 3.0 g, 5.1 mmol) and compound 495Ai (3.78 g, 10.0 mmol) in a polymer synthesis tube. The mixture turned into a yellow gel and was vigorously shaken (wrist action shaker for 4 h.). All the solvents were absorbed by the resin and it looked dry. The resin was washed in portions with CH_2Cl_2 (200 mL) and the washes were combined and extracted with 200 mL 1N HCl. The HCl fraction was re-extracted with ethyl acetate (200 mL). The organic fractions were combined and extracted with water (50 mL), brine (50 mL) and the organic fractions were dried over sodium sulfate, filtered and concentrated to give 2.1 g of resin bound compound 496A (89% loaded based on recovered unbound compound 495Ai). The resin was washed consecutively with DMF (5X), DMF : water (3:1, 5X), THF (3X) and CH_2Cl_2 (3X) (~30 mL each wash). The resin was dried *in vacuo* for 1 h to yield 5.35 g of resin. The resin was still wet and was re-treated with the alcohol. The above described loading process was repeated using the recovered un-reacted compound 495Ai from the above procedure. Recovered compound 495Ai (2.1 g, 5.6 mmol) and anhydrous dichloromethane (15 mL) and pyridine (15 mL) and the resin were combined and subjected to the reaction conditions described above. The resulting resin was washed as described previously and dried *in vacuo* overnight to yield 4.49 g of resin (87% loaded based on recovered

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unbound compound 495Ai). The starting alcohol was recovered from the dichloromethane:pyridine mixture as described previously (2.04 g of white solid, which would suggest a 92% loading based on recovered alcohol). The resin weigh increase is usually more accurate for loading assessment. The resin loading was calculated to be 0.87 (determined by resin weight increase) X 1.08 mmol/g (calculated 100% loading) = 0.94 mmol/g. The resin was used as is for the next step.

B. [3a*R*-(3aα,4β,7β,7aα)]-4-[4-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (496Bi) & [3a*R*-(3aα,4β,7β,7aα)]-4-[4-[2-(5-Chloro-2-oxo-1(2H)-pyridinyl)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (496Bii)

The following procedure describes a general process by which arrays of compounds of Formula I can be made using automated approaches. Additional information on such automated synthetic approaches can be found in Example 8. Compounds 496Bi & 496Bii are an example of compounds made by such a procedure. For compounds 496Bi & 496Bii, 4-chloropyridinol represents the nuceophile reagent. A broader definition of the term nucleophile is contained in the body of this document and is well understood by one skilled in the art. A Bohdan MiniReactor equipped with a heating/cooling block was used with 0.5 Dram vials stacked over one another to achieve the same level as the reactor tubes. Resin (compound 496A) was measured into the individual vials by using each Bohdan resin Transfer module plate "10 mg" and "20 mg" once. The weights of resin delivered ranged from 17-23 mg (0.016-0.022 mmol). Cesium carbonate was added using the Bohdan "20 mg" plate which delivered ~57-60 mg (0.17-0.18 mmol). The nucleophiles were weighted into 1 Dram vials and were diluted in THF to 0.06 M using a Tecan eight channel liquid handler. The resulting solutions (250 μL, 0.015 mmol) were added manually via a micro-pipette to each of the reaction vials containing resin and the resulting array of reaction vials were placed in a Bohdan reactor. When the nucleophiles are amines, ~13 μL of diisopropylethylamine was

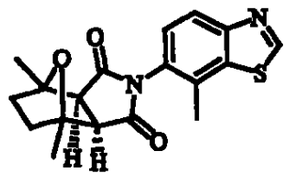
added to the THF solution of the amine. The vials were capped (Teflon-lined) and the reactions were heated with orbital shaking (short stroke 500 rpm) at 70°C for 24 h. The reactions were cooled to 25°C and 1 mL of a mixture of heptane and ethyl acetate (1:1) was added followed by 0.5 mL of water. The organic layer was extracted manually and individually transferred to a synthesis block tube containing magnesium sulfate (~150 mg). The array of synthesis block tubes were simultaneously filtered and the filtrates were individually collected into microtubes (96 well block). The aqueous layer was re-extracted with 1 mL of a mixture of heptane and ethyl acetate (1:1), the organic layer was filtered as described above and the filtrate was individually collected as described above into the existing microtubes.

Analysis of the array of compounds prepared by the above procedure was performed using the following automated approach. A 120 µl portion of each of the above reaction (filtrates) was aliquoted into two 96 deep well blocks for analysis. The solvent was concentrated *in vacuo* and the plates were re-diluted with methanol (500 µL). One plate was analyzed by LCMS (Phenomenex ODS column, 4.6 x 50 mm, 4 mL/min, gradient 0% A to 100% B (A: 90% water, 10% MeOH, 0.1% TFA; B: A: 90% MeOH, 10% water, 0.1% TFA) and the other by flow-NMR (Varian Inova-500 MHz, MeOH, WET solvent suppression pulse sequence, 128 scans, 60 µl flow cell probe). The criteria for submission was: correct molecular ion present and HPLC/NMR purity >70%. Compounds which did not meet the desired criteria were purified by reverse phase preparative HPLC (Shimadzu UP-ODS column, 20 x 50 mm, 20 mL/min, gradient 40% B to 100% B in 6 min with 2 min hold (A: 90% water, 10% MeOH, 0.1% TFA; B: A: 90% MeOH, 10% water, 0.1% TFA). HPLC purification yielded 3.4 mg (21%) of compound **496BI** as a glassy solid and 6.8 mg (41%) of compound **496BII** as a glassy solid. Compound **496BI**: HPLC: 96% at 3.47 min & 3.62 min (atropisomers, retention time) (Phenominex ODS column, 4.6 x 50 mm, 4 mL/min, gradient 0% A to 100% B (A: 90% water, 10% MeOH, 0.1% TFA; B: A: 90% MeOH, 10% water, 0.1% TFA), monitoring at 220 nm). MS (ES): m/z 487.94 $[M+H]^+$. Compound **496BII**: HPLC: 96% at 3.00 min & 3.12 min (atropisomers, retention time) (Phenominex ODS column, 4.6 x 50 mm, 4 mL/min, gradient 0% A to 100% B (A: 90% water, 10% MeOH, 0.1% TFA; B: A: 90

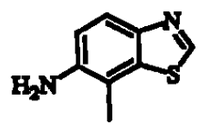
MeOH, 10% water, 0.1% TFA), monitoring at 220 nm). MS (ES): m/z 488.12 $[M+H]^+$. Additional compounds made by this procedure are set forth in Table 17.

Example 497

(3aα,4β,5β,7β,7aα)-Hexahydro-4,7-dimethyl-2-(7-methyl-6-benzothiazolyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione (497B)



A. 6-Amino-7-methylbenzothiazole (497A)



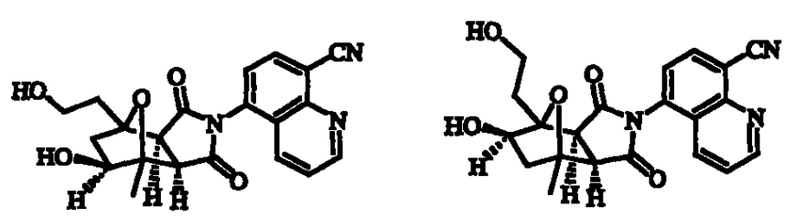
7-Methyl-6-nitrosobenzothiazole was prepared from 6-nitrobenzothiazole according to the general procedure described by Bartoli *et al. Synlett* 270 (1976). To a solution of 7-methyl-6-nitrosobenzothiazole (889 mg, 5.00 mmol) in AcOH (40 mL) at 70°C was added iron powder (325 mesh, 559 mg, 10.0 mmol) in a single portion. The resulting dark reaction mixture was stirred for 15 min before it was cooled and concentrated *in vacuo* to leave a residue which was partitioned between 1N HCl (50 mL) and CH_2Cl_2 (50 mL). The layers were separated and the organic layer was washed once with 1N HCl (25 mL). The combined aqueous layers were made basic by the addition of solid $NaHCO_3$ and were extracted twice with EtOAc. The organic phases were combined, dried over $MgSO_4$ and concentrated *in vacuo* to give 534 mg (65%) of compound 497A as a light brown solid. HPLC: 96% at 0.55 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm Ballistic, 10-90% aqueous methanol over 4 min containing 0.2% H_3PO_4, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 165.0 $[M+H]^+$.

B. (3aα,4β,5β,7β,7aα)-Hexahydro-4,7-dimethyl-2-(7-methyl-6-benzothiazolyl)-4,7-epoxy-1H-isoindole-1,3(2H)-dione (497B)

6-Amino-7-methylbenzothiazole (29 mg, 0.18 mmol), $MgSO_4$ (54 mg, 0.45 mmol), triethylamine (125 µL, 0.897 mmol) and compound **20A** (52 mg, 0.26 mmol) were taken up in 0.18 mL of DME and placed in a sealed tube. The sealed tube was heated at 135°C for 14 h. The cooled reaction mixture was filtered through a short pad of Celite eluting with EtOAc and the solvent was removed *in vacuo*. The residue was purified by reverse phase preparative HPLC (YMC S5 ODS column, 20 x 100 mm, eluting with 30-100% aqueous methanol over 10 min containing 0.1% TFA, 20 mL/min, monitoring at 220 nm). Concentration of the desired fractions afforded a residue which was partitioned between CH_2Cl_2 (10 mL) and sat. $NaHCO_3$ solution (10 mL). The aqueous layer was extracted once with CH_2Cl_2 and the combined organic phases were dried over Na_2SO_4 and concentrated *in vacuo* to give 42 mg (68) of compound **497B** as a tan solid. HPLC: 2.36 min & 2.55 min (atropisomers, retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 343.3 $[M+H]^+$.

Example 498

(3aα,4β,5β,7β,7aα)-5-[Octahydro-5-hydroxy-7-(2-hydroxyethyl)-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile (498i) & (3aα,4β,5β,7β,7aα)-5-[Octahydro-5-hydroxy-4-(2-hydroxyethyl)-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile (498ii)



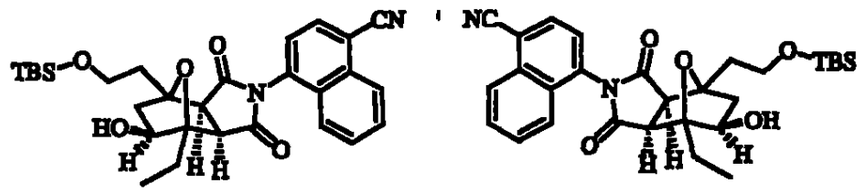
Compound **464E** (0.500 g, 1.02 mmol) was dissolved in THF (5.00 mL) and cooled to 0°C. BH_3•DMS (0.193 mL, 2.04 mmol) was then added slowly followed by warming to 25°C. After 1 h, the reaction was cooled to 0°C and pH 7 phosphate buffer (15.0 mL) was added resulting in the evolution of gas. EtOH (7.0 mL) and

hydrogen peroxide (30%, 1.5 mL) were then added and the reaction was warmed to 25°C over 2 h. After 3 h, the mixture was extracted with methylene chloride (3 x 50 mL). The combined organic layers were washed once with brine and dried over anhydrous sodium sulfate. The product was complexed to boron after workup. All attempts to break up this complex failed to give the free product. The crude material was taken on to the next step without further purification.

The crude reaction mixture was dissolved in 2% conc. HCl/MeOH (5.0 mL) at rt. After 1 h, the volatiles were removed *in vacuo* and the resulting residue was dissolved in methylene chloride and washed once with sat. aq. sodium bicarbonate and dried over anhydrous sodium sulfate. Solvent removal *in vacuo* gave the crude mixture of compounds **498i** and **498ii** as a yellow solid. The mixture of compounds was separated by reverse phase preparative HPLC: Compound **498i**: 17.994 min (retention time) & compound **498ii**: 19.767 min (retention time) (YMC S5 ODS column, 30 x 250 mm, 25 mL/min, 10-90% aqueous methanol over 35 min containing 0.1% TFA, monitoring at 220 nm). Solvent removal *in vacuo* gave 0.012 g (3%) of compound **498i** as a white solid and 0.009 g (2%) of compound **498ii** as a white solid. Compound **498i**: HPLC: 85% at 1.843 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2 phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 394.21 $[M+H]^+$. Compound **498ii**: HPLC: 98% at 1.650 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2 phosphoric acid, 4 mL/min, monitoring at 220 nm): MS (ES): m/z 394.21 $[M+H]^+$.

Example 499

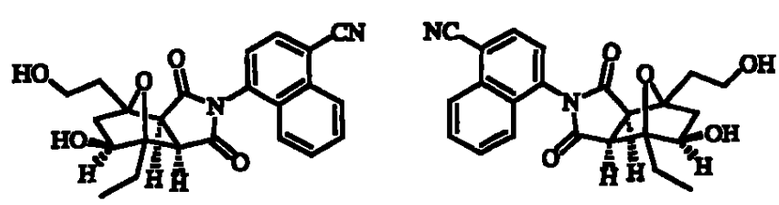
[3a*R*-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]-4-ethyloctahydro-5-hydroxy-1,3-dioxo-4,7-epoxy-2*H*-isoindol-2-yl]- 1-naphthalenecarbonitrile (499i) & [3a*S*-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]-4-ethyloctahydro-5-hydroxy-1,3-dioxo-4,7-epoxy-2*H*-isoindol-2-yl]- 1-naphthalenecarbonitrile (499ii)



The racemic compound 434C was separated into its individual antipodes by normal phase preparative chiral HPLC using a Chiracel AD column (5 cm x 50 cm), eluting with 8% EtOH in hexane at 50 mL/min to give the faster eluting compound 499i (Chiral HPLC: 6.74 min; CHIRALCEL AD 4.6 x 250 mm column; isocratic elution with 10% EtOH in hexane at 2 mL/min) and the slower eluting compound 499ii (Chiral HPLC: 9.99 min; CHIRALCEL AD 4.6 x 250 mm column; isocratic elution with 10% EtOH in hexane at 2 mL/min). For either compound 499i or 499ii: HPLC: 100% at 3.96 min (retention time) (YMC CombiSreen ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol containing 0.2% phosphoric acid over 4 min, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 521.25 $[M+H]^+$. The absolute stereochemistry for compounds 499i & 499ii was not established. For simplicity in nomenclature, compound 499i is designated herein as having an "R" configuration and compound 499ii as having an "S" configuration. Enantiomerically pure products derived from compound 499i are designated herein as having a "R" configuration and enantiomerically pure products derived from compound 499ii are designated herein as having an "S" configuration.

Example 500

[3a*R*-(3aα,4β,5β,7β,7aα)]-4-[4-Ethyloctahydro-5-hydroxy-7-(2-hydroxyethyl)-1,3-dioxo-4,7-epoxy-2*H*-isoindol-2-yl]-1-naphthalenecarbonitrile (500i) & [3a*S*-(3aα,4β,5β,7β,7aα)]-4-[4-Ethyloctahydro-5-hydroxy-7-(2-hydroxyethyl)-1,3-dioxo-4,7-epoxy-2*H*-isoindol-2-yl]-1-naphthalenecarbonitrile (500ii)



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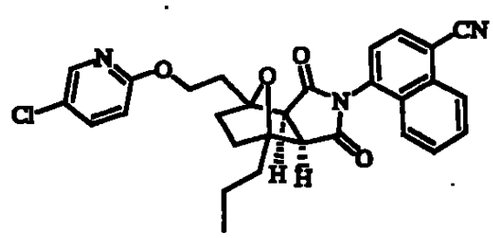
Compound **499i** (24.0 mg, 0.0461 mmol) was dissolved in 2% conc. HCl/EtOH (0.8 mL) and the mixture was stirred at rt for 20 min. Cold sat. $NaHCO_3$ was added to the mixture until the solution reached pH 8, then extracted with EtOAc. The organic layers were combined, washed with brine and dried over anhydrous sodium sulfate. Concentration *in vacuo* gave 14.7 mg (78%) of compound **500i** as a white solid which did not require further purification. HPLC: 95% at 2.40 min (retention time) (YMC S5 ODS 4.6 x 50 mm, 10%-90% aqueous methanol over 4 min gradient with 0.2% H_3PO_4, monitoring at 220 nm).

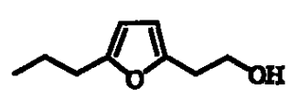
Compound **499ii** (18.0 mg, 0.0346 mmol) was dissolved in 2% conc. HCl/EtOH (0.6 mL) and the mixture was stirred at rt for 20 min. Cold sat. $NaHCO_3$ was added to the mixture until the solution reached pH 8, then extracted with EtOAc. The organic layers were combined, washed with brine and dried over anhydrous sodium sulfate. Concentration *in vacuo* gave 14.1 mg (99%) of compound **500ii** as a white solid which did not require further purification. HPLC: 95% at 2.40 min (retention time) (YMC S5 ODS 4.6 x 50 mm, 10%-90% aqueous methanol over 4 min gradient with 0.2% H_3PO_4, monitoring at 220 nm).

Example 501

[3a*R*-(3aα,4β,7β,7aα)]-4-[4-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]octahydro-1,3-dioxo-7-propyl-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (501D)



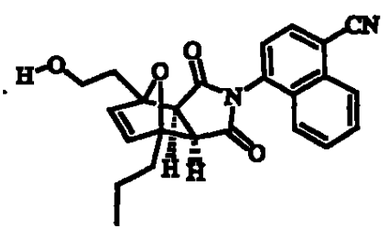
A. 2-(5-Propyl-furan-2-yl)-ethanol (501A)



To a solution of 2-propylfuran (3.00 g, 31.2 mmol) in THF (31 mL) at –78°C was added *n*-BuLi (15.0 mL, 2.5 M, 37.4 mmol) dropwise over 10 min. The reaction

was warmed to rt and stirred for 3.5 h. After cooling to 0°C, ethylene oxide (2.33 mL, 46.8 mmol) was added, the reaction was warmed to rt and stirring was continued for 19 h. The reaction was then cooled to 0°C and quenched with sat. NH_4Cl (20 mL), followed by extraction with Et_2O (2 x 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated to give 4.38 g (91) of compound **501A** as a bright orange oil. This material was used without further purification. HPLC: 94% at 2.91 min (retention time) (YMC Combiscreen ODS-A column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol containing 0.2 phosphoric acid over 4 min, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 137.13 $[M-H_2O+H]^+$.

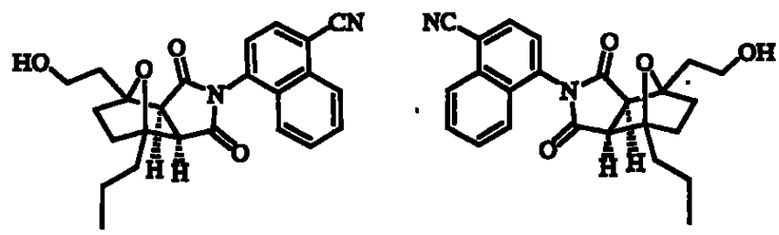
B. (3aα,4β,7β,7aα)-4-[1,3,3a,4,7,7a-Hexahydro-4-(2-hydroxyethyl)-1,3-dioxo-7-propyl-4,7-epoxy-2*H*-isoindol-2-yl]-1-naphthalenecarbonitrile (501B)



A suspension of 2-(5-propyl-furan-2-yl)-ethanol (2.50 g, 16.2 mmol) and 4-(2,5-dihydro-2,5-dioxo-1H-1-yl)-1-naphthalenecarbonitrile (4.02 g, 16.2 mmol) in benzene (16 mL) was warmed to 60°C. After 3 h, the reaction was concentrated *in vacuo* to give a brown foam. Methanol (17 mL) was added and the mixture was sonicated to give a fine beige solid with a brown supernatant. Filtration gave 1.75 g (27%) of compound **501B** as an off-white solid. This material was used without further purification. HPLC: 85% at 3.02 min & 3.14 min (atropisomers, retention time) (YMC Combiscreen ODS-A column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol containing 0.2% phosphoric acid over 4 min, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 403.31 $[M+H]^+$.

C. [3a*R*-(3aα,4β,7β,7aα)]-4-[Octahydro-4-(2-hydroxyethyl)-1,3-dioxo-7-propyl-4,7-epoxy-2H-isoindol-2-yl]-1-

naphthalenecarbonitrile (501Ci) & [3aS-(3aα,4β,7β,7aα)]-4-[Octahydro-4-(2-hydroxyethyl)-1,3-dioxo-7-propyl-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (501Cii)



To a suspension of compound **501B** (1.60 g, 3.97 mmol) in ethyl acetate (79.5 mL) was added 10% Pd/C (0.422 g, 0.397 mmol). Hydrogen gas was bubbled through the reaction for several minutes and the reaction was allowed to stir under a hydrogen atmosphere for 3 h. The reaction was filtered through Celite and the filtrate was concentrated *in vacuo* to give a white solid (1.74 g). The crude material was dissolved in minimum amount of methylene chloride and loaded on a 120 g silica gel ISCO cartridge. Elution with a step gradient of 0 to 100% ethyl acetate/hexane gave 1.06 g (66%) of the racemic mixture of compounds **501Ci** & **501Cii** as a white foam. A 500 mg portion of the racemic mixture was separated by normal phase preparative chiral HPLC (Chiralpak AD; 5 x 50 cm column; isocratic elution with 13 MeOH/EtOH (1:1) in heptane at 50 mL/min, monitoring at 220 nm) to give 245 mg of the faster eluting enantiomer, compound **501Ci** and 245 mg of the slower eluting enantiomer, compound **501Cii**, both as a white foams. Compound **501Ci**: Normal phase preparative chiral HPLC: 28.0 min (retention time), >95% ee (Chiralpak AD 4.6 x 250 mm column, eluting with 12% MeOH/EtOH (1:1) in heptane at 1.0 mL/min). HPLC: 99% at 3.04 & 3.17 min (atropisomers, retention time) (YMC Combiscreen ODS-A column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). HRMS m/z Calc'd for $C_{24}H_{23}N_2O_4$ $[M-H]^-$: 403.1658. Found 403.1644. Compound **501Cii**: Chiral HPLC: 65.7 min (retention time), >95% ee (Chiral HPLC: 65.7 min; >95% ee; Chiralpak AD 4.6 x 250 mm column; eluting with 12% MeOH/EtOH (1:1) in heptane at 1.0 mL/min). HPLC: 98% at 3.02 & 3.15 min (atropisomers, retention

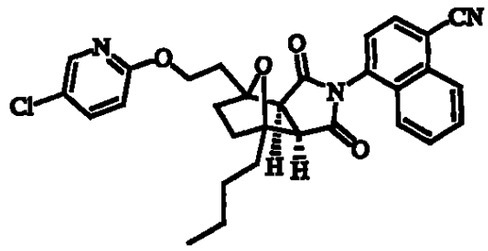
time) (YMC Combiscreen ODS-A column, 4.6 x 50 mm, eluting with 10-90%aqueous methanol over 4 min containing 0.2% phosphoric acid, 4mL/min, monitoring at 220 nm). The absolute stereochemistry for compounds 501Ci & 501Cii was not established. For simplicity in nomenclature, compound 501Ci is designated herein as having an "R" configuration and compound 501Cii as having an "S" configuration. Enantiomerically pure products derived from compound 501Ci are designated herein as having a "R" configuration and enantiomerically pure products derived from compound 501Cii are designated herein as having an "S" configuration.

D. [3a*R*-(3aα,4β,7β,7aα)]-4-[4-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]octahydro-1,3-dioxo-7-propyl-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (501D)

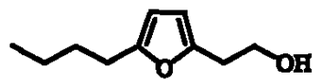
To a solution of DBAD (17.1 mg, 0.0741 mmol) in THF (0.5 mL) was added PPh_3 (19.4 mg, 0.0741 mmol). After 10 min, 5-chloro-2-pyridinol (9.6 mg, 0.074 mmol) was added. After 5 min, compound 501Ci (20.0 mg, 0.0494 mmol) was added. After 1 h, DBAD (17.1 mg, 0.0741 mmol), PPh_3 (19.4 mg, 0.0741 mmol), and 5-chloro-2-pyridinol (9.6 mg, 0.074 mmol) were added. After 3 h, the solvent was removed *in vacuo* to give a yellow residue. Preparative reverse phase HPLC (YMC ODS column, 20 x 100 mm, eluting with 40-100% aqueous methanol containing 0.1% TFA over 30 min, 25 mL/min, monitoring 220 nm) gave 9.5 mg (37%) of the trifluoracetic acid salt of compound 501D as a clear, colorless residue. HPLC: 99% at 7.88 min & 8.11 min (atropisomers, retention time) (Zorbax SB C18 4.6 x 75 mm, eluting with 10-90% aqueous methanol over containing 0.2% phosphoric acid over 8 min, 2.5 mL/min, monitoring at 220 nm). HRMS m/z Calc'd for $C_{29}H_{27}N_3O_4Cl$ $[M+H]^+$: 516.1690. Found 516.1676.

Example 502

[3a*R*-(3aα,4β,7β,7aα)]-4-[4-Butyl-7-[2-[(5-chloro-2-pyridinyl)oxy]ethyl]octahydro-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (502D)

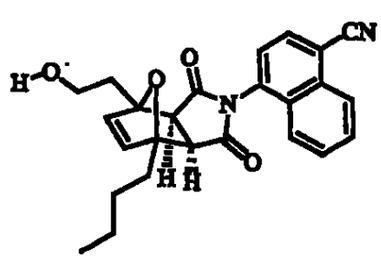


A. 2-(5-Butyl-furan-2-yl)-ethanol (502A)



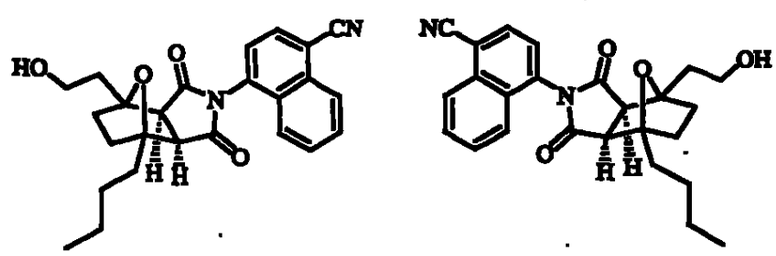
To a solution of 2-butylfuran (3.00 g, 24.2 mmol) in THF (24 mL) at -78°C was added *n*-BuLi (11.6 mL, 2.5 M, 29.0 mmol) dropwise over 10 min. The reaction was warmed to rt and stirred for 3.5 h. After cooling to 0°C, ethylene oxide (1.81 mL, 36.2 mmol) was added, the reaction was warmed to rt and stirring was continued for 19 h. The reaction was then cooled to 0°C and quenched with sat. NH_4Cl (20 mL), followed by extraction with diethyl ether (2 x 50 mL). The combined organic layers were washed with brine, dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give 4.07 g (100%) compound **502A** as a bright orange oil. This material was used without further purification. HPLC: 96% at 3.23 min (retention time) (YMC Combiscreen ODS-A column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol containing 0.2% phosphoric acid over 4 min, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 169.22 $[M+H]^+$.

B. (3aα,4β,7β,7aα)-4-[4-Butyl-1,3,3a,4,7,7a-hexahydro-7-(2-hydroxyethyl)-1,3-dioxo-4,7-epoxy-2*H*-isoindol-2-yl]- 1-naphthalenecarbonitrile (502B)



A suspension of compound 502A (2.50 g, 14.9 mmol) and 4-(2,5-dihydro-2,5-dioxo-1H-1-yl)-1-naphthalenecarbonitrile (3.70 g, 14.9 mmol) in benzene (15 mL) was warmed to 60°C. After 3 h, the reaction was concentrated *in vacuo* to give a brown foam. Methanol (17 mL) was added and the mixture was sonicated to give a fine beige solid with an orange-brown supernatant. Filtration of the precipitate gave 2.64 g (44%) of compound 502B as an off-white solid. This material was used without further purification. HPLC: 95% at 3.25 min & 3.35 min (atropisomers, retention time) (YMC Combiscreen ODS-A column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol containing 0.2% phosphoric acid over 4 min, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 417.29 $[M+H]^+$.

C. **[3a*R*-(3aα,4β,7β,7aα)]-4-[4-Butyloctahydro-7-(2-hydroxyethyl)-1,3-dioxo-4,7-epoxy-2*H*-isoindol-2-yl]-1-naphthalenecarbonitrile (502Ci) & [3a*S*-(3aα,4β,7β,7aα)]-4-[4-Butyloctahydro-7-(2-hydroxyethyl)-1,3-dioxo-4,7-epoxy-2*H*-isoindol-2-yl]-1-naphthalenecarbonitrile (502Cii)**



To a suspension of compound 502C (1.47 g, 3.52 mmol) in ethyl acetate (70 mL) was added 10% Pd/C (0.375 g, 0.352 mmol). Hydrogen was bubbled through the reaction for several minutes and the reaction was allowed to stir under a hydrogen atmosphere for 3 h. The reaction was filtered through Celite®, rinsing with ethyl acetate (2 x 70 mL). The filtrate was concentrated *in vacuo* to give a white foam (1.50 g). The crude material was dissolved in a minimum amount of methylene chloride and loaded on a 120 g silica gel ISCO cartridge. Elution with a step gradient of 0 to 100% ethyl acetate/hexane gave 1.05 g (74%) a racemic mixture of compounds 502Ci & 502Cii as a white foam. A 438 mg portion of racemic mixture of compounds 502Ci & 502ii was separated by normal phase preparative chiral HPLC

(Chirapak AD column, 5 x 50 cm, isocratic elution with 12 MeOH/EtOH (1:1) in heptane at 50 mL/min, monitoring at 220 nm) to yield 178 mg of the faster eluting enantiomer, compound **502Ci** as a white foam and 132 mg of the slower eluting enantiomer, compound **502Cii**, as a clear, viscous oil. Compound **502Ci**: Chiral HPLC: 25.5 min (retention time), >95% ee (Chiral HPLC: Chiralpak AD 4.6 x 250 mm column, eluting with 12% MeOH/EtOH (1:1) in heptane at 1.0 mL/min) and HPLC: 99% at 6.50 min & 6.71 min (atropisomers, retention time) (YMC Combiscreen ODS-A column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol containing 0.2% phosphoric acid over 4 min, 4 mL/min, monitoring at 220 nm) HRMS m/z Calc'd for $C_{25}H_{25}N_2O_4$ $[M-H]^-$: 417.1814. Found 417.1800. Compound **502Cii**: HPLC: 55.6 min (retention time), >95% ee (Chiral HPLC: Chiralpak AD 4.6 x 250 mm column; eluting with 12% MeOH/EtOH (1:1) in heptane at 1.0 mL/min). HPLC: 99% at 3.26 min & 3.38 min (atropisomers, retention time) (YMC Combiscreen ODS-A column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol containing 0.2% phosphoric acid over 4 min, 4 mL/min, monitoring at 220 nm). The absolute stereochemistry for compounds **502Ci** & **502Cii** was not established. For simplicity in nomenclature, compound **502Ci** is designated herein as having an "R" configuration and compound **502Cii** as having an "S" configuration. Enantiomerically pure products derived from compound **502Ci** are deaignated herein as having a "R" configuration and enantiomerically pure products derived from compound **502Cii** are designated herein as having an "S" configuration.

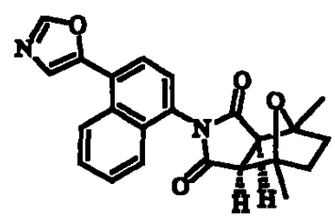
D. [3a*R*-(3aα,4β,7β,7aα)]-4-[4-Butyl-7-[2-[(5-chloro-2-pyridinyl)oxy]ethyl]octahydro-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (502D)

To a solution of compound **502Ci** (20.0 mg, 0.0478 mmol), PPh_3 (37.6 mg, 0.143 mmol) and 5-chloro-2-pyridinol (18.6 mg, 0.143 mmol) in THF (0.5 mL) was added DBAD (33.0 mg, 0.143 mmol). The resulting solution was stirred at rt for 15.5 h. The solvent was removed *in vacuo* to give a yellow residue. Preparative HPLC (Shimadzu VP ODS column, 20 x 250 mm, eluting with 40-100% aqueous methanol containing 0.1% TFA over 30 min and 100% for 25 min, 25 mL/min, monitoring at

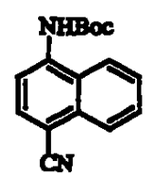
220 nm) gave 9.4 mg (37%) of the trifluoracetic acid salt of compound 502D as a clear, colorless residue. HPLC: 99% at 8.14 min & 8.36 min (atropisomers, retention time) (Zorbax SB C18 column, 4.6 x 75 mm, eluting with 10-90% aqueous methanol containing 0.2% phosphoric acid over 8 min, 2.5 mL/min, monitoring at 220 nm). HRMS m/z Calc'd for $C_{30}H_{29}N_3O_4Cl$ $[M+H]^+$: 530.1847. Found 530.1855.

Example 503

(3aα,4β,7β,7aα)-Hexahydro-4,7-dimethyl-2-[4-(5-oxazolyl)-1-naphthalenyl]-4,7-epoxy-1H-isoindole-1,3(2H)-dione (503E)



A. (4-Cyano-naphthalen-1-yl)-carbamic acid tert-butyl ester (503A)



To a solution of 4-amino-1-naphthalenecarbonitrile (9.67 g, 57.5 mmol) in THF (100 mL) at rt was added, over 10 min, sodium hexamethyldisilazane (1.0 M in THF, 133 mL, 133 mmol). After stirring for 15 min, a solution of di-*t*-butyldicarbonate (15.1 g, 69.0 mmol) in THF (20 mL) was added. After stirring for 18 h at rt, the reaction mixture was partitioned between Et_2O (400 mL) and saturated potassium bisulfate solution (200 mL). The organic layer was washed with saturated potassium bisulfate solution (200 mL), saturated sodium bicarbonate solution (200 mL) and brine (100 mL). Drying over anhydrous magnesium sulfate, treatment with decolorizing carbon and concentration *in vacuo*, afforded a residue that was partially purified by flash chromatography on silica gel eluting with 20% ethyl acetate in hexane. The partially purified material was crystallized from ethyl acetate/hexane to give 5.26 g of compound 503A as a colorless crystals. The mother liquor was

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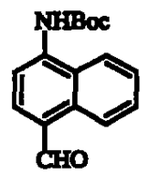
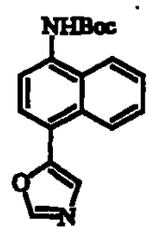
concentrated and crystallized from ethyl acetate/hexane to give an additional 2.8 g of compound **503A** to yield a total of 8.06 g (52%) of compound **503A**. ^{1}HNMR (400 MHz, DMSO-d^6): δ 9.81(s, 1H), 8.36 (d, 1H, J = 8.5 Hz), 8.11(m, 2H), 7.92 (d, 1H, J = 8 Hz), 7.78 (m, 1H), 7.67 (m, 1H), 1.53 (s, 9H).

B. (4-Formyl-naphthalen-1-yl)-carbamic acid tert-butyl ester (503B)



A mixture of compound **503A** (4.02 g, 15.0 mmol), Raney nickel (1.5 g), sodium hypophosphite (9.00 g, 86.5 mmol), pyridine (50 mL), water (25 mL) and acetic acid (25 mL) was stirred at 45°C for 5 h. The mixture was filtered through celite and the filter cake was rinsed with warm ethanol (100 mL). After adding water (600 mL) to the filtrate and allowing it to stand for 1 h, the resulting precipitate was filtered and rinsed with water. Drying *in vacuo* afforded 3.38 g of a white solid which was a 3:1 mixture of compounds **503B** & **503A**. The material was used in the next step without further purification. ^{1}HNMR (400 MHz, DMSO-d^6): δ 10.28 (s, 1H), 9.77 (s, 1H), 9.27 (d, 1H, J = 8.5 Hz), 8.31 (m, 1H), 8.13 (m, 1H), 8.00 (d, 1H, J = 8 Hz), 7.80 (m, 1H), 7.70 (m, 1H), 1.54 (s, 9H).

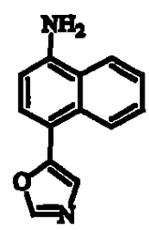
C. (4-Oxazol-5-yl-naphthalen-1-yl)-carbamic acid *tert*-butyl ester (503C)



The above mixture of compounds **503A** & **503B** (3.37 g, 10.0 mmol; corrected for presence of compound **503A**), toluene-sulfonylisocyanide (2.15 g, 11.0 mmol) and potassium carbonate (1.66 g, 12.0 mmol) in 50 mL of methanol was

refluxed for 4 h. The reaction mixture was partitioned between water (200 mL) and chloroform (200 mL). After extracting the aqueous layer with chloroform (100 mL), the combined organic layers were dried over magnesium sulfate and concentrated *in vacuo*. The crude residue was purified by flash chromatography on silica gel eluting with a gradient of 10-40% ethyl acetate in hexane to give 1.35 g (44%) of compound 503C as a white solid. ^{1}HNMR (400 MHz, DMSO-d^6): δ 9.45 (s, 1H), 8.57 (s, 1H), 8.20 (m, 2H), 7.76 (m, 2H), 7.64 (s, 1H), 7.62 (m, 2H), 1.51 (s, 9H).

D. 4-Oxazol-5-yl-naphthalen-1-ylamine (503D)



Compound 503C (1.34 g, 4.3 mmol) was dissolved in trifluoroacetic acid (10 mL) and the resulting mixture was allowed to stand for 1 h at room temperature. After removing the volatiles *in vacuo*, the residue was co-evaporated from ethyl acetate/heptane (2 x 50 mL) to remove traces of trifluoroacetic acid. After partitioning the residue between ethyl acetate (100 mL) and 1N NaOH (75 mL), the organic layer was washed with brine (50 mL), dried over magnesium sulfate and concentrated *in vacuo* to afford 900 mg (99%) of compound 503D as a yellow crystalline solid. HPLC conditions: 95% at 0.92 min (retention time) (Phenomenex 5 micron ODScolumn, 4.6 x 30 mm, 10%-90% aqueous methanol over 2 min gradient with 0.1% TFA, monitoring at 254 nm.). MS (ES): m/z 211.22 $[M+H]^+$.

E. (3aα,4β,7β,7aα)-Hexahydro-4,7-dimethyl-2-[4-(5-oxazolyl)-1-naphthalenyl]-4,7-epoxy-1H-isoindole-1,3(2H)-dione (503E)

A mixture of compound 503D (42 mg, 0.020 mmol) and 20A (78 mg, 0.40 mmol) in acetic acid (1.0 mL) was refluxed for 18 h. The reaction mixture was cooled to rt, concentrated *in vacuo* and the residue was partitioned between ethyl

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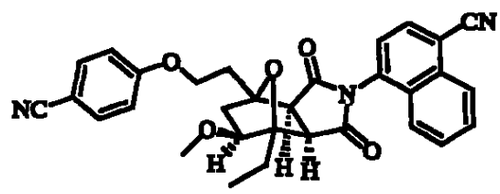
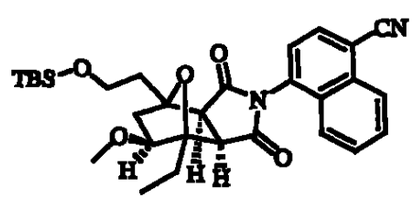
acetate (30 mL) and saturated sodium bicarbonate solution (30 mL). The organic layer was isolated, dried over magnesium sulfate and concentrated *in vacuo*. Purification by flash chromatography on a 2.5 x 15 cm silica gel column, using a gradient of 40-60% ethyl acetate in hexane gave 28 mg (37%) of compound **503E** as a white powder. HPLC: 99% at 1.46 min & 1.36 min (atropisomers, retention time) (Phenomenex 5 micron ODS 4.6 x 30 mm, 10%-90% aqueous methanol over 2 min gradient with 0.1% TFA, monitoring at 254 nm.). MS (ES): m/z 389.10 $[M+H]^+$.

Example 504

[3a*S*-(3aα,4β,5β,7β,7aα)]-4-[7-[2-(4-Cyanophenoxy)ethyl]-4-ethyloctahydro-5-methoxy-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (504C)



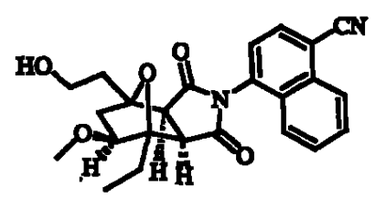
A. **[3a*S*-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]-4-ethyloctahydro-5-methoxy-1,3-dioxo-4,7-epoxy-2*H*-isoindol-2-yl]- 1-naphthalenecarbonitrile (504A)**



To a solution of compound **499II** (0.235 g, 0.451 mmol) in CH_3CN (6 mL) was added silver oxide (0.523 g, 2.26 mmol) and iodomethane (0.56 mL, 9.0 mmol, stirred over K_2CO_3 before addition). The resulting suspension was placed in a preheated oil bath (80°C). After 24 h, the reaction was cooled to rt, diluted with CH_3CN (20 mL), filtered through a plug of Celite, and concentrated *in vacuo* to give a

brown gum. Purification by flash chromatography on silica gel eluting with 30% ethyl acetate/hexanes gave 0.156 g (65%) of compound 504A as a white solid. HPLC: 95% at 4.17 min & 4.25 min (atropisomers, retention time) (YMC CombiSreen ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol containing 0.2% phosphoric acid over 4 min, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 521.25 $[M+H]^+$.

B. (3aα,4β,5β,7β,7aα)-4-[4-Ethyloctahydro-7-(2-hydroxyethyl)-5-methoxy-1,3-dioxo-4,7-epoxy-2*H*-isoindol-2-yl]-1-naphthalenecarbonitrile (504B)



To a solution of compound 504A (0.156 g, 0.292 mmol) in ethanol (6 mL) was added 1N HCl (0.44 mL, 0.44 mmol). After 20 min, the reaction was cooled to 0°C and quenched with sat. aq. $NaHCO_3$ (2 mL) to give a white suspension. Added H_2O until the solid dissolved. The mixture was extracted with ethyl acetate (3 x 30 mL). The combined organic layers were washed with brine (20 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a white solid. Purification by flash chromatography on silica gel eluting with 5% $MeOH/CH_2Cl_2$ gave 120 mg (99%) of compound 504A as a white solid. HPLC: 98% at 5.17 and 5.44 min (atropisomers, retention time) (YMC CombiSreen ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol containing 0.2% phosphoric acid over 8 min, 2.5 mL/min, monitoring at 220 nm). HRMS m/z Calc'd for $C_{24}H_{24}N_2O_5$ $[M - H]^+$: 419.1607. Found 419.1611.

C. [3a*S*-(3aα,4β,5β,7β,7aα)]-4-[7-[2-(4-Cyanophenoxy)ethyl]-4-ethyloctahydro-5-methoxy-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (504C)

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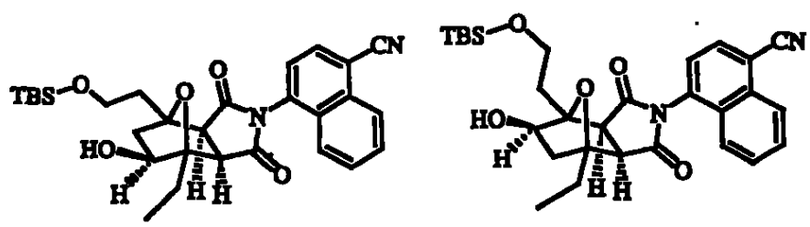
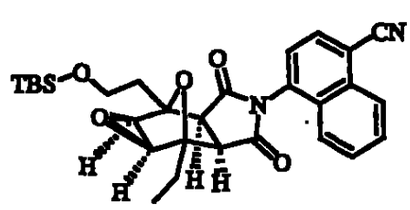
To a solution of compound 504B (20 mg, 0.048 mmol) in anhydrous THF (0.5 mL) was added PPh_3 (37.0 mg, 0.143 mmol), *para*-cyanophenol (17.0 mg, 0.143 mmol) and DBAD (32.0 mg, 0.143 mmol). After 30 min, the solution was concentrated to give a brown gum. Purification by reverse phase preparative HPLC (YMC S5 ODS column, 20 x 250 mm, eluting with 10-90% aqueous methanol containing 0.2% phosphoric acid over 35 min, 20 mL/min, monitoring at 220 nm) gave 16 mg (64%) of compound 504C as a clear, colorless oil. HPLC 98% at 6.84 and 7.10 min (atropisomers, retention time) (Zorbax SB C18column, 4.6 x 75 mm, eluting with 10-90% aqueous methanol containing 0.2% phosphoric acid over 8 min, 2.5 mL/min, monitoring at 220 nm). HRMS m/z Calc'd for $C_{31}H_{27}N_3O_5$ $[M + NH_4]^+$: 539.2295. Found 539.2302.

Example 505

(3aα,4β,5β,7β,7aα)-4-[7-[2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]-4-ethyloctahydro-5-hydroxy-1,3-dioxo-4,7-epoxy-2*H*-isoindol-2-yl]- 1-naphthalenecarbonitrile (505Bi) & (3aα,4β,5β,7β,7aα)-4-[4-[2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]-7-ethyloctahydro-5-hydroxy-1,3-dioxo-4,7-epoxy-2*H*-isoindol-2-yl]- 1-naphthalenecarbonitrile (505Bii)



A. **(1aα,2β,2aα,5aα,6β,7aα)-4-[2-[2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]-6-ethyloctahydro-3,5-dioxo-2,6-epoxy-4*H*-oxireno[*f*]isoindol-4-yl]- 1-naphthalenecarbonitrile (505A)**



To a solution of compound **434B** (1.01 g, 2.01 mmol) in methylene chloride (20 mL) was added 60% *m*-CPBA (0.863 g, 3.00 mmol). After 48 h, the reaction was diluted with methylene chloride (50 mL) and washed with sat. Na_2SO_3 (20 mL) and sat. $NaHCO_3$ (20 mL). The combined aqueous layers were extracted with CH_2Cl_2 (20 mL). The combined organic layers were washed with brine (30 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give 1.01 g (97%) of compound **505A** as a yellow solid. This material used without further purification. HPLC: 95% at 4.22 min (retention time) (Phenominex Luna C18 column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol containing 0.2% phosphoric acid over 4 min, 4 mL/min, monitoring at 220 nm). HRMS m/z Calc'd for $C_{29}H_{34}N_2O_5Si$ $[M-H]^+$: 517.2159. Found 517.2163.

B. (3aα,4β,5β,7β,7aα)-4-[7-[2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]-4-ethyloctahydro-5-hydroxy-1,3-dioxo-4,7-epoxy-2*H*-isoindol-2-yl]- 1-naphthalenecarbonitrile (505Bi) & (3aα,4β,5β,7β,7aα)-4-[4-[2-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]ethyl]-7-ethyloctahydro-5-hydroxy-1,3-dioxo-4,7-epoxy-2*H*-isoindol-2-yl]- 1-naphthalenecarbonitrile (505Bii)

To a red solution of titanocene dichloride (0.500 g, 2.00 mmol) in anhydrous THF (4.0 mL) was added zinc dust (0.392 g, 6.00 mmol). The resulting suspension was vigorously stirred for 1 h under an argon atmosphere to give a green suspension. Excess zinc was removed by filtration through a 0.45 μm microfilter to give a green solution of dicyclopentadienyl titanium (III) chloride. To a solution of compound **505A** (0.207 g, 0.399 mmol) and 1,4-cyclohexadiene (0.380 mL, 4.02 mmol) in anhydrous THF (1 mL) was added dropwise a 0.5 M solution of the above described dicyclopentadienyl titanium (III) chloride (0.9 mL, 0.45 mmol). After 1 h, an additional aliquot of the 0.5 M solution of dicyclopentadienyl titanium (III) chloride (0.9 mL, 0.45 mmol) was added and stirring was continued for 1 h. The reaction was then quenched with water (2 mL) and diluted with ethyl acetate (10 mL). The layers

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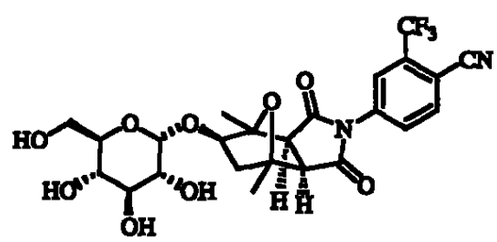
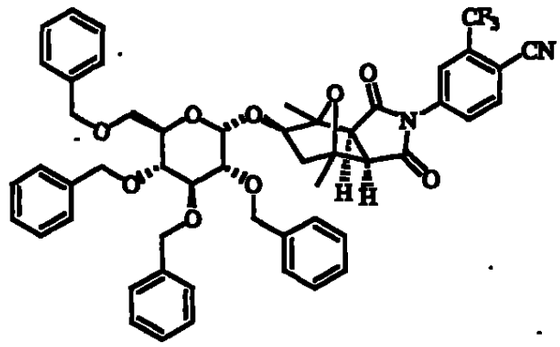
were separated and the organic layer was washed with brine (5 mL), dried over Na_2SO_4, filtered, and concentrated *in vacuo* to give a yellow gum. The crude material was dissolved in a minimum amount of methylene chloride and loaded on a 35 g silica gel ISCO column. Gradient elution with 0-80% ethyl acetate in hexane gave 0.043 g (21%) of compound **505Bi** as a white solid and 0.023 g (11%) of compound **505Bii** as a white solid. Compound **505Bi**: HPLC: 3.92 min (retention time) (YMC CombiSreen ODS-A column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol containing 0.2% phosphoric acid over 4 min, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 521.36 $[M+H]^+$. Compound **505Bii** : HPLC: 91% at 3.97 min (retention time) (YMC CombiScreen ODS-A column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol containing 0.2% phosphoric acid over 4 min, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 521.34 $[M+H]^+$.

Example 506

4-[[3a*S*-(3aα,4β,5β,7β,7aα)]-5-(α-D-Glucopyranosyloxy)octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile (506B)



A. [3a*S*-(3aα,4β,5β,7β,7aα)]-4-[Octahydro-4,7-dimethyl-1,3-dioxo-5-[[2,3,4,6-tetrakis-*O*-(phenylmethyl)-α-D-glucopyranosyl]oxy]-4,7-epoxy-2*H*-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile (506A)



2,3,4,6-Tetra-*O*-benzyl-α-D-glucopyranosyl bromide was made according to the procedure by Spohr *et al. Can. J. Chem.* 71, 1928-42 (1993). Oxalyl bromide (0.48 mL, 0.95 mmol, 2 M in CH_2Cl_2) was added dropwise to a solution of 2,3,4,6-tetra-*O*-benzyl-D-glucopyranose (412 mg, 0.763 mmol) in CH_2Cl_2 (5 mL) and DMF (0.28 mL) at rt under Ar. The reaction mixture was stirred for 20 min, poured onto a mixture of ice and H_2O (1:1, 30 mL) and diluted with CH_2Cl_2 (30 mL). The layers were separated and the organic layer was washed with cold H_2O (2 x 30 mL) and brine (1 x 30 mL) and dried over $MgSO_4$. Concentration *in vacuo* gave the desired bromide as a brown oil. This oil was taken up in CH_2Cl_2 (2 mL) and DMF (1 mL). Compound 471Dii (100 mg, 0.763 mmol), tetrabutylammonium bromide (111 mg, 0.526 mmol) and 4 Å sieves (600 mg) were added to this solution and the reaction was stirred under Ar for 4 d. The reaction was quenched with MeOH (2 mL), stirred for 0.5 h, diluted with CH_2Cl_2 (10 mL) and then filtered through a medium porosity fritted funnel, rinsing with CH_2Cl_2 (5 mL). The solvent was removed *in vacuo* and the resulting residue was dissolved in CH_2Cl_2 (25 mL). The organic solution was washed with sat. aq. $NaHCO_3$ (1 x 20 mL) and H_2O (1 x 20 mL) and dried over $MgSO_4$. Purification by flash chromatography on SiO_2 eluting with 50% EtOAc/hexanes gave 79 mg (33%) of 506A as a white solid. HPLC: 99% at 4.56 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 902 $[M+H]^+$.

B. 4-[[3a*S*-(3aα,4β,5β,7β,7aα)]-5-(α-D-Glucopyranosyloxy)octahydro-4,7-dimethyl-1,3-dioxo-4,7-

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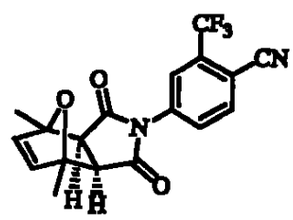
epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile (506B)

Palladium hydroxide (62 mg, 20 wt.% Pd (dry basis) on carbon, wet) was added to a solution of 506A (65 mg, 0.07 mmol) in EtOAc (2 mL) and the mixture was stirred under a hydrogen atmosphere introduced via a balloon. After 5 h, the reaction was complete as was evident by HPLC, so the mixture was filtered through a medium porosity fritted funnel rinsing with MeOH (2 mL) and concentrated *in vacuo*. The resulting residue was dissolved in MeOH (2 mL) and filtered through a Gelman Acrodisc CR 13 mm syringe filter with a 0.45 μM PTFE membrane. Concentration yielded 38 mg of 506B as a white solid. HPLC: 90% at 2.16 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 543.20 $[M+H]^+$. A 10 mg portion was recrystallized from MeOH:H_2O to give crystals suitable for X-ray crystal diffraction studies to elucidate the exact stereochemistry of compound 506B as referenced to the known fixed stereochemistry of the D-glucoside appendage.

Example 507

(3aα,4β,7β,7aα)-4-(1,3,3a,4,7,7a-Hexahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (507)

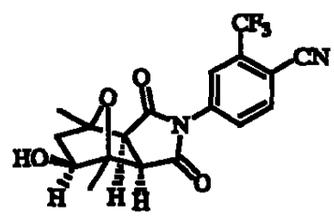


To 25 g (94.2 mmol) of compound 471A was added neat 2,5-dimethylfuran (30 mL, 280 mmol), and the resulting slurry was heated to 60 °C for 1 to 3 h with mechanical agitation. The resulting slurry was cooled to 0-5 °C, and diluted with cold toluene (25 mL, 0-10 °C). The cold slurry was filtered under vacuum. The flask and filter cake were washed with cold toluene (2 x 25 mL), and the cake was deliquored with house vacuum. The precipitate was dried *in vacuo* to yield 31.3 g (91.6%) of a compound 507 as a tan solid. HPLC: 99.6%, 19.43 min (retention time) (Column:

Zorbax™ SB-C18, 4.6 x 15 cm; Mobile Phase: 40% CH_3CN/60% H_2O w/ 0.1% v/v TFA, isocratic; Flow Rate: 1 mL/min; Detection: λ_{max} 210 nm; Temperature: 30 °C; Injection Volume: 5 μL).

Example 508

(3aα,4β,5β,7β,7aα)-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (508)

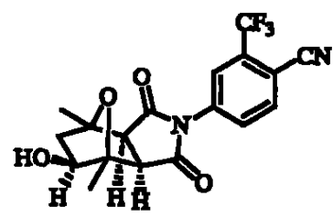


To THF (275 mL) that had been cooled to −3 °C was added compound **507** (55.0 g, 152 mmol), which resulted in a slurry. To the slurry was added borane methylsulfide (14.4 mL, 152 mmol), at a rate such that the temperature did not exceed 0 °C. The reaction mixture was slowly warmed to 20 °C over 2.5 h. The temperature of the reaction mixture was then returned to 0 °C, where upon phosphate buffer (1056 mL, pH 7) was carefully added at a rate to control the hydrogen gas evolution and maintain a temperature ≤ 20 °C. The resulting suspension was dissolved by adding ethanol (528 mL, 190 proof). At 15 °C, hydrogen peroxide (55 mL, 30 wt%) was added at a rate to maintain the temperature ≤ 20 °C. The homogeneous solution was left stirring for 12 h at 20 °C and pH 7.8, whereby crystallization occurred. The resulting slurry was collected by filtration and washed with water (4 X 100 mL) and methyl-*tert*-butyl ether (2 X 100 mL). Drying *in vacuo* afforded 37.3 g (64.6%) of compound **508**. The aqueous mother liquor was extracted with ethyl acetate (3 X 500 mL). The combined rich organics were washed with 10 wt% aqueous sodium sulfite (1 X 100 mL), and 25 wt% aqueous sodium chloride (1 X 100 mL). The organics were dried over sodium sulfate, filtered, and concentrated to recover 8.9 g (15.4%) of compound **508**, and a third 11.5 g (20%) fraction of compound **508** was recovered from the methyl-*tert*-butyl ether cake wash. The above three solid samples of crude material were separately recrystallized from 190 proof ethanol (1 g / 10 mL) to afford

a total of 35.6 g (61.7%) of compound **508** having a purity level of 98.7% as determined by HPLC analysis (conditions as below). A second crop of compound **508** was isolated from the mother liquor to afford 9.3 g (16.1%) of solid having a purity level of 98.4% as determined by HPLC analysis. The remaining mother liquor was purified by silica gel chromatography using 200 g of SiO_2 and eluting with 4 L of 50V% ethyl acetate and 50 V% heptane to yield 5.6 g (9.7%) of compound **508**, having a purity level of 94.0% as determined by HPLC analysis. HPLC conditions: 9.74 minute retention time on a YMC S5 ODS-AQ column (4.6 x 150 mm) using a gradient elution from 100% solvent A to 100% solvent B over 15 minutes at 1.0 mL/min. Solvent A = 95 V% water (0.01 M NH_4OAc); 5 V% acetonitrile. Solvent B = 5 V% water (0.01 M NH_4OAc); 95 V% acetonitrile. Duel wavelength detector set at 210 and 245 nm. MS (ES): m/z 381.11 $[M+H]^+$.

Example 509

(3aα,4β,5β,7β,7aα)-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (509)

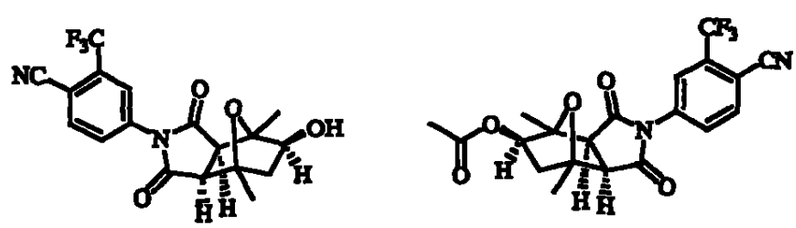


Compound **471A** (0.37 g, 1.4 mmol) and 2,5-dimethylfuran (0.73 mL, 6.9 mmol) were combined to form a slurry which was heated to 60 °C for 1 h. The reaction mixture was cooled to −10 °C and THF (1.0 mL) was added followed by the addition of borane tetrahydrofuran (2.1 mL, 1 M). The reaction mixture was stirred for 30 minutes at 0 °C and 30 minutes at +10 °C. To the reaction mixture was added acetone (3.0 mL), and the resulting mixture was warmed to 20 °C and maintained at 20 °C for 1 h. To this solution was added sodium bicarbonate (1.5 mL, pH 9, 8 wt%) and the mixture was then cooled to 5 °C before adding hydrogen peroxide (0.3 mL, 30 wt%). Addition of hydrogen peroxide was exothermic bringing the temperature to 20 °C. A solution of sodium sulfite (4.0 mL, 10 wt%) was added at 20 °C resulting in an

exotherm to 30 °C. The biphasic mixture was allowed to stand at 25 °C for 12 h. After the phases were separated, the aqueous waste was back extracted twice with ethyl acetate (5 mL) and the combined organic layers were washed with water (2 mL) followed by sodium chloride (2 mL, 25 wt%). The organic layers were concentrated *in vacuo* to yield a yellow oil which rapidly crystallized. To the crude product was added 190 proof ethanol (5.0 mL) and the mixture was heated to 60 °C to afford complete dissolution. Cooling to 20 °C for 17 h resulted in crystallization. The crystal slurry was collected by filtration, washed with heptane (5 mL), and dried at 60 °C under vacuum (30 in/Hg) to afford 0.23 g (44 %) of compound **509** having 93.1 HPLC Area%. HPLC conditions: 9.74 minute retention time on a YMC S5 ODS-AQ column (4.6 x 150 mm) using a gradient elution from 100% solvent A to 100% solvent B over 15 minutes at 1.0 mL/min. Solvent A = 95 V% water (0.01 M NH_4OAc); 5 V% acetonitrile. Solvent B = 5 V% water (0.01 M NH_4OAc); 95 V% acetonitrile. Detector set at 245 nm. MS (ES): m/z 381.11 $[M+H]^+$.

Example 510

[3aR-(3aα,4β,5β,7β,7aα)]-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (510i) & [3aS-(3aα,4β,5β,7β,7aα)-4-[5-(Acetyloxy)octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile (510ii)



Compound **509** (4 mg), vinyl acetate (0.1 mL) and toluene (2 mL) were combined and 20 mg of each of the enzymes shown in Table 12 were added. The mixture was stirred with a magnetic stirring bar at rt in a 16 x 100 mm capped tube for the time period listed in Table 12. The enantioselective acetylation of the racemic mixture resulted in the formation of compound **510i** and the acetylated compound **510ii**. The enantiomeric purity of compound **510i** was determined by chiral HPLC

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(method below) and the results for each enzyme are as shown in Table 12. The resulting information was used to prepare a large scale batch of compounds 510i & 510ii as described below.

Table 12:

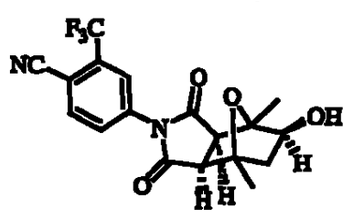
Enzyme	Supplier	Source	Time	Comp. 510i	Comp. 510i	Comp. 510i	Comp. 510ii
			H	mg/mL	% yield	% ee	mg/mL
AK-20	Amano	*Pseudomonas fluorescens*	15	0.74	39	100	1.02
AP-12	Amano	*Aspergillus niger*	144	1.10	58	55.4	0.74
PS-30	Amano	*Pseudomonas cepacia*	15	0.46	24	100	1.24
Acylase 30000	Amano	*Aspergillus*	15	0.51	27	12.2	1.26
Chirazyme L3	Boehringer	*Candida rugosa*	144	0.81	42	87.2	1.04
Lipase type VII	Sigma	*Candida rugosa*	144	0.74	39	100	1.06

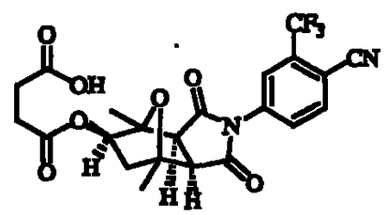
To a 500 mL jacketed flask were added Amano lipase AK20 from *Pseudomonas fluorescens* (25 g), compound 509 (25 g), methyl-isobutyl-ketone (475 mL) and vinyl acetate (25 mL). The flask was maintained at 25°C with a circulating water bath and stirred with a magnetic stir bar. The incubation was continued for 42 h, at which point the enantiomeric excess of compound 510i reached 100%. The solution was filtered through Whatman 4 filter paper to remove enzyme and the filter cake was washed with 50 mL methyl isobutyl ketone. The filtrate was concentrated *in vacuo* and the resulting residue was dissolved in EtOAc (50 mL) followed by the addition of heptane (50 mL). This solution was loaded onto a Phenomenex cartridge column (silica 800 g) in a Biotage 75L system and the column was eluted with 75% EtOAc / heptane at flow rate 110 mL/min. Fractions were collected (500 mL) which contained compound 510ii and then the eluting solvent was changed to 100% EtOAc to elute off compound 510i. The desired fractions were pooled and the solvent was

removed *in vacuo* to yield 11.0 g of compound 510i, (44%, 100%ee) and 12.10 g of compound 510ii (44%). Compound 510i was re-crystallized from 95% EtOH (5 mL/g) in two crops to afford 9.61 g (38%) of compound 510i as a white crystalline solid. Compounds 510i: Chiral HPLC: 10.02 min (retention time) (CHIRALPAK AD 4.6 x 250 mm column; isocratic elution with 20% MeOH/EtOH (1:1) in heptane at 1 mL/min). HPLC: 99% at 2.45 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 381.11 $[M+H]^+$.

Example 511

[3aR-(3aα,4β,5β,7β,7aα)]-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (511i) & Butanedioic acid, mono[3aS-(3aα,4β,5β,7β,7aα)]-[2-[4-cyano-3-(trifluoromethyl)phenyl]octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-1H-isoindol-5-yl]ester - (511ii)





A mixture of the racemic compound 509 (10 mg), succinic anhydride (100 mg) and lipase AK-20 Amano (50 mg) in toluene or MTBE (5 mL) was stirred at rt for 20 hours. After 16 and 20 h, samples (0.1 mL) were taken out from each reaction mixture, evaporated, redissolved in acetonitrile (1 mL) and analyzed by reversed phase HPLC (YMC Pro-pack ODS-A, 3μ, 15 X 0.6 cm, acetonitrile:water 20:80 to 90:10 in 12 min) to determine the area ratio of products compound 511i (RT = 8.8 min) and compound 511ii (RT = 9.9 min). A second sample (0.1 mL) of each reaction mixture was removed, evaporated and redissolved in 1 mL isopropyl alcohol-heptane (1:1) and analyzed by Chiral HPLC (Chiralpak AD, 25 X 0.46 cm, 20 °C, heptane:ethanol 85:15, 0.5 mL/min, UV 210 nm) to determine the % ee of compound 511i (RT = 32.2 min) and compound 471Dii (RT = 34.8 min). After 20 h, the

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reaction mixtures were filtered off to separate the insoluble components (enzyme, etc.). The filtrates were washed with 5% aqueous $NaHCO_3$ (3 X 1 volume) and water (3 X 1 volume), evaporated *in vacuo* and analyzed by HPLC as described above. The results showed an average yield of 48% (theoretical max yield is 50%) and 100% ee for compound **511i**. Complete separation of compound **511ii** was achieved via the above described $NaHCO_3$ extraction. Table 13 gives the details of each reaction as determined by the methods described above. Compound **511i**: Chiral HPLC: 10.02 min; CHIRALPAK AD 4.6 x 250 mm column; isocratic elution with 20% MeOH/EtOH (1:1) in heptane at 1 mL/min, 100% ee. HPLC: 99% at 2.45 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 381.11 $[M+H]^+$.

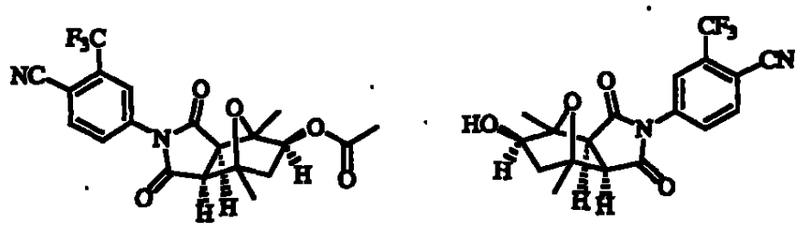
Table 13.

Solvent	Solvent	Comp. 509	Lipase AK-20	Succinic Anhydride	Time	Comp. 511i	Comp. 511ii	Comp 511i	Comp 471Dii	Comp. 511i
	Vol., ml	mg	mg	mg	Hr	8.8 min	9.9 min	32.2 min	34.8 min	ee%
						Area Ratio	Area Ratio	%	%	
Toluene	5	10	50	100	16	53%	47%	93.1%	6.9%	86.2%
					20	54%	46%	96.0%	4.0%	92.0%
Toluene Wash NaHCO3						100%	0%	96.1%	3.9%	92.2%
MTBE	5	10	50	100	16	49%	51%	100.0%	0.0%	100.0%
					20	50%	50%	100.0%	0.0%	100.0%
MTBE Wash NaHCO3						100%	0%	100.0%	0.0%	100.0%

Example 512

[3aR-(3aα,4β,5β,7β,7aα)-4-[5-(Acetyloxy)octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile (512i) & [3aS-

(3aα,4β,5β,7β,7aα)]-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (512ii)



A series of 50 mL flasks were arranged and enzymes (see Table 14 for enzyme type and amounts) were weighed into each followed by the addition of phosphate buffer (BF45, 5 mL, 100 mM, pH 7). A solution of compound 473 (5 mg) in DMSO (50 µL) was added to each flask. The flasks were shaken at 200 rpm at 28 °C for 24 hours. After 24 hours, the reaction mixtures were extracted with EtOAc (10 mL). A portion of the EtOAc extract (1 mL) was evaporated, redissolved in acetonitrile (1 mL) and analyzed by reversed phase HPLC (C-18, acetonitrile:water 20:80 to 90:10 in 12 min) to determine the area ratio of compound 512i (RT = 11.0 min) and compound 512ii, (RT = 8.9 min). Another portion of EtOAc extract (4 mL) was evaporated, redissolved in 1 mL isopropyl alcohol-heptane (1:1) and analyzed by chiral HPLC (Chiralpak AD, heptane:ethanol 85:15, 0.5 mL/min) to determine the % ee of the compound 512ii (RT = 34.8 min) and compound 471Di (RT = 32.2 min) in this system. Table 14 gives details for an array of different enzymes examined and the resulting yields and% ee for the desired products.

Table 14.

Enzyme	Supplier	Source	Enz Amt mg	Area Ratio by HPLC Comp. 512ii	Comp. 512i	Exo-Alcohol Comp 471Di	Exo-Alcohol Comp. 511ii	% ee of Comp 512ii
Lipase AP-12	Amano	Aspergillus niger	5	18%	82%	18.8%	81.2%	62.5%
Lipase AP-12	Amano	Aspergillus niger	25	50%	50%	41.0%	59.0%	17.9%
Lipase PS	Amano	Pseudomonas cepacia	5	20%	80%	31.3%	68.7%	37.4%
Lipase PS	Amano	Pseudomonas cepacia	25	46%	54%	40.2%	59.8%	19.6%
Acylase 150000	Amano	Aspergillus sp	5	30%	70%	52.0%	48.0%	-9.9%
Acylase 150001	Amano	Aspergillus sp	25	71%	29%	50.4%	49.6%	-0.8%
Newlase F	Amano	Rhizopus niveus	50	3%	97%	31.3%	68.7%	37.5%
Newlase F	Amano	Rhizopus niveus	100	5%	97%	25.7%	74.3%	48.6%
Acylase I	Sigma	Aspergillus melleus	5	10%	90%	9.7%	90.3%	80.6%
Acylase I	Sigma	Aspergillus melleus	25	28%	72%	10.9%	89.1%	78.2%
Esterase	Sigma	Porcine liver	5	76%	24%	36.0%	64.0%	27.9%

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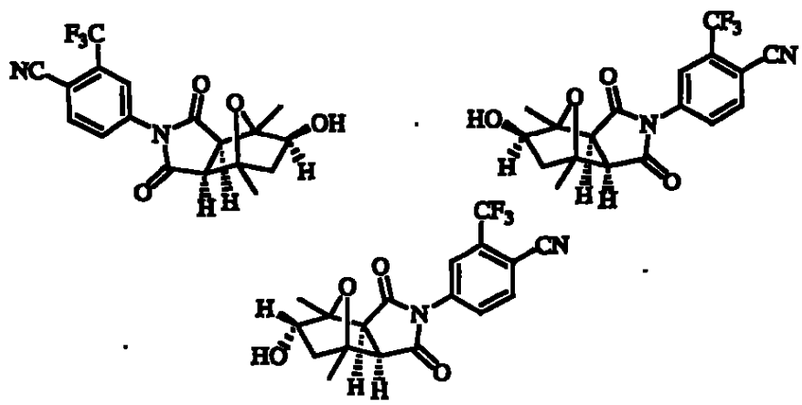
Example 513

[3aR-(3aα,4β,5β,7β,7aα)]-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (513i) & [3aS-(3aα,4β,5β,7β,7aα)]-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile & (513ii) & (3aα,4β,5α,7β,7aα)-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (513iii)



A series of microbial biotransformation reactions were set up to generate compounds 513i, 513ii & 513iii. The details of the reactions for several microorganisms are shown in Table 15 and a general procedure is described below. One thawed vial of the microbe (1 mL culture) was inoculated into sterile soybean-glucose media (10 mL) in a 50 mL flask. The microbes were grown by shaking at 200 rpm at 28°C for 40 h. A solution of compound 472 (10 mg in 100 μL DMSO) was added to each flask and the flasks were shaken at 200 rpm at 28 °C. At 24 and 48 h, 5 mL of the reaction mixtures were extracted by EtOAc (10 mL). A portion of EtOAc extract (1 mL) was evaporated, redissolved in acetonitrile (1 mL) and analyzed by reversed phase HPLC (C-18, acetonitrile: water 20:80 to 90:10 in 12 min) to determine the area ratio of compound 472 (RT = 11.2 min) and the product compounds 513i (RT = 8.9 min), 513ii (RT = 8.9 min) & 513iii (RT = 9.6 min). A second portion of the EtOAc extract (4 mL) was evaporated, redissolved in isopropyl alcohol-heptane (1:1, 1 mL) and analyzed by chiral HPLC (Chiralpak AD,

Heptane:Ethanol 85:15, 0.5 mL/min) to determine the % ee of compounds 513i (RT = 32.2 min) compound 513ii (RT = 34.8 min) in this system.

Table 15.

Microorganism	ID	Time	Analysis by Reversed Phase HPLC (Area Ratio)			Analysis for % ee by HPLC		% ee of
		Hrs	Comp 513i	Comp 513ii	Comp 472	Comp 513i	Comp 513ii	Comp 513i
Streptomyces sp	SC1754	24	7%	0%	93%	96.9%	3.1%	93.9%
		48	12%	0%	88%	96.7%	3.3%	93.3%
Streptomyces sp	SC3740	24	1%	0%	99%	88.0%	12.0%	76.0%
		48	2%	0%	98%	85.8%	14.2%	71.7%
Nocardia interforma	ATCC 21072	24	5%	0%	95%	93.2%	6.8%	86.3%
		48	8%	0%	92%	92.6%	7.4%	85.1%
Streptomyces antibioticus	ATCC 14890	24	11%	1%	88%	95.7%	4.3%	91.4%
		48	48%	13%	39%	94.1%	5.9%	88.2%
Streptomyces medocidicus	ATCC 13278	24	1%	0%	99%	82.0%	18.0%	64.1%
		48	7%	0%	93%	79.4%	20.6%	58.8%
Streptomyces griseus	NRRL B8090	24	23%	0%	77%	85.0%	15.0%	70.0%
		48	28%	0%	72%	85.9%	14.1%	71.8%
Amycolatopsis orientalis	ATCC 43490	24	12%	1%	86%	81.3%	18.7%	62.5%
		48	25%	4%	71%	77.4%	22.6%	54.9%

Example 514

[3aR-(3aα,4β,5β,7β,7aα)]-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (514i) & [3aS-(3aα,4β,5β,7β,7aα)]-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile & (514ii) & (3aα,4β,5α,7β,7aα)-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (514iii)

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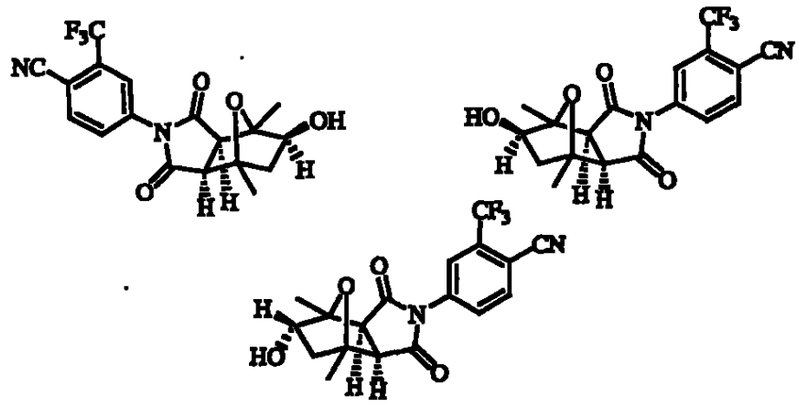


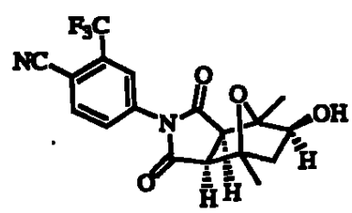
A series of microbial biotransformation reactions were set up to generate compounds 514i, 514ii & 514iii. The details of the reactions for several microorganisms are shown in Table 16 and a general procedure is described below. A 1 mL culture of *Streptomyces griseus* SC13971 from a frozen vial was used to inoculate 100 mL of medium (0.5% toasted nutrisoy, 2% glucose, 0.5% yeast extract, 0.5% K_2HPO_4, 0.5% NaCl, adjusted to pH 7 with 1N HCl (R. V. Smith and J. P. Rosazza, Arch. Biochem. Biophys., 161, 551-558 (1974)) in a 500 mL Erlenmeyer flask and the flask was incubated at 28°C at 200 rpm for 3 days. 10 mL of this culture was used to inoculate 100 mL of medium (as above) in a 500 mL Erlenmeyer flask and the flask was incubated at 28°C at 200 rpm for 1 day. For the filamentous fungi *Mucor rouxii* and *Cunninghamella echinulata*, 1 mL of spore suspension, prepared by washing a slant with 10 mL water, was used to inoculate 100 mL of medium (as above) in a 500 mL Erlenmeyer flask and the flask was incubated at 28° C at 200 rpm for 1 day. Compound 472 (30 mg in 1 mL methanol) was added to each culture and the incubations were continued for 6 to 10 days. Samples of 10 mL of the culture broth in each flask were removed and extracted with ethyl acetate (20 mL). Samples of 10 mL of the organic layers were each individually evaporated to dryness at 40 °C under a nitrogen stream. The residues were dissolved in 1.2 mL isopropanol and analyzed by reversed phase HPLC (YMC Pak ODS 150x6mm, 3 μ C-18, acetonitrile: water 20:80 to 90:10 in 12 min, 1 mL/min, 40 °C) to determine the concentration of compound 472 (RT = 11.2 min) and product compounds 514i (RT = 8.9 min), 514ii (RT = 8.9 min) & 514iii (RT = 9.6 min). The same samples were analyzed by chiral HPLC (Chiralpak AD, heptane:ethanol 85:15, 0.5 mL/min) to determine the % ee of compounds 514i (RT = 32.2 min) compound 514ii (RT = 34.8 min) in this system.

Table 16.

strain	SC	ATCC	time	Comp. 472	Comp. 514i	Comp 514i	Comp514iii
			days	mg/ml	mg/ml	ee %	mg/ml
1. *Mucor rouxii*	13920	24905	3	0.30	0.01	100.00	0.000
			6	0.27	0.01	100.00	0.000
2. *Streptomyces griseus*	13971	13273	3	0.29	0.01	100.00	0.000
			6	0.30	0.01	100.00	0.000
3. *Cunninghamella echinulata*	16027	9244	3	0.34	0.02	100.00	0.002
			6	0.06	0.02	100.00	0.001
			10	0.16	0.02	100.00	0.001

Example 515

[3aR-(3aα,4β,5β,7β,7aα)]-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (515)



Microbial transformation of compound 472 to compound 515 was conducted on a 3 L scale in a 5 L fermentor, using *Cunninghamella echinulata* SC 16027 (ATCC 9244) and a medium consisting of the following: 0.5% toasted nutrisoy, 2% glucose, 0.5% yeast extract, 0.5% K_2HPO_4, 0.5% NaCl, adjusted to pH 7 with 1N HCl (R. V. Smith and J. P. Rosazza, Arch. Biochem. Biophys., 161, 551-558 (1974)). The fermentor was batched with 0.05% SAG antifoam before sterilization. Spore inoculum was prepared by washing the spores from a 10 day slant culture of *Cunninghamella echinulata* SC 16027 (ATCC 9244) with 0.9% saline / 0.1% Tween 80. The inoculum stage was prepared by adding 1 mL of spore inoculum into 100 mL medium in a 500 mL flask, then the cultures were grown at 28° C at 200 rpm for 1 day. 10% inoculum from the flask was blended in a sterile Waring blender and used to inoculate the sterile fermentor, containing 3 L of sterile media. The fermentor was run at 28°C at 600 rpm and 1 vvm aeration. A sterile solution of three antibiotics was

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added to the fermentor after inoculation; 12 mg of tetracycline chloride, 12 mg of kanamycin sulfate, and 60 mg of cephalexin hydrate in 10 mL of deionized water. After 22 hours of growth in the fermentor, a sterile substrate solution was added containing 0.75 g of compound **472** dissolved in 30 mL of methanol, this step was repeated two hours later for a total of 0.5 g/L of compound **472** in the bioconversion. The fermentation conditions were maintained at 28° C at 600 rpm and 1 vvm aeration. pH 6.5 was maintained by the automatic addition of 10% H_2SO_4 or 10% NaOH. Periodically, 10 mL aseptic samples were taken and extracted with two 10 mL portions of ethyl acetate. The ethyl acetate layer was isolated, dried under a nitrogen stream at 40 °C, and the residue was dissolved in 2.0 mL of isopropyl alcohol. The samples were analyzed by reverse phase HPLC (method below) to determine the ratio of compound **472** and the product compound **515**. In addition, each sample was analyzed by chiral HPLC (method below) in order to determine the % ee of compound **515**. During the bioconversion process, a sterile solution of 30% cerelose and 1.5% yeast extract was fed into the reaction at ~5 mL / hour. After 114 h from the time of substrate addition, reverse phase HPLC analysis indicated the production of a 78% yield of compound **515**. Chiral HPLC analysis measured the % e.e. of compound **515** at 94.9%. The above process was repeated in another 3 L bioconversion, and the reaction was conducted at 28°C at 600 rpm, 1 vvm aeration, with 0.5 g/L of compound **472** input. After 44 h, this reaction gave a 80% yield of compound **515** with 95% e.e. The broth was flittered through a pad of HyFlo™ to provide a clarified fermentation broth. The broth was flittered through a pad of HyFlo™ to provide a clarified fermentation broth. Compound **515** was completely adsorbed onto 55 g of XAD-16 and extracted back into a 1:1 mixture of EtOAc and acetone (3 X 100 mL) or methyl-*tert*-butyl ether (3 X 100 mL). The solvent was removed *in vacuo* and the resulting residue was purified by silica pad (5 g), eluting with EtOAc. The desired fractions were collected and treated with activated carbon (0.5 g) to declorize the solution and the solvent was removed *in vacuo* to yield 1.27 g of compound **515**. Re-crystallization of this material from EtOAc/heptane (10 mL/20 mL) resulted 950 mg of crystalline compound **515** having 97% purity by reverse phase HPLC and 95% ee by chiral HPLC. Reverse Phase HPLC: YMC Pak ODS-A C18 column, 4.6 x 50 mm, eluting with a gradient of : 0 min 20% acetonitrile/80%

0.1% TFA in water, 12 min 90% acetonitrile/10% 0.1% TFA in water, 12.01-15 min 20% acetonitrile/80% 0.1% TFA in water, monitoring at 250 nm, 40°C, 5 μL injection volume). Compound 515: RT = 8.86 min. Chiral HPLC: CHIRALPAK OD 25x0.46 cm column; isocratic elution with 15% ethanol/85% heptane at 0.5 mL/min, 18 °C, monitoring at 220 nm, injection volume: 20 μL. Compound 515: RT = 36.5 min.

In an alternate recovery process, the fermentation broth (1L) from the above biohydroxylation reaction was filtered and the cake of cells was washed with 100 mL of water. Clear broth was extracted with ethyl acetate (2 X 600 mL) and the cake of cells was extracted with 400 mL of ethyl acetate. The combined ethyl acetate layers were concentrated and the resulting residue was dissolved in 5 mL of 1:1 heptane / ethyl acetate and loaded on to silica gel pad pad (70 g in 250 mL fritted glass filter). The silica gel pad was eluted with a gradient of 80 to 90% EtOAc/heptane. Fractions were collected and the fractions containing compound 515 were pooled. The solvent was removed *in vacuo* and resulting product was crystallized from EtOAc/heptane to give a 90% yield of compound 515 with 98% purity by reverse phase HPLC and 95% ee by chiral HPLC. Reverse Phase HPLC: YMC Pak ODS-A C18 column, 4.6 x 50 mm, eluting with a gradient of : 0 min 20% acetonitrile/80% 0.1% TFA in water, 12 min 90% acetonitrile/10% 0.1% TFA in water, 12.01-15 min 20% acetonitrile/80% 0.1% TFA in water, monitoring at 250 nm, 40°C, 5 μL injection volume). Compound 472: RT = 11.12 min. Compound 515: RT = 8.86 min. Chiral HPLC: CHIRALPAK OD 25x0.46 cm column; isocratic elution with 15% ethanol/85% heptane at 0.5 mL/min, 18 °C, monitoring at 220 nm, injection volume: 20 μL. Compound 472: RT = 27.4 min. Compound 515: RT = 36.5 min. Compound (514iii) RT = 39.1 min.

Example 516

4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-2-trifluoromethylbenzonitrile (516B)

The following Example demonstrates preparation of an intermediate useful for preparing compounds of the formula I of the present invention.

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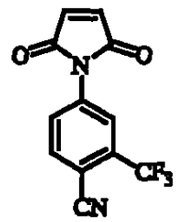
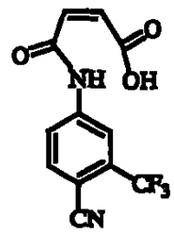


A. 3-(4-Cyano-3-trifluoromethylphenylcarbamoyl)acrylic acid (516A)



5-amino-2-cyanobenzotrifluoride (210.6 mmoles; 40.00 g) and butyl acetate (80 mL) were added to a 250 mL round bottom flask, followed by the addition of maleic anhydride (231.9 mmoles, 23.20 g). The resulting suspension was heated to 60 °C for 3.5 h. The reaction mixture was cooled to 25 °C and then heptane (160 mL) was added dropwise over a period of 25 minutes. The resulting suspension was filtered and washed with a mixture of 4:1, hepatane:butyl acetate (30 mL) and heptane (45 mL). The cake was dried *in vacuo* to give 60 g (95% yield) of compound 516A.

B. 4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-2-trifluoromethyl-benzonitrile(516B)

Compound 516A (17.42 mmoles, 5.000 g) was added to the reaction flask followed by the addition of zinc bromide (17.58 mmoles, 3.960 g) and then toluene (50.00 mL, 43.25 g) was added to the mixture. The resulting suspension was stirred for 20 min. Hexamethyldisilazane (26.35 mmoles, 5.560 mL, 4.253 g) was added to this suspension which was then heated to 60 °C for 4.5 h. The reaction mixture was diluted with EtOAc (25 mL) and then poured into a 1N HCl solution (30 mL) at 25 °C. The organic phase was collected and the aqueous phase was extracted with EtOAc (15 mL). The organic phase was isolated, combined with the earlier organic phase and washed consecutively with saturated $NaHCO_3$ (15 mL), a mixture of 1:1

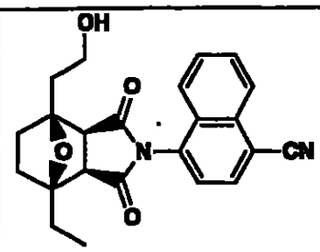
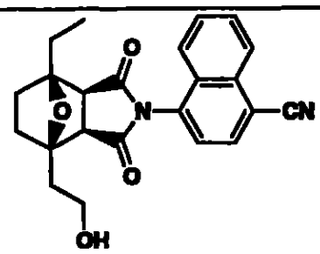
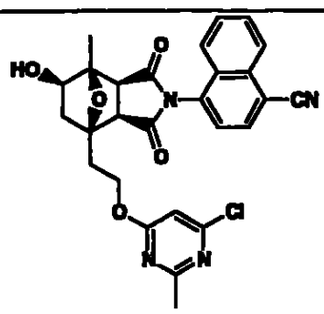
water:brine solution (15 mL) and brine (15 mL). The resulting solution was dried over $MgSO_4$, filtered and concentrated *in vacuo* to a 50 mL suspension. Heptane (125 mL) was added dropwise to this suspension with agitation. The resulting thicker suspension was filtered and washed with a mixture of 2:1 heptane:toluene (15 mL) and then heptane (15 mL) to give 4 g (85% yield) of compound **516B**. HPLC: 100% at 2.11 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm).

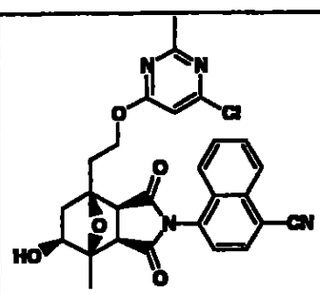
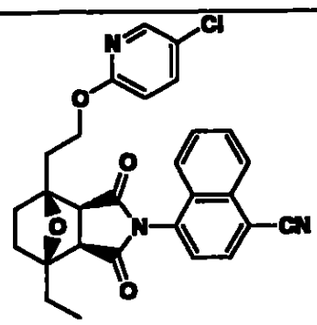
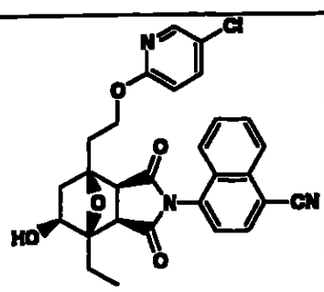
Examples 517 to 746

Additional compounds of the present invention were prepared by procedures analogous to those described above. The compounds of Examples 517 to 746 have the structures shown in the following Table 17.

Table 17 also provides the compound name, retention time/molecular mass, and the procedure employed for preparation of these compounds. The chromatography techniques used to determine the compound retention times of Table 17 are as follows: LC and LCMS were described in Examples 439 to 454 (Table 9). The molecular mass of the compounds listed in Table 17, where provided, was determined by MS (ES) by the formula m/z.

Ex. No.	Compound Structure	Compound Name	Retention Time Min. / Molecular Mass	Pro. of Ex.

517		[3a*R*-(3aα,4β,7β,7aα)]-4-[4-Ethyloctahydro-7-(2-hydroxyethyl)-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	2.84 LC $[M + H]^+$= 391.16	245 & 461
518		[3a*S*-(3aα,4β,7β,7aα)]-4-[4-Ethyloctahydro-7-(2-hydroxyethyl)-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	2.84 LC $[M + H]^+$= 391.16	245 & 461
519		[3a*S*-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[(6-Chloro-2-methyl-4-pyrimidinyl)oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.04 LC $[M + H]^+$= 519.0	243 & 244

520		[3a*R*-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[(6-Chloro-2-methyl-4-pyrimidinyl)oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.04 LC $[M + H]^+$= 519.0	243 & 244
521		[3a*R*-(3aα,4β,7β,7aα)]-4-[4-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]-7-ethyloctahydro-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.90 LC $[M + H]^+$= 502.28	245 & 461
522		[3a*R*-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]-4-ethyloctahydro-5-hydroxy-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.37 LC $[M + H]^+$= 518.28	435, 499 & 500

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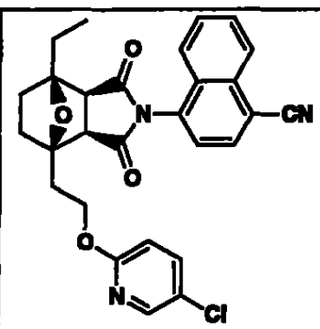
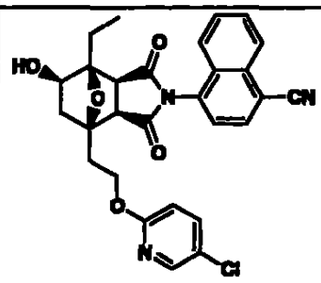
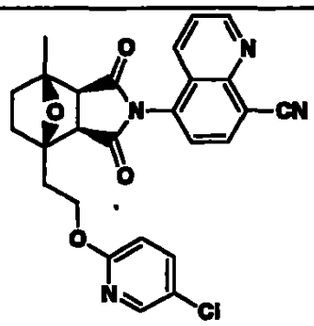
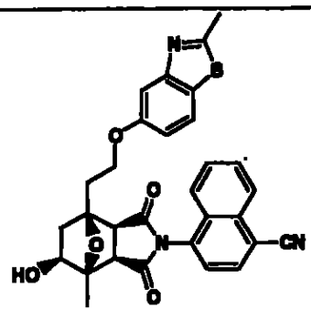
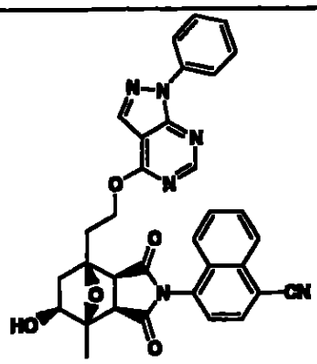
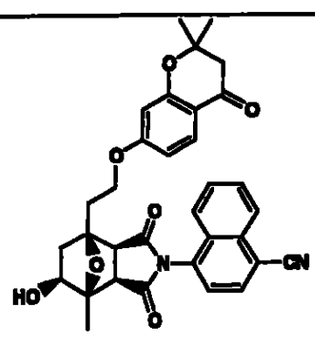
523		[3a*S*-(3aα,4β,7β,7aα)]-4-[4-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]-7-ethyloctahydro-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.90 LC $[M+H]^+$= 502.27	245 & 461
524		[3a*S*-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]-4-ethyloctahydro-5-hydroxy-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.40 LC $[M+H]^+$= 518.27	435, 499 & 500
525		(3aα,4β,7β,7aα)-5-[4-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile	3.32 LC $[M+H]^+$= 489.26	467

526		[3a*R*-(3aα,4β,5β,7β,7aα)]-4-[Octahydro-5-hydroxy-4-methyl-7-[2-[(2-methyl-5-benzothiazolyl)oxy]ethyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.36 LC $[M + H]^+$= 540.0	243 & 244
527		[3a*R*-(3aα,4β,5β,7β,7aα)]-4-[Octahydro-5-hydroxy-4-methyl-1,3-dioxo-7-[2-[(1-phenyl-1H-pyrazolo[3,4-d]pyrimidin-4-yl)oxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.35 LC $[M + OAc]^-$ = 644.8	243 & 244
528		[3a*R*-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[(3,4-Dihydro-2,2-dimethyl-4-oxo-2H-1-benzopyran-7-yl)oxy]ethyl]octahydro-5-hydroxy-4-	3.37 LC $[M + OAc]^-$ = 391.16	243 & 244

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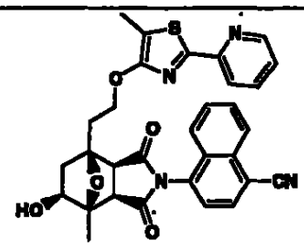
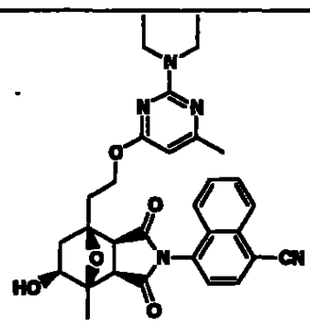
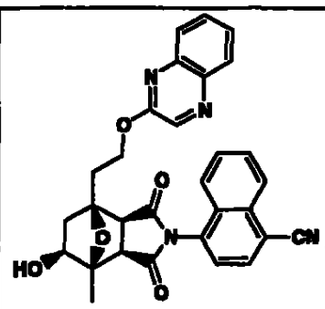
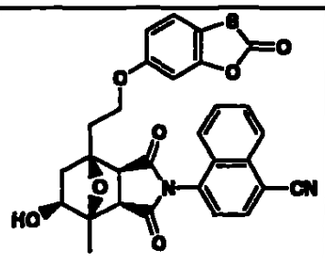
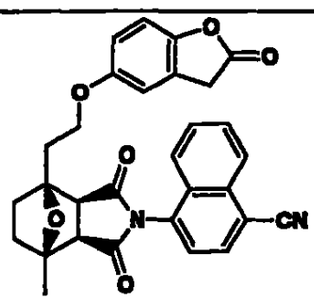
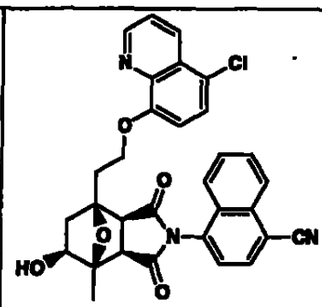
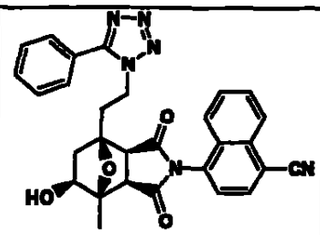
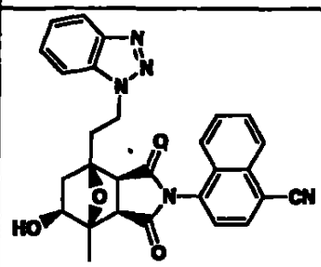
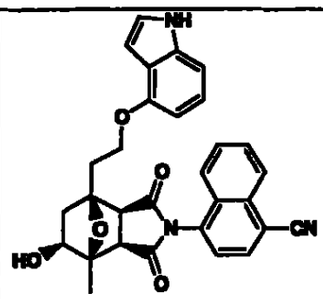
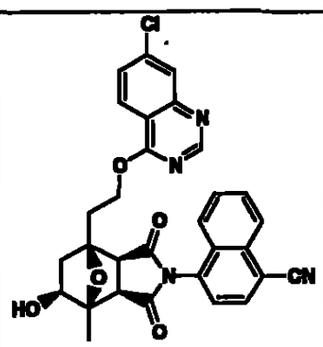
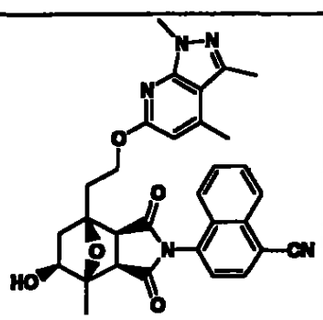
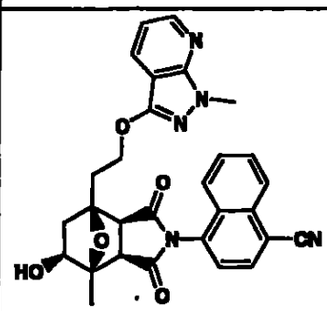
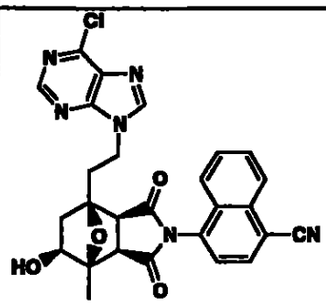
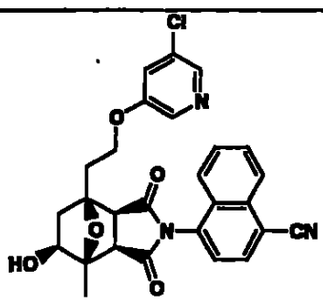
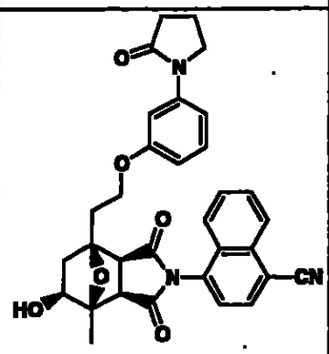
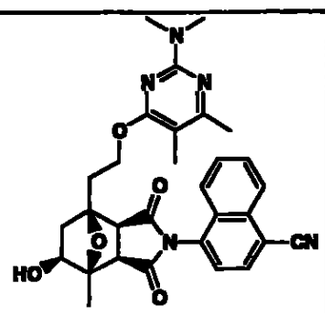
		methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile		
529		[3a*R*-(3aα,4β,5β,7β,7aα)]-4-[Octahydro-5-hydroxy-4-methyl-7-[2-[[5-methyl-2-(2-pyridinyl)-4-thiazolyl]oxy]ethyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.47 LC $[M + H]^+$= 566.9	243 & 244
530		[3a*R*-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[[2-(Diethylamino)-6-methyl-4-pyrimidinyl]oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.47 LC $[M + H]^+$= 556.1	243 & 244

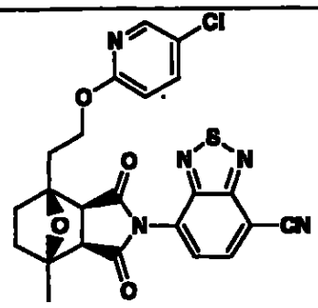
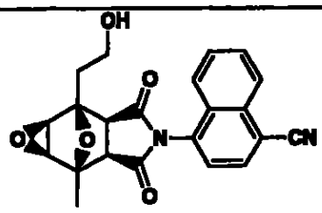
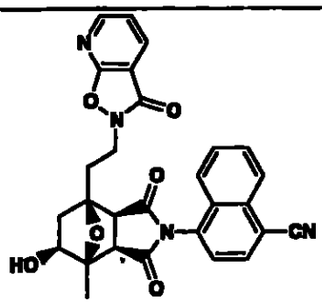
531		[3a*R*-(3aα,4β,5β,7β,7aα)]-4-[Octahydro-5-hydroxy-4-methyl-1,3-dioxo-7-[2-(2-quinoxalinyloxy)ethyl]-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.39 LC $[M + H]^+$= 520.6	243 & 244
532		[3a*R*-(3aα,4β,5β,7β,7aα)]-4-[Octahydro-5-hydroxy-4-methyl-1,3-dioxo-7-[2-[(2-oxo-1,3-benzoxathiol-5-yl)oxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.35 LC $[M + OAc]^-$ = 600.8	243 & 244
533		(3aα,4β,7β,7aα)-4-[4-[2-[(2,3-Dihydro-2-oxo-5-benzofuranyl)oxy]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.28 LC $[M + OAc]^-$ = 566.6	223 & 250

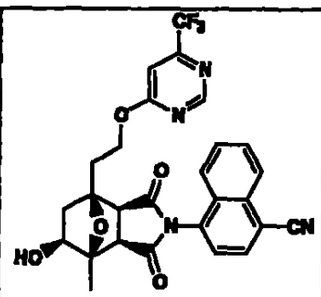
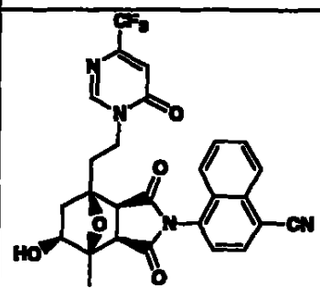
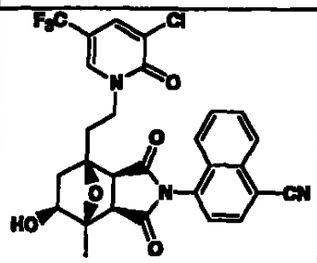
534		[3a*R*-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[(5-Chloro-8-quinolinyl)oxy]ethyl] octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.18 LC $[M + H]^+$= 553.6	243 & 244
535		[3a*R*-(3aα,4β,5β,7β,7aα)]-4-[Octahydro-5-hydroxy-4-methyl-1,3-dioxo-7-[2-(5-phenyl-1H-tetrazol-1-yl)ethyl]-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.32 LC [M + H] = 521.5	243 & 244
536		[3a*R*-(3aα,4β,5β,7β,7aα)]-4-[7-[2-(1H-1,2,3-Benzotriazol-1-yl)ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.15 LC $[M + H]^+$= 493.8	243 & 244

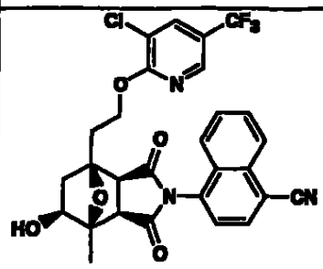
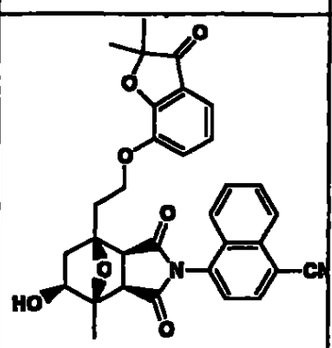
537		[3a*R*-(3aα,4β,5β,7β,7aα)]-4-[Octahydro-5-hydroxy-7-[2-(1H-indol-4-yloxy)ethyl]-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.05 LC $[M]^+$= 507.6	243 & 244
538		[3a*R*-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[(7-Chloro-4-quinazolinyl)oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.33 LC $[M + H]^+$= 555.2	243 & 244
539		[3a*R*-(3aα,4β,5β,7β,7aα)]-4-[Octahydro-5-hydroxy-4-methyl-1,3-dioxo-7-[2-[(1,3,4-trimethyl-1H-pyrazolo[3,4-b]pyridin-6-yl)oxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-1-	3.48 LC $[M + H]^+$= 552.2	243 & 244

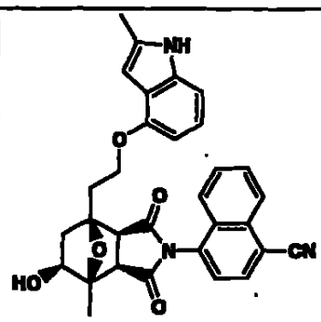
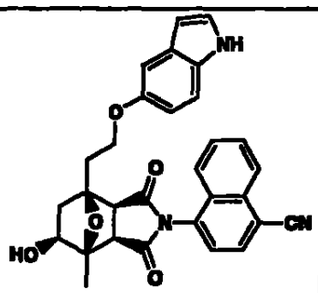
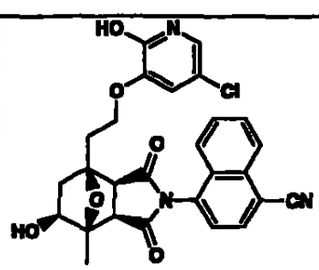
		naphthalenecarbonitrile		
540		[3a*R*-(3aα,4β,5β,7β,7aα)]-4-[Octahydro-5-hydroxy-4-methyl-7-[2-[(1-methyl-1H-pyrazolo[3,4-b]pyridin-3-yl)oxy]ethyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.08 LC $[M + H]^+$= 524.2	243 & 244
541		[3a*R*-(3aα,4β,5β,7β,7aα)]-4-[7-[2-(6-Chloro-9H-purin-9-yl)ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	2.70 LC $[M + H]^+$= 529.0	243 & 244
542		[3a*R*-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[(5-Chloro-3-pyridinyl)oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-	3.17 LC $[M + H]^+$= 504.1	243 & 244

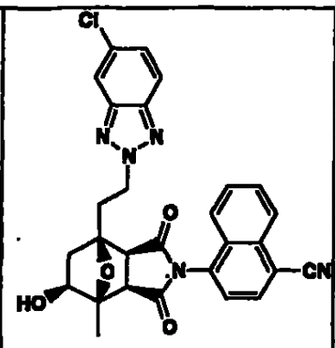
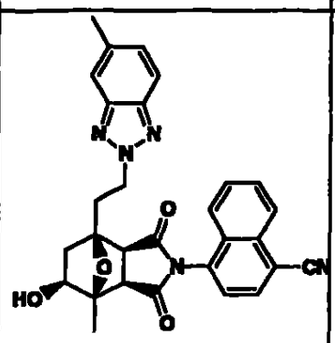
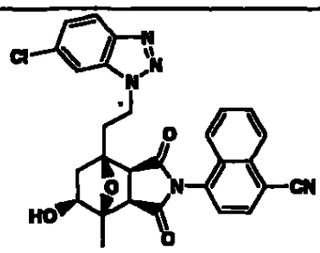
		isoindol-2-yl]-1-naphthalenecarbonitrile		
543		[3a*R*-(3aα,4β,5β,7β,7aα)]-4-[Octahydro-5-hydroxy-4-methyl-1,3-dioxo-7-[2-[3-(2-oxo-1-pyrrolidinyl)phenoxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.10 LC $[M + H]^+$= 552.3	243 & 244
544		[3a*R*-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[[2-(Dimethylamino)-5,6-dimethyl-4-pyrimidinyl]oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	2.40 LC $[M + H]^+$= 542.3	243 & 244

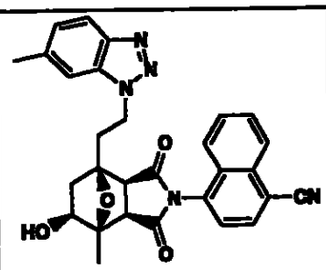
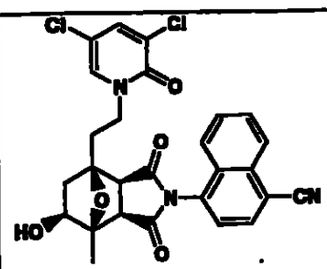
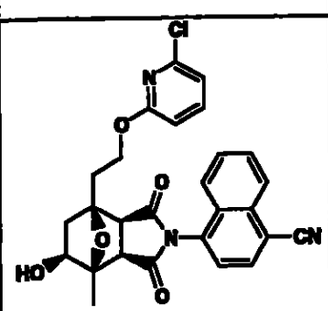
545		(3aα,4β,7β,7aα)-7-[4-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2,1,3-benzothiadiazole-4-carbonitrile	3.52 LC $[M + H]^+$= 495.6	424A, 204, 482F & 482G
546		(1aα,2β,2aα,5aα,6β,6aα)-4-[Octahydro-2-(2-hydroxyethyl)-6-methyl-3,5-dioxo-2,6-epoxy-4H-oxireno[f]isoindol-4-yl]-1-naphthalenecarbonitrile	2.36 LC $[M + H]^+$= 391.31	460 & 228
547		[3a*R*-(3aα,4β,5β,7β,7aα)]-4-[Octahydro-5-hydroxy-4-methyl-1,3-dioxo-7-[2-(3-oxoisoxazolo[5,4-b]pyridin-2(3H)-yl)ethyl]-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	2.92 LC $[M + OAc]^-$ = 568.6	243 & 244

548		[3a*R*-(3aα,4β,5β,7β,7aα)]-4-[Octahydro-5-hydroxy-4-methyl-1,3-dioxo-7-[2-[[6-(trifluoromethyl)-4-pyrimidinyl]oxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.18 LC [M + OAc]⁻ = 596.7	243 & 244
549		[3a*R*-(3aα,4β,5β,7β,7aα)]-4-[Octahydro-5-hydroxy-4-methyl-1,3-dioxo-7-[2-[6-oxo-4-(trifluoromethyl)-1(6H)-pyrimidinyl]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	2.94 LC [M + OAc]⁻ = 596.5	243 & 244
550		[3a*R*-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[3-Chloro-2-oxo-5-(trifluoromethyl)-1(2H)-pyridinyl]ethyl]octahydro-5-hydroxy-4-	3.39 LC [M + OAc]⁻ = 629.3	243 & 244

		methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile		
551		[3a*R*-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[[3-Chloro-5-(trifluoromethyl)-2-pyridinyl]oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.76 LC [M + OAc]⁻ = 629.6	243 & 244
552		[3a*R*-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[(2,3-Dihydro-2,2-dimethyl-3-oxo-7-benzofuranyl)oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.26 LC [M + OAc]⁻ = 611.5	243 & 244

553		[3a*R*-(3aα,4β,5β,7β,7aα)]-4-[Octahydro-5-hydroxy-4-methyl-7-[2-[(2-methyl-1H-indol-4-yl)oxy]ethyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.16 LC $[M + H]^+$= 522.5	243 & 244
554		[3a*R*-(3aα,4β,5β,7β,7aα)]-4-[Octahydro-5-hydroxy-7-[2-(1H-indol-5-yloxy)ethyl]-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.03 LC $[M + H]^+$= 506.3	243 & 244
555		[3a*R*-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[(5-Chloro-1,2-dihydro-2-oxo-3-pyridinyl)oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	2.85 LC $[M + H]^+$= 520.5	243 & 244

556		[3a*R*-(3aα,4β,5β,7β,7aα)]-4-[7-[2-(5-Chloro-2H-1,2,3-benzotriazol-2-yl)ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.53 LC [M + OAc]⁻ = 586.3	243 & 244
557		[3a*R*-(3aα,4β,5β,7β,7aα)]-4-[Octahydro-5-hydroxy-4-methyl-7-[2-(5-methyl-2H-1,2,3-benzotriazol-2-yl)ethyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.35 LC [M + H]⁺= 508.5	243 & 244
558		[3a*R*-(3aα,4β,5β,7β,7aα)]-4-[7-[2-(6-Chloro-1H-1,2,3-benzotriazol-1-yl)ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.32 LC [M + H]⁺= 528.3	243 & 244

559		[3a*R*-(3aα,4β,5β,7β,7aα)]-4-[Octahydro-5-hydroxy-4-methyl-7-[2-(6-methyl-1H-1,2,3-benzotriazol-1-yl)ethyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	2.97 LC $[M + H]^+$= 508.4	243 & 244
560		[3a*R*-(3aα,4β,5β,7β,7aα)]-4-[7-[2-(3,5-Dichloro-2-oxo-1(2H)-pyridinyl)ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.22 LC $[M + H]^+$= 538.3	243 & 244
561		[3a*R*-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[(6-Chloro-2-pyridinyl)oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonit	3.30 LC $[M + H]^+$= 504.3	243 & 244

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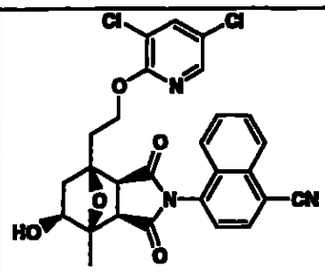
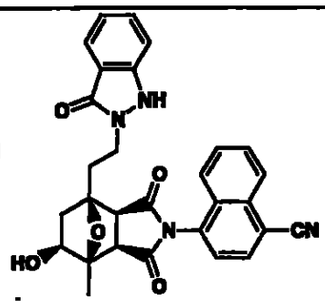
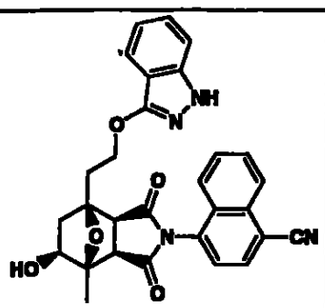
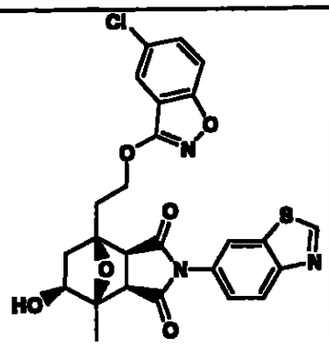
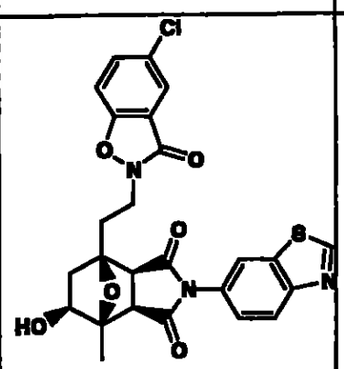
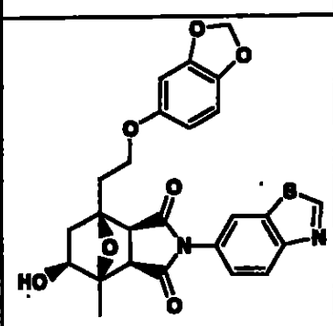
562		[3a*R*-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[(3,5-Dichloro-2-pyridinyl)oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.67 LC $[M + H]^+$= 596.3	243 & 244
563		[3a*R*-(3aα,4β,5β,7β,7aα)]-4-[7-[2-(1,3-Dihydro-3-oxo-2H-indazol-2-yl)ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	2.82 LC $[M + H]^+$= 509.1	243 & 244
564		[3a*R*-(3aα,4β,5β,7β,7aα)]-4-[Octahydro-5-hydroxy-7-[2-(1H-indazol-3-yloxy)ethyl]-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-	3.19 LC $[M + H]^+$= 509.2	243 & 244

		naphthalenecarbonitrile		
565		[3a*R*-(3aα,4β,5β,7β,7aα)]-2-(6-Benzothiazolyl)-7-[2-[(5-chloro-1,2-benzisoxazol-3-yl)oxy]ethyl]hexahydro-5-hydroxy-4-methyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.21 LC $[M+H]^+$= 526.2	481
566		[3a*R*-(3aα,4β,5β,7β,7aα)]-2-(6-Benzothiazolyl)-7-[2-(5-chloro-3-oxo-1,2-benzisoxazol-2(3H)-yl)ethyl]hexahydro-5-hydroxy-4-methyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione	2.81 LC $[M+H]^+$= 526.2	481
567		[3a*R*-(3aα,4β,5β,7β,7aα)]-7-[2-(1,3-Benzodioxol-5-yloxy)ethyl]-2-(6-benzothiazolyl)hexahydro-5-hydroxy-4-methyl-4,7-epoxy-	2.80 LC $[M+H]^+$= 495.2	481

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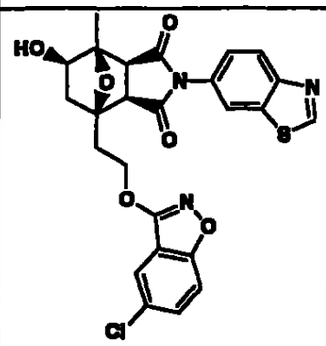
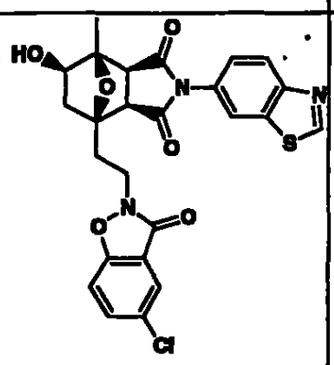
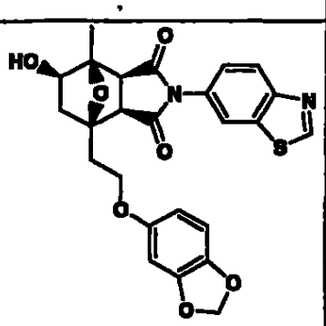
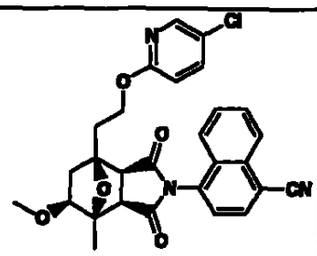
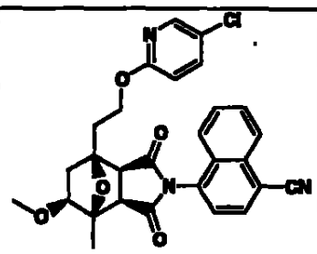
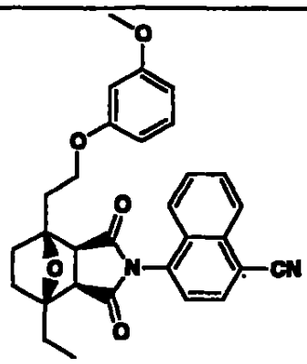
		1H-isoindole-1,3(2H)-dione		
568		[3a*S*-(3aα,4β,5β,7β,7aα)]-2-(6-Benzothiazolyl)-7-[2-[(5-chloro-1,2-benzisoxazol-3-yl)oxy]ethyl]hexahydro-5-hydroxy-4-methyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.21 LC $[M+H]^+$= 526.1	481
569		[3a*S*-(3aα,4β,5β,7β,7aα)]-2-(6-Benzothiazolyl)-7-[2-(5-chloro-3-oxo-1,2-benzisoxazol-2(3H)-yl)ethyl]hexahydro-5-hydroxy-4-methyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione	2.84 LC $[M+H]^+$= 391.16	481
570		[3a*S*-(3aα,4β,5β,7β,7aα)]-7-[2-(1,3-Benzodioxol-5-yloxy)ethyl]-2-(6-benzothiazolyl)hexahydro-5-hydroxy-4-methyl-4,7-epoxy-	2.82 LC $[M+H]^+$= 495.2	481

		1H-isoindole-1,3(2H)-dione		
571		(3aα,4β,5β,7β,7aα)-4-[7-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]octahydro-5-methoxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.64 & 3.76 atropisomers LCMS $[M + H]^+$= 518.19	491
572		[3a*R*-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]octahydro-5-methoxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.50 LC $[M + H]^+$= 518.28	491
573		[3a*R*-(3aα,4β,7β,7aα)]-4-[4-Ethyloctahydro-7-[2-(3-methoxyphenoxy)ethyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	7.49 & 7.75 atropisomers LC HRMS $[M + CH_3CO_2]^-$= 555.2144	245C, 461 & 462

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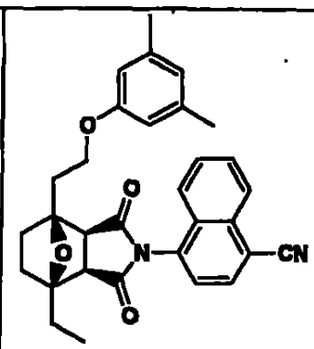
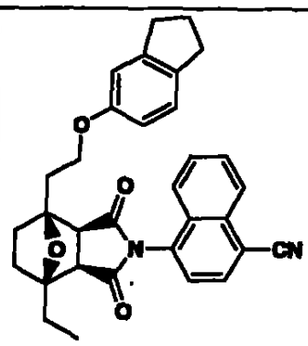
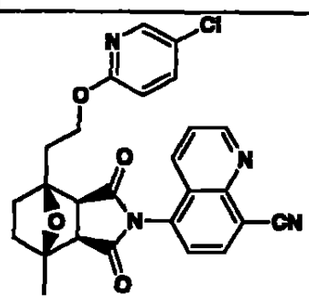
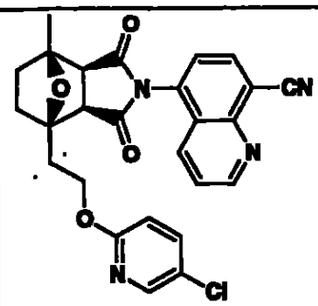
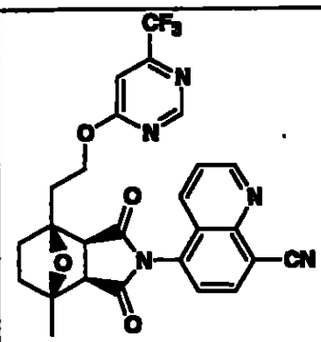
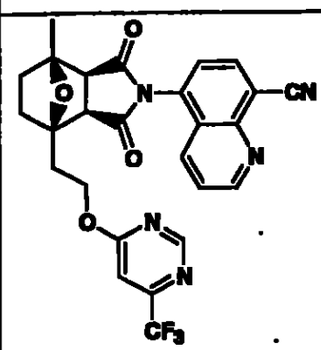
574		[3a*R*-(3aα,4β,7β,7aα)]-4-[4-[2-(3,5-Dimethylphenoxy)ethyl]-7-ethyloctahydro-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	8.10 & 8.31 atropisomers HRMS [M + CH_3CO_2]$^-$ = 553.2363	**245C, 461 & 462**
575		[3a*R*-(3aα,4β,7β,7aα)]-4-[4-[2-[(2,3-Dihydro-1H-inden-5-yl)oxy]ethyl]-7-ethyloctahydro-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	8.17 & 8.37 atropisomers HRMS [M + CH_3CO_2]$^-$ = 565.2326	245C, 461 & 462
576		[3a*R*-(3aα,4β,7β,7aα)]-5-[4-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile	3.45 LC [M + H]$^+$ = 489.0	467 & 487

577		[3a*S*-(3aα,4β,7β,7aα)]-5-[4-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile	3.45 LC $[M + H]^+$= 488.99	467 & 487
578		[3a*R*-(3aα,4β,7β,7aα)]-5-[Octahydro-4-methyl-1,3-dioxo-7-[2-[[6-(trifluoromethyl)-4-pyrimidinyl]oxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile	3.25 LC $[M + H]^+$= 524.0	467 & 487
579		[3a*S*-(3aα,4β,7β,7aα)]-5-[Octahydro-4-methyl-1,3-dioxo-7-[2-[[6-(trifluoromethyl)-4-pyrimidinyl]oxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile	3.45 LC $[M + H]^+$= 523.98	467 & 487

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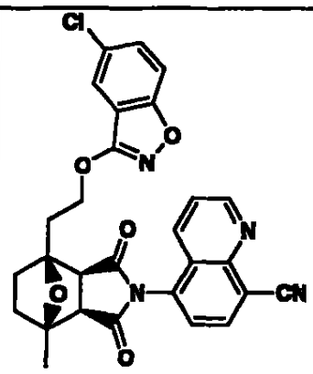
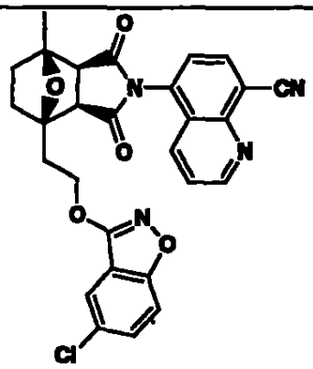
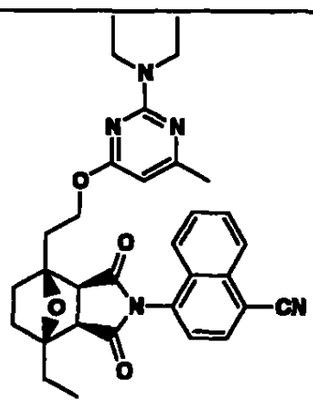
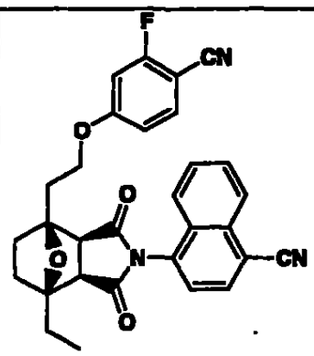
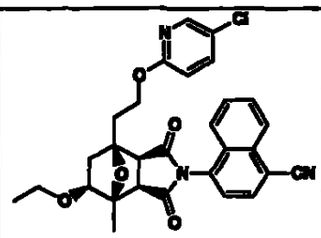
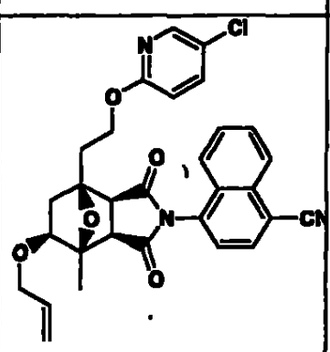
580		[3a*R*-(3aα,4β,7β,7aα)]-5-[4-[2-[(5-Chloro-1,2-benzisoxazol-3-yl)oxy]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile	3.66 LC $[M + H]^+$= 529.16	467 & 487
581		[3a*S*-(3aα,4β,7β,7aα)]-5-[4-[2-[(5-Chloro-1,2-benzisoxazol-3-yl)oxy]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile	3.66 LC $[M + H]^+$= 529.16	467 & 487
582		[3a*R*-(3aα,4β,7β,7aα)]-4-[4-[2-[[2-(Diethylamino)-6-methyl-4-pyrimidinyl]oxy]ethyl]-7-ethyloctahydro-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	5.85 & 6.06 atropisomers LC $[M + H]^+$= 554.26	245C, 461 & 462

583		[3a*R*-(3aα,4β,7β,7aα)]-4-[4-[2-(4-Cyano-3-fluorophenoxy)ethyl]-7-ethyloctahydro-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	7.23 & 7.50 atropisomers HRMS $[M - H]^-$ = 508.1682	245C, 461 & 462
584		[3a*R*-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]-5-ethoxyoctahydro-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.60 LC $[M + H]^+$ = 532.23	223, 495 & 496
585		[3a*R*-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]octahydro-4-methyl-1,3-dioxo-5-(2-propenyloxy)-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.68 LC $[M + H]^+$ = 544.23	491

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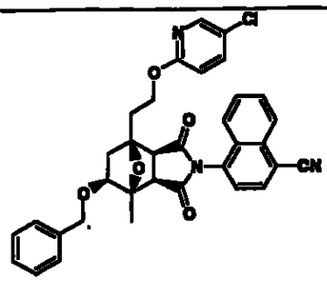
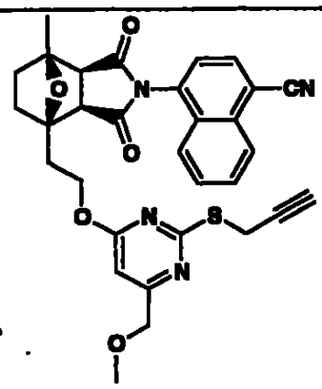
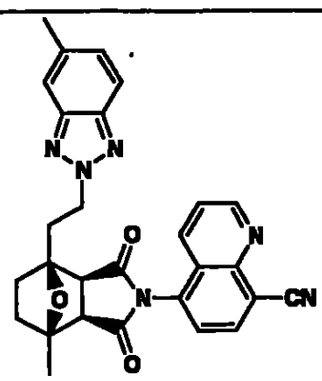
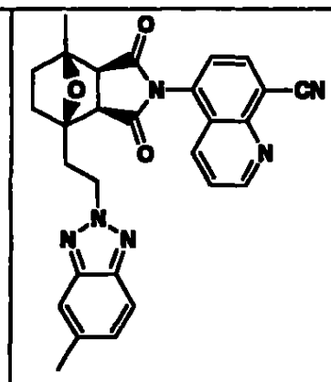
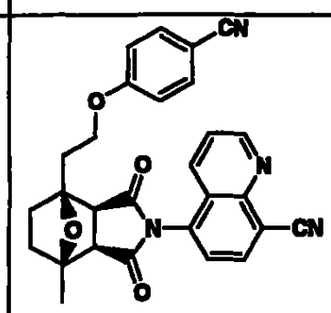
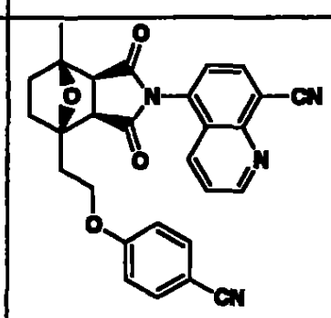
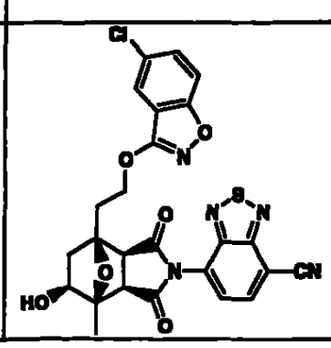
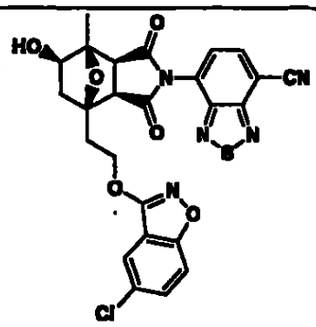
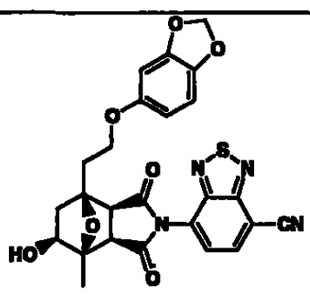
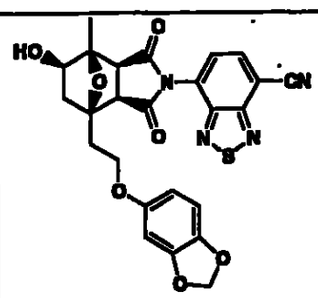
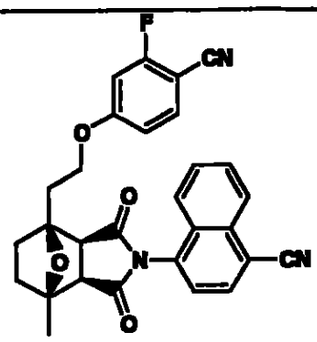
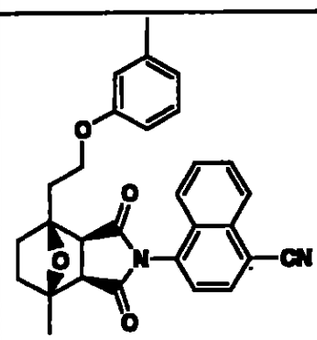
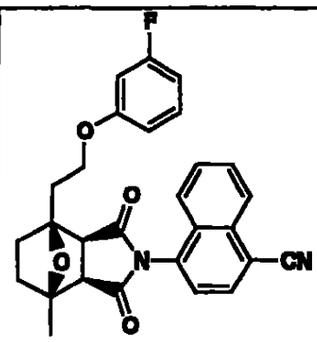
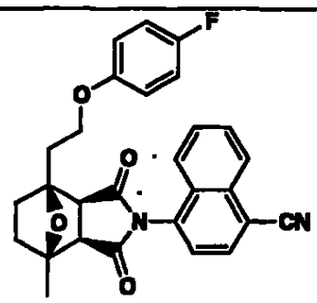
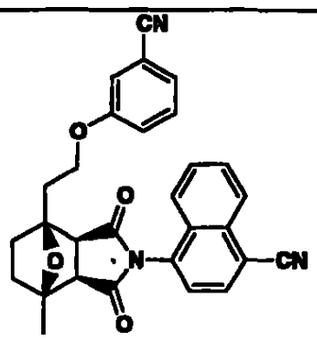
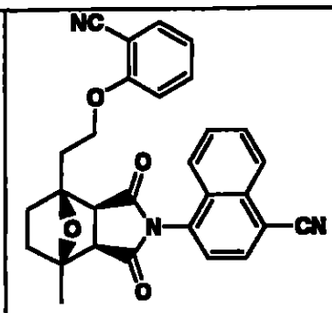
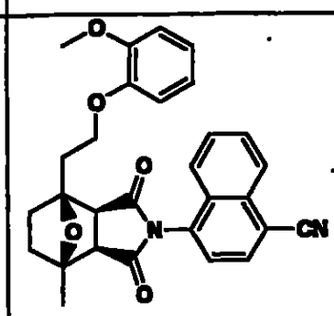
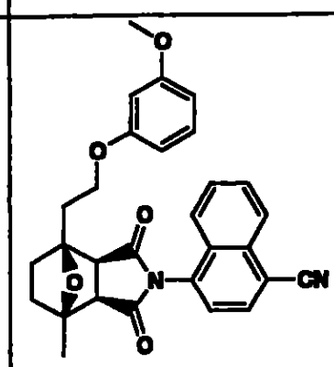
586		[3a*R*-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]octahydro-4-methyl-1,3-dioxo-5-(phenylmethoxy)-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.63 LC $[M + H]^+$= 594.26	491
587		[3a*S*-(3aα,4β,7β,7aα)]-4-[Octahydro-4-[2-[[6-(methoxymethyl)-2-(2-propynylthio)-4-pyrimidinyl]oxy]ethyl]-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	4.02 LC $[M + H]^+$= 567.31	491
588		[3a*R*-(3aα,4β,7β,7aα)]-5-[Octahydro-4-methyl-7-[2-(5-methyl-2H-1,2,3-benzotriazol-2-yl)ethyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile	3.37 LC $[M + H]^+$= 493.24	467 & 487

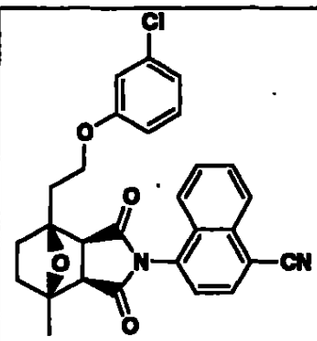
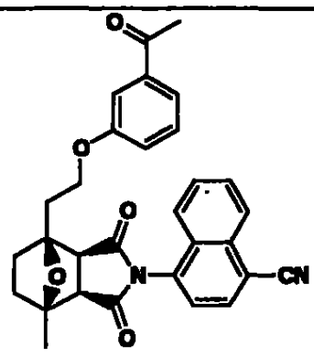
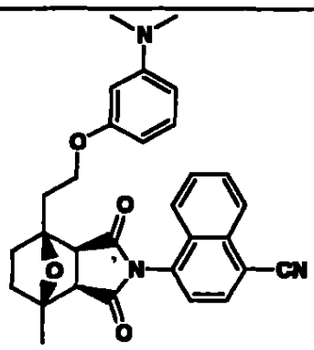
589		[3a*S*-(3aα,4β,7β,7aα)]-5-[Octahydro-4-methyl-7-[2-(5-methyl-2H-1,2,3-benzotriazol-2-yl)ethyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile	3.37 LC $[M+H]^+$= 493.24	467 & 487
590		[3a*R*-(3aα,4β,7β,7aα)]-5-[4-[2-(4-Cyanophenoxy)ethyl] octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile	3.14 LC $[M+H]^+$= 479.22	467 & 487
591		[3a*S*-(3aα,4β,7β,7aα)]-5-[4-[2-(4-Cyanophenoxy)ethyl] octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile	3.14 LC $[M+H]^+$= 479.22	467 & 487
592		[3a*R*-(3aα,4β,5β,7β,7aα)]-7-[7-[2-[(5-Chloro-1,2-benzisoxazol-3-yl)oxy]ethyl]octahydro-5-hydroxy-4-	3.38 LC $[M+H]^+$= 552.12	482

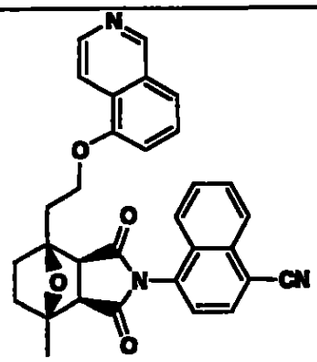
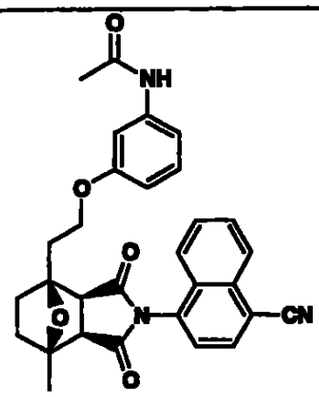
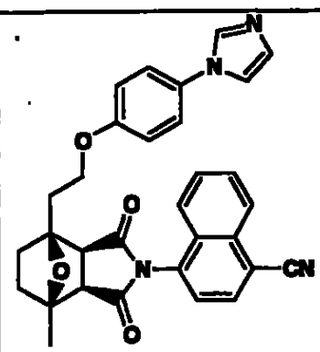
		methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2,1,3-benzothiadiazole-4-carbonitrile		
593		[3a*S*-(3aα,4β,5β,7β,7aα)]-7-[7-[2-[(5-Chloro-1,2-benzisoxazol-3-yl)oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2,1,3-benzothiadiazole-4-carbonitrile	3.39 LC $[M + H]^+$= 552.10	482
594		[3a*R*-(3aα,4β,5β,7β,7aα)]-7-[7-[2-(1,3-Benzodioxol-5-yloxy)ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2,1,3-benzothiadiazole-4-carbonitrile	3.00 LC $[M + H]^+$= 521.15	482

595		[3a*S*-(3aα,4β,5β,7β,7aα)]-7-[7-[2-(1,3-Benzodioxol-5-yloxy)ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2,1,3-benzothiadiazole-4-carbonitrile	2.99 LC $[M + H]^+$= 521.14	482
596		[3a*R*-(3aα,4β,7β,7aα)]-4-[4-[2-(4-Cyano-3-fluorophenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.76 LCMS $[M + H]^+$= 496.2	496
597		[3a*R*-(3aα,4β,7β,7aα)]-4-[Octahydro-4-methyl-7-[2-(3-methylphenoxy)ethyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	1.79 LCMS $[M + H]^+$= 467.2	496

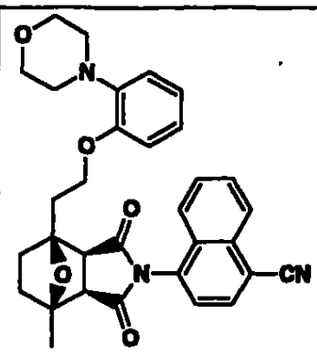
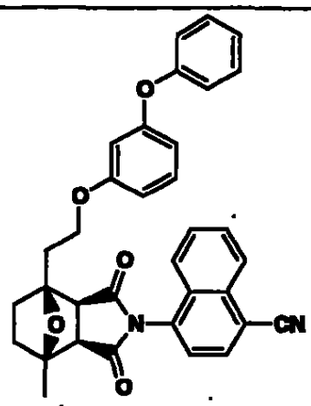
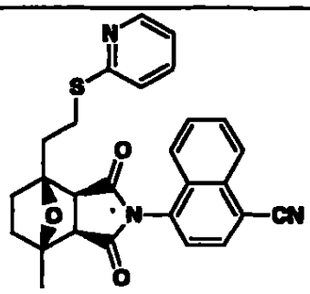
598		[3a*R*-(3aα,4β,7β,7aα)]-4-[4-[2-(3-Fluorophenoxy)ethyl] octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	2.01 LCMS $[M + H]^+$= 471.2	496
599		[3a*R*-(3aα,4β,7β,7aα)]-4-[4-[2-(4-Fluorophenoxy)ethyl] octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	1.98 LCMS $[M + H]^+$= 471.2	496
600		[3a*R*-(3aα,4β,7β,7aα)]-4-[4-[2-(3-Cyanophenoxy)ethyl] octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	1.88 LCMS $[M + H]^+$= 478.2	496

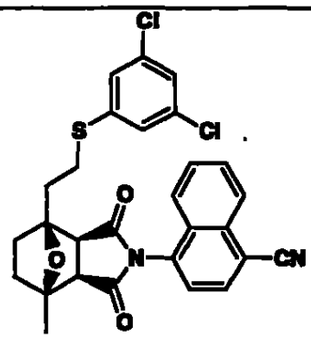
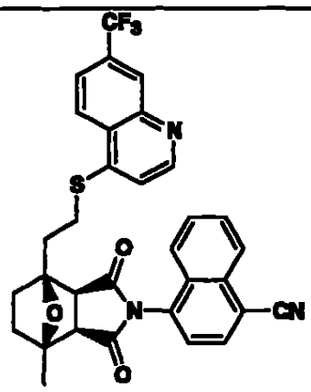
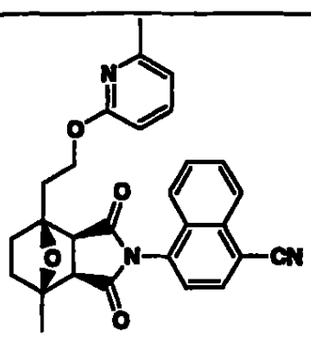
601		[3a*R*-(3aα,4β,7β,7aα)]-4-[4-[2-(2-Cyanophenoxy)ethyl] octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.42 LCMS $[M + H]^+$= 478.2	496
602		[3a*R*-(3aα,4β,7β,7aα)]-4-[Octahydro-4-[2-(2-methoxyphenoxy)ethyl]-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	1.83 LCMS $[M + H]^+$= 483.2	496
603		[3a*R*-(3aα,4β,7β,7aα)]-4-[Octahydro-4-[2-(3-methoxyphenoxy)ethyl]-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	2.14 LCMS $[M + H]^+$= 483.2	496

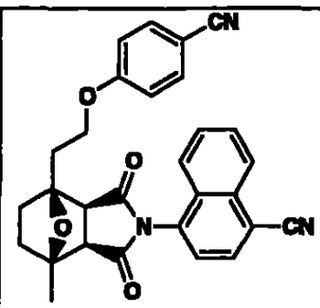
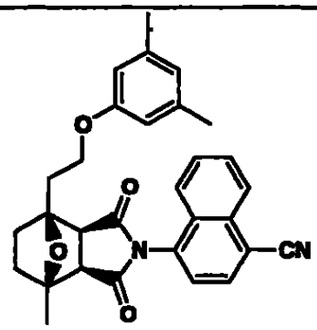
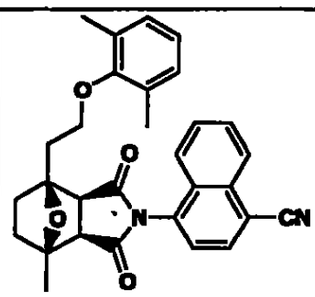
604		[3a*R*-(3aα,4β,7β,7aα)]-4-[4-[2-(3-Chlorophenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	2.09 LCMS $[M+H]^+$= 487.2	496
605		[3a*R*-(3aα,4β,7β,7aα)]-4-[4-[2-(3-Acetylphenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	2.20 LCMS $[M+H]^+$= 495.2	496
606		[3a*R*-(3aα,4β,7β,7aα)]-4-[4-[2-[3-(Dimethylamino)phenoxy]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	1.94 LCMS $[M+H]^+$= 496.2	496

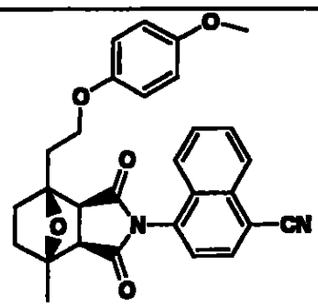
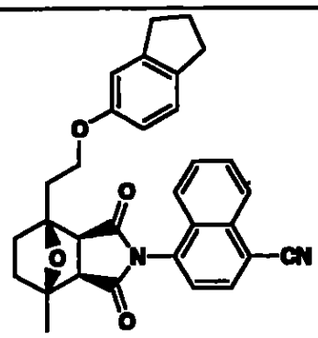
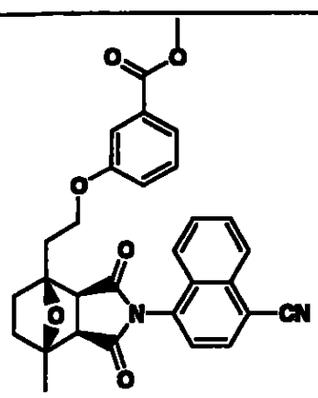
607		[3a*R*-(3aα,4β,7β,7aα)]-4-[Octahydro-4-[2-(5-isoquinolinyloxy)ethyl]-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	1.89 LCMS $[M + H]^+$= 504.2	496
608		*N*-[3-[2-[3a*R*-(3aα,4β,7β,7aα)]-2-(4-Cyano-1-naphthalenyl)octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindol-4-yl]ethoxy]phenylacetamide	1.97 LCMS $[M + H]^+$= 510.6	496
609		[3a*R*-(3aα,4β,7β,7aα)]-4-[Octahydro-4-[2-[4-(1H-imidazol-1-yl)phenoxy]ethyl]-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.81 LCMS $[M + H]^+$= 519.6	496

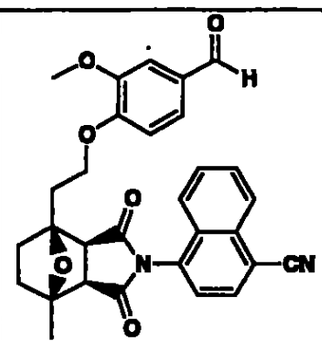
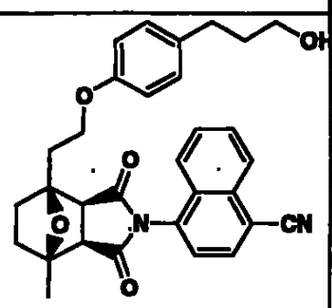
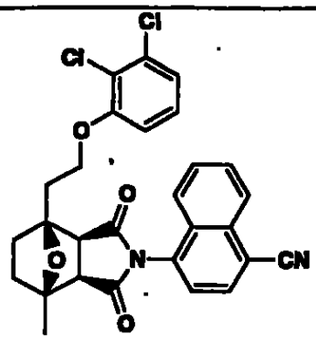
254

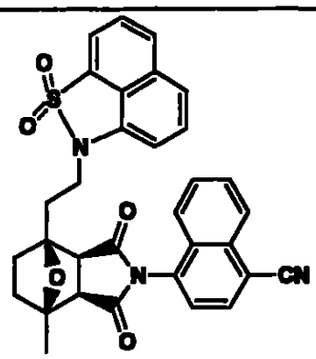
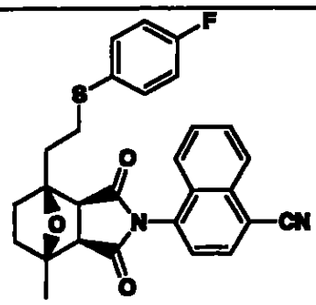
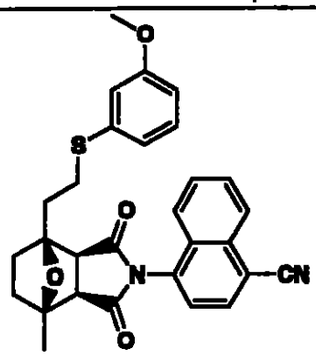
610		[3a*R*-(3aα,4β,7β,7aα)]-4-[Octahydro-4-methyl-7-[2-[2-(4-morpholinyl)phenoxy]ethyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	2.16 LCMS $[M + H]^+$= 538.2	496
611		[3a*R*-(3aα,4β,7β,7aα)]-4-[Octahydro-4-methyl-1,3-dioxo-7-[2-(3-phenoxyphenoxy)ethyl]-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	1.89 LCMS $[M + H]^+$= 545.2	496
612		[3a*R*-(3aα,4β,7β,7aα)]-4-[Octahydro-4-methyl-1,3-dioxo-7-[2-(2-pyridinylthio)ethyl]-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	1.91 LCMS $[M + H]^+$= 469.6	496

613		[3a*R*-(3aα,4β,7β,7aα)]-4-[4-[2-[(3,5-Dichlorophenyl)thio]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	1.53 LCMS $[M + H]^+$= 537.1	496
614		[3a*R*-(3aα,4β,7β,7aα)]-4-[Octahydro-4-methyl-1,3-dioxo-7-[2-[[7-(trifluoromethyl)-4-quinolinyl]thio]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	1.49 LCMS $[M + H]^+$= 588.2	496
615		[3a*R*-(3aα,4β,7β,7aα)]-4-[Octahydro-4-methyl-7-[2-[(6-methyl-2-pyridinyl)oxy]ethyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	1.79 LCMS $[M + H]^+$= 467.5	496

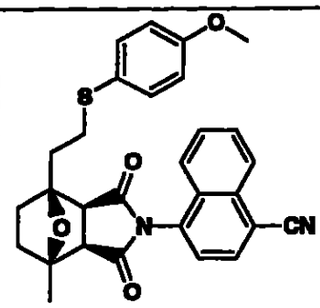
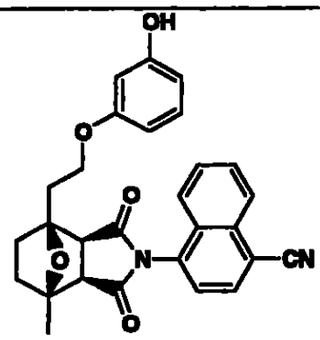
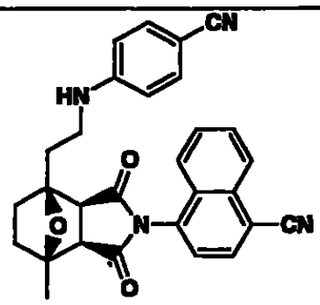
616		[3a*R*-(3aα,4β,7β,7aα)]-4-[4-[2-(4-Cyanophenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	1.98 LCMS $[M + H]^+$= 478.2	496
617		[3a*R*-(3aα,4β,7β,7aα)]-4-[4-[2-(3,5-Dimethylphenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	1.80 LCMS $[M + H]^+$= 481.2	496
618		[3a*R*-(3aα,4β,7β,7aα)]-4-[4-[2-(2,6-Dimethylphenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	1.88 LCMS $[M + H]^+$= 481.2	496

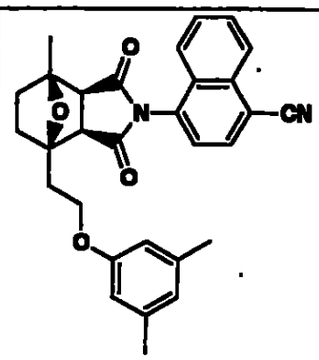
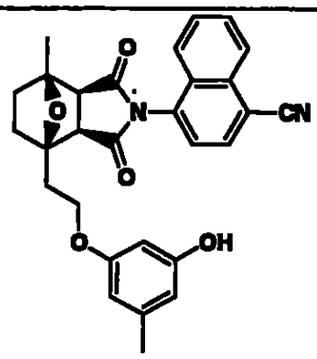
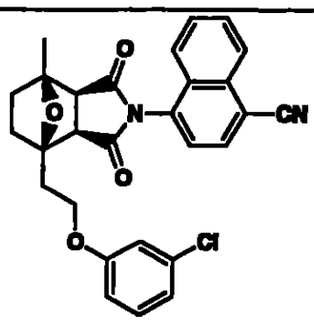
619		[3a*R*-(3aα,4β,7β,7aα)]-4-[Octahydro-4-[2-(4-methoxyphenoxy)ethyl]-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	1.50 LCMS $[M + H]^+$= 483.2	496
620		[3a*R*-(3aα,4β,7β,7aα)]-4-[4-[2-[(2,3-Dihydro-1H-inden-5-yl)oxy]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	2.14 LCMS $[M + H]^+$= 493.3	496
621		3-[2-[[3a*R*-(3aα,4β,7β,7aα)]-2-(4-Cyano-1-naphthalenyl)octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindol-4-yl]ethoxy]benzoic acid, methyl ester	3.99 LCMS $[M + H]^+$= 511.2	496

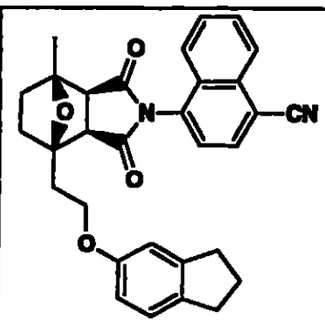
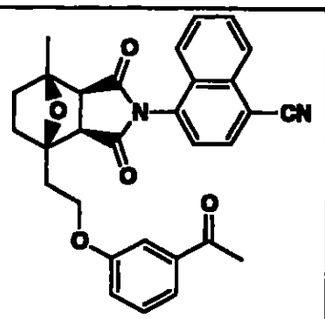
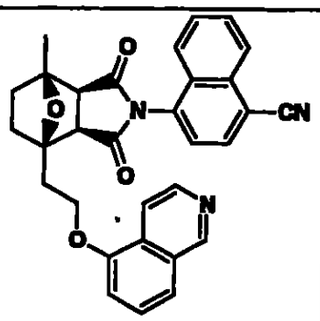
622		[3a*R*-(3aα,4β,7β,7aα)]-4-[4-[2-(4-Formyl-2-methoxyphenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	2.01 LCMS $[M + H]^+$= 511.2	496
623		[3a*R*-(3aα,4β,7β,7aα)]-4-[Octahydro-4-[2-[4-(3-hydroxypropyl)phenoxy]ethyl]-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	1.93 LCMS $[M + H]^+$= 511.3	496
624		[3a*R*-(3aα,4β,7β,7aα)]-4-[4-[2-(2,3-Dichlorophenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	1.79 LCMS $[M + H]^+$= 521.1	496

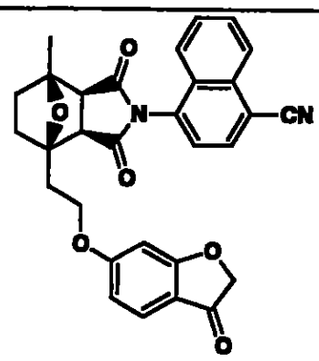
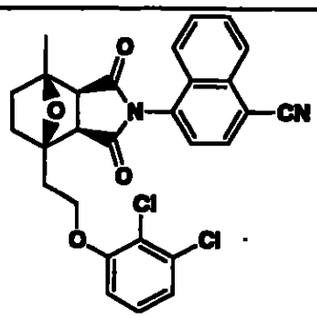
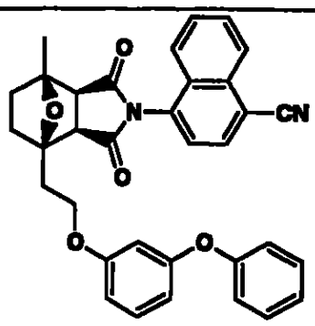
625		[3a*R*-(3aα,4β,7β,7aα)]-4-[4-[2-(1,1-Dioxido-2H-naphtho[1,8-cd]isothiazol-2-yl)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	1.69 LCMS $[M + H]^+$= 564.2	496
626		[3a*R*-(3aα,4β,7β,7aα)]-4-[4-[2-[(4-Fluorophenyl)thio]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	2.03 LCMS $[M + H]^+$= 487.2	496
627		[3a*R*-(3aα,4β,7β,7aα)]-4-[Octahydro-4-[2-[(3-methoxyphenyl)thio]ethyl]-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	2.02 LCMS $[M + H]^+$= 499.2	496

257

628		[3a*R*-(3aα,4β,7β,7aα)]-4-[Octahydro-4-[2-[(4-methoxyphenyl)thio]ethyl]-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	1.99 LCMS $[M + H]^+$= 499.2	496
629		[3a*R*-(3aα,4β,7β,7aα)]-4-[Octahydro-4-[2-(3-hydroxyphenoxy)ethyl]-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	2.27 LCMS $[M + H]^+$= 469.2	496
630		[3a*R*-(3aα,4β,7β,7aα)]-4-[4-[2-[(4-Cyanophenyl)amino]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.56 LCMS $[M + H]^+$= 477.2	496

631		[3a*S*-(3aα,4β,7β,7aα)]-4-[4-[2-(3,5-Dimethylphenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	4.10 LCMS $[M+H]^+$= 481.2	496
632		[3a*S*-(3aα,4β,7β,7aα)]-4-[Octahydro-4-[2-(3-hydroxy-5-methylphenoxy)ethyl]-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.56 LCMS $[M+H]^+$= 483.2	496
633		[3a*S*-(3aα,4β,7β,7aα)]-4-[4-[2-(3-Chlorophenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	4.03 LCMS $[M+H]^+$= 487.1	496

634		[3a*S*-(3aα,4β,7β,7aα)]-4-[4-[2-[(2,3-Dihydro-1H-inden-5-yl)oxy]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	4.15 LCMS $[M + H]^+$= 493.2	496
635		[3a*S*-(3aα,4β,7β,7aα)]-4-[4-[2-(3-Acetylphenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.65 LCMS $[M + H]^+$= 495.2	496
636		[3a*S*-(3aα,4β,7β,7aα)]-4-[Octahydro-4-[2-(5-isoquinolinyloxy)ethyl]-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, trifluoroacetate (1:1)	3.67 LCMS $[M + H]^+$= 504.2	496

637		[3a*S*-(3aα,4β,7β,7aα)]-4-[4-[2-[(2,3-Dihydro-3-oxo-6-benzofuranyl)oxy]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	2.90 LCMS $[M + H]^+$= 509.2	496
638		[3a*S*-(3aα,4β,7β,7aα)]-4-[4-[2-(2,3-Dichlorophenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	2.80 LCMS $[M + H]^+$= 521.1	496
639		[3a*S*-(3aα,4β,7β,7aα)]-4-[Octahydro-4-methyl-1,3-dioxo-7-[2-(3-phenoxyphenoxy)ethyl]-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.54 LCMS $[M + H]^+$= 545.2	496

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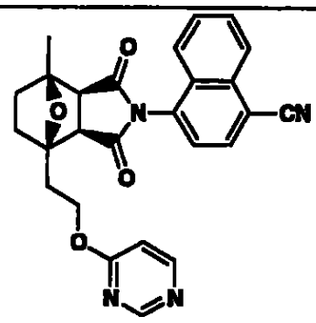
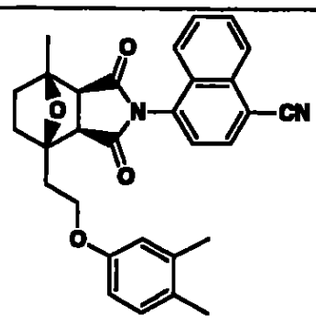
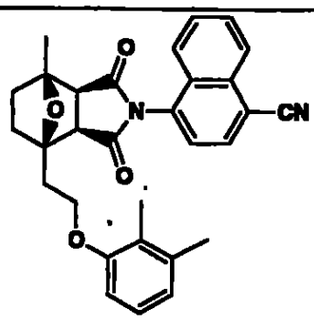
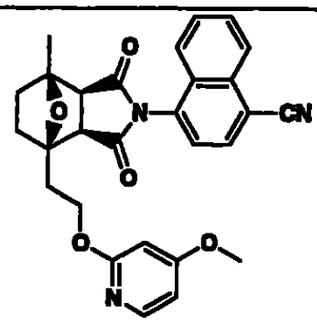
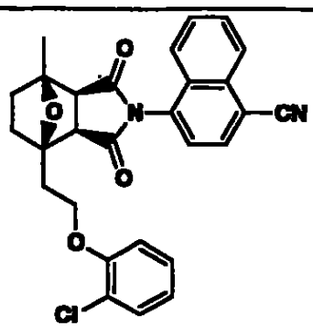
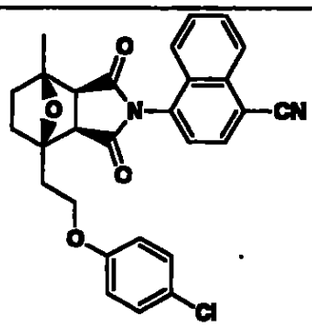
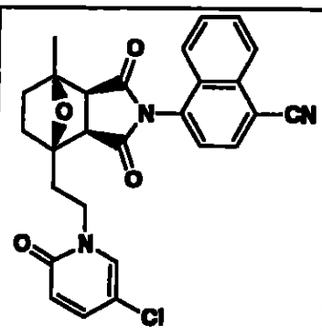
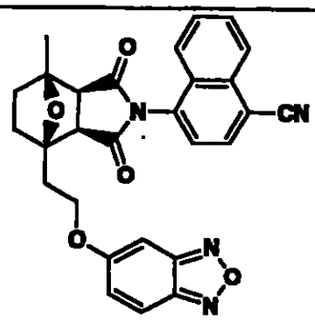
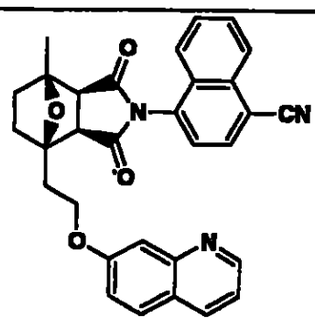
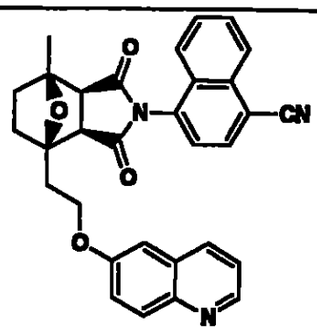
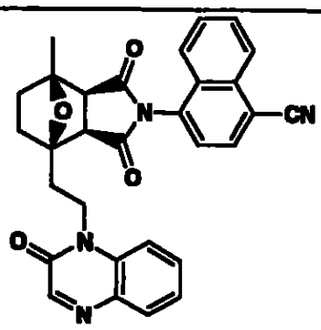
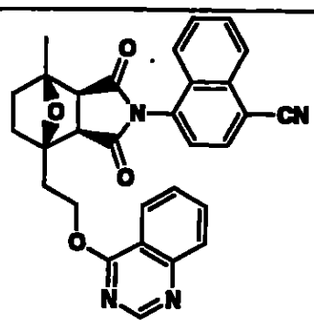
640		[3a*S*-(3aα,4β,7β,7aα)]-4-[Octahydro-4-methyl-1,3-dioxo-7-[2-(4-pyrimidinyloxy)ethyl]-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	4.13 LCMS $[M + H]^+$= 455.2	496
641		[3a*S*-(3aα,4β,7β,7aα)]-4-[4-[2-(3,4-Dimethylphenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	4.19 LCMS $[M + H]^+$= 481.2	496
642		[3a*S*-(3aα,4β,7β,7aα)]-4-[4-[2-(2,3-Dimethylphenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	2.80 LCMS $[M + H]^+$= 481.2	496

643		[3a*S*-(3aα,4β,7β,7aα)]-4-[Octahydro-4-[2-[(4-methoxy-2-pyridinyl)oxy]ethyl]-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	2.72 LCMS $[M + H]^+$= 484.2	496
644		[3a*S*-(3aα,4β,7β,7aα)]-4-[4-[2-(2-Chlorophenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	2.63 LCMS $[M + H]^+$= 487.1	496
645		[3a*S*-(3aα,4β,7β,7aα)]-4-[4-[2-(4-Chlorophenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	4.07 LCMS $[M + H]^+$= 487.1	496

646		[3a*S*-(3aα,4β,7β,7aα)]-4-[4-[2-(5-Chloro-2-oxo-1(2H)-pyridinyl)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	4.13 LCMS [M + H]$^+$= 488.1	496
647		[3a*S*-(3aα,4β,7β,7aα)]-4-[4-[2-(2,1,3-Benzoxadiazol-5-yloxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.15 LCMS [M + H]$^+$= 495.2	496
648		[3a*S*-(3aα,4β,7β,7aα)]-4-[Octahydro-4-methyl-1,3-dioxo-7-[2-(7-quinolinyloxy)ethyl]-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, trifluoroacetate (1:1)	3.93 LCMS [M + H]$^+$= 504.2	496

649		[3a*S*-(3aα,4β,7β,7aα)]-4-[Octahydro-4-methyl-1,3-dioxo-7-[2-(6-quinolinyloxy)ethyl]-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, trifluoroacetate (1:1)	4.01 LCMS $[M + H]^+$= 504.2	496
650		[3a*S*-(3aα,4β,7β,7aα)]-4-[Octahydro-4-methyl-1,3-dioxo-7-[2-(2-oxo-1(2H)-quinoxalinyl)ethyl]-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, trifluoroacetate (1:1)	3.38 LCMS $[M + H]^+$= 505.2	496
651		[3a*S*-(3aα,4β,7β,7aα)]-4-[Octahydro-4-methyl-1,3-dioxo-7-[2-(4-quinazolinyloxy)ethyl]-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, trifluoroacetate (1:1)	3.39 LCMS $[M + H]^+$= 505.2	496

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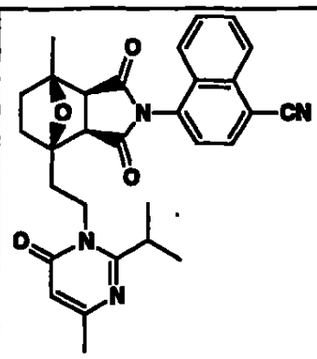
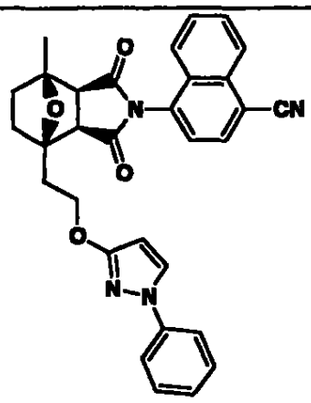
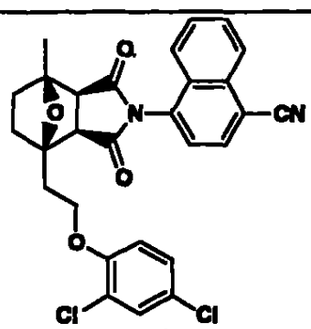
652		[3a*S*-(3aα,4β,7β,7aα)]-4-[Octahydro-4-methyl-7-[2-[4-methyl-2-(1-methylethyl)-6-oxo-1(6H)-pyrimidinyl]ethyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.72 LCMS $[M + H]^+$= 511.3	496
653		[3a*S*-(3aα,4β,7β,7aα)]-4-[Octahydro-4-methyl-1,3-dioxo-7-[2-[(1-phenyl-1H-pyrazol-3-yl)oxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, trifluoroacetate (1:1)	3.48 LCMS $[M]^+$= 519.2	496
654		[3a*S*-(3aα,4β,7β,7aα)]-4-[4-[2-(2,4-Dichlorophenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonit	2.85 LCMS $[M + H]^+$= 521.1	496

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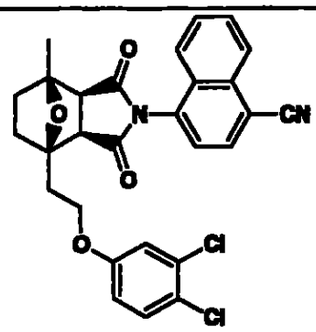
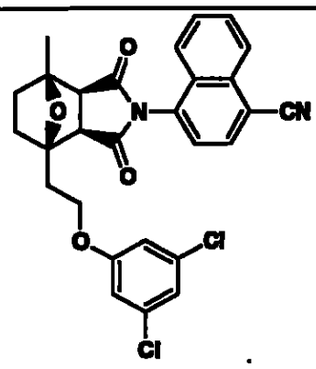
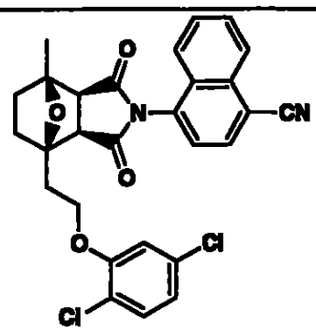
655		[3a*S*-(3aα,4β,7β,7aα)]-4-[4-[2-(3,4-Dichlorophenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	2.86 LCMS $[M+H]^+$= 521.1	496
656		[3a*S*-(3aα,4β,7β,7aα)]-4-[4-[2-(3,5-Dichlorophenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.47 LCMS $[M+H]^+$= 521.1	496
657		[3a*S*-(3aα,4β,7β,7aα)]-4-[4-[2-(2,5-Dichlorophenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.33 LCMS $[M+H]^+$= 521.1	496

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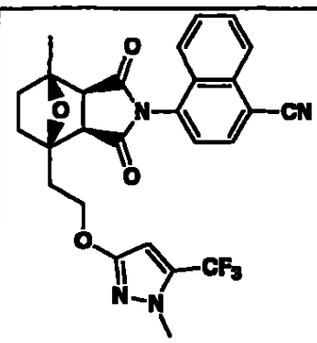
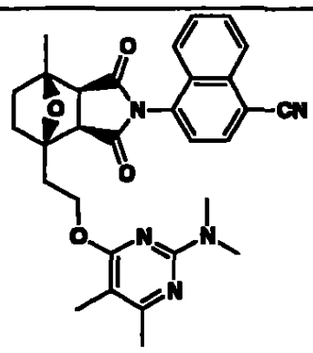
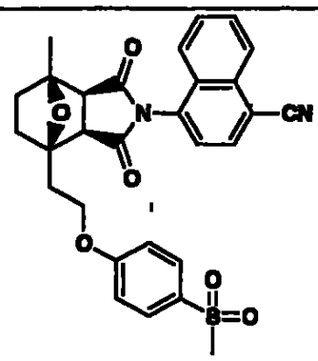
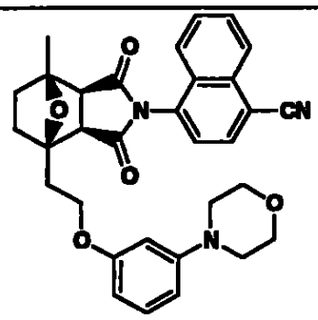
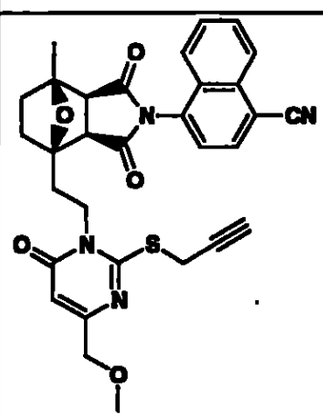
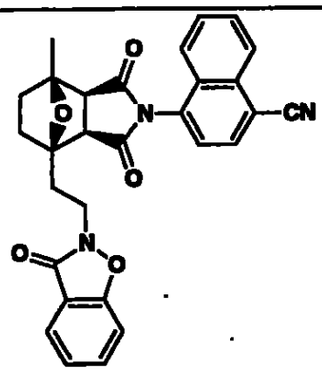
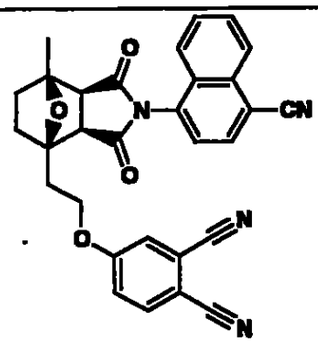
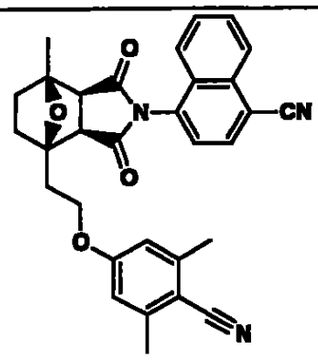
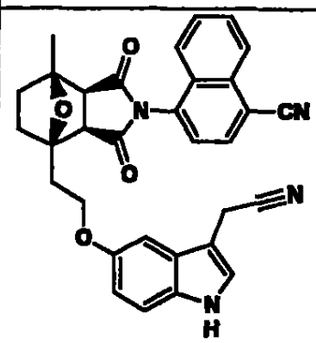
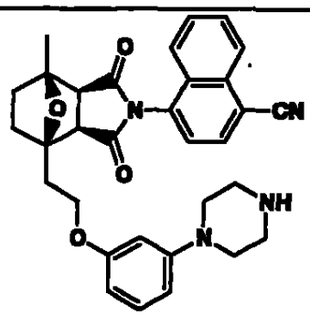
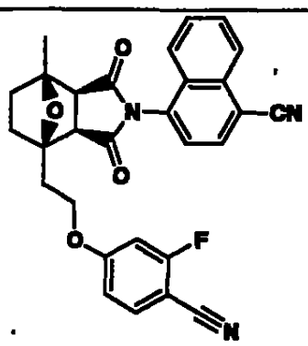
658		[3a*S*-(3aα,4β,7β,7aα)]-4-[Octahydro-4-methyl-7-[2-[[1-methyl-5-(trifluoromethyl)-1H-pyrazol-3-yl]oxy]ethyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, trifluoroacetate (1:1)	3.87 LCMS $[M + H]^+$= 525.2	496
659		[3a*S*-(3aα,4β,7β,7aα)]-4-[4-[2-[[2-(Dimethylamino)-5,6-dimethyl-4-pyrimidinyl]oxy]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, trifluoroacetate (1:1)	2.71 LCMS $[M + H]^+$= 526.2	496

660		[3a*S*-(3aα,4β,7β,7aα)]-4-[Octahydro-4-methyl-7-[2-[4-(methylsulfonyl)phenoxy]ethyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	2.91 LCMS $[M + H]^+$= 531.2	496
661		[3a*S*-(3aα,4β,7β,7aα)]-4-[Octahydro-4-methyl-7-[2-[3-(4-morpholinyl)phenoxy]ethyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, trifluoroacetate (1:1)	3.78 LCMS $[M + H]^+$= 538.2	496
662		[3a*S*-(3aα,4β,7β,7aα)]-4-[Octahydro-4-[2-[4-(methoxymethyl)-6-oxo-2-(2-propynylthio)-1(6H)-pyrimidinyl]ethyl]-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-	4.18 LCMS $[M + H]^+$= 569.2	496

		naphthalenecarbonitrile, trifluoroacetate (1:1)		
663		[3a*S*-(3aα,4β,7β,7aα)]-4-[Octahydro-4-methyl-1,3-dioxo-7-[2-(3-oxo-1,2-benzisoxazol-2(3H)-yl)ethyl]-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	4.18 LCMS $[M + H]^+$= 494.2	496
664		[3a*S*-(3aα,4β,7β,7aα)]-4-[2-[2-(4-Cyano-1-naphthalenyl)octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindol-4-yl]ethoxy]-1,2-benzenedicarbonitrile	4.30 LCMS $[M + H]^+$= 503.1	496
665		[3a*S*-(3aα,4β,7β,7aα)]-4-[4-[2-(4-Cyano-3,5-dimethylphenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-	4.13 LCMS $[M + H]^+$= 506.2	496

		naphthalenecarbonitrile		
666		[3a*S*-(3aα,4β,7β,7aα)]-5-[2-[2-(4-Cyano-1-naphthalenyl)octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindol-4-yl]ethoxy]-1H-indole-3-acetonitrile, trifluoroacetate (1:1)	3.36 LCMS $[M+H]^+$= 531.2	496
667		[3a*S*-(3aα,4β,7β,7aα)]-4-[Octahydro-4-methyl-1,3-dioxo-7-[2-[3-(1-piperazinyl)phenoxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, trifluoroacetate (1:1)	3.81 LCMS $[M+H]^+$= 537.2	496
668		[3a*S*-(3aα,4β,7β,7aα)]-4-[4-[2-(4-Cyano-3-fluorophenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	2.89 LCMS $[M+H]^+$= 496.2	496

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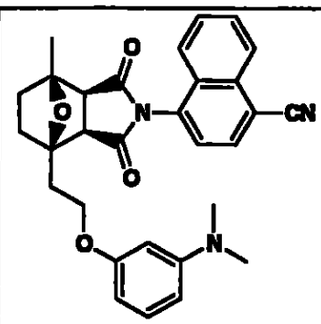
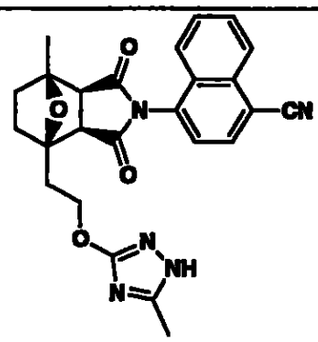
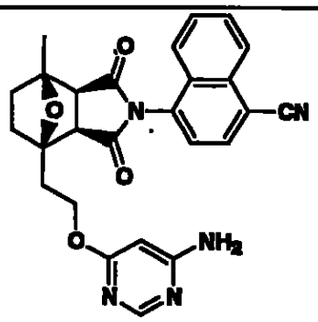
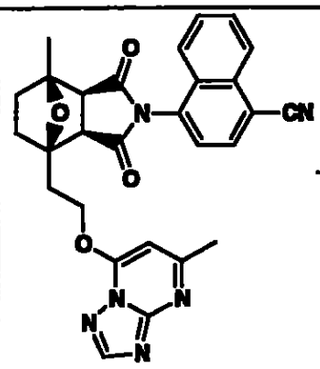
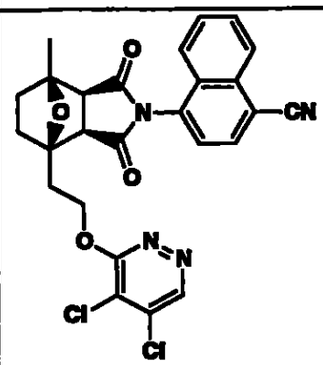
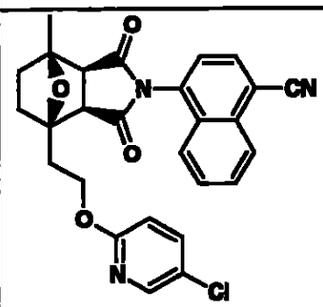
669		[3a*S*-(3aα,4β,7β,7aα)]-4-[4-[2-[3-(Dimethylamino)phenoxy]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, trifluoroacetate (1:1)	3.37 LCMS $[M + H]^+$= 496.2	496
670		[3a*S*-(3aα,4β,7β,7aα)]-4-[Octahydro-4-methyl-7-[2-[(5-methyl-1H-1,2,4-triazol-3-yl)oxy]ethyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, trifluoroacetate (1:1)	3.26 LCMS $[M + H]^+$= 458.2	496
671		[3a*S*-(3aα,4β,7β,7aα)]-4-[4-[2-[(6-Amino-4-pyrimidinyl)oxy]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonit	2.97 LCMS $[M + H]^+$= 470.2	496

		rile, trifluoroacetate (1:1)		
672		[3aS-(3aα,4β,7β,7aα)]-4-[Octahydro-4-methyl-7-[2-[(5-methyl[1,2,4]triazolo[1,5-a]pyrimidin-7-yl)oxy]ethyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, trifluoroacetate (1:1)	3.45 LCMS $[M + H]^+$= 509.2	496
673		[3aS-(3aα,4β,7β,7aα)]-4-[4-[2-[(4,5-Dichloro-3-pyridazinyl)oxy]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.79 LCMS $[M + H]^+$= 528.1	496
674		[3aS-(3aα,4β,7β,7aα)]-4-[4-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonit	3.86 LCMS $[M + H]^+$= 488.4	496

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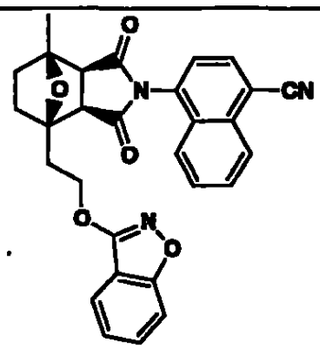
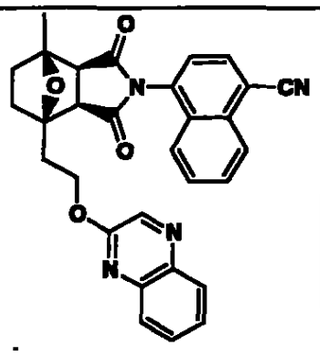
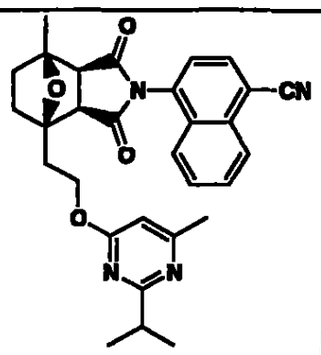
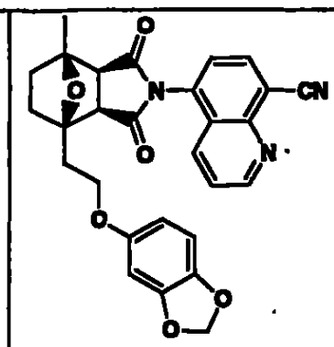
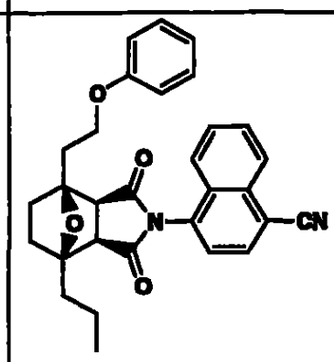
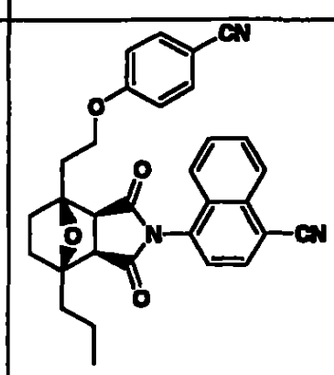
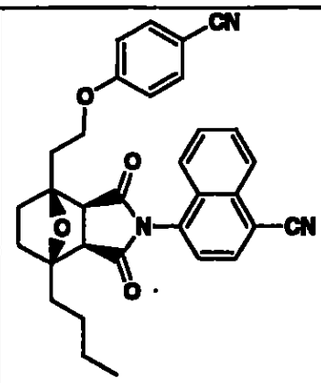
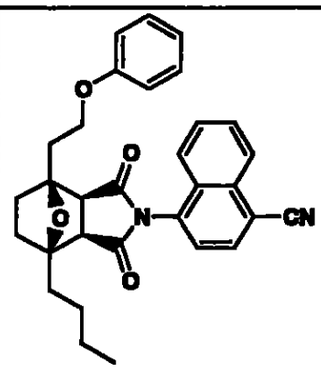
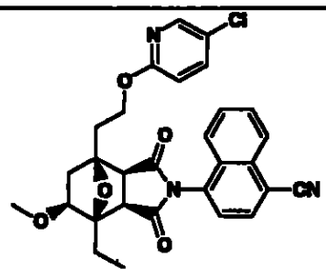
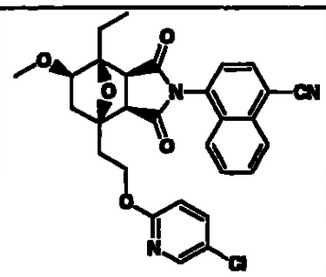
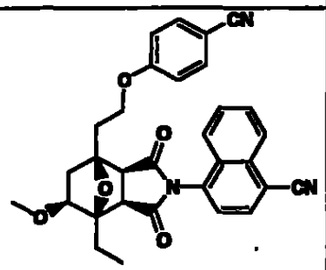
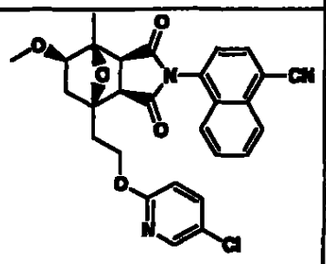
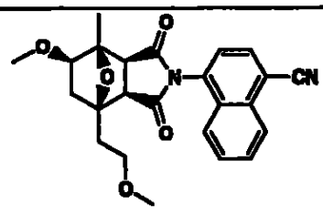
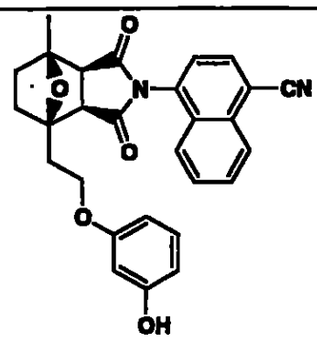
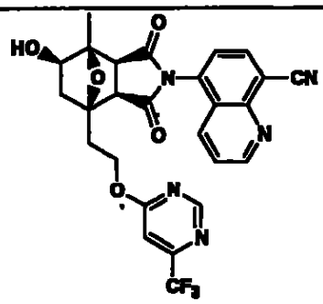
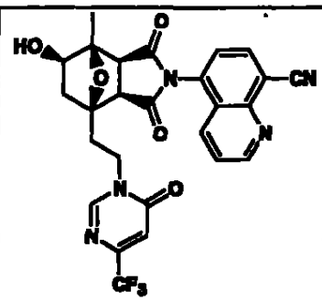
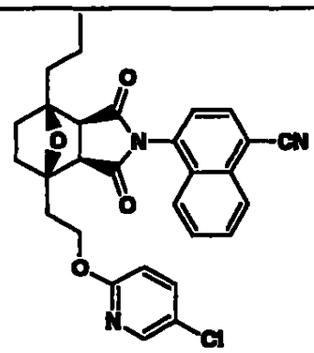
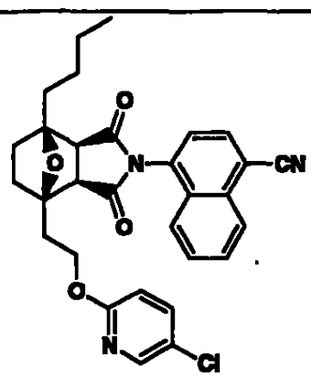
675		[3a*S*-(3aα,4β,7β,7aα)]-4-[4-[2-(1,2-Benzisoxazol-3-yloxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.78 LCMS [M + H]⁺= 494.41	496
676		[3a*S*-(3aα,4β,7β,7aα)]-4-[Octahydro-4-methyl-1,3-dioxo-7-[2-(2-quinoxalinyloxy)ethyl]-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.83 LCMS [M + H]⁺= 505.43	496
677		[3a*S*-(3aα,4β,7β,7aα)]-4-[Octahydro-4-methyl-7-[2-[[6-methyl-2-(1-methylethyl)-4-pyrimidinyl]oxy]ethyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.52 LCMS [M + H]⁺= 511.49	496

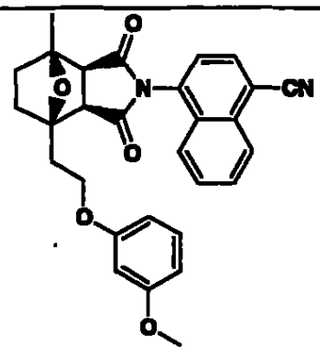
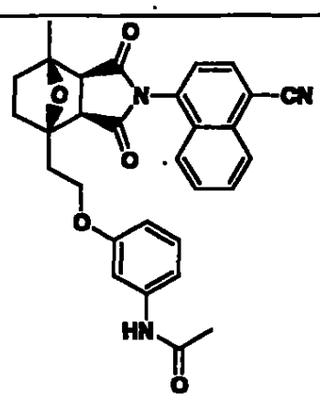
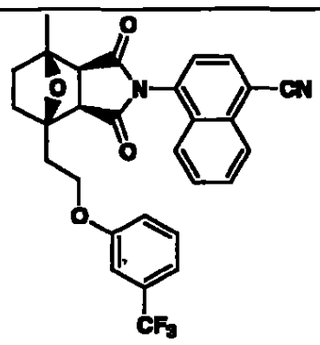
678		[3a*S*-(3aα,4β,7β,7aα)]-5-[4-[2-(1,3-Benzodioxol-5-yloxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile	3.327 LC [M + H]⁺= 498.24	467 & 487
679		[3a*R*-(3aα,4β,7β,7aα)]-4-[Octahydro-1,3-dioxo-4-(2-phenoxyethyl)-7-propyl-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	7.77 & 8.01 atropisomers LC [M + H]⁺= 481.4	501
680		[3a*R*-(3aα,4β,7β,7aα)]-4-[4-[2-(4-Cyanophenoxy)ethyl]octahydro-1,3-dioxo-7-propyl-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	7.42 & 7.68 atropisomers LC [M + H]⁺= 506.38	501

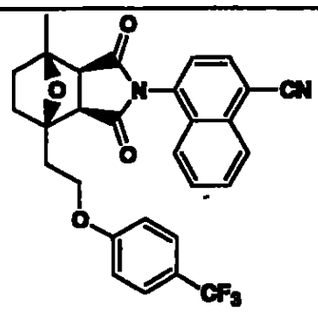
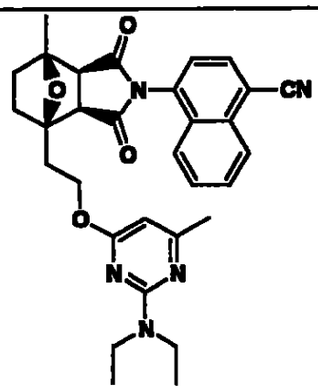
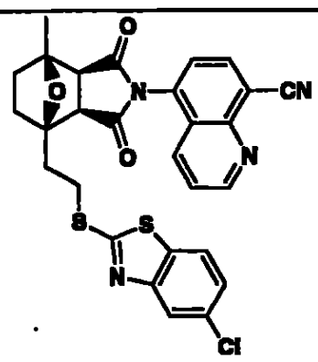
681		[3a*R*-(3aα,4β,7β,7aα)]-4-[4-Butyl-7-[2-(4-cyanophenoxy)ethyl] octahydro-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	7.69 & 7.92 atropisomers LC $[M + H]^+$= 520.38	502
682		[3a*R*-(3aα,4β,7β,7aα)]-4-[4-Butyloctahydro-1,3-dioxo-7-(2-phenoxyethyl)-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	8.02 & 8.23 atropisomers LC $[M + H]^+$= 495.33	502
683		[3a*R*-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]-4-ethyloctahydro-5-methoxy-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, trifluoroacetate (1:1)	7.31 & 7.55 atropisomers LC $[M + H]^+$= 532.3	504

684		[3a*S*-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]-4-ethyloctahydro-5-methoxy-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, trifluoroacetate (1:1)	7.31 & 7.55 atropisomers LC $[M + H]^+$= 532.3	504
685		[3a*R*-(3aα,4β,5β,7β,7aα)]-4-[7-[2-(4-Cyanophenoxy)ethyl]-4-ethyloctahydro-5-methoxy-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	6.84 & 7.10 atropisomers LC $[M + H]^+$= 522.33	504
686		[3a*S*-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]octahydro-5-methoxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.37 & 3.52 atropisomers LC $[M + H]^+$= 518.16	491

687		[3a*S*-(3aα,4β,5β,7β,7aα)]-4-[Octahydro-5-methoxy-7-(2-methoxyethyl)-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	2.57 & 2.75 atropisomers LC $[M+H]^+$= 421.18	491
688		[3a*S*-(3aα,4β,7β,7aα)]-4-[Octahydro-4-[2-(3-hydroxyphenoxy)ethyl]-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.38 LCMS $[M+H]^+$= 469.38	496
689		[3a*S*-(3aα,4β,5β,7β,7aα)]-5-[Octahydro-5-hydroxy-4-methyl-1,3-dioxo-7-[2-[[6-(trifluoromethyl)-4-pyrimidinyl]oxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile	2.833 LC $[M+H]^+$= 540.17	485, 486, 487 & 488

690		[3a*S*-(3aα,4β,5β,7β,7aα)]-5-[Octahydro-5-hydroxy-4-methyl-1,3-dioxo-7-[2-[6-oxo-4-(trifluoromethyl)-1(6H)-pyrimidinyl]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile	2.59 LC $[M + H]^+$= 540.16	485, 486, 487 & 488
691		[3a*S*-(3aα,4β,7β,7aα)]-4-[4-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]octahydro-1,3-dioxo-7-propyl-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	7.91 & 8.15 atropisomers LC $[M + H]^+$= 516.25	501
692		[3a*S*-(3aα,4β,7β,7aα)]-4-[4-Butyl-7-[2-[(5-chloro-2-pyridinyl)oxy]ethyl]octahydro-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	8.18 & 8.39 atropisomers LC $[M + H]^+$= 530.28	502

693		[3a*S*-(3aα,4β,7β,7aα)]-4-[Octahydro-4-[2-(3-methoxyphenoxy)ethyl]-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.97 LCMS $[M + H]^+$= 483.1	496
694		*N*-[3-[2-[3a*S*-(3aα,4β,7β,7aα)]-2-(4-Cyano-1-naphthalenyl)octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindol-4-yl]ethoxy]phenylacetamide	3.42 LCMS $[M + H]^+$= 510.1	496
695		[3a*S*-(3aα,4β,7β,7aα)]-4-[Octahydro-4-methyl-1,3-dioxo-7-[2-[3-(trifluoromethyl)phenoxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.83 LCMS $[M + H]^+$= 521.1	496

696		[3a*S*-(3aα,4β,7β,7aα)]-4-[Octahydro-4-methyl-1,3-dioxo-7-[2-[4-(trifluoromethyl)phenoxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.86 LCMS $[M+H]^+$= 521.2	496
697		[3a*S*-(3aα,4β,7β,7aα)]-4-[4-[2-[[2-(Diethylamino)-6-methyl-4-pyrimidinyl]oxy]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.63 LCMS $[M+H]^+$= 540.2	496
698		[3a*S*-(3aα,4β,7β,7aα)]-4-[4-[2-[(5-Chloro-2-benzothiazolyl)thio]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonit	4.15 LCMS $[M]^+$= 560.0	496

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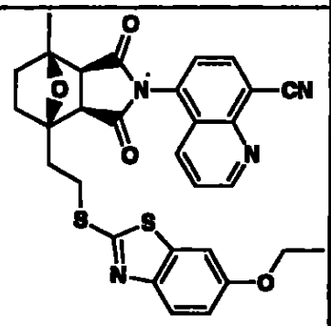
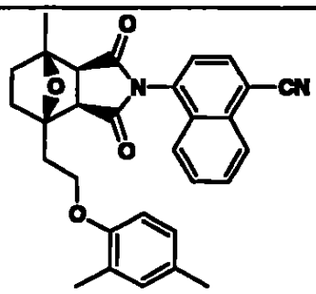
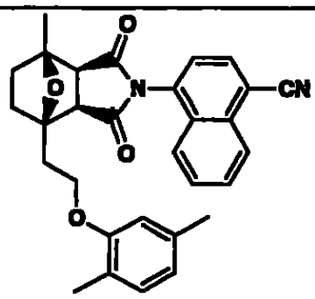
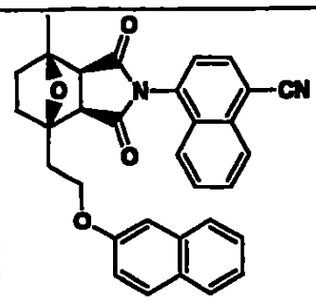
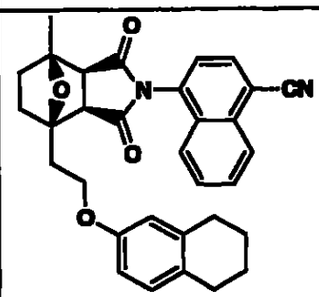
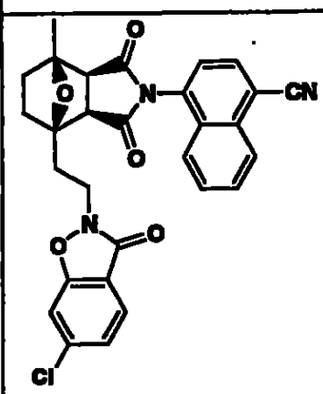
699		[3a*S*-(3aα,4β,7β,7aα)]-4-[4-[2-[(6-Ethoxy-2-benzothiazolyl)thio]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	4.15 LCMS $[M + H]^+$= 570.1	496
700		[3a*S*-(3aα,4β,7β,7aα)]-4-[4-[2-(2,4-Dimethylphenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.71 LCMS $[M + H]^+$= 481.2	496
701		[3a*S*-(3aα,4β,7β,7aα)]-4-[4-[2-(2,5-Dimethylphenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.79 LCMS $[M + H]^+$= 481.2	496

702		[3a*S*-(3aα,4β,7β,7aα)]-4-[Octahydro-4-methyl-7-[2-(2-naphthalenyloxy)ethyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	2.66 LCMS $[M + H]^+$= 503.2	496
703		[3a*S*-(3aα,4β,7β,7aα)]-4-[Octahydro-4-methyl-1,3-dioxo-7-[2-[(5,6,7,8-tetrahydro-2-naphthalenyl)oxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	2.72 LCMS $[M + H]^+$= 507.2	496
704		[3a*S*-(3aα,4β,7β,7aα)]-4-[4-[2-(6-Chloro-3-oxo-1,2-benzisoxazol-2(3H)-yl)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonit	2.71 LCMS $[M + H]^+$= 528.1	496

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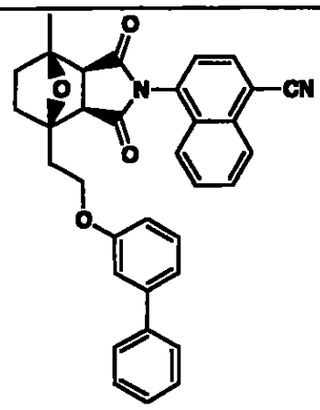
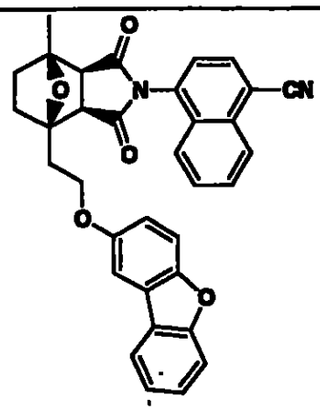
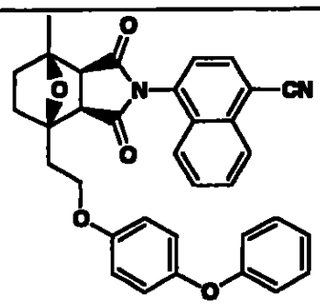
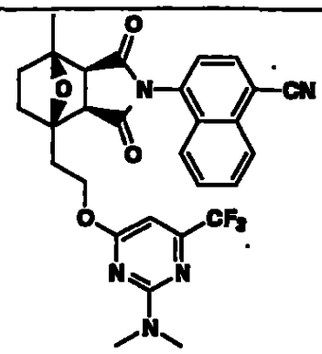
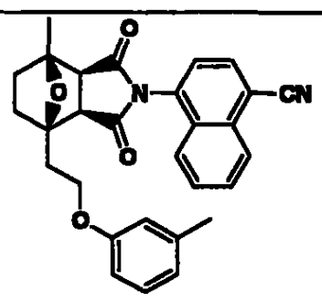
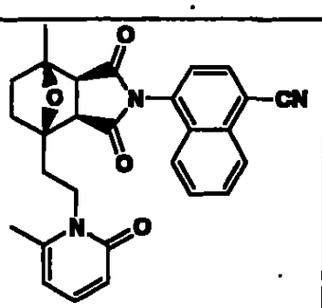
705		[3a*S*-(3aα,4β,7β,7aα)]-4-[4-[2-([1,1'-Biphenyl]-3-yloxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.03 LCMS [M + H]$^+$= 529.2	496
706		[3a*S*-(3aα,4β,7β,7aα)]-4-[4-[2-(2-Dibenzofuranyloxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.51 LCMS [M + H]$^+$= 543.2	496
707		[3a*S*-(3aα,4β,7β,7aα)]-4-[Octahydro-4-methyl-1,3-dioxo-7-[2-(4-phenoxyphenoxy)ethyl]-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.73 LCMS [M + H]$^+$= 545.2	496

708		[3aS-(3aα,4β,7β,7aα)]-4-[4-[2-[[2-(Dimethylamino)-6-(trifluoromethyl)-4-pyrimidinyl]oxy]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, trifluoroacetate (1:1)	4.15 LCMS $[M + H]^+$= 566.2	496
709		[3aS-(3aα,4β,7β,7aα)]-4-[Octahydro-4-methyl-7-[2-(3-methylphenoxy)ethyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.17 LCMS $[M + H]^+$= 466.5	496
710		[3aS-(3aα,4β,7β,7aα)]-4-[Octahydro-4-methyl-7-[2-(6-methyl-2-oxo-1(2H)-pyridinyl)ethyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonit	3.41 LCMS $[M + H]^+$= 468.2	496

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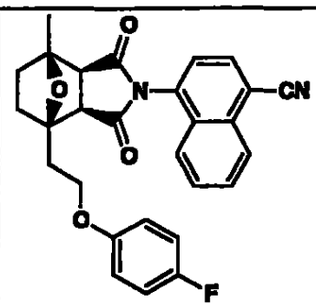
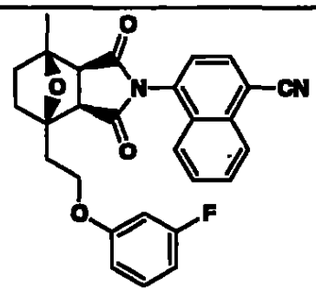
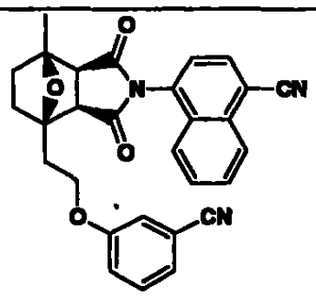
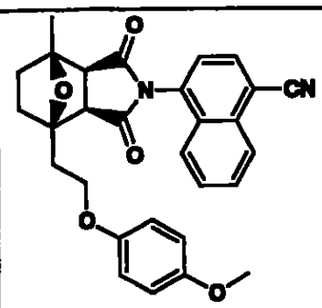
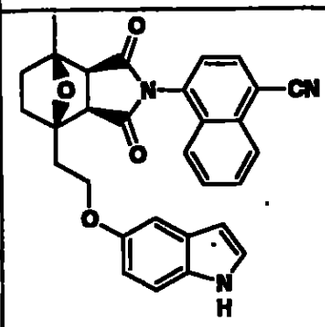
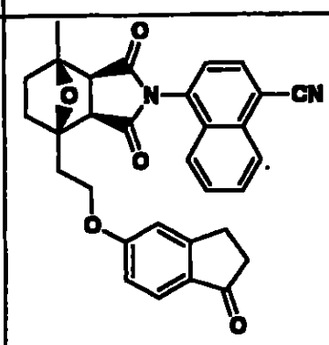
711		[3a*S*-(3aα,4β,7β,7aα)]-4-[4-[2-(4-Fluorophenoxy)ethyl] octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	4.10 LCMS $[M + H]^+$= 471.2	496
712		[3a*S*-(3aα,4β,7β,7aα)]-4-[4-[2-(3-Fluorophenoxy)ethyl] octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.56 LCMS $[M + H]^+$= 471.2	496
713		[3a*S*-(3aα,4β,7β,7aα)]-4-[4-[2-(3-Cyanophenoxy)ethyl] octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	4.28 LCMS $[M + H]^+$= 478.2	496

714		[3a*S*-(3aα,4β,7β,7aα)]-4-[Octahydro-4-[2-(4-methoxyphenoxy)ethyl]-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.58 LCMS $[M + H]^+$= 483.2	496
715		[3a*S*-(3aα,4β,7β,7aα)]-4-[Octahydro-4-[2-(1H-indol-5-yloxy)ethyl]-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.40 LCMS $[M + H]^+$= 492.2	496
716		[3a*S*-(3aα,4β,7β,7aα)]-4-[4-[2-[(2,3-Dihydro-1-oxo-1H-inden-5-yl)oxy]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.20 LCMS $[M + H]^+$= 507.2	496

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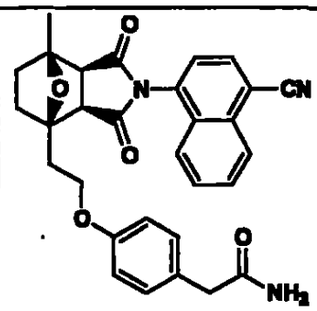
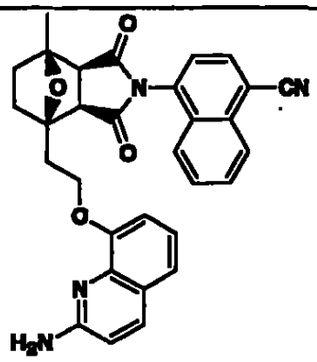
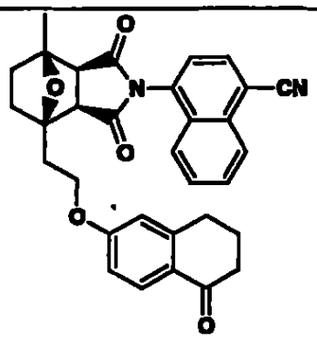
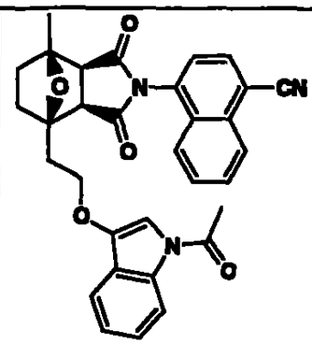
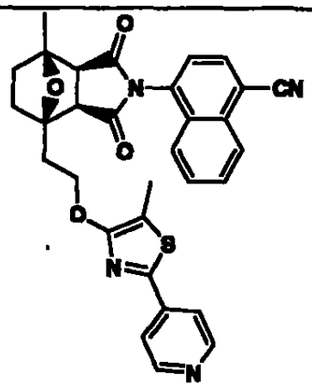
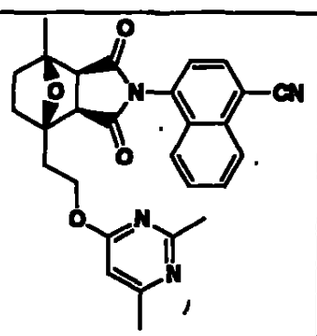
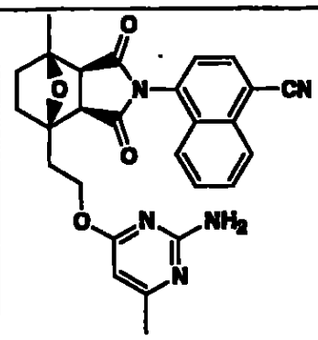
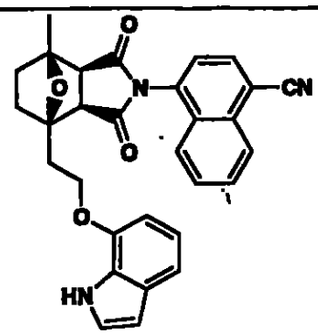
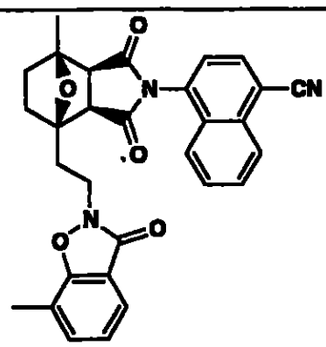
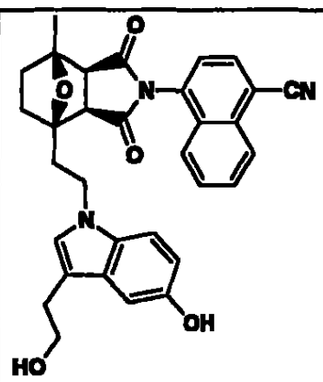
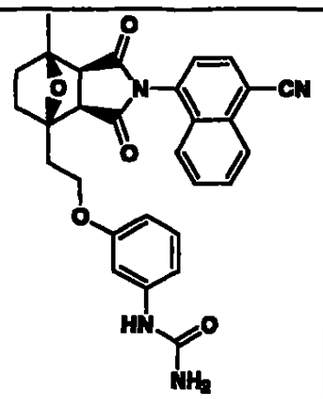
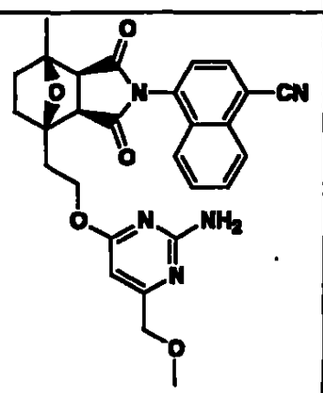
717		[3a*S*-(3aα,4β,7β,7aα)]-4-[2-[2-(4-Cyano-1-naphthalenyl)octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindol-4-yl]ethoxy]benzeneacetamide	3.26 LCMS $[M + H]^+$= 510.2	496
718		[3a*S*-(3aα,4β,7β,7aα)]-4-[4-[2-[(2-Amino-8-quinolinyl)oxy]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, trifluoroacetate (1:1)	2.77 LCMS $[M + H]^+$= 519.2	496
719		[3a*S*-(3aα,4β,7β,7aα)]-4-[Octahydro-4-methyl-1,3-dioxo-7-[2-[(5,6,7,8-tetrahydro-5-oxo-2-naphthalenyl)oxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	2.88 LCMS $[M + H]^+$= 521.2	496

720		[3a*S*-(3aα,4β,7β,7aα)]-1-Acetyl-3-[2-[2-(4-cyano-1-naphthalenyl)octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindol-4-yl]ethoxy]-1H-indole	4.03 LCMS $[M + H]^+$= 534.2	496
721		[3a*S*-(3aα,4β,7β,7aα)]-4-[Octahydro-4-methyl-7-[2-[[5-methyl-2-(4-pyridinyl)-4-thiazolyl]oxy]ethyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile, trifluoroacetate (1:1)	4.02 LCMS $[M + H]^+$= 551.2	496
722		[3a*S*-(3aα,4β,7β,7aα)]-4-[4-[2-[(2,6-Dimethyl-4-pyrimidinyl)oxy]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.74 LCMS $[M + H]^+$= 483.2	496

273

723		[3a*S*-(3aα,4β,7β,7aα)]-4-[4-[2-[(2-Amino-6-methyl-4-pyrimidinyl)oxy]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.71 LCMS $[M + H]^+$= 484.2	496
724		[3a*S*-(3aα,4β,7β,7aα)]-4-[Octahydro-4-[2-(1H-indol-7-yloxy)ethyl]-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	4.23 LCMS $[M + H]^+$= 492.2	496
725		[3a*S*-(3aα,4β,7β,7aα)]-4-[Octahydro-4-methyl-7-[2-(7-methyl-3-oxo-1,2-benzisoxazol-2(3H)-yl)ethyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.02 LCMS $[M + H]^+$= 508.2	496

726		[3a*S*-(3aα,4β,7β,7aα)]-4-[Octahydro-4-[2-[5-hydroxy-3-(2-hydroxyethyl)-1H-indol-1-yl]ethyl]-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	2.94 LCMS $[M + H]^+$= 536.2	496
727		*N*-[3-[2-[[3a*S*-(3aα,4β,7β,7aα)]-2-(4-Cyano-1-naphthalenyl)octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindol-4-yl]ethoxy]phenyl]urea	4.26 LCMS $[M + H]^+$= 511.2	496
728		[3a*S*-(3aα,4β,7β,7aα)]-4-[4-[2-[[2-Amino-6-(methoxymethyl)-4-pyrimidinyl]oxy]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	4.18 LCMS $[M + H]^+$= 514.2	496

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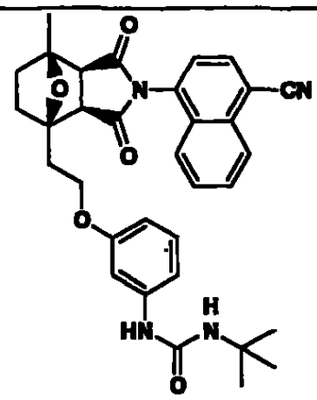
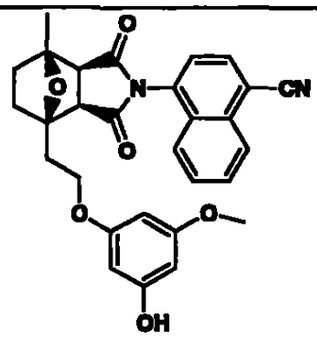
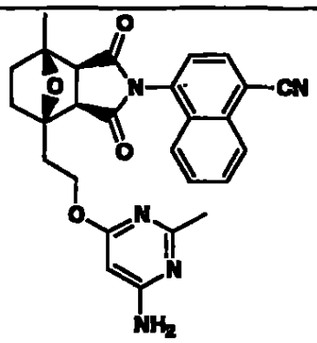
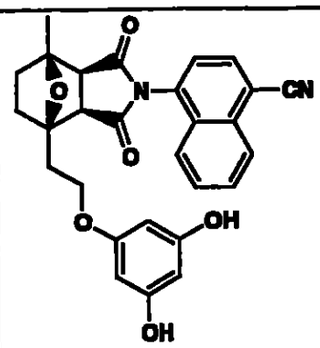
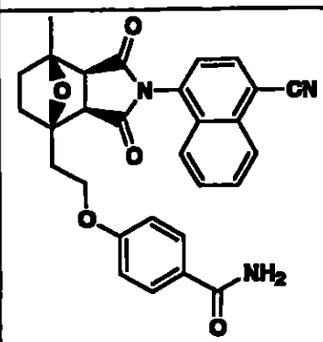
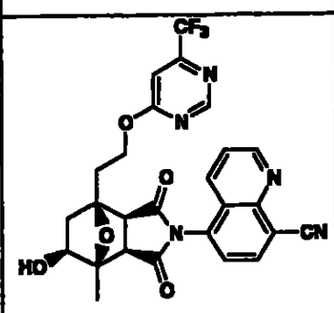
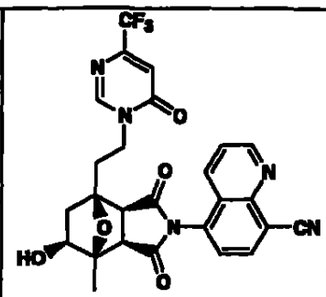
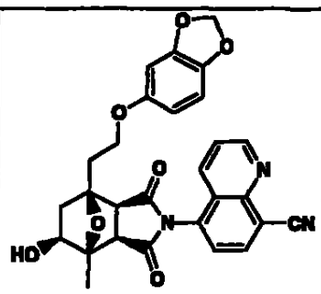
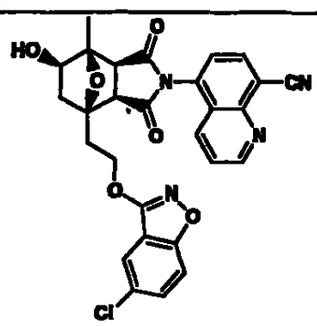
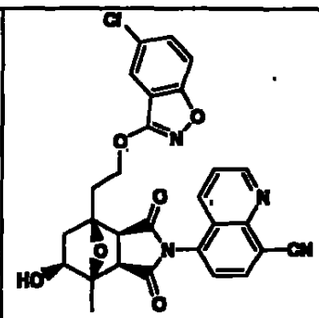
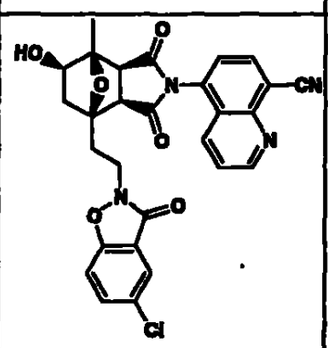
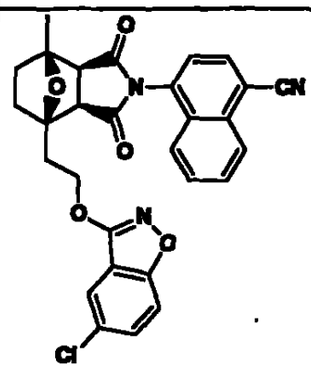
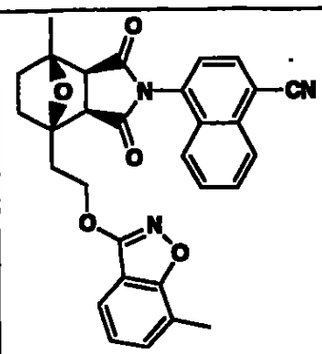
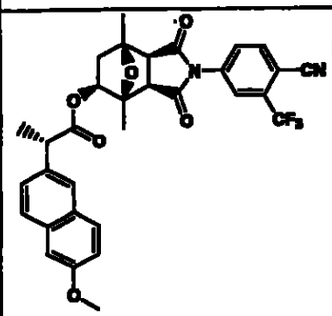
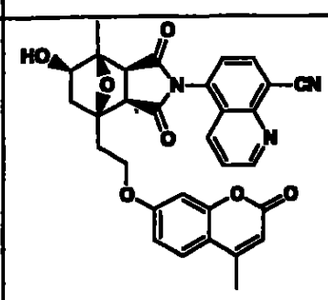
729		*N*-[3-[2-[[3a*S*-(3aα,4β,7β,7aα)]-2-(4-Cyano-1-naphthalenyl)octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindol-4-yl]ethoxy]phenyl]-*N'*-(1,1-dimethylethyl)urea	3.13 LCMS [M + H]⁺= 567.2	496
730		[3a*S*-(3aα,4β,7β,7aα)]-4-[Octahydro-4-[2-(3-hydroxy-5-methoxyphenoxy)ethyl]-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	4.22 LCMS [M + H]⁺= 499.2	496
731		[3a*S*-(3aα,4β,7β,7aα)]-4-[4-[2-[(6-Amino-2-methyl-4-pyrimidinyl)oxy]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	4.19 LCMS [M + H]⁺= 484.2	496

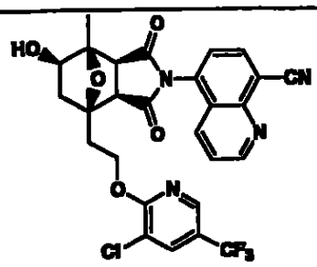
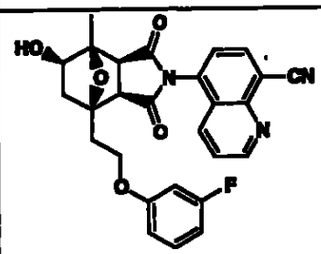
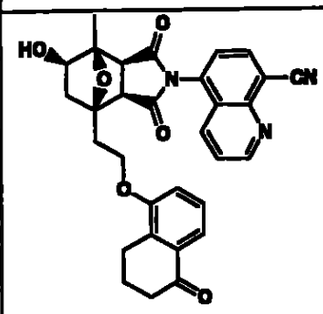
732		[3a*S*-(3aα,4β,7β,7aα)]-4-[4-[2-(3,5-Dihydroxyphenoxy)ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.73 LCMS $[M+H]^+$= 485.1	496
733		[3a*S*-(3aα,4β,7β,7aα)]-4-[2-[2-(4-Cyano-1-naphthalenyl)octahydro-7-methyl-1,3-dioxo-4,7-epoxy-4H-isoindol-4-yl]ethoxy]benzamide	4.11 LCMS $[M+H]^+$= 496.2	496
734		[3a*R*-(3aα,4β,5β,7β,7aα)]-5-[Octahydro-5-hydroxy-4-methyl-1,3-dioxo-7-[2-[[6-(trifluoromethyl)-4-pyrimidinyl]oxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile	2.847 LC $[M+H]^+$= 540.14	485, 486, 487 & 488

735		[3a*R*-(3aα,4β,5β,7β,7aα)]-5-[Octahydro-5-hydroxy-4-methyl-1,3-dioxo-7-[2-[6-oxo-4-(trifluoromethyl)-1(6H)-pyrimidinyl]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile	2.577 LCMS $[M + H]^+$= 540.14	485, 486, 487 & 488
736		[3a*R*-(3aα,4β,5β,7β,7aα)]-5-[7-[2-(1,3-Benzodioxol-5-yloxy)ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile	2.867 LCMS $[M + H]^+$= 514.16	485, 486, 487 & 488
737		[3a*S*-(3aα,4β,5β,7β,7aα)]-5-[7-[2-[(5-Chloro-1,2-benzisoxazol-3-yl)oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile	3.24 LCMS $[M + H]^+$= 545.12	485, 486, 487 & 488

738		[3a*R*-(3aα,4β,5β,7β,7aα)]-5-[7-[2-[(5-Chloro-1,2-benzisoxazol-3-yl)oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile	3.25 LCMS $[M + H]^+$= 545.12	485, 486, 487 & 488
739		[3a*S*-(3aα,4β,5β,7β,7aα)]-5-[7-[2-(5-Chloro-3-oxo-1,2-benzisoxazol-2(3H)-yl)ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile	2.863 LCMS $[M + H]^+$= 545.12	485, 486, 487 & 488
740		[3a*S*-(3aα,4β,7β,7aα)]-4-[4-[2-[(6-Chloro-1,2-benzisoxazol-3-yl)oxy]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	4.04 LCMS $[M + H]^+$= 528.1	496

276

741		[3a*S*-(3aα,4β,7β,7aα)]-4-[Octahydro-4-methyl-7-[2-[(7-methyl-1,2-benzisoxazol-3-yl)oxy]ethyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile	3.94 LCMS $[M + H]^+$= 508.1	496
742		(α*S*)-6-Methoxy-α-methyl-2-naphthaleneacetic acid, [3a*R*-(3aα,4β,5β,7β,7aα)]-2-[4-cyano-3-(trifluoromethyl)phenyl]octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-1H-isoindol-5-yl ester	$[M - H]^-$= 591.3	483
743		[3a*S*-(3aα,4β,5β,7β,7aα)]-5-[Octahydro-5-hydroxy-4-methyl-7-[2-[(4-methyl-2-oxo-2H-1-benzopyran-7-yl)oxy]ethyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile	2.89 LCMS $[M + H]^+$= 552.19	485, 486, 487 & 488

744		[3a*S*-(3aα,4β,5β,7β,7aα)]-5-[7-[2-[[3-Chloro-5-(trifluoromethyl)-2-pyridinyl]oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile	3.46 LCMS $[M + H]^+$= 573.12	485, 486, 487 & 488
745		[3a*S*-(3aα,4β,5β,7β,7aα)]-5-[7-[2-(3-Fluorophenoxy)ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile	3.05 LCMS $[M + H]^+$= 488.03	485, 486, 487 & 488
746		[3a*S*-(3aα,4β,5β,7β,7aα)]-5-[Octahydro-5-hydroxy-4-methyl-1,3-dioxo-7-[2-[(5,6,7,8-tetrahydro-5-oxo-1-naphthalenyl)oxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile	2.98 LCMS $[M + H]^+$= 538.23	485, 486, 487 & 488

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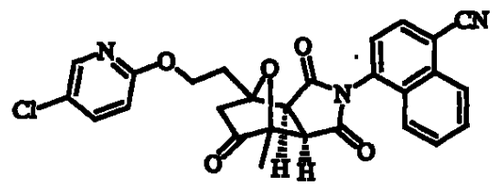
Example 747

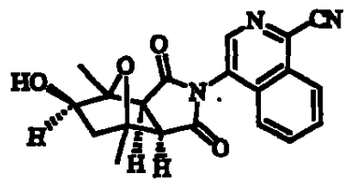
[3a*R*-(3aα,4β,7β,7aα)]-4-[7-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]octahydro-4-methyl-1,3,5-trioxo-4,7-epoxy-2H-isoindol-2-yl]-1-naphthalenecarbonitrile (747)



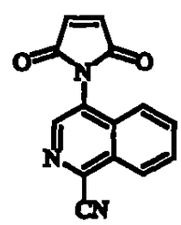
Dess-Martin periodinane (122 mg, 0.29 mmol, prepared as described in Ishiharas, J., T. Fukuzakia, *et al. Tetrahedron Letters* 40(10), 1907-1910 (1999)) was added to a solution of the compound 490A (120 mg, 0.24 mmol) in dichloromethane (2.5 mL) under nitrogen and the mixture was stirred for 4h. The reaction was half concentrated under a stream of nitrogen and was applied on a flash cartridge (Jones 2 g) with celite on top and was eluted with chloroform:heptane (9:1) to chloroform:acetone (4:1) to give 148 mg of a still impure white solid. The solid was disolved in dichloromethane (5 mL) and heptane (3 mL) and the precipitate was filtered over 1 g silica and was eluted with dichloromethane to chloroform:acetone (4:1). Fractions 3-9 (58.8 mg white solid) was almost pure and fractions 10-13 (68 mg white foam) were still impure. Fractions 3-9 were purified over silica (1 g) using heptane to heptane:ethyl acetate (1:1) as eluant to give 35.8 mg (30% yield) compound 747 as a white solid. Fractions 10-13 were purified by adding ~400 mg of silica to an excess solution of crude compound 747 in ethyl acetate and heptane and concentrating it. The silica was then put on top of a preconditioned (heptane) silica column (1 g) and was eluted with a gradient from heptane to heptane ethyl acetate (1:1) to give an additional 36.7 mg (31% yield) of compound 747 as a white solid. HPLC: 94% at 3.46 & 3.59 min (atropisomers, retention time) (YMC S5 ODS 4.6 X 50 mm, 4 mL min, 4 min gradient 100% A to 100% B (A: 10% methanol, 89.1% water, 0.1% TFA; B: 10% water, 89.1% methanol, 0.1% TFA, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 502.11 $[M+H]^+$.

Example 748

(3aα,4β,5β,7β,7aα)-4-[Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-isoquinolinecarbonitrile (748D)

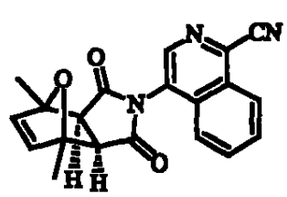


A. 4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-isoquinoline-1-carbonitrile (748A)



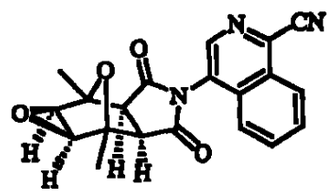
A mixture of compound 470D (200 mg, 1.18 mmol) and maleic anhydride (470 mg, 4.7 mmol) in glacial acetic acid (5 mL) was heated to reflux for 4 hours. After removing the volatiles *in vacuo*, the residue was partitioned between ethyl acetate (50 mL) and water (50 mL). The organic layer was washed with saturated sodium bicarbonate solution (2 x 50 mL) and brine (50 mL). After drying over magnesium sulfate, the organic layer was filtered through a 1 x 5 cm plug of silica gel. The filtrate was concentrated to afford 263 mg (90%) of 748a as an off-white solid. HPLC: 99% at 1.12 min (Phenomenex 5 micron ODS 4.6X30 mm, 10%-90% aqueous methanol over 2 minute gradient with 0.1% TFA, detecting at 254 nm). MS (ES): m/z 250.2 $[M+H]^+$.

B. (3aα,4β,7β,7aα)-4-(1,3,3a,4,7,7a-Hexahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-1-isoquinolinecarbonitrile (748B)



A mixture of compound **748A** (250 mg, 1 mmol) and 2,5-dimethylfuran (4 mL) was heated to 60°C for 2 h. At 15 min, the reaction mixture became homogeneous. A precipitate formed at 45 minutes. After cooling to 25°C, the reaction mixture was diluted with hexane and the filter cake was washed with ethyl ether:hexane, 1:1. Drying under high vacuum afforded 270 mg (78%) of compound **748B** as a light yellow solid. ^{1}HNMR-400 MHz ($CDCl_3$): δ 8.55 (s, 1H), 8.54 (m, 1H), 7.86 (m, 3H), 6.45 (s, 2H), 3.18 (s, 2H), 1.81 (s, 6H).

C. (1aα,2β,2aα,5aα,6β,6aα)-4-[Octahydro-2,6-dimethyl-3,5-dioxo-2,6-epoxy-4H-oxireno[f]isoindol-4-yl]-1-isoquinolinecarbonitrile (748C)



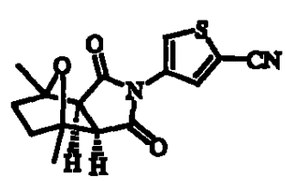
m-CPBA, (70%, 110 mg, 0.45 mmol) was added to a solution of compound **748B** (100 mg, 0.29 mmol) in 3 mL of dichloromethane at 25°C. After 1 h, additional *m*-CPBA, (70%, 110 mg, 0.45 mmol) was added and the reaction mixture was stirred an additional 18 h. After partitioning the reaction mixture between ethyl acetate (30 mL) and water (30 mL), the organic layer was washed with saturated sodium bisulfite solution (30 mL), saturated sodium bicarbonate solution (2 x 30 mL) and brine (30 mL). The sample was dried over magnesium sulfate and concentration to yield 103 mg (98%) of compound **748C** as an off-white solid. HPLC: 99% at 1.09 & 1.22 min (atropisomers, retention time) (Phenomenex 5 micron ODS 4.6X30 mm, 10%-90% aqueous methanol over a 2 min gradient with 0.1% TFA, detecting at 254 nm). MS (ES): m/z 362.07 $[M+H]^+$.

D. (3aα,4β,5β,7β,7aα)-4-[Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-isoquinolinecarbonitrile (748D)

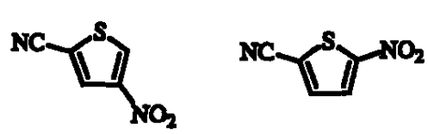
A 0.5 M solution of bis(cyclopentadienyl)titanium chloride in THF (1.2 mL, 0.6 mmol) was added dropwise over 20 min to a well stirred suspension of compound 748C (103 mg, 0.29 mmol) in THF (2.5 mL) and 1,4-cyclohexadiene (1.2 mL) at 60°C. After stirring 1 h at 60°C, the reaction mixture was partitioned between 1N HCl (40 mL) and ethyl acetate (50 mL). The pH of the aqueous layer was adjusted to 7 with solid sodium bicarbonate. After extracting the aqueous with ethyl acetate, the combined organic layers were dried over sodium sulfate. Decolorizing carbon (~1 g) was added and the mixture was allowed to stand for 18 h. Filtration and concentration of the filtrate *in vacuo* afforded a yellow oil that was chromatographed on a 2.5 x 15 cm silica gel column, using dichloro-methane:acetone, 6:4 as the mobile phase. Concentration of the product containing fractions *in vacuo* gave a partially purified residue that was subjected to preparative thin layer silica gel chromatography, using dichloromethane:acetone, 6:4 as the mobile phase. Extraction of the desired band with CH_2Cl_2, filtration and concentration of the filtrate *in vacuo* yielded 3 mg (31%) of compound 748D as an off-white solid. HPLC conditions: 95% at 1.46 min (Phenomenex 5 micron ODS 4.6X30 mm, 10%-90% aqueous methanol over 2 minute gradient with 0.1% TFA, detecting at 254 nm). MS (ES): m/z 364.19 $[M+H]^+$.

Example 749

(3aα,4β,7β,7aα)-4-[Octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-thiophenecarbonitrile (749C)



A. 2-Cyano-4-nitrothiophene (749Ai) & 2-Cyano-5-nitrothiophene (749Aii)



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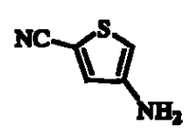
Fuming nitric acid (21 mL) was slowly added to glacial acetic acid (105 mL) and the mixture was then cooled in an ice-bath. 2-Cyanothiophene (7.98 g, 73.1 mmol) was dissolved in 20 mL of acetic anhydride and added dropwise to the above acid mixture such that the temperature did not exceed 25°C. Upon completion of the addition, the reaction mixture was warmed to 22°C and stirred for 48 h. The reaction was poured over 400 mL of ice and extracted with 200 mL of diethylether. The ether layer was isolated, washed with water, followed by brine and dried over $MgSO_4$. Filtration and concentration *in vacuo* gave a sticky, orange residue which was purified by column chromatography using 1:1 hexanes/ methylene chloride as the eluent to give 1.69 g (15%) of compound **749Ai** as a white solid and 1.71 g (15%) of compound **749Aii** as a yellow crystalline substance. . Compound **749Ai**: HPLC: 0.73 minutes (retention time) (Phenomenex column 30 x 4.6 mm eluting with 10-90% aqueous methanol over 2 minutes containing 0.1% TFA, 5 mL/min, monitoring at 220 nm). Compound **749Aii**: HPLC: 99% at 0.89 minutes (retention time) (Phenomenex column 30 x 4.6 mm eluting with 10-90% aqueous methanol over 2 minutes containing 0.1% TFA, 5 mL/min, monitoring at 220 nm).

B. 4-Amino-2-cyanothiophene (749B)



To a 100 mL 3-necked flask was added compound **749Ai** (1.42 g, 9.21 mmol) dissolved in ethyl acetate (20 mL) followed by a 10% acetic acid solution (20 mL). The biphasic mixture was heated to 65°C and then iron powder (2.95 g, 52.9 mmol) was added portion-wise over 5 minutes. After stirring for 1.5 h at 65°C, the reaction was filtered through a bed of Celite and the pad was washed with ethyl acetate. The organic layer was separated, washed with water (3 x 20 mL), brine and dried over $MgSO_4$. Filtration and concentration *in vacuo* gave a dark amber residue which was purified by column chromatography using 30% diethyl ether / methylene chloride as the eluent to give 84 mg (73%) of compound **749B** as a brown solid. HPLC: 93.4 at 0.26 minutes (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-

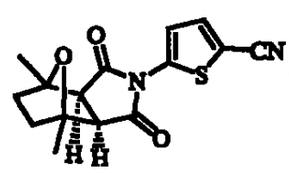
90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm).

C. (3aα,4β,7β,7aα)-4-[Octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-thiophenecarbonitrile (749C)

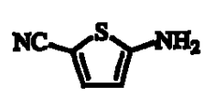
To a Pyrex tube was added compound 749B (0.06 g, 0.5 mmol), toluene (1 mL), triethylamine (0.25 g, 0.35 mL, 2.5 mmol), $MgSO_4$ (0.15 g, 1.3 mmol), and compound 20A. The tube was sealed with a teflon cap and heated overnight at 145°C. The reaction was cooled, diluted with methylene chloride and filtered through Celite. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography using 10% ether / methylene chloride as the eluent to give 14 mg (95%) of compound 749C as a light yellow crystalline solid. HPLC: 94.6% at 2.6 minutes (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm. MS (ES): m/z 303.05 $[M+H]^+$.

Example 750

(3aα,4β,7β,7aα)-5-[Octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-thiophenecarbonitrile (750B)



A. 5-Amino-2-cyanothiophene (750A)



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To a 100 mL 3-necked flask was added compound **749Aii** (1.63 g, 10.1 mmol) dissolved in ethyl acetate (20 mL) followed by a 10% solution of acetic acid (20 mL). The biphasic mixture was heated to 65°C and then iron powder (2.95 g, 52.9 mmol) was added portion-wise over 5 minutes. After stirring for 1.5 h at 65°C, the reaction was filtered through a bed of Celite and the pad was washed with ethyl acetate. The organic layer was separated, washed with water (3 x 20 mL), brine and dried over $MgSO_4$. Filtration and concentration *in vacuo* gave a dark amber residue which was purified by column chromatography using 10% diethyl ether / methylene chloride as the eluent to give 87 mg (66%) of compound **750A** as a brown solid. HPLC: 94.2% at 1.05 minutes (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm).

B. (3aα,4β,7β,7aα)-5-[Octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-thiophenecarbonitrile (750B)

To a Pyrex tube was added compound **750A** (0.06 g, 0.5 mmol), toluene (1 mL), triethylamine (0.25 g, 0.35 mL, 2.5 mmol), $MgSO_4$ (0.15 g, 1.3 mmol), and compound **20B**. The tube was sealed with a teflon cap and heated overnight at 145° C. The reaction was cooled, diluted with methylene chloride and filtered through Celite. The filtrate was concentrated *in vacuo* and the residue was purified by column chromatography using 10% ether/ methylene chloride as the eluent to yield 143 mg (96%) of compound **750B** as a light yellow crystalline solid. HPLC: 92.7% at 2.93 minutes (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm. MS (ES): m/z 303.21 $[M+H]^+$.

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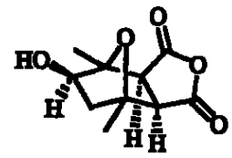
Example 751

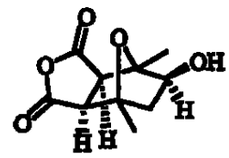
[3aS-(3aα,4β,7β,7aα)]-Hexahydro-5-hydroxy-4,7-dimethyl-4,7-epoxyisobenzofuran-1,3-dione (751)



To a solution of compound 471Dii (2.36 g, 6.21 mmol) in tetrahydrofuran (THF, 20 mL) cooled in an ice-bath (~5 °C) was added, in one portion, aq 1M NaOH solution (10 mL, 10 mmol). The resulting light yellow reaction mixture was stirred for 30 min then acidified by addition of aq 1M HCl solution (12 mL, 12 mmol) and partitioned between water (100 mL) and EtOAc (40 mL). The aqueous layer was separated and extracted with EtOAc (25 mL). The organic phases were combined, dried rapidly over sodium sulfate and filtered, rinsing with hot THF to dissolve some precipitated solid product. The filtrate was concentrated *in vacuo* to give the crude ring opened amido-acid intermediate as a white solid. A slurry of the crude material suspended in 60 mL of dry THF and 25 mL of glacial HOAc and was heated with stirring to 60 °C during which time the mixture became homogeneous. After 9 h, the reaction mixture was cooled and concentrated *in vacuo* to give a pale yellow solid. The solid was triturated with 30 mL of toluene, warmed (~50 °C), then allowed to cool to rt. The insoluble product was collected on a Buchner funnel, washed with toluene and dried under vacuum to afford compound 751 (75%) as a white solid. 400 MHz ^{1}H NMR (DMSO-d_6) δ 1.34 (s, 3H), 1.34 (m, 1H), 1.45 (s, 3H), 2.32 (dd, J=7.3, 13.1, 1H), 3.20 (d, J=7.3, 1H), 3.28 (d, J=7.2, 1H), 3.79 (m, 1H), 5.11 (d, J=6.1, 1H); 100 MHz ^{13}C NMR (DMSO-d_6) δ 169.6, 86.7, 82.3, 72.8, 52.9, 50.3, 46.5, 16.0, 11.2. The absolute stereochemistry of compound 751 is established by the known stereochemistry of the intermediate compound 471Dii and the retention of configuration therein. The absolute stereochemistry is as drawn in the above figure.

Example 752

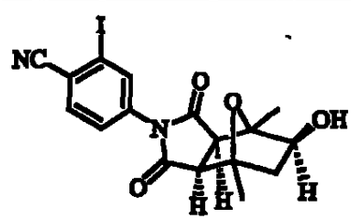
[3a*R*-(3aα,4β,7β,7aα)]-Hexahydro-5-hydroxy-4,7-dimethyl-4,7-epoxyisobenzofuran-1,3-dione (752)



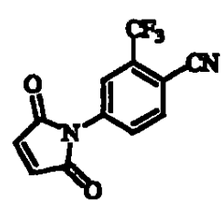
Compound 752 was synthesized as described in example 751 with the exception that the starting compound 471Di was utilized as the starting material rather than compound 471Dii. 400 MHz ^{1}H NMR (DMSO-d_6) δ 1.34 (s, 3H), 1.34 (m, 1H), 1.45 (s, 3H), 2.32 (dd, J=7.3, 13.1, 1H), 3.20 (d, J=7.3, 1H), 3.28 (d, J=7.2, 1H), 3.79 (m, 1H), 5.11 (d, J=6.1, 1H); 100 MHz ^{13}C NMR (DMSO-d_6) δ 169.6, 86.7, 82.3, 72.8, 52.9, 50.3, 46.5, 16.0, 11.2. The absolute stereochemistry of compound 752 is established by the known stereochemistry of the intermediate compound 471Di and the retention of configuration therein. The absolute stereochemistry is as drawn in the above figure.

Example 753

[3a*R*-(3aα,4β,5β,7β,7aα)]-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-iodobenzonitrile (753G)

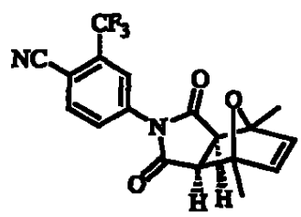


A. 4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-2-trifluoromethyl-benzonitrile (453A)



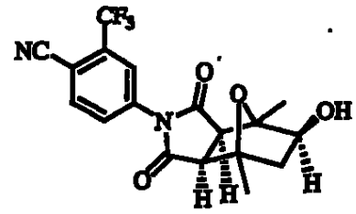
A mixture of 3-trifluoromethyl-4-cyano-aniline (24.0 g, 129 mmol) and maleic anhydride (14.0 g, 143 mmol) in 50 mL of acetic acid was heated at 115°C overnight. A precipitate was obtained during the heating period. The reaction was allowed to stand at rt for an additional overnight period. The solid was removed by filtration, the filter cake was washed with diethyl ether and dried to give 21 g (79 mmol, 61%) of compound 753A as an off white solid. HPLC: 100% at 2.11 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm).

B. (3aα,4β,7β,7aα)-4-(1,3,3a,4,7,7a-Hexahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (753B)



A slurry of 4-(2,5-dihydro-2,5-2,5-dioxo-1H-pyrrol-1-yl)-2-trifluoromethyl-benzonitrile (15.0g, 56.35 mmol) and 2,5-dimethylfuran (32.5g, 338 mmol) was stirred at 60°C for 3h, followed by continued stirring for another 14h at 23°C. The mixture was diluted with cold (~5°C) toluene (15 mL) and the resulting off white solid was collected by filtration while cold. The filter cake was washed with cold toluene (20 mL) and dried at 23°C in vacuum oven for 24 h to provide compound 753B (18.6g, 91% yield) with a purity of 98.7% as judged by HPLC.

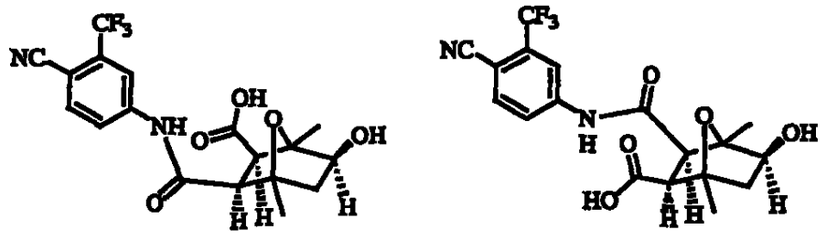
C. [3aR-(3aα,4β,5β,7β,7aα)]-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (753C)



A slurry of compound 753B (5.0g, 13.81 mmol), allylpalladium chloride dimer (10mg, 0.027 mmol) and (R)-2-methoxy-2'-diphenylphosphino-1, 1'-binaphthyl (R-MOP, 26mg, 0.055 mmol) in THF (14 mL) was purged with nitrogen and cooled to 10°C. To the above mixture, was added trichlorosilane (3.7g, 27.62 mmol) slowly over a period of 10 minand the resulting heterogeneous mixture was stirred for 24 h at 10°C. The mixture was diluted with THF (85 mL) and further cooled to -20°C. To the above mixture, a solution of triethylamine (9.76g, 96.67 mmol) in ethanol (6.35g, 138.1 mmol) was added slowly keeping the temperature <25°C and stirred for another 2 h at rt. The white solid was filtered and the filter cake was washed with THF (50 mL) and the filtrate was evaporated under the reduced pressure. The oily residue was dissolved in ethyl acetate (100 mL) and stirred at 23°C in the presence of trithiocyanuric acid (TMT, 500mg) and charcoal (500mg) for 5h. The slurry was filtered through a pad of celite and silica gel and the filtrate was evaporated under the reduced pressure. The residue was dissolved in a mixture of THF (175 mL) and methanol (125 mL), and to this mixture was added anhydrous potassium fluoride (2.0g, 34.5 mmol), potassium hydrogencarbonate (6.9g, 69 mmol), followed by urea-hydrogen peroxide adduct (6.5g, 69 mmol). This suspension was stirred at rt for 14 h and an additional amount of potassium fluoride (800 mg, 13.81 mmol), potassium hydrogencarbonate (1.38 g, 13.81 mmol) and urea-hydrogen peroxide adduct (2.59 g, 27.62 mmol) was added. Stirring continued for another 12 h and the slurry was filtered and the filter cake was washed with ethyl acetate (100 mL). The filtrate was washed consecutively with 10% aqueous sodium hydrogensulfite (50 mL x 2), water (50 mL) and brine (50 mL). The solvent was evaporated under the reduced pressure to provide a light brown foam. Column chromatography of this foam using silica gel and EtOAc-heptane (2:3) afforded compound 753C (4.72g, 90%, >99% pure by HPLC) as an off white solid. This material has an enantiomeric purity of >96% ee by chiral HPLC and LC-MS: m/z 379 ($M+H^+$). The abosolute stereochemistry of compound

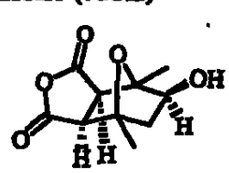
753C was established by comparison to existing material of known stereochemistry as described in Example 483.

D. [1*S*-(1β,2α,3α,4β,6β)]-3-[[(4-Cyano-3-(trifluoromethyl)phenyl)amino]carbonyl]-6-hydroxy-1,4-dimethyl-7-oxa-bicyclo[2.2.1]heptane-2-carboxylic acid & [1*R*-(1β,2α,3α,4β,5β)]-3-[[(4-Cyano-3-(trifluoromethyl)phenyl)amino]carbonyl]-5-hydroxy-1,4-dimethyl-7-oxa-bicyclo[2.2.1]heptane-2-carboxylic acid (753Di &753Dii)



Compound 753C (25.0 g, 65.7 mmol) was dissolved in THF (100 mL) at 22°C and 1 N NaOH (100 mL) was added. After 1 h, THF (100 mL), 1 N HCl (110 mL) and brine (100 mL) were added. The mixture was then extracted once with EtOAc (200 mL) and twice with 1:1 THF/EtOAc (200 mL). The combined organics were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give compounds 753Di and 753Dii (1:1 by HPLC) as a white solid. No purification was necessary. HPLC: 100% at 2.217 and 2.413 min (retention time) (YMC S5 ODS-A column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 mincontaining 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm).

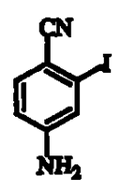
E. [3a*R*-(3aα,4β,7β,7aα)]-Hexahydro-5-hydroxy-4,7-dimethyl-4,7-epoxyisobenzofuran-1,3-dione (753E)



Compounds 753Di and 753Dii were suspended in a mixture of THF (500 mL) and AcOH (200 mL) and heated to 60°C for 16 h. The reaction became homogenous after 4 h. The reaction was cooled to 22°C and concentrated *in vacuo*. Toluene (200 mL) was then added and the mixture was heated to 90°C for 4 h until all product was

dissolved. The mixture was then cooled to 22°C and left standing for 20 h. Compound 753E precipitates from solution over the 20 h period. The resulting solid was filtered and rinsed with toluene followed by drying *in vacuo*. A yield of 11.93 g of crude compound 753E was obtained as an off-white solid. Crude compound 753E (10 g) was dissolved in 350 ml of warm EtOAc (the solution was turbid), and then 5 g of decolorizing carbon was added and the mixture was stirred at rt for 40 mins. After filtering through celite, the filter cake was washed with hot EtOAc (2 x 50 ml). Concentration of the filtrate afforded an off-white solid that was dissolved in 40 ml of hot acetonitrile. After carefully adding 200 ml of ethyl ether, 300 ml of hexane was added and the flask was allowed to stand 18 hrs at rt. Filtration and drying afforded 8.32 g of compound 753E as a colorless crystalline solid. ^{1}H NMR(DMSO-d^6): δ = 5.11 (d, 1H, J = 6.0 Hz), 3.78 (dd, 1H, J = 7.2, 30.6 Hz), 3.27 (d, 1 H, J = 7.2 Hz), 3.20 (d, 1 H, J = 7.3 Hz), 2.27 (dd, 1H, J = 7.3, 13.1 Hz), 1.44 (s, 3H), 1.33 (s, 3 H) and 1.32 ppm (m, 1H).

F. 4-Amino-2-iodo-benzonitrile (753F)



2-Iodo-4-nitro-benzonitrile (1.00 g, 3.65 mmol, was prepared by the method given in *J. Med. Chem.* 2000, *43*, 3344-47) was dissolved in THF (20 mL) at 60°C with mechanical stirring. EtOH (25 mL) was then added followed by aq NH_4Cl (0.293 g, 5.48 mmol in 20 mL H_2O). Iron powder (325 mesh, 0.815 g, 14.6 mmol) was then added with vigorous stirring. After 2 h, reaction was complete. Cooled to 22°C and filtered through celite rinsing with EtOAc. The mixture was then concentrated to ~20 mL and then diluted with EtOAc (200 mL) and washed once with 1 N NaOH (50 mL), once with brine (50 mL) and dried over anhydrous $MgSO_4$, to give, compound 753F (0.710 g) as a light yellow solid. No additional purification was needed. HPLC: 99 at 2.147 min (retention time) (YMC S5 ODS column, 4.6 x

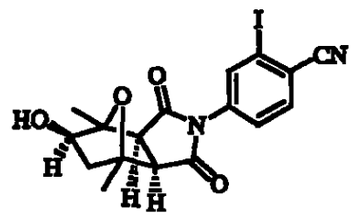
50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm).

G. [3a*R*-(3aα,4β,5β,7β,7aα)]-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-iodobenzonitrile (753G)

A mixture of compound **753E** (1.60 g, 7.57 mmol), compound **753F** (1.32 g, 5.41 mmol), 4Å molecular sieves (2.0 g) in dimethylacetamide (8 mL) was stirred in a 175°C oil bath for 4 h. The resulting dark mixture was cooled, diluted with EtOAc (50 mL) then filtered to remove sieves and rinsed with EtOAc. The filtrate was partitioned between EtOAc (50 mL) and water (75 mL). The organic phase was separated, washed with water (2 x 75 mL), brine (50 mL), then diluted with tetrahydrofuran (20 mL), dried over sodium sulfate and concentrated *in vacuo* to give a solid foam. The crude material was triturated with diethyl ether (100 mL) then stirred for 1.5 h. The solid precipitate was collected on a Buchner funnel then suspended in diethyl ether (50 mL) and stirred for 16 h. The resulting solid was collected on a Buchner funnel, rinsed with diethyl ether and dried under vacuum (90°C) to afford compound **753G** (67%) as an off-white solid. HPLC: 96% at 3.00 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90 aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 438.90 $[M+H]^+$. The absolute stereochemistry of compound **753G** is established by the known stereochemistry of the intermediate compound **753C** and the retention of configuration therein. The absolute stereochemistry is as drawn in the above figure and rendered by the nomenclature.

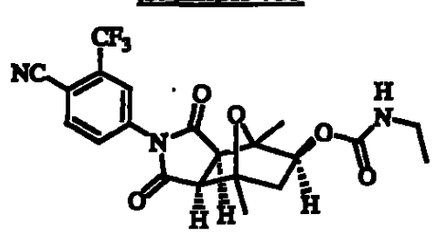
Example 754

[3a*S*-(3aα,4β,5β,7β,7aα)]-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-iodobenzonitrile (754)



A mixture of compound 751 (850 mg, 4.01 mmol), 4-cyano-3-iodo-aniline (975 mg, 4.01 mmol), 4Å molecular sieves (1.2 g) in dimethylacetamide (4.5 mL) was stirred in a 175 °C oil bath for 4 h. The resulting dark mixture was cooled, filtered to remove sieves and rinsed with EtOAc. The filtrate was partitioned between EtOAc (50 mL) and water (50 mL). The organic phase was separated, washed with water (2 x 50 mL), brine (25 mL), dried over sodium sulfate and concentrated *in vacuo*. The crude material was dissolved in tetrahydrofuran and purified by silica gel flash chomatography, eluting with 1:4 acetone/methylene chloride to give an impure white solid. The impure material was suspended in diethyl ether (75 mL), stirred for 18 h then collected on a Buchner funnel to afford 650 mg (37%) of compound 754 as a white solid. HPLC: 100% at 2.90 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 438.95 $[M+H]^+$. The absolute stereochemistry of compound 754 is established by the known stereochemistry of the intermediate compound 751 and the retention of configuration therein. The absolute stereochemistry is as drawn in the above figure and rendered by the nomenclature.

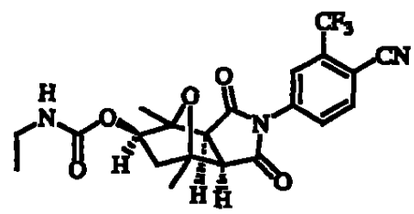
<u>Example 755</u>



A solution of compound 471Di (80 mg, 0.21 mmol), ethyl isocyanate (30 mg, 0.43 mmol) and 4-dimethyaminopyridine (5 mg, 0.04 mmol) in dry tetrahydrofuran (1

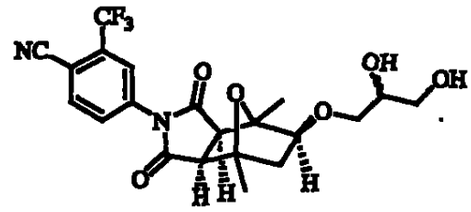
mL) was heated to 55 °C for 2 h, then additional ethyl isocyanate (30 mg) was added and heated for another 2 h. A final portion of EIC (30 mg) was added, then after 16 h the reaction mixture was cooled, concentrated *in vacuo* and purified by silica gel flash chomatography on SiO_2 eluting with 2:1 EtOAc/heptane to give 80 mg (86%) of compound **755** as a white solid. HPLC: 94% at 3.51 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 452.29 $[M+H]^+$. The absolute stereochemistry of compound **755** is established by the known stereochemistry of the intermediate compound **471Di** and the retention of configuration therein. The absolute stereochemistry is as drawn in the above figure and rendered by the nomenclature.

Example 756

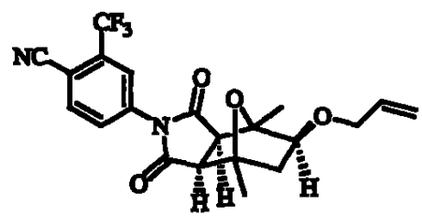


A solution of compound **471Dii** (80 mg, 0.21 mmol), ethyl isocyanate (100 mg, 1.4 mmol) and 4-dimethyaminopyridine (8 mg, 0.07 mmol) in dry tetrahydrofuran (2 mL) was heated to 60 °C for 16 h, then cooled, MeOH was added and the solution was concentrated *in vacuo*. The reaction mixture was purified by silica gel flash chomatography, eluting with 2:1 EtOAc/heptane to give 84 mg (90%) of compound **756** as a white solid foam. HPLC: 94% at 3.54 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 452.34 $[M+H]^+$. The absolute stereochemistry of compound **756** is established by the known stereochemistry of the intermediate compound **471Dii** and the retention of configuration therein. The absolute stereochemistry is as drawn in the above figure and rendered by the nomenclature.

Example 757

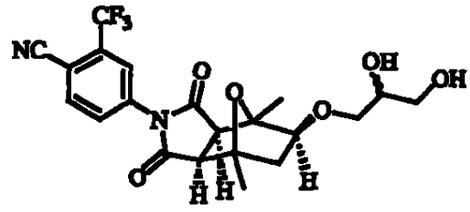


A. (757A)



A mixture of compound 471Di (620 mg, 1.63 mmol), silver(I) oxide (3.78 g, 16.3 mmol), allyl iodide (2.74 g, 16.3 mmol) and dry MeCN (15 mL) was stirred rapidly at 75-80 °C for 7.5 h. The resulting mixture was cooled and filtered though a pad of Celite rinsing with EtOAc. The filtrate was concentrated *in vacuo* and the crude material purified by silica gel flash chomatography on SiO_2 eluting with 1:1 EtOAc/heptane to give 570 mg (83%) of compound 757A as a glass. HPLC: 96 at 3.72 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 421.27 $[M+H]^+$.

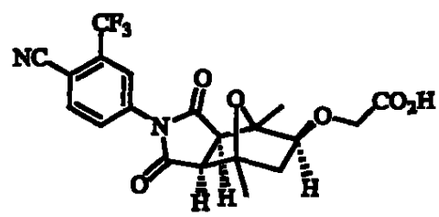
B. (757B)



To a mixture of compound 757A (85mg, 0.20 mmol), 4-methylmorpholine-N-oxide (26mg, 0.22 mmol) and acetone (1.6 mL) at rt was added water (0.4 mL) and then 2.5% osmium tetroxide solution in t-butanol (17mg, 0.002 mmol). The reaction mixture was stirred for 5 h, then filtered through a pad of Florosil. The filtrate was

concentrated *in vacuo* and the residue partitioned between EtOAc and 1M aq HCl solution. The organic phase was separated, dried over sodium sulfate, concentrated *in vacuo* and the crude material purified by silica gel flash chomatography on SiO_2 eluting with 2:1 acetone/heptane to give compound **757B** (52 mg, 55%) as a white solid. HPLC: 100% at 3.11 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 455 $[M+H]^+$. The absolute stereochemistry of compound **757B** is established by the known stereochemistry of the intermediate compound **471DI** and the retention of configuration there in. The absolute stereochemistry is as drawn in the above figure and rendered by the nomenclature.

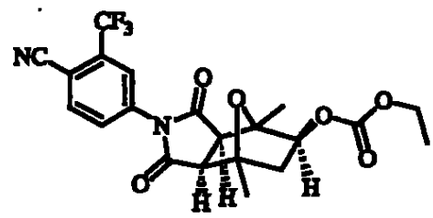
Example 758



To a solution of compound **757A** (45 mg, 0.11 mmol), carbon tetrachloride (0.50 mL), acetonitrile (0.5 mL) and water (0.75 mL) at rt was added sodium periodate (94 mg, 0.44 mmol) then after several minutes, ruthenium(III) chloride hydrate (50 mg, 0.24 mmol). After 30 min the dark mixture was partitioned between methylene chloride (20 mL) and water (20 mL). The mixture was filtered to remove solids, then the organic phase was separated, dried over sodium sulfate and concentrated *in vacuo*. The crude material purified by silica gel flash chomatography on SiO_2 eluting with 1:20 MeOH/EtOAc then 1:5:100 HOAc/MeOH/EtOAc to give compound **758** (19 mg, 36%) as a white solid foam. HPLC: 99% at 3.31 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 437.23 $[M-H]^-$. The absolute stereochemistry of compound **758** is

established by the known stereochemistry of the intermediate compound 471Di and the retention of configuration therein. The absolute stereochemistry is as drawn in the above figure and rendered by the nomenclature.

Example 759



To a solution of compound 471Di (100 mg, 0.26 mmol) and triethylamine (50 mg, 0.50 mmol) in dry methylene chloride (3 mL) cooled in an ice-bath was added ethyl chloroformate (40 µL, 0.40 mmol). The reaction was warmed to rt for 2 h and an additional portion of ethyl chloroformate (40 µL), triethylamine (50 mg), 4-dimethylaminopyridine (10 mg, 0.08 mmol) was added. The reaction mixture was stirred for 18 h at rt, then partitioned between 25 mL of EtOAc and 25 mL of 1M aq HCl solution. The organic phase was separated, washed with 1M aq HCl (2 x 25 mL), brine (1 x 25 mL), dried (sodium sulfate) and concentrated *in vacuo*. Purification by silica gel flash chomatography eluting with 1:1 EtOAc/heptane followed by recrystallization (EtOAc/heptane) afforded 76 mg (65%) of compound 759 as a white solid. HPLC: 100% at 3.85 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 453.01 $[M+H]^+$. The absolute stereochemistry of compound 759 is established by the known stereochemistry of the intermediate compound 471Di and the retention of configuration therein. The absolute stereochemistry is as drawn in the above figure and rendered by the nomenclature.

Example 760

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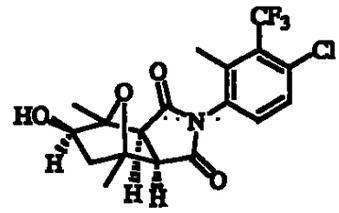
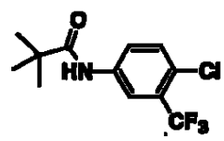
[3aS-(3aα,4β,5β,7β,7aα)]-2-(4-Chloro-2-methyl-3-(trifluoromethyl)phenyl)hexahydro-5-hydroxy-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione (760D)

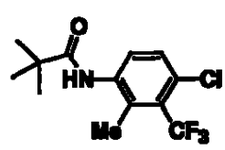


A. *N*-(4-Chloro-3-trifluoromethylphenyl)-2,2-dimethylpropionamide (760A)



To a solution of commercially available 4-chloro-3-(trifluoromethyl)aniline (15.0 g, 76.7 mmol) in anhydrous THF (200 mL) cooled to 0-5 °C was added triethylamine (11.7 mL, 84.4 mmol) followed by pivaloyl chloride (10.4 mL, 84.4 mmol) over 30 min. The ice bath was removed and the mixture stirred at rt for 1 h. The mixture was diluted with ether and filtered. The filtrate was washed with water (2X) and brine, dried over $MgSO_4$, filtered and concentrated. The residue was triturated with hexanes and the solid was filtered and dried *in vacuo* to afford compound 760A (20.4 g, 95%); MS (ES): m/z = 280 $[M+1]^+$.

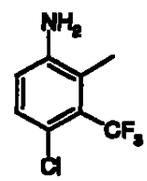
B. *N*-(4-Chloro-2-methyl-3-trifluoromethylphenyl)-2,2-dimethyl-propionamide (760B)



To a solution of *N*-(4-chloro-3-trifluoromethylphenyl)-2,2-dimethylpropionamide (2.29 g, 8.19 mmol) in anhydrous THF (25 mL) cooled to 0-5 °C was added a solution of 1.6M *n*-butyllithium in hexanes (12.3 mL, 19.7

mmol) slowly so that the reaction temperature was maintained below 5 °C. The solution was stirred at 0-5 °C for 1.5 h. A solution of iodomethane (0.56 mL, 9.01 mmol) in petroleum ether (2 mL) was added over 20 min while maintaining the temperature below 5 °C. The suspension was stirred at 0-5 °C for 1 h and diluted with water and ether. The aqueous layer was extracted with ether and the combined organic layers washed with brine, dried over $MgSO_4$, filtered and concentrated. The residue was chomatographed (silica gel) eluting with CH_2Cl_2 to afford compound **760B** (1.60 g, 67%). MS (ES): m/z = 294 $[M+1]^+$.

C. 4-Chloro-2-methyl-3-trifluoromethylaniline (760C)



N-(4-Chloro-2-methyl-3-trifluoromethylphenyl)-2,2-dimethyl-propionamide 1.0 g, 3.4 mmol) was added to a 1:1 mixture (15 mL) of concentrated HCl and ethanol and heated at reflux for overnight. The reaction was cooled and concentrated *in vacuo* to give a tan solid which was then partitioned between EtOAc and saturated $NaHCO_3$. The organic layer was separated, washed with water, brine, dried (Na_2SO_4), filtered and concentrated to give compound **760C** (0.54g, 76%) as a brown oily solid.

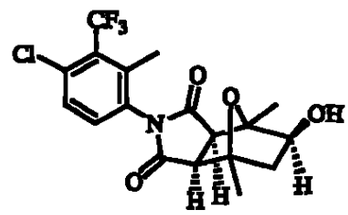
D. [3a*S*-(3aα,4β,5β,7β,7aα)]-2-(4-Chloro-2-methyl-3-(trifluoromethyl)phenyl)hexahydro-5-hydroxy-4,7-dimethyl-4,7-epoxy-1*H*-isoindole-1,3(2H)-dione (760D)

To a Pyrex sealable tube was added 4-chloro-2-methyl-3-trifluoromethylaniline (0.1g, 0.48 mmol), compound **751** (0.15g, 0.72 mmol), TEA (0.24g, 0.33 mL, 2.4 mmol), $MgSO_4$ (0.14g, 1.2 mmol), and toluene (0.5 mL). The reaction was heated in the sealed tube at 150 °C for 18 h. The cooled reaction was diluted with EtOAc, filtered, concentrated and purified by Prep-TLC using CH_2Cl_2 as

eluent to give compound **760D** (0.078g, 40%) as an off-white solid. HPLC: 90% at 3.26 min(YMC S5 ODS column) eluting with 10-90% aqueous methanol containing 0.2% phosphoric acid over a 4 min gradient monitoring at 220 nm. MS (ES): m/z 404.01 $[M+H]^+$. The absolute stereochemistry of compound **760D** is established by the known stereochemistry of the intermediate compound **751** and the retention of configuration therein. The absolute stereochemistry is as drawn in the above figure and rendered by the nomenclature.

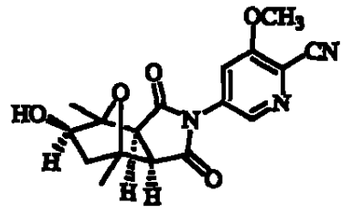
Example 761

[3a*R*-(3aα,4β,5β,7β,7aα)]-2-(4-Chloro-2-methyl-3-(trifluoromethyl)phenyl)hexahydro-5-hydroxy-4,7-dimethyl-4,7-epoxy-1H-Isoindole-1,3(2H)-dione (761)

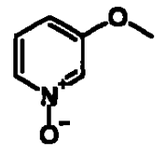


To a Pyrex sealable tube was added compound **760C** (0.1g, 0.48 mmol), compound **752** (0.15g, 0.72 mmol), TEA (0.24g, 0.33 mL, 2.4 mmol), $MgSO_4$ (0.14g, 1.2 mmol), and toluene (0.5 mL). The reaction was heated in the sealed tube at 150 °C for 18 h. The cooled reaction was diluted with EtOAc, filtered, concentrated and purified by SiO_2 Prep-TLC using CH_2Cl_2 as eluent to give compound **761** (0.056g, 29%) as an off-white solid. HPLC: 90% at 3.27 min(YMC S5 ODS column) eluting with 10-90% aqueous methanol containing 0.2% phosphoric acid over a 4 min gradient monitoring at 220 nm. MS (ES): m/z 403.91 $[M+H]^+$. The absolute stereochemistry of compound **761** is established by the known stereochemistry of the intermediate compound **752** and the retention of configuration therein. The absolute stereochemistry is as drawn in the above figure and rendered by the nomenclature.

Example 762

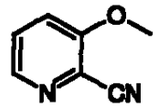


A. 3-Methoxypyridine-1-oxide (762A)



3-Methoxypyridine (20.08g, 209 mmol) was dissolved in 100 mL of acetic acid. 30% H_2O_2 (28.3 mL, 275 mmol) was added and the reaction mixture was heated at 70 °C for six h. The cooled reaction mixture was concentrated and the residue dissolved in CH_2Cl_2 and stirred overnight with 20 g of solid potassium carbonate. The mixture was filtered and concentrated to give compound 762A (25.2g, 100%) as a light yellow solid which was characterized by ^{1}H NMR and carried on to the next step.

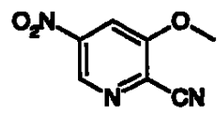
B. 2-Cyano-3-methoxypyridine (762B)



3-Methoxypyridine-1-oxide (25.2g, 209 mmol) was dissolved in acetonitrile (260mL). Trimethylsilycyanide (66.35g, 669 mmol) and triethylamine (45.13g, 446 mmol) were added and the reaction mixture heated at reflux for overnight. The cooled solution was concentrated *in vacuo* to give a brown solid which was partitioned between CH_2Cl_2 and 3M Na_2CO_3. The organic layer was separated, washed with brine, dried ($MgSO_4$), filtered and concentrated *in vacuo*. The residue was purified by silica gel chomatography using 1:1 EtOAc/hexanes as eluent. Compound 762B was isolated (17.63g, 63) as a light yellow solid. HPLC: 96.2% at

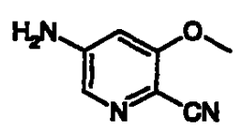
1.37 min(YMC S5 ODS column) eluting with 10-90% aqueous methanol containing 0.2% phosphoric acid over a 4 min gradient monitoring at 220 nm. MS (ES): m/z 134.88 $[M+H]^+$.

C. 2-Cyano-3-methoxy-5-nitropyridine (762C)



2-Cyano-3-methoxypyridine (17.63g, 131.4 mmol) was dissolved in CH_2Cl_2 (400 mL) and cooled in an ice bath. Tetrabutylammonium nitrate (52.02g, 170.8 mmol) and trifluoroacetic anhydride (35.88g, 170.8 mmol) were dissolved in 200 mL of CH_2Cl_2 and added in a thin stream via addition funnel. The mixture was warmed to 23°C and stirred for 60 h. The reaction mixture was stirred for one h with saturated sodium bicarbonate. The organic layer was separated, washed with brine, dried ($MgSO_4$), filtered, concentrated *in vacuo*, and purified by silica gel column chomatography using CH_2Cl_2 as eluent to give compound 762C (18.07g, 79%) as a light yellow crystalline solid. HPLC: 100% at 1.67 min(YMC S5 ODS column) eluting with 10-90% aqueous methanol containing 0.2% phosphoric acid over a 4 min gradient monitoring at 220 nm. MS (ES): m/z 179.93 $[M+H]^+$.

D. 5-Amino-2-cyano-3-methoxypyridine (762D)



2-Cyano-3-methoxy-5-nitropyridine (1.0g, 5.6 mmol) was dissolved in 1:1 EtOAc/ AcOH (10 mL) and heated to 65 °C. Iron powder (1.61g, 28 mmol, 325 mesh) was added and the mixture stirred for two h. The mixture was filtered though Celite and the filtrate concentrated *in vacuo*. The residue was partitioned between

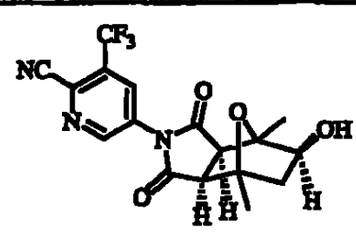
EtOAc and saturated aqueous sodium bicarbonate. The organic layer was separated, washed with brine, dried ($MgSO_4$), filtered and concentrated. The residue was purified by SiO_2 Prep-TLC using CH_2Cl_2 as the eluent to give the compound 762D (0.805g, 97%) as an off-white solid. HPLC: 100% at 1.31 min(YMC S5 ODS column) eluting with 10-90% aqueous methanol containing 0.2% phosphoric acid over a 4 min gradient monitoring at 220 nm. MS (ES): m/z 149.90 $[M+H]^+$.

E. (762E)

5-Amino-2-cyano-3-methoxypyridine (0.1g, 0.67 mmol), 4Å molecular sieves (0.4g), compound 751 (0.142g, 0.67 mmol), and N,N-dimethylacetamide (0.67 mL) were combined in a sealable Pyrex tube and heated at 170 °C for 1 h. The cooled reaction mixture was diluted with EtOAc and filtered. The filtrate was washed 3x with 1:1 saturated NH_4Cl / water and then brine. The filtrate was dried over Na_2SO_4, filtered, concentrated and purified by Prep-TLC using 4:1 chloroform/acetone as the eluent to give the compound 762E (0.062g, 27%) as a white solid. HPLC: 94% at 1.85 min(YMC S5 ODS column) eluting with 10-90% aqueous methanol containing 0.2% phosphoric acid over a 4 min gradient monitoring at 220 nm. MS (ES): m/z 344.02 $[M+H]^+$. The absolute stereochemistry of compound 762E is established by the known stereochemistry of the intermediate compound 751 and the retention of configuration therein. The absolute stereochemistry is as drawn in the above figure and rendered by the nomenclature.

Example 763

[3a*R*-(3aα,4β,5β,7β,7aα)]-5-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-3-(trifluoromethyl)-2-pyridinecarbonitrile (763F)



A. 3-Bromopyridine-1-oxide (763A)

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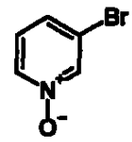
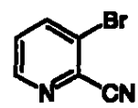


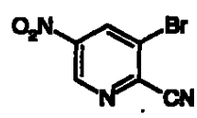
3-Bromopyridine (11.06g, 70 mmol), 30% H_2O_2 (14 mL, 140 mmol), and methyltrioxorhenium (0.035g, 0.14 mmol) were added to 28 mL of CH_2Cl_2 and stirred at rt overnight. A 25 mg portion of manganese dioxide was added and the reaction was stirred until the evolution of oxygen was complete (~1 h). The organic layer was separated, washed with brine, dried over $MgSO_4$, filtered, and concentrated *in vacuo* to give compound 673A (9.84g (81%) as a yellow oil.

B. 3-Bromo-2-cyanopyridine (763B)



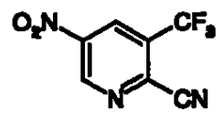
3-Bromopyridine-1-oxide was converted to compound 763B as described in example 762B. The crude product was purified by silica gel chomatography using CH_2Cl_2 as eluent to give compound 763B (6.64g, 65%) as an off-white solid. The product was characterized by ^{1}H NMR.

C. 3-Bromo-2-cyano-5-nitropyridine (763C)



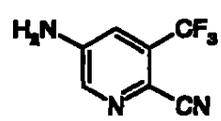
3-Bromo-2-cyanopyridine was converted to compound 763C as described in example 762C. The crude product was purified by silica gel chomatography using 20% hexanes / CH_2Cl_2 as eluent to give compound 763C (1.27g, 16%) as an off-white solid. The product was characterized by ^{1}H NMR.

D. 2-Cyano-5-nitro-3-trifluoromethylpyridine (763D)



3-Bromo-2-cyano-5-nitropyridine (0.23g, 1 mmol) was dissolved in DMF (3 mL). copper iodide (0.023g, 0.12 mmol) and methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (0.1g, 0.5 mmol) were added and the reaction mixture heated at 80 °C for 7 h. Additional methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (0.05g, 0.25 mmol) was added and heating at 80 °C was continued for an additional 8 h. The cooled reaction mixture was poured into water to give a dark oil. Water was decanted and the oil was dissolved in EtOAc and washed with water and brine. The organic layer was dried over $MgSO_4$, filtered, and concentrated *in vacuo*. The residue was purified by silica gel chomatography using CH_2Cl_2 as eluent to compound 763D (0.065g, 43%) as a yellow oil. HPLC: 90% at 2.09 min(YMC S5 ODS column) eluting with 10-90% aqueous methanol containing 0.2% phosphoric acid over a 4 min gradient monitoring at 220 nm.

E. 5-Amino-2-cyano-3-trifluoromethylpyridine (763E)



2-Cyano-5-nitro-3-trifluoromethylpyridine (0.065g, 0.3 mmol) was reacted in the same manner as described in example 762D to give the desired compound 763E (0.046g, 82%) as a gold colored solid after trituration with ether. HPLC: 100 at 2.07 min(YMC S5 ODS column) eluting with 10-90% aqueous methanol containing 0.2% phosphoric acid over a 4 min gradient monitoring at 220 nm. MS (ES): m/z 187.82 $[M+H]^+$.

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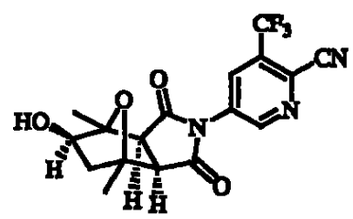
F. [3a*R*-(3aα,4β,5β,7β,7aα)]-5-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-3-(triflu romethyl)-2-pyridinecarbonitrile (763F)

5-Amino-2-cyano-3-trifluoromethylpyridine (0.044g, 0.24 mmol) was reacted with compound 752 (0.087g, 0.41 mmol) according to the procedure described for the synthesis of compound 762. The crude product was purified by SiO_2 Prep-TLC using 15% acetone / $CHCl_3$ as eluent to give compound 763F (0.058g, 65%) as an off-white solid. HPLC: 92% at 2.58 min(YMC S5 ODS column) eluting with 10-90% aqueous methanol containing 0.2% phosphoric acid over a 4 min gradient monitoring at 220 nm. MS (ES): m/z 382.33 $[M+H]^+$. The absolute stereochemistry of compound 763F is established by the known stereochemistry of the intermediate compound 752 and the retention of configuration there in. The absolute stereochemistry is as drawn in the above figure and rendered by the nomenclature.

Example 764

[3a*S*-(3aα,4β,5β,7β,7aα)]-5-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-3-(trifluoromethyl)-2-pyridinecarbonitrile (764)

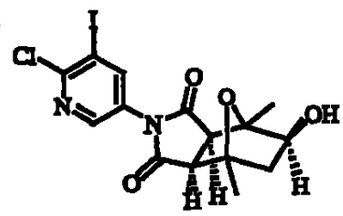


5-Amino-2-cyano-3-trifluoromethylpyridine (0.2g, 1.07 mmol) was reacted with compound 751 (0.386g, 1.82 mmol) according to the procedure described in example 763F. The crude product was purified by SiO_2 Prep-TLC using 15% acetone / $CHCl_3$ as the eluent to give compound 764 (0.293g, 72%) as an off-white solid. HPLC: 92% at 2.58 min(YMC S5 ODS column) eluting with 10-90% aqueous methanol containing 0.2% phosphoric acid over a 4 min gradient monitoring at 220 nm. MS (ES): m/z 382.23 $[M+H]^+$. The absolute stereochemistry of compound 764 is established by the known stereochemistry of the intermediate compound 751 and

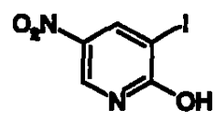
the retention of configuration therein. The absolute stereochemistry is as drawn in the above figure and rendered by the nomenclature.

Example 765

(765D)

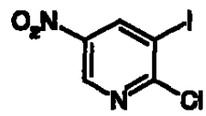


A. 2-Hydroxy-3-iodo-5-nitropyridine (765A)



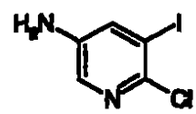
2-Hydroxy-5-nitropyridine (7.0g, 50 mmol) was suspended in 100 mL of 20 sulfuric acid and then treated with potassium iodate (4.2g, 19.6 mmol) dissolved in 10 mL of water. The mixture was heated to 100 °C and potassium iodide (8.0g, 48.2 mmol) dissolved in 20 mL of water was added dropwise over one h. The reaction mixture turns a purplish-red and a precipitate forms. After 0.5 h, the reaction mixture is cooled and filtered. The solid is stirred for 15 minwith 10% sodium *meta*-bisulfite solution, filtered, washed with water and dried at 80 °C overnight on a vacuum pump to give the desired compound 765A (12.32 g, 92%) as a yellow solid. The product was characterized by ^{1}H NMR.

B. 2-Chloro-3-iodo-5-nitropyridine (765B)



2-Hydroxy-3-iodo-5-nitropyridine (2.55g, 9.5 mmol), phosphorous pentachloride (2.60g, 12 mmol) and phosphorous oxychloride (2 mL) were combined in a flask under nitrogen and heated to 140 °C for 45 mins. The cooled reaction mixture was poured over ice to give a solid which was partitioned between CH_2Cl_2 and water. The organic layer was separated, washed with brine, dried ($MgSO_4$), filtered, and the solvent was removed *in vacuo* to give compound 765B (2.25 g, 83%) as a yellow solid. HPLC: 98.5% at 2.75 min(YMC S5 ODS column) eluting with 10-90% aqueous methanol containing 0.2% phosphoric acid over a 4 min gradient monitoring at 220 nm.

C. 5-Amino-2-chloro-3-iodopyridine (765C)



2-Chloro-3-iodo-5-nitropyridine (0.25g, 0.88 mmol) was reacted with iron powder (0.25g, 4.4 mmol) in the manner described in example 762D. Removal of the solvent *in vacuo* gave compound 765C (0.172g, 77%). as a golden yellow solid. HPLC: 100% at 2.32 min(YMC S5 ODS column) eluting with 10-90% aqueous methanol containing 0.2% phosphoric acid over a 4 min gradient monitoring at 220 nm. MS (ES): m/z 255.03 $[M+H]^+$.

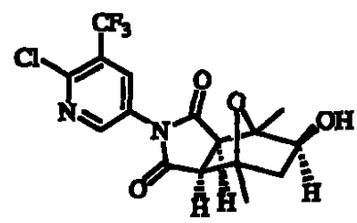
D. (765D)

5-Amino-2-chloro-3-iodopyridine (0.06g, 0.24 mmol) and compound 752 (0.085g, 0.4 mmol) was reacted as previously described in example 762E. The crude product obtained after workup was purified by SiO_2 Prep-TLC using 10 acetone/$CHCl_3$ as eluent to give compound 765D (0.067g, 62%) as an off-white foam. HPLC: 95% at 2.65 min(YMC S5 ODS column) eluting with 10-90% aqueous methanol containing 0.2% phosphoric acid over a 4 min gradient monitoring at 220 nm. MS (ES): m/z 448.96 $[M+H]^+$. The absolute stereochemistry of compound 765D is established by the known stereochemistry of the intermediate compound 752

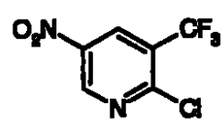
and the retention of configuration therein. The absolute stereochemistry is as drawn in the above figure and rendered by the nomenclature.

Example 766

[3a*R*-(3aα,4β,5β,7β,7aα)]-2-(4-Chloro-3-(trifluoromethyl)pyridinyl)hexahydro-5-hydroxy-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione (766C)

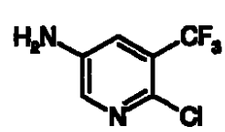


A. 2-Chloro-5-nitro-3-trifluoromethylpyridine (766A)



2-Chloro-3-iodo-5-nitropyridine (1.0g, 3.5 mmol), methyl 2,2-difluoro-2-(fluorosulfonyl)acetate (0.35g, 1.82 mmol), and copper iodide (0.083g, 0.44 mmol) were reacted in DMF (10 mL) according to the method described in example 763D. The crude product was purified by silica gel chomatography using 30% CH_2Cl_2 / hexane as the eluent to give compound 766A (0.278g, 35%) as a colorless oil. The product was characterized by ^{1}H NMR and ^{19}F NMR.

B. 5-Amino-2-chloro-3-trifluoromethylpyridine (766B)



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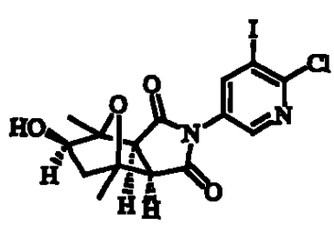
2-Chloro-5-nitro-3-trifluoromethylpyridine (0.16g, 0.68 mmol) and iron powder (0.2g, 3.42 mmol, 325 Mesh) were reacted as described in example 762D. Purification of the crude product by Prep-TLC using 10% ether / CH_2Cl_2 as eluent gave compound 766B (0.098g, 73%) as a yellow solid. HPLC: 89% at 2.52 min(YMC S5 ODS column) eluting with 10-90% aqueous methanol containing 0.2% phosphoric acid over a 4 min gradient monitoring at 220 nm. MS (ES): m/z 197.01 $[M+H]^+$.

C. **[3a*R*-(3aα,4β,5β,7β,7aα)]-2-(4-Chloro-3-(trifluoromethyl)pyridinyl)hexahydro-5-hydroxy-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione (766C)**

5-Amino-2-chloro-3-trifluoromethylpyridine (0.045g, 0.23 mmol) and compound 751 (0.085g, 0.4 mmol) were reacted as described in example 762E. After workup, the crude product was purified by Prep-TLC using 10% acetone/$CHCl_3$ as the eluent to give compound 766C (0.038g, 42%) as an off-white solid. HPLC: 100% at 2.92 min(YMC S5 ODS column) eluting with 10-90% aqueous methanol containing 0.2% phosphoric acid over a 4 min gradient monitoring at 220 nm. MS (ES): m/z 391.06 $[M+H]^+$. The absolute stereochemistry of compound 766C is established by the known stereochemistry of the intermediate compound 751 and the retention of configuration therein. The absolute stereochemistry is as drawn in the above figure and rendered by the nomenclature.

Example 767

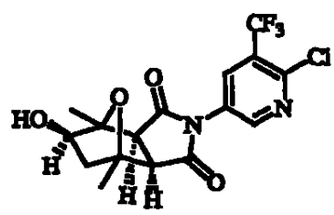


5-Amino-2-chloro-3-iodopyridine (0.06g, 0.24 mmol) and compound 752 (0.085g, 0.4 mmol) were reacted as described in example 762E. The crude reaction

product was purified by Prep-TLC using 20% acetone/$CHCl_3$ as the eluent to give compound 767 (0.061g, 58%) as a yellow solid. HPLC: 100% at 2.64 min(YMC S5 ODS column) eluting with 10-90% aqueous methanol containing 0.2% phosphoric acid over a 4 min gradient monitoring at 220 nm. MS (ES): m/z 449.02 $[M+H]^+$. The absolute stereochemistry of compound 767 is established by the known stereochemistry of the intermediate compound 752 and the retention of configuration therein. The absolute stereochemistry is as drawn in the above figure and rendered by the nomenclature.

Example 768

[3aS-(3aα,4β,5β,7β,7aα)]-2-(4-Chloro-3-(trifluoromethyl)pyridinyl)hexahydro-5-hydroxy-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione (768)



6-Chloro-5-trifluoromethyl-pyridin-3-ylamine (0.045g, 0.23 mmol) and compound 752 (0.085g, 0.4 mmol) were reacted as described in example 762E. The crude product was puified by SiO_2 Prep-TLC using 10% acetone/$CHCl_3$ as the eluent to give compound 768 (0.048g, 54%) as a white solid. HPLC: 100% at 2.91 min(YMC S5 ODS column) eluting with 10-90% aqueous methanol containing 0.2% phosphoric acid over a 4 min gradient monitoring at 220 nm. MS (ES): m/z 391.21 $[M+H]^+$. The absolute stereochemistry of compound 768 is established by the known stereochemistry of the intermediate compound 752 and the retention of configuration therein. The absolute stereochemistry is as drawn in the above figure and rendered by the nomenclature.

Example 769

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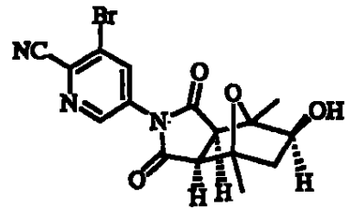
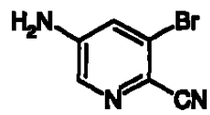


A. 5-Amino-3-bromo-2-cyanopyridine (769A)

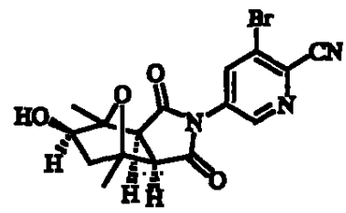


3-Bromo-2-cyano-5-nitropyridine (0.4g, 1.75 mmol) and iron powder (0.51g, 8.8 mmol, 325 Mesh) were reacted as described in example 762D. The crude solid obtained by trituration with ether was purified by SiO_2 Prep-TLC using 4:1 CH_2Cl_2 / ether as eluent to give compound 769A (0.16 g, (65%) as an off-white solid. HPLC: 100% at 1.77 min(YMC S5 ODS column) eluting with 10-90% aqueous methanol containing 0.2% phosphoric acid over a 4 min gradient monitoring at 220 nm. MS (ES): m/z 197.93 $[M+H]^+$.

B. (769B)

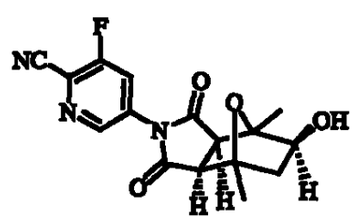
5-Amino-3-bromo-2-cyanopyridine (0.06g, 0.3 mmol) and compound 752 (0.096g, 0.45 mmol) were reacted as previously in example 762E. The crude product was purified by SiO_2 Prep-TLC using 20% acetone/$CHCl_3$ as the eluent to give compound 769B (0.036g, 30%) as an off-white solid. HPLC: 100% at 2.29 min(YMC S5 ODS column) eluting with 10-90% aqueous methanol containing 0.2 phosphoric acid over a 4 min gradient monitoring at 220 nm. MS (ES): m/z 393.33 $[M+H]^+$. The absolute stereochemistry of compound 769B is established by the known stereochemistry of the intermediate compound 752 and the retention of configuration therein. The absolute stereochemistry is as drawn in the above figure and rendered by the nomenclature.

Example 770

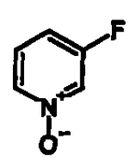


5-Amino-3-bromo-2-cyanopyridine (0.06g, 0.3 mmol) and compound 751 (0.096g, 0.45 mmol) were reacted as previously in example 762E. The crude product was purified by SiO_2 Prep-TLC using 20% acetone/$CHCl_3$ to give compound 770 (0.038g (31%) as an off-white solid. HPLC: 99.2% at 2.28 min(YMC S5 ODS column) eluting with 10-90% aqueous methanol containing 0.2% phosphoric acid over a 4 min gradient monitoring at 220 nm. MS (ES): m/z 392.27 $[M]^+$. The absolute stereochemistry of compound 770 is established by the known stereochemistry of the intermediate compound 751 and the retention of configuration therein. The absolute stereochemistry is as drawn in the above figure and rendered by the nomenclature.

Example 771



A. 3-Fluoropyridine-1-oxide (771A)



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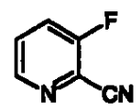
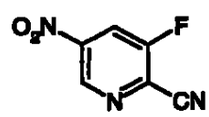
3-Fluoropyridine (9.71g, 100 mmol), 30% H_2O_2 (20 mL, 200 mmol), and methyltrioxorhenium (0.13g, 0.5 mmol) were reacted in 40 mL of CH_2Cl_2 according to the same procedure described in example 760C. Filtration and concentration of the solvent *in vacuo* gave compound 771A (8.79g, 78%) as a yellow solid.

B. 2-Cyano-3-fluoropyridine (771B)



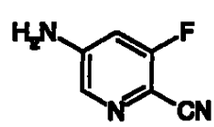
3-Fluoropyridine-1-oxide (10.0g, 88.4 mmol), trimethylsilylcyanide (26.32g, 265.3 mmol), and triethylamine (17.89g, 177 mmol) were reacted in 90 mL of acetonitrile utilizing the procedure described in example 762B. Purification of the crude by silica gel chomatography using CH_2Cl_2 as eluent gives compound 771B (7.5g, 70%) as a light yellow solid.

C. 2-Cyano-3-fluoro-5-nitropyridine (771C)



2-Cyano-3-fluoropyridine (6.5g, 53.2 mmol), tetrabutylammonium nitrate (21.07g, 69.2 mmol), and trifluoroacetic anhydride (14.53g, 69.2 mmol) were reacted in 245 mL of CH_2Cl_2 utilizing the procedure described in example 762C. Purification of the crude by silica gel chomatography using 20% hexanes/ CH_2Cl_2 gave compound 771C (0.12g, 1.3%) as a yellow oil.

D. 5-Amino-2-cyano-3-fluoropyridine (771D)

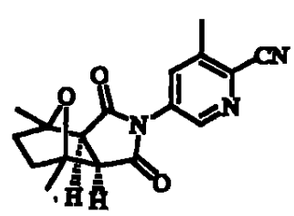


2-Cyano-3-fluoro-5-nitropyridine (0.12g, 0.72 mmol) and iron powder (0.21g, 3.6 mmol, 325 Mesh) were reacted in 1:1 EtOAc/AcOH (10 mL) utilizing the procedure described in example 762D. Trituration of the crude product with ether gave compound 771D (0.093g, 94%) as a pale yellow solid. HPLC: 99% at 1.27 min(YMC S5 ODS column) eluting with 10-90% aqueous methanol containing 0.2% phosphoric acid over a 4 min gradient monitoring at 220 nm. MS (ES): m/z 138.02 $[M+H]^+$.

E. (771E)

5-Amino-2-cyano-3-fluoropyridine (0.45g, 0.33 mmol) and compound 752 (0.104g, 0.49 mmol) were reacted in 0.33 mL of dimethylacetamide utilizing the procedure described in example 762E. The crude residue was purified by Prep-TLC using 20% acetone/$CHCl_3$ as the eluent, yielding compound 771E (0.026g, 23%) as a pale peach-colored solid. HPLC: 90.2% at 1.97 min(YMC S5 ODS column) eluting with 10-90% aqueous methanol containing 0.2% phosphoric acid over a 4 min gradient monitoring at 220 nm. MS (ES): m/z 332.2 $[M+H]^+$. The absolute stereochemistry of compound 771E is established by the known stereochemistry of the intermediate compound 752 and the retention of configuration therein. The absolute stereochemistry is as drawn in the above figure and rendered by the nomenclature.

Example 772



A. 2-Cyano-3-methyl-5-nitropyridine (772A)

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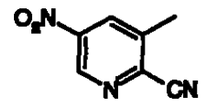
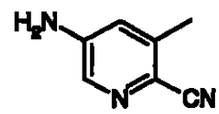


Commercially available 2-cyano-3-methylpyridine (2.36g, 20 mmol), tetrabutylammonium nitrate (6.7g, 22 mmol) and trifluoroacetic anhydride (4.20g, 20 mmol) were reacted in 65 mL of CH_2Cl_2 utilizing the procedure described in example **762B**. Purification of the crude by silica gel chomatography using 20% hexanes/ CH_2Cl_2 as the eluent gives compound **772A** (1.05g (32%) as a light yellow solid.

B. 5-Amino-2-cyano-3-methylpyridine (772B)

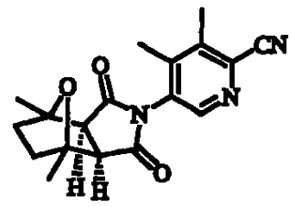


2-Cyano-3-methyl-5-nitropyridine (0.2 g, 1.23 mmol) was dissolved in 6 mL of 90% ethanol and calcium chloride (0.07g, 0.64 mmol) was added followed by iron powder (0.62g, 11.1 mmol, 325 Mesh). The heterogeneous mixture was stirred for one h. The mixture was filtered though Celite and concentrated to give compound **772B** (0.13g, 81%) as a light-brown solid.

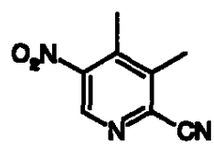
C. (772C)

5-Amino-2-cyano-3-methylpyridine (0.067g, 0.5 mmol), compound **20A** (0.103g, 0.53 mmol), $MgSO_4$ (0.15g, 1.25 mmol), triethylamine (0.25g, 2.5 mmol) and 1 mL of toluene were combined in a sealed tube and heated at 145 °C for 16 h. The cooled mixture was diluted with CH_2Cl_2, filtered, and purified by silica gel chomatography using 5% ether/ CH_2Cl_2 as the eluent to give compound **772C** (0.055g, 35%) as an off-white solid. HPLC: 100% at 2.49 min(YMC S5 ODS column) eluting with 10-90% aqueous methanol containing 0.2% phosphoric acid over a 4 min gradient monitoring at 220 nm. MS (ES): m/z 312.2 $[M+H]^+$.

Example 773

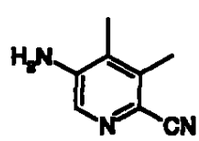


A. 2-Cyano-3,4-dimethyl-5-nitropyridine (773A)



2-Cyano-3-methyl-5-nitropyridine (0.33g, 2 mmol) was dissolved in 10 mL of THF and cooled in a dry ice/acetone bath under nitrogen. Methylmagnesium bromide (1.33 mL, 4 mmol) was added via syringe over five mins. The reaction was stirred for 2 h at -70°C. DDQ (0.068g, 3 mmol) in 7 mL of THF was added and the mixture warmed to 25 °C. The solvent was removed *in vacuo* and the residue was purified by silica gel chomatography using CH_2Cl_2 as the eluent to give compound 773A (0.15g, 42%) as a red oil.

B. 5-Amino-2-cyano-3,4-dimethylpyridine (773B)



2-Cyano-3,4-dimethyl-5-nitropyridine (0.15g, 0.85 mmol), calcium chloride (0.05g, 0.42 mmol), and iron powder (0.44g, 7.8 mmol, 325 Mesh) were reacted as described in example 772B. Purification of the crude product by silica gel chomatography using 1:1 ether/ CH_2Cl_2 as the eluent gave compound 773B (0.054g, 50%) as a yellow solid.

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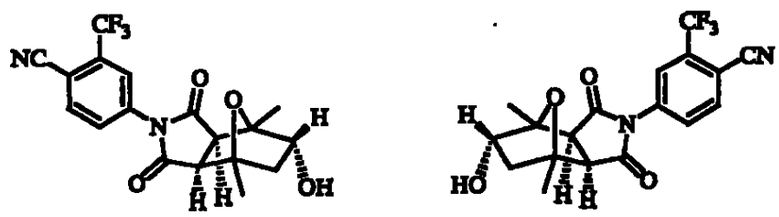
C. (773C)

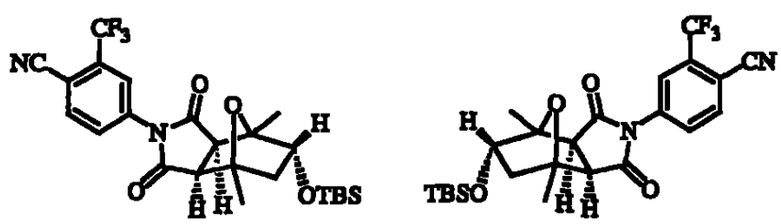
5-Amino-2-cyano-3,4-dimethylpyridine (0.05g, 0.34 mmol) and compound **20A** (0.1g, 0.5 mmol) were reacted as described in example 772C. The crude product obtained after filtration though Celite was purified by silica gel chomatography using 10% ether/ CH_2Cl_2 as the eluent to give compound 773C (0.33g, 30%). as a yellow solid. HPLC: 90% at 2.58 min(YMC S5 ODS column) eluting with 10-90% aqueous methanol containing 0.2% phosphoric acid over a 4 min gradient monitoring at 220 nm. MS (ES): m/z 326.22 $[M+H]^+$.

Example 774

[3a*R*-(3aα,4β,5α,7β,7aα)]-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile & [3a*S*-(3aα,4β,5α,7β,7aα)]-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (774Bi and 774Bii)



A. **[3a*R*-(3aα,4β,5α,7β,7aα)]-4-[5-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile & [3a*S*-(3aα,4β,5α,7β,7aα)]-4-[5-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile (774Ai & 774Aii)**



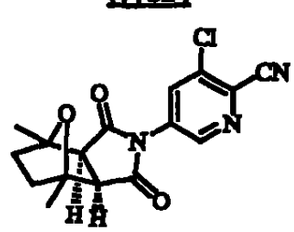
Racemic compound **222C** was separated into its enantiomers by normal phase preparative chiral HPLC (CHIRALPAK AD 5x50 cm column; eluting with 7% EtOH in hexanes (isocratic) at 50 mL/min) to give the faster eluting compound **774Ai** (18 mins) and the slower eluting compound **774Aii**.

B. [3a*R*-(3aα,4β,5α,7β,7aα)]-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile & [3a*S*-(3aα,4β,5α,7β,7aα)]-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (774Bi & 774Bii)

774Ai and **774Aii** (0.12g, 0.25 mmol) were each dissolved in 2 mL of THF and 2 mL of 10% HCl/MeOH was added and the reactions stirred overnight at rt. Saturated sodium bicarbonate and EtOAc were added and the organic layer was separated, washed with brine, dried (Na_2SO_4), filtered, and concentrated *in vacuo* to givecompound **774Bi** (0.084mg, 88%) and compound **774Bii** (0.076g, 82%). as white solids. Compound **774Bi**: HPLC: 100% at 2.89 min(YMC S5 ODS column) eluting with 10-90% aqueous methanol containing 0.2% phosphoric acid over a 4 min gradient monitoring at 220 nm. MS (ES): m/z 381.19 [M+H]. Compound **774Bii**: HPLC: 100% at 2.89 min(YMC S5 ODS column) eluting with 10-90% aqueous methanol containing 0.2% phosphoric acid over a 4 min gradient monitoring at 220 nm. MS (ES): m/z 381.16 $[M+H]^+$. The absolute stereochemistry of compounds **774Bi** & **774Bii** has not been established. Although each compound represents a single antipode, the nomenclature and structure shown does not reflect the absolute stereochemistry of the compound.

Example 775

(775F)



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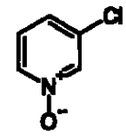
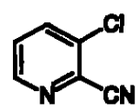
A. 3-Chloropyridine-1-oxide (775A)



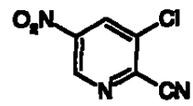
Commercially available 3-chloropyridine (11.36g, 100 mmol) was dissolved in 60 mL of acetic acid and 30% hydrogen peroxide (15 mL) was added. The reaction mixture was heated to 70 °C for 16 h. The cooled reaction mixture was diluted with chloroform and stirred with solid potassium carbonate. The mixture was filtered and solvent removed *in vacuo* to give compound 775A (10.21g, 79%) as a yellow-green oil.

B. 3-Chloro-2-cyanopyridine (775B)



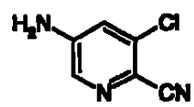
3-Chloropyridine-1-oxide (2.59g, 20 mmol), trimethylsilyl cyanide (5.95g, 60 mmol), and triethylamine (4.05g, 40 mmol) were combined in 40 mL of acetonitrile and reacted as described in example 763A. The solvent was removed *in vacuo* and the residue partitioned between CH_2Cl_2 and 3M potassium carbonate. The organic layer was separated, washed with brine, dried ($MgSO_4$), and concentrated *in vacuo*. Purification of the crude product by silica gel chomatography using 5% ether/ CH_2Cl_2 as the eluent gave compound 775B (1.84g, 67%) as a white crystalline solid. HPLC: 100% at 1.64 min(YMC S5 ODS column) eluting with 10-90% aqueous methanol containing 0.2% phosphoric acid over a 4 min gradient monitoring at 220 nm. MS (ES): m/z 139.0 $[M+H]^+$.

C. 3-Chloro-2-cyano-5-nitropyridine (775C)



3-Chloro-2-cyanopyridine (1.75g, 12.7 mmol), tetrabutylammonium nitrate (5.02g, 16.5 mmol), and trifluoroacetic anhydride (3.15g, 15 mmol) were combined in 65 mL of CH_2Cl_2 and reacted as described in example 762C. The crude product was purified by silica gel chomatography using CH_2Cl_2 as the eluent to give compound 775C (0.43g, 16%) as a pale yellow solid.

D. 5-Amino-3-chloro-2-cyanopyridine (775D)



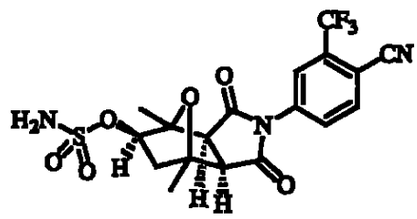
3-Chloro-2-cyano-5-nitropyridine (0.35g, 1.9 mmol), iron powder (0.56g, 10 mmol, 325 Mesh) and calcium chloride (0.06g, 0.55 mmol) were combined in 10 mL of 90% ethanol and as described in example 772B. Purification of the crude product via silica gel chomatography using 10% ether/ CH_2Cl_2 as the eluent gives compound 775D (0.14g, 43%) as a light brown solid. HPLC: 95.5% at 1.69 min(YMC S5 ODS column) eluting with 10-90% aqueous methanol containing 0.2% phosphoric acid over a 4 min gradient monitoring at 220 nm. MS (ES): m/z 154.03 $[M+H]^+$.

E. (775E)

5-Amino-3-chloro-2-cyanopyridine (0.05g, 0.33 mmol) and compound 20A (0.07g, 0.36 mmol) were reacted as described in example 772C. The crude product obtained after workup was purified by silica gel chomatography using 5% ether/ CH_2Cl_2 to give compound 775E (0.054g, 50%) as an off-white solid. HPLC: 97.6 at 2.86 min(YMC S5 ODS column) eluting with 10-90% aqueous methanol containing 0.2% phosphoric acid over a 4 min gradient monitoring at 220 nm. MS (ES): m/z 332.16 $[M+H]^+$.

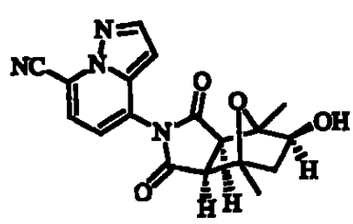
300

Example 776

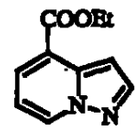


To a clear solution of compound 741Di (190 mg, 0.5 mmol) in anhydrous dioxane (3.5 mL) was added Burgess Reagent (143 mg, 0.6 mmol) at rt under Argon. After the mixture was stirred at rt for 70 min, bis(cyclopentadienyl) titanium dichloride (137 mg, 0.55 mmol) was added. The mixture was stirred at 100 °C for 1 day, then cooled to rt. H_2O and a saturated aqueous solution of $KHSO_4$ were added. The mixture was extracted with EtOAc (3X). The combined extracts were dried over Na_2SO_4 and concentrated under reduced pressure. Purification by silica gel flash chomatography eluting with EtOAc/heptane (gradient from 1:4 to 1:0 ratio) gave compound 776 (170 mg, 74%) as a yellow glassy solid. HPLC: 99% at 3.27 min (retention time) (YMC S5 ODS-A column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 mincontaining 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 458 [M-H]. The absolute stereochemistry of compound 776 is established by the known stereochemistry of the intermediate compound 741Di and the retention of configuration therein. The absolute stereochemistry is as drawn in the above figure and rendered by the nomenclature.

Example 777

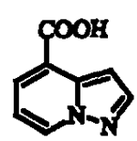


A. Pyrazolo[1,5-a]pyridine-4-carboxylic acid ethyl ester (777A)



To a clear solution of 2-methyl-nicotinic acid ethyl ester (50.6 g, 306 mmol) in anhydrous methylene chloride (200 mL) was added O-mesitylenesulfonylhydroxylamine (73 g, 337 mmol; prepared according to a literature procedure described in Krause; J.G., Syntheais 1972, 140); in portions at 0 °C. The solution obtained was stirred at 0 °C for 15 min, and then at rt for 1 h. Concentration under reduced pressure gave a yellow solid. After the solid was dissolved in anhydrous DMF (300 mL), N,N-dimethylformamide dimethyl acetal (122 mL, 918 mmol) was added at 0°C. The mixture was stirred at 0°C for 15 min, and then at 90°C for 3 h. The reaction mixture was concentrated under reduced pressure, mixed with H_2O (200 mL), and extracted with Et_2O (3x180 mL). The combined organic solutions were washed sequentially with brine (50 mL), 1N aqueous HCl (50 mL), and brine (50 mL), and dried over Na_2SO_4. Filtration through a SiO_2 column, which was then eluted with 30% EtOAc in heptane, gave compound 777A (43.3 g, 74%) as a yellow solid. HPLC: 80% at 3.20 min (retention time) plus 20% corresponding methyl ester at 2.83 min (retention time) (YMC S5 ODS-A column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 mincontaining 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 191 $[M+H]^+$.

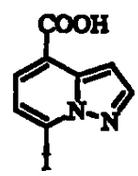
B. Pyrazolo[1,5-a]pyridine-4-carboxylic acid (777B)



To a stirred mixture of pyrazolo[1,5-a]pyridine-4-carboxylic acid ester (35.1 g, 185 mmol), KOH (85%, 25 g, 379 mmol), and MeOH (200 mL), cooled to rt in a water bath, was added H_2O slowly. The reaction mixture obtained was stirred at rt for 1.5 h and then concentrated under reduced pressure to remove MeOH. A minimal amount of H_2O was added to the residue to make a clear solution that was then

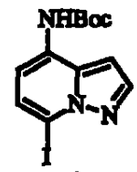
acidified to pH=1 at 0°C with aqueous HCl (concentrated HCl, 11 mL; 5N HCl, 10 mL, Then 2N and 1N HCl). After heating on a steam bath, the mixture was cooled. The solid was filtered, washed with H_2O, and dried under vacuum to give compound 777B (29 g, 97%) as a yellow solid. HPLC: 100% at 2.14 min (retention time) (YMC S5 ODS-A column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 mincontaining 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 163 $[M+H]^+$.

C. 7-Iodo-pyrazolo[1,5-a]pyridine-4-carboxylic acid (777C)



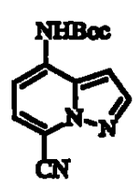
To a stirred suspension of pyrazolo[1,5-a]pyridine-4-carboxylic acid (29 g, 179 mmol) in anhydrous THF (1000 mL) cooled at 0°C was added lithium hexamethyldisilazide solution (1M in THF, 200 mL, 200 mmol). After the mixture was stirred at 0°C for 30 min, additional LHMDS solution (1M in THF, 320 mL, 320 mmol) was added at -4°C. After the mixture was stirred for 10 min, iodine (55 g, 215 mmol) was added in portions. The reaction mixture was stirred at -4°C for 1.5 h, at rt for 1 h, and then cooled to 0°C. Aqueous HCl (5N, 40 mL) and NaS_2O_3 solution (10 g in 40 mL of H_2O) were added. The mixture was stirred at 0°C for 30 min, and then concentrated under reduced pressure. The residual mixture was mixed with sat. $NaHCO_3$ solution (100 mL), ethyl ether (150 mL), and H_2O (130 mL). The ether solution was separated and extracted with H_2O (50 mL). The combined aqueous solutions were washed with ethyl ether (150 mL), acidified to pH=1 with saturated aqueous solution of $KHSO_4$, heated in a steam bath, and then cooled. The solid was filtered, washed with H_2O, and then dried to give compound 777C (50 g, 97%) as a yellow solid. HPLC: 100% at 2.88 min (retention time) (YMC S5 ODS-A column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 mincontaining 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 289 $[M+H]^+$.

D. (7-Iodo-pyrazolo[1,5-a]pyridin-4-yl)-carbamic acid tert-butyl ester (777D)



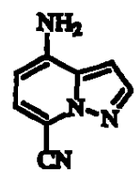
To a clear solution of 7-iodo-pyrazolo[1,5-a]pyridine-4-carboxylic acid (23.4 g, 81.2 mmol) and diisopropylethylamine (65 mL) in tert-butanol (250 mL) and anhydrous toluene (200 mL) was added diphenyl phosphoryl azide (25 mL, 114 mmol) under argon. After the mixture was stirred at rt for 30 min, the temperature was raised slowly to 90°C. The mixture was stirred at 90°C overnight and concentrated under reduced pressure to remove the solvents. The residue was partitioned between EtOAc (200 mL) and aqueous NaOH solution (2N, 75 mL). The aqueous solution was separated and extracted with EtOAc (100 mL). The combined organic solutions were washed with aqueous NaOH solution (1N, 75 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification by silica gel flash chomatography eluting with EtOAc/heptane (gradient from 0:1 to 1:1 ratio) gave a brownish solid. Recrystallization in heptane with some EtOAc gave compound 777D (19.6 g, 67%) as a yellow solid. HPLC: 95% at 3.83 min (retention time) (YMC S5 ODS-A column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 mincontaining 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 360 $[M+H]^+$.

E. (7-Cyano-pyrazolo[1,5-a]pyridin-4-yl)-carbamic acid tert-butyl ester (777E)



A mixture of (7-iodo-pyrazolo[1,5-a]pyridin-4-yl)-carbamic acid tert-butyl ester (36 mg, 0.1 mmol), zinc cyanide (24 mg, 0.2 mmol), tetrakis(triphenylphosphine) palladium (0) (23 mg, 0.02 mmol), and anhydrous DMF (1 mL) was degassed with argon. Then, the mixture was stirred at 80°C for 4.5 h, cooled to rt, mixed with EtOAc (6 mL), and filtered. The filtrate was concentrated under reduced pressure. Purification by silica gel flash chomatography eluting with EtOAc/heptane (gradient from 1:4 to 1:2 ratio) gave compound 777E (24 mg, 93%) as a white solid. HPLC: 93% at 3.64 min (retention time) (YMC S5 ODS-A column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 mincontaining 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 259 $[M+H]^+$.

F. 4-Amino-pyrazolo[1,5-a]pyridine-7-carbonitrile (777F)



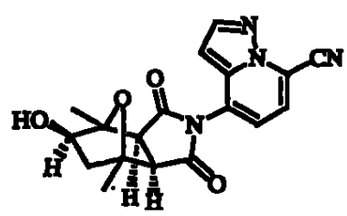
To a clear solution of (7-cyano-pyrazolo[1,5-a]pyridin-4-yl)-carbamic acid tert-butyl ester (3 g, 11.6 mmol) in methylene chloride (40 mL) was added TFA (8 mL). The mixture was stirred at rt for 3 h, and then concentrated under reduced pressure. The residue was partitioned between EtOAc (100 mL) and sat. $NaHCO_3$ solution (50 mL). The aqueous solution was separated and extracted with EtOAc (2x50 mL). The combined organic solutions were dried over Na_2SO_4, filtered though SiO_2 pad, and concentrated under reduced pressure. Crystallization in EtOAc and 95% EtOH gave compound 777F (1.07 g, 58%) as a dark yellow solid. HPLC: 97% at 1.96 min (retention time) (YMC S5 ODS-A column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 mincontaining 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 159 $[M+H]^+$.

G. (777G)

A mixture of 4-amino-pyrazolo[1,5-a]pyridine-7-carbonitrile (135 mg, 0.85 mmol), compound 752 (225 mg, 1.06 mmol), 4Å molecular sieve powder (850

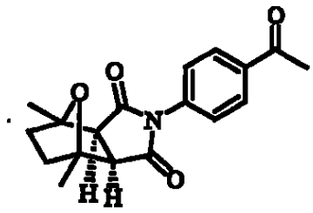
mg), and DMA (0.85 mL) was stirred under argon at rt for 10 min, at 170°C for 3 h, and then cooled to rt. The molecular sieve powder was filtered off, and the filtrate was concentrated under reduced pressure. Purification by silica gel flash chomatography eluting with EtOAc (gradient with MeOH from 0% to 5%) gave compound 777G (98 mg, 33%) as a yellowish solid. HPLC: 99% at 2.28 min (retention time) (YMC S5 ODS-A column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 mincontaining 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 353 $[M+H]^+$. The absolute stereochemistry of compound 777G is established by the known stereochemistry of the intermediate compound 752 and the retention of configuration therein. The absolute stereochemistry is as drawn in the above figure and rendered by the nomenclature.

Example 778



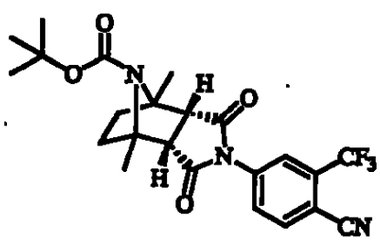
A mixture of 4-amino-pyrazolo[1,5-a]pyridine-7-carbonitrile (60 mg, 0.38 mmol), compound 751 (110 mg, 0.52 mmol), $MgSO_4$ (360 mg, 3 mmol), diisopropylethylamine (0.35 mL, 2 mmol), and anhydrous toluene (0.6 mL) was stirred at 135°C under argon for 20 h. Purification by silica gel flash chomatography eluting with EtOAc (gradient with MeOH from 0% to 5%) gave compound 778 (115 mg, 86%) as a greyish solid. HPLC: 98% at 2.28 min (retention time) (YMC S5 ODS-A column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 mincontaining 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 353 $[M+H]^+$. The absolute stereochemistry of compound 778 is established by the known stereochemistry of the intermediate compound 751 and the retention of configuration therein. The absolute stereochemistry is as drawn in the above figure and rendered by the nomenclature.

Example 779

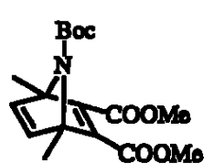


A clear solution of compound 20A (50 mg, 0.25 mmol), p-aminoacetophenone (68 mg, 0.5 mmol), and N,N-dimethylformamide dimethyl acetal (0.065 mL, 0.49 mmol) in anhydrous N,N-dimethylformamide (0.2 mL) was stirred at 100°C under argon for 18 h, and then concentrated. Purification by silica gel flash chomatography on SiO_2 eluting with EtOAc/heptane (gradient from 1:4 to 1:0 ratio) gave a solid that was crystallized in a mixture of EtOAc and heptane to give compound 779 (11 mg, 14%) as a white solid. HPLC: 98% at 2.89 min (retention time) (YMC S5 ODS-A column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 mincontaining 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 314 $[M+H]^+$.

Example 780

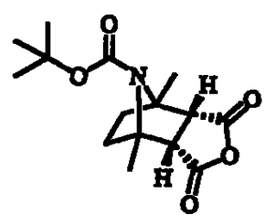


A. **1,4-Dimethyl-7-aza-bicyclo[2.2.1]hepta-2,5-diene-2,3,7-tricarboxylic acid 7-tert-butyl ester 2,3-dimethyl ester (780A)**



A mixture of crude 2,5-dimethyl-pyrrole-1-carboxylic acid tert-butyl ester (prepared according to a literature (Haiser, H.-P.; et al. J. Org. Chem. 1984 49(22) 4203-4209); 500 mg) and dimethyl acetylenedicarboxylate (0.5 mL, ca 4 eq) was stirred at 120°C under argon for 2 h. Purification by silica gel flash chomatography on SiO_2 eluting with EtOAc/heptane (gradient from 1:20 to 1:2 ratio) gave compound **780A** (166 mg, 50% yield) as a colorless liquid. HPLC: 90% at 3.67 min (retention time) (YMC S5 ODS-A column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 mincontaining 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm).

B. (780B)

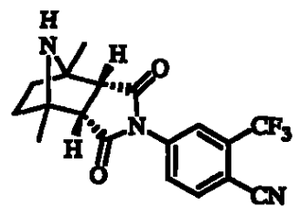


To a clear solution of 1,4-dimethyl-7-aza-bicyclo[2.2.1]hepta-2,5-diene-2,3,7-tricarboxylic acid 7-tert-butyl ester 2,3-dimethyl ester (1.5 g, 4.4 mmol) in MeOH (10 mL) and H_2O (5 mL) cooled in ice water was added KOH (2.9 g, 44 mmol) in portions. More H_2O (5 mL) was then added. After the reaction mixture was stirred at rt for 1 h, hydrazine (1.4 mL, 44 mmol), HCl (2N aqueous solution, 17mL, 34 mmol), and hydrogen peroxide (50% aqueous solution, 1.27mL, 22 mmol) were added sequentially at 0°C. The reaction mixture was stirred at rt for 3 h, and then concentrated under reduced pressure to remove MeOH. The aqueous solution obtained was acidified to pH=1 with saturated aqueous solution of $KHSO_4$ and extracted with EtOAc (3X). The combined extracts were dried over Na_2SO_4, and concentrated under reduced pressure to give a yellow solid. The yellow solid above was dissolved in acetic anhydride (15 mL). The solution was stirred at 100°C for 1 h. Concentration under reduced pressure gave 1.3 g (100%) of compound **780B** as an orange solid.

C. (780C)

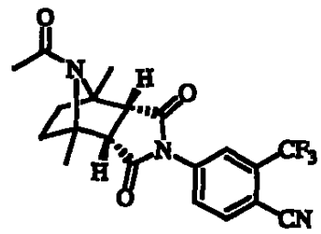
A mixture of compound **780B** (0.8g, 2.7 mmol), 4-amino-2-trifluoromethylbenzonitrile (0.5 g, 2.7 mmol), $MgSO_4$ (2.6 g, 22 mmol), diisopropylethylamine (2.35 mL, 13.5 mmol), and anhydrous toluene (2.9 mL) was stirred at 135°C under argon for 15 h. The solid was filtered and washed with EtOAc. The filtrate was concentrated under reduced pressure. Purification by silica gel flash chomatography eluting with EtOAc/heptane (gradient from 1:4 to 1:2 ratio) gave compound **780C** (1.03 g, 82%) as a glassy solid. HPLC: 100% at 4.26 min (retention time) (YMC S5 ODS-A column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 mincontaining 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 462.34 $[M-H]^-$.

Example 781



To a solution of compound **780C** (770 mg, 1.66 mmol) in methylene chloride (10 mL) was added trifloroacetic acid (5 mL). The reaction mixture was stirred at rt for 40 min. The mixture was then concentrated under reduced pressure, basified with sat. $NaHCO_3$ solution, and extracted with EtOAc (3X). The combined extracts were dried over Na_2SO_4 and concentrated under reduced pressure to give compound **781** (600 mg, 99%) as an orange solid. HPLC: 100% at 2.55 min (retention time) (YMC S5 ODS-A column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 mincontaining 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 364 $[M+H]^+$.

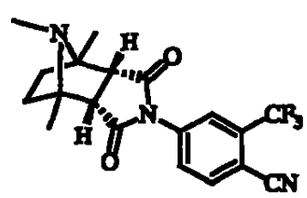
Example 782



To a clear solution of compound 781 (27 mg, 0.074 mmol) and triethylamine (0.061 mL, 0.44 mmol) in anhydrous methylene chloride (3 mL) was added acetyl chloride (0.016 mL, 0.22 mmol) at 0°C under argon. After the mixture was stirred at 0°C for 30 min and at rt for 30 min, sat. $NaHCO_3$ solution was added. After the mixture was stirred for 15 min, the organic solution was separated, dried over Na_2SO_4, and filtered though a SiO_2 pad that was then rinsed with EtOAc. The filtrate was concentrated under reduced pressure. Crystallization in a mixture of EtOAc and heptane gave compound 782 (19 mg, 63%) as a white solid. HPLC: 99% at 3.56 min (retention time) (YMC S5 ODS-A column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 mincontaining 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 406 $[M+H]^+$.

Example 783

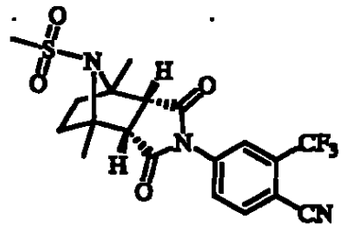
(3aα,4β,7β,7aα)-4-(Octahydro-4,7,8-trimethyl-1,3-dioxo-4,7-imino-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (783)



A mixture of compound 781 (180 mg, 0.5 mmol), formaldehyde (37% aqueous solution, 0.11 mL, 1.5 mmol), $NaHB(OAc)_3$ (318 mg, 1.5 mmol), and 1,2-dichloroethane (9 mL) was stirred at rt under argon overnight, and then dried over Na_2SO_4. Purification by silica gel flash chomatography eluting with EtOAc (gradient with triethylamine from 2% to 10%) gave compound 783 (160 mg, 84%) as a white solid. HPLC: 100% at 2.46 min (retention time) (YMC S5 ODS-A column 4.6 x 50

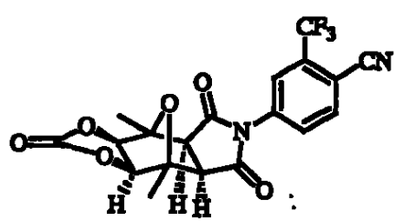
mm eluting with 10-90% aqueous methanol over 4 mincontaining 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 378 $[M+H]^+$.

Example 784



To a clear solution of compound **781** (20 mg, 0.055 mmol) and triethylamine (0.04 mL, 0.24 mmol) in anhydrous methylene chloride (1 mL) cooled at 0°C was added methanesulfonyl chloride (0.01 mL, 0.13 mmol). After the reaction mixture was stirred at 0°C for 30 min, sat. $NaHCO_3$ solution (0.1 mL) was added. The mixture was stirred for 10 min, dried over Na_2CO_3, and filtered though a SiO_2 pad that was then rinsed with EtOAc. The filtrate was concentrated under reduced pressure. Crystallization in a mixture of EtOAc and heptane gave compound **784** (14 mg, 58%) as a white solid. HPLC: 98% at 3.58 min (retention time) (YMC S5 ODS-A column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 mincontaining 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 440 $[M-H]^-$.

Example 785

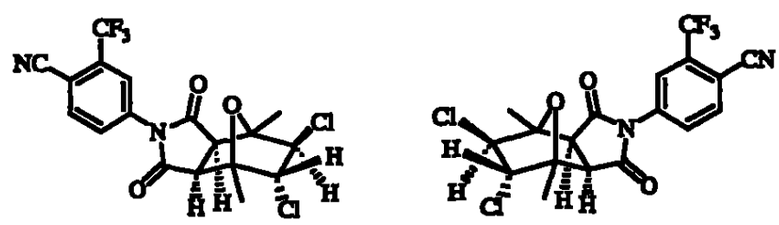


To a stirred solution of compound **230Bi** (50 mg, 0.13 mmol) and triethylamine (0.09 mL, 0.65 mmol) in anhydrous methylene chloride (5 mL) was added phosgene (20% in toluene, 0.25 mL, 0.48 mmol) dropwise. After the reaction

was completed, sat. $NaHCO_3$ solution was added. The mixture was extracted with EtOAc (3X). The combined extracts were dried over Na_2SO_4, filtered though a SiO_2 pad, and concentrated under reduced pressure. Crystallization in a mixture of EtOH and H_2O gave compound 785 (40 mg, 73%) as a white solid. HPLC: 100% at 3.55 min (retention time) (YMC S5 ODS-A column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 mincontaining 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 377 [M-CO2-H]$^-$.

Examples 786i & 786ii

[3a*R*-(3aα,4β,5β,6α,7β,7aα)]-4-(Octahydro-5,6-dichloro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile & [3a*R*-(3aα,4β,5β,6α,7β,7aα)]-4-(Octahydro-5,6-dichloro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (786i & 786ii)



To a stirred mixture of compound 230Bi (544 mg, 1.5 mmol), acetone (10 mL), acetic acid (2 mL), and brine (2 mL) cooled at 0°C was added bleach (5 mL) dropwise. The clear solution obtained was stirred at rt for 1 h, and then concentrated under reduced pressure. The residual mixture was extracted with EtOAc (3X). The combined extracts were dried over Na_2SO_4, and concentrated under reduced pressure. Purification by silica gel flash chomatography on SiO_2 eluting with EtOAc/heptane (gradient from 1:9 to 1:2 ratio) gave a white solid that was crystalized in a mixture of EtOAc and heptane to give 301 mg (46%) of racemic mixture of compounds 786i & 786ii as a white solid. HPLC: 100% at 4.11 min (retention time) (YMC S5 ODS-A column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 mincontaining 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 395 [M-HCl-H]$^-$.

Chiral HPLC separation the raacemic mixture gave two enantiomers: compound **786i** & compound **786ii**.

Chiral HPLC conditions employed for the separation:

Chiral HPLC Condition

Column:	CHIRALPAK AD	
	50 x 500 mm, 20 µ	
Temperature:	rt	
Injection Volume:	20 mL	
Mobile Phase:	A:	IPA with 0.1% diethylamine
	B:	Heptane with diethylamine
	Isocratic, 45% of A, 60 min.	
Flow Rate:	50 mL/min.	
UV Detection:	245 nm	

Chiral HPLC conditions employed for the analysis:

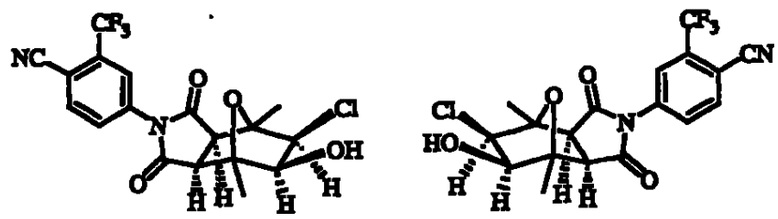
Chiral HPLC Condition

Column:	CHIRALPAK AD	
	4.6 x 250 mm, 10 µ	
Temperature:	25°C	
Injection Volume:	10 µL	
Mobile Phase:	A:	IPA with 0.1% diethylamine
	B:	Heptane with diethylamine
	Isocratic, 45% of A, 15 min.	
Flow Rate:	1 mL/min.	
UV Detection:	245 nm	
RT:	Compound **786i**	10.6 min
	Compound **786ii**	7.0 min

The absolute stereochemistry of compounds 785i & 785ii has not been established. Although each compound represents a single antipode, the nomenclature and structure shown does not reflect the absolute stereochemistry of the compound.

Example 787i & 787ii

[3a*R*-(3aα,4β,5β,6β,7β,7aα)]-4-(Octahydro-5-chloro-6-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile & [3a*S*-(3aα,4β,5β,6β,7β,7aα)]-4-(Octahydro-5-chloro-6-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (787i & 787ii)



To a stirred solution of compound 230Bi (181 mg, 0.5 mmol) in anhydrous methylene chloride (4 mL) cooled at –78°C under argon was added chromyl chloride (0.048 mL, 0.6 mmol) dropwise. After the reaction mixture was stirred at –78°C for 1 h, the reaction temperature was raised slowly to rt. The reaction mixture was stirred at rt for 2 h. Sat. $NaHCO_3$ solution (10 mL) was then added at 0°C with vigorous stirring. The mixture was extracted with EtOAc (3X). The combined extracts were dried over Na_2SO_4, and concentrated under reduced pressure. Purification by silica gel flash chomatography on SiO_2 eluting with EtOAc/heptane (gradient from 1:4 to 1:0 ratio) gave 98 mg (47%) of racemic mixture of compounds 787i & 787ii as a white solid. HPLC: 100% at 3.32 min (retention time) (YMC S5 ODS-A column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 mincontaining 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 377 $[M-HCl-H]^-$.

Chiral HPLC separation of the racemate gave two enantiomers: compound 787i & compound 787ii.

Chiral HPLC conditions employed for the separation:

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Chiral HPLC Condition

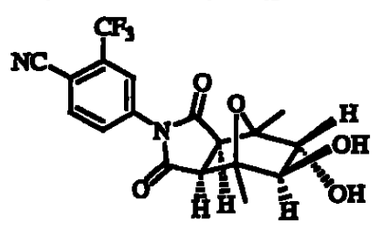
Column:	CHIRALCEL OD	
	50 x 500 mm, 20 μ	
Temperature:	rt	
Injection Volume:	20 mL	
Mobile Phase:	A:	IPA with 0.1% diethylamine
	B:	Heptane with 0.1% diethylamine
	Isocratic, 35% of A, 90 min.	
Flow Rate:	50 mL/min.	
UV Detection:	245 nm	

RT:	Compound 787i	41 min
	Compound 787ii	51 min

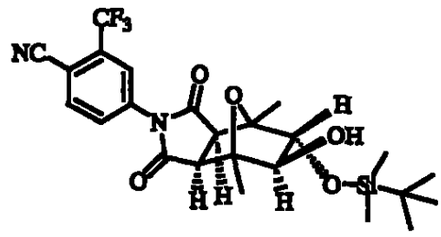
The absolute stereochemistry of compounds 787i & 787ii has not been established. Although each compound represents a single antipode, the nomenclature and structure shown does not reflect the absolute stereochemistry of the compound.

Example 788

(3aα,4β,5β,6α,7β,7aα)-4-(Octahydro-5,6-dihydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (788B)



A. **(3aα,4β,5α,6β,7β,7aα)-4-(Octahydro-5-[[(1,1-dimethylethyl)dimethylsilyl]oxy]-6-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (788A)**

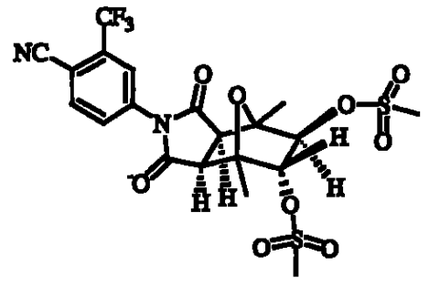


To a stirred solution of compound 222B (1.49 g, 3 mmol) in anhydrous THF (31 mL) was added borane-methyl sufide complex (0.61 mL, 6.1 mmol) dropwise at rt under argon. After the reaction mixture was stirred at rt for 1.5 h, EtOH (20 mL) was added slowly at 0°C, followed by phosphate buffer (pH = 7.2, 39 mL), and H_2O_2 (30% aqueous, 12 mL). The mixture was vigorously stirred at 0°C for 30 min, at rt for 21 h, and then concentrated under reduced pressure at rt to remove THF. The residue was partitioned between EtOAc (160 mL) and brine (160 mL). The organic solution was separated, washed with 5% Na_2SO_3 solution (120 mL), dried over Na_2SO_4, and concentrated under reduced pressure. Purification by silica gel flash chomatography on SiO_2 eluting with EtOAc/heptane (gradient from 1:8 to 1:0 ratio) compound 788A (1.15 g, 75%) as a foam solid.

B. [3a*S*-(3aα,4β,5β,6α,7β,7aα)]-4-(Octahydro-5,6-dihydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (788B)

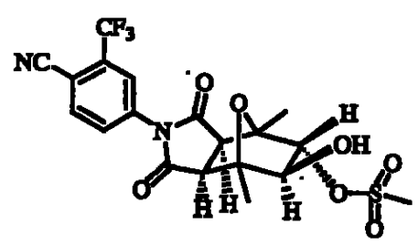
To a stirred solution of compound 788A (0.67 g, 1.3 mmol) in EtOH (100%, 19 mL) was added concentrated HCl (3.7 mL). The mixture was stirred at rt for 21 h, at 40°C for 3 h, and then concentrated under reduced pressure. Purification by silica gel flash chomatography eluting with EtOAc/heptane (gradient from 1:1 to 1:0 ratio) gave compound 788B (0.47 mg, 92%) as a glassy solid. HPLC: 98% at 3.07 min (retention time) (YMC S5 ODS-A column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 mincontaining 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 397 $[M+H]^+$. Compound 788B represents a racemic mixture of antipodes. The nomenclature and structure shown does not reflect the absolute stereochemistry of the compound.

Example 789



To a stirred solution of compound 788B (40 mg, 0.1 mmol) and triethylamine (0.16 mL, 1.1 mmol) in anhydrous methylene chloride (1 mL) was added methanesulfonyl chloride (0.042 mL, 0.54 mmol) at 0°C under argon. The reaction mixture was stirred at 0°C for 10 min, and at rt for 30 min. Purification by silica gel flash chomatography eluting with EtOAc/heptane (gradient from 1:2 to 1:0 ratio) gave compound 789 (50 mg, 90%) as a glassy solid. HPLC: 100% at 3.66 min (retention time) (YMC S5 ODS-A column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 mincontaining 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 575 $[M+Na]^+$. Compound 789 represents a racemic mixture of antipodes. The nomenclature and structure shown does not reflect the absolute stereochemistry of the compound.

Example 790

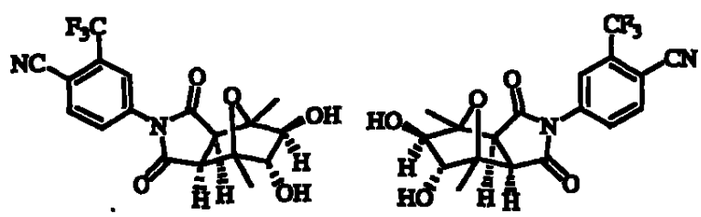


A clear solution of compound 788B (40 mg, 0.1 mmol), pyridine (0.04 mL, 0.49 mmol), and methanesulfonyl chloride (0.032 mL, 0.41 mmol) in anhydrous methylene chloride (1 mL) was stirred at rt for 1 day. Purification by preparative HPLC (YMC S5 ODS column 20 x 100 mm, 20 mL/min, monitoring at 245 nm, gradient elution with 10-100% solvent B over 10 mins. Solvent A: 10% MeOH-90%

H2O-0.1% TFA. Solvent B: 90% MeOH-10% H_2O-0.1% TFA.) gave compound 790 (23 mg, 48%) as a glassy solid. HPLC: 98% at 3.46 min (retention time) (YMC S5 ODS-A column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 mincontaining 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 475 $[M+H]^+$. Compound 790 represents a racemic mixture of antipodes. The nomenclature and structure shown does not reflect the absolute stereochemistry of the compound.

Example 791

[3aS-(3aα,4β,5β,6α,7β,7aα)]-4-(Octahydro-5,6-dihydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile & [3aR-(3aα,4β,5β,6α,7β,7aα)]-4-(Octahydro-5,6-dihydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (791i &791ii)

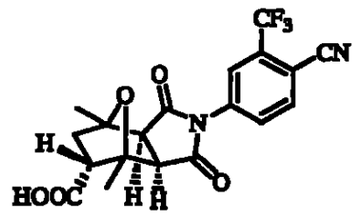


Racemic compound 788B (1g) was separated into its enantiomers by normal phase preparative chiral HPLC (CHIRALPAK OJ 5 x 50 cm column; eluting with 20% MeOH/EtOH (1:1) in heptane (isocratic) + 0.1% diethylamine at 50 mL/min) to give 296 mg of faster eluting compound 791i (Chiral HPLC: 8.92 min; CHIRALPAK OJ 4.6 x 250 mm column; eluting with 20% MeOH/EtOH (1:1) in heptane + 0.1 diethylamine at 1 mL/min); HPLC: 95% at 1.25 min (retention time) (Phenomenex S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 2 mincontaining 0.1% TFA, 4 mL/min, monitoring at 254 nm); MS (ES): m/z 397.37 $[M+H]^+$and 274 mg of the slower eluting 791ii (Chiral HPLC: 11.25 min; CHIRALPAK OJ 4.6 x 250 mm column; eluting with 20% MeOH/EtOH (1:1) in heptane + 0.1% diethylamine at 1 mL/min); HPLC: 95% at 1.25 min (retention time) (Phenomenex S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 2 mincontaining 0.1% TFA, 4 mL/min, monitoring at 254 nm); MS (ES): m/z

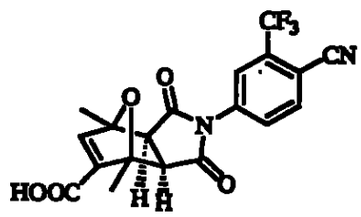
397.43 $[M+H]^+$. The absolute stereochemistry of compounds 791i & 791ii has not been established. Although each compound represents a single antipode, the nomenclature and structure shown does not reflect the absolute stereochemistry of the compound.

Example 792

(3aα,4β,5α,7β,7aα)-2-(4-Cyano-3-(trifluoromethyl)phenyl)hexahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-1H-isoindole-5-carboxylic acid (792B)



A. **(3aα,4β,7β,7aα)-2-(4-Cyano-3-(trifluoromethyl)phenyl)tetrahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-1H-isoindole-5-carboxylic acid (792A)**



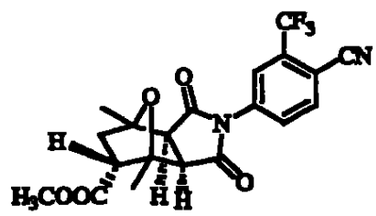
A mixture of 2,5-dimethyl-3-furoic acid (11.2 g; 80 mmol) and 4-(2,5-dihydro-2,5-2,5-dioxo-1H-pyrrol-1-yl)-2-trifluoromethylbenzonitrile (5.32 g; 20 mmol) in 20 mL of THF was heated to 65°C. for 2 h. After cooling to rt, the solid residue was slurried in EtOAc and loaded onto a 5 x 30 cm silica gel column packed in hexanes. The column was eluted with 2 L of EtOAc, followed by 1.5 L of 1% AcOH/EtOAc. Fractions containing the desired acrylic acid were concentrated and the residue was co-evaporated from EtOAc/Heptane (3 x 100 mL). After dissolving the solid residue in ~15 mL of EtOAc, heptane (~50 mL) was added and the mixture was concentrated to ~25 mL volume. The suspension was filtered and the filter cake was washed with hexane. Removing the solvent *in vacuo* afforded compound 792A (1.5g, 16%) as a white powder.

B. (3aα,4β,5α,7β,7aα)-2-(4-Cyano-3-(trifluoromethyl)phenyl)hexahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-1H-isoindole-5-carboxylic acid (792B)

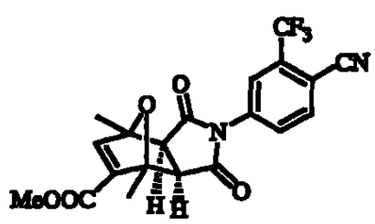
Compound 792A (220 mg; 0.54 mmol) was hydrogenated at 1 atm. in EtOAc (5 mL) over 10% Pd/C (20 mg) for 4 hs. After filtering though Celite, the filtrate was concentrated and the residue was chomatographed on a 2.5 x 15 cm silica gel column eluting with EtOAc:Heptane, 1:1 + 0.5% AcOH. Pure fractions were concentrated to afford compound 792B (173 mg, 79%) as a colorless glass. HPLC: 95.7% at 1.64 min (retention time) (Phenomonex S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 2 mincontaining 0.1% TFA, 4 mL/min, monitoring at 254 nm); MS (ES): m/z 409.23 $[M+H]^+$.

Example 793

(3aα,4β,5α,7β,7aα)-2-(4-Cyano-3-(trifluoromethyl)phenyl)hexahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-1H-isoindole-5-carboxylic acid, methyl ester (793B)



A. (3aα,4β,7β,7aα)-2-(4-Cyano-3-(trifluoromethyl)phenyl)tetrahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-1H-isoindole-5-carboxylic acid, methyl ester (793A)



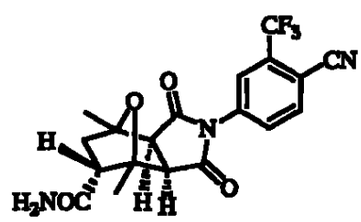
A mixture of methyl-2,5-dimethyl-3-furoate (30 mL; 200 mmol) and 4-(2,5-dihydro-2,5-2,5-dioxo-1H-pyrrol-1-yl)-2-trifluoromethylbenzonitrile (13.3 g; 50 mmol) was heated to 120°C. for 5 h. After cooling slowly to rt over 18 h, ethyl ether

(~150 mL) was added and the resulting thick suspension was filtered. Rinsing thoroughly with ethyl ether and drying afforded compound 793A (11.3 g, 54%) as a white powder.

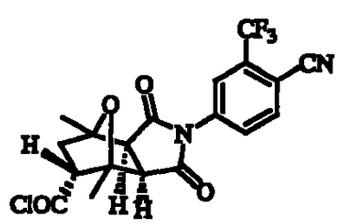
B. (3aα,4β,5α,7β,7aα)-2-(4-Cyano-3-(trifluoromethyl)phenyl)hexahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-1H-isoindole-5-carboxylic acid, methyl ester (793B)

Compound 793A (1 g; 2.38 mmol) was hydrogenated at 1 atm. in EtOAc (25 mL) over 10% Pd/C (100 mg) for 2 h. After filtering though Celite, the filtrate was concentrated and the residue was chomatographed on a 2.5 x 15 cm silica gel column eluting with EtOAc:Hexane, 1:3. Pure fractions were concentrated to afford compound 793B (665 mg, 65%) as a yellow powder. HPLC: 99% at 1.67 min (retention time) (Phenominex S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 2 mincontaining 0.1% TFA, 4 mL/min, monitoring at 254 nm); MS (ES): m/z 423.27 $[M+H]^+$. Compound 793B represents a racemic mixture of antipodes. The nomenclature and structure shown does not reflect the absolute stereochemistry of the compound.

Example 794B



A. (794A)

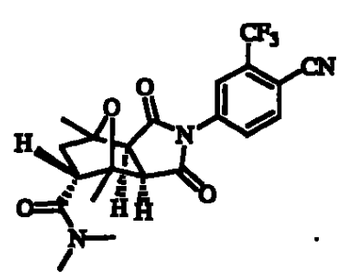


One drop of DMF was added to a solution of compound 792B (160 mg; 0.4 mmol) and oxalyl chloride (0.09 mL; 1 mmol) in methylene chloride (4 mL) at rt. After stirring 1 h at rt, the volatiles were removed in vacuo and the residue was dissolved in 2 mL of THF to afford a 0.2M solution of compound 794A in THF.

C. (794B)

A 0.2M solution of compound 794A in THF (1 mL; 0.2 mmol) was added to a 0.5M solution of ammonia in dioxane (5 mL; 2.5 mmol) at rt. After standing 1 h at rt, the reaction mixture was partitioned between EtOAc (25 mL) and water (25 mL). The organic layer was washed with saturated potassium bisulfate solution (25 mL) and brine (25 mL). Drying over $MgSO_4$ followed by concentration *in vacuo* gave a solid residue that was triturated with ethyl ether to afford compound 794B (60 mg, 74%) as a white solid. HPLC: 95.6% at 1.41 min (retention time) (Phenominex S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 2 mincontaining 0.1% TFA, 4 mL/min, monitoring at 254 nm); MS (ES): m/z 408.03 $[M+H]^+$. Compound 794B represents a racemic mixture of antipodes. The nomenclature and structure shown does not reflect the absolute stereochemistry of the compound.

Example 795

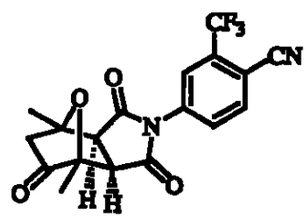


A 0.2M solution of compound 794A in THF (1 mL; 0.2 mmol) was added to a 2.0M solution of dimethylamine in dioxane (2.5 mL; 5 mmol) at rt. After standing 1 h at rt, the reaction mixture was partitioned between EtOAc (25 mL) and water (25

mL). The organic layer was washed with saturated potassium bisulfate solution (25 mL) and brine (25 mL). Drying over $MgSO_4$ followed by concentration *in vacuo* gave a residue that was purified by preparative TLC (EtOAc:Hexane, 3:2) to afford compound **795** (45 mg, 52%) as a white powder. HPLC: 99% at 1.52 min (retention time) (Phenominex S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 2 mincontaining 0:1% TFA, 4 mL/min, monitoring at 254 nm); MS (ES): m/z 435.10 $[M+H]^+$. Compound **795** represents a racemic mixture of antipodes. The nomenclature and structure shown does not reflect the absolute stereochemistry of the compound.

Example 796

[3a*R*-(3aα,4β,7β,7aα)]-4-(Octahydro-4,7-dimethyl-1,3,5-trioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (796)

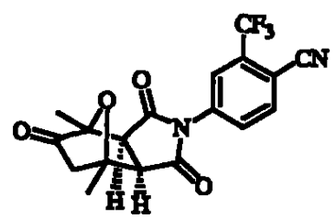


Compound **471Di** (0.10 g, 0.263 mmol) was dissolved in a mixture of CH_2Cl_2 (1.0 mL) and THF (2.0 mL) at 22°C. Dess-Martin periodinane (0.279 g, 0.658 mmol) was added with stirring. After 3 h, the reaction was quenched with a 1:1 mixture of sat aq $NaHCO_3$ and sat aq $NaHSO_3$ (5 mL). After stirring for 15 min, the mixture was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organics were dried over Na_2SO_4. The crude material was purified by silica gel flash chomatography eluting with 5 – 10 – 20% acetone in chloroform to give compound **796** (0.090 g) as a white solid. HPLC: 100% at 3.170 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 mincontaining 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm), MS (ES): m/z 379.11 $[M+H]^+$. Chiral analytical HPLC using a Chiracel OD column, 4.6X250 mm, eluting with 20% (1:1) EtOH/MeOH in hexanes at 2.0 mL/min and monitoring at 220 nm gave a retention time of 9.097 mins. The absolute stereochemistry of compound **796** is established by the known stereochemistry of the intermediate compound **741Di** and the retention of

configuration therein. The absolute stereochemistry is as drawn in the above figure and rendered by the nomenclature.

Example 797

[3a*S*-(3aα,4β,7β,7aα)]-4-(Octahydro-4,7-dimethyl-1,3,5-trioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (797)

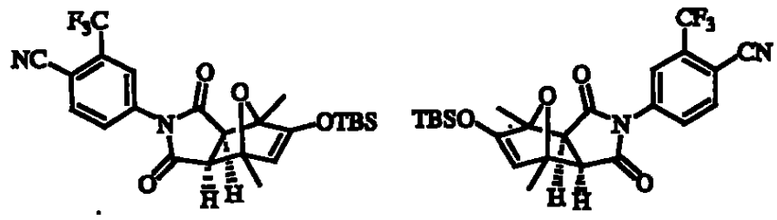


Compound 471Dii (0.10 g, 0.263 mmol) was dissolved in a mixture of CH_2Cl_2 (1.0 mL) and THF (2.0 mL) at 22°C. Dess-Martin periodinane (0.279 g, 0.658 mmol) was added with stirring. After 3 h, the reaction was quenched with a 1:1 mixture of sat aq $NaHCO_3$ and sat aq $NaHSO_3$ (5 mL). After stirring for 15 min, the mixture was extracted with CH_2Cl_2 (3 x 10 mL) and the combined organics were dried over Na_2SO_4. The crude material was purified by silica gel flash chomatography on SiO_2 eluting with 5 – 10 – 20% acetone in chloroform to give compound 797 (0.094 g) as a white solid. HPLC: 100% at 3.170 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 mincontaining 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm), MS (ES): m/z 379.11 $[M+H]^+$. Chiral analytical HPLC using a Chiracel OD column, 4.6X250 mm, eluting with 20% (1:1) EtOH/MeOH in hexanes at 2.0 mL/min and monitoring at 220 nm gave a retention time of 5.710 mins. The absolute stereochemistry of compound 797 is established by the known stereochemistry of the intermediate compound 471Dii and the retention of configuration therein. The absolute stereochemistry is as drawn in the above figure and rendered by the nomenclature.

Example 798

[3a*R*-(3aα,4β,7β,7aα)]-4-[5-[[(1,1-Dimethylethyl)dimethylsilyl]oxy]tetrahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile & [3a*R*-(3aα,4β,7β,7aα)]-4-[5-[[(1,1-

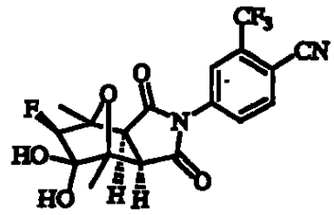
Dimethylethyl)dimethylsilyl]oxy]tetrahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzonitrile (798i and 798ii)



The individual enantiomers of compound 222B were separated by preparative-chiral HPLC using a Chiracel OD column, 50X500 mm, eluting with 12% EtOH in hexanes at 50 mL/min and monitoring at 220 nm. Compound 798i has a retention time of 22 min(>99% ee by analytical) and Compound 798ii had a retention time of 40 min(95% ee by analytical). Absolute stereochemistry was confirmed by acid hydrolysis of the silyl enol ether to the corresponding ketone (compounds 796 & 797). Comparison by chiral analytical HPLC clearly demonstrated that the ketone product derived from compound 798i had an identical retention time to that seen for compound 796 and the ketone product derived from compound 798ii had an identical retention time to that seen for compound 797. In this fashion, the absolute configuration of compounds 798i & 798ii can be inferred by the known absolute configuration of compounds 796 & 797. Compound 798i: HPLC: 100% at 4.211 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 mincontaining 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). Compound 798ii: HPLC: 100% at 4.210 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 mincontaining 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm).

Example 799

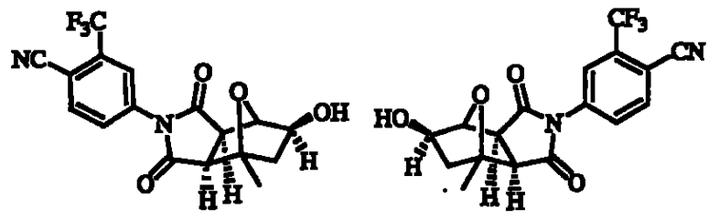
[3aS-(3aα,4β,6β,7β,7aα)]-4-(Octahydro-6-fluoro-5,5-dihydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (799)



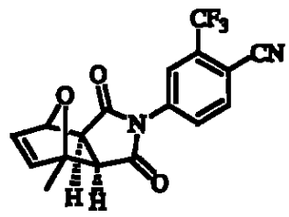
Compound 798i (2.20 g, 4.47 mmol) was dissolved in acetonitrile (45 mL) and cooled to 0°C. 1-Fluoro-4-hydroxy-1,4-diazoniabicyclo[2.2.2]octane bis-(tetrafluoroborate) (50% w/w on alumina, 5.75 g, 8.94 mmol) was then added with vigorous stirring. After 0.5 h, the reaction was quenched with sat aq $NaHCO_3$ (20 mL) and brine (20 mL). The resulting mixture was extracted with EtOAc (3 x 50 mL). The combined organics were dried over anhydrous $MgSO_4$ and concentrated *in vacuo*. The crude material was purified by silica gel flash chomatography on SiO_2 eluting with 0 – 35% acetone in chloroform to give a mixture of ketone and hydrate. The mixture was dissolved in CH_3CN (50 mL) and water (5.0 mL) was added. The mixture was stirred for 3 h and then concentrated *in vacuo* followed by azeotroping with additional CH_3CN three times and then dried *in vacuo* at 50°C for 12 h to give compound 799 (1.09 g) as a white solid. Compound 799 was shown to be the hydrate only by ^1H and ^{19}F NMR spectroscopy. HPLC: 100% at 2.687 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 mincontaining 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm), MS (ES): m/z 413.27 $[M-H]^+$. The absolute stereochemistry of compound 799 is established by the known stereochemistry of the intermediate compound 798i and the retention of configuration therein. The absolute stereochemistry is as drawn in the above figure and rendered by the nomenclature.

Example 800

[3aS-(3aα,4β,6β,7β,7aα)]-4-(Octahydro-6-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile & [3aR-(3aα,4β,6β,7β,7aα)]-4-(Octahydro-6-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (799Ci and 799Cii)

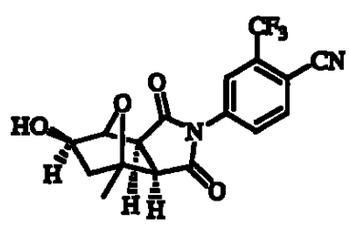


A. (800A)



2-Methyl furan (5.33 mL, 59.1 mmol) was added to 4-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-2-trifluoromethyl-benzonitrile (1.50 g, 5.91 mmol) and the mixture was heated at 60°C for 3 h. Upon heating, the reaction became homogenous followed shortly by the product crashing out of solution. The mixture was cooled to 22°C and diluted with heptane (25 mL) and filtered, rinsing with cold heptane. Concentration *in vacuo* gave compound **800A** (1.76 g) as a white solid. This compound was taken forward without further purification. HPLC: 100% at 2.250 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 mincontaining 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm).

B. **(3aα,4β,6β,7β,7aα)]-4-(Octahydro-6-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (800B)**



Compound **800A** (0.500 g, 1.49 mmol) was dissolved in dry THF (15 mL) and Wilkinson's catalyst (0.028 g, 0.029 mmol) was added. After stirring for 10 min, catecholborane (1.0 M soln in THF, 3.00 mL, 3.00 mmol) was then added over a 5

min period. After 1 h, the reaction was cooled to 0°C followed by sequential addition of EtOH (7.0 mL), pH 7.4 phosphate buffer (16.0 mL) and 30% aq H_2O_2 (1.5 g). The mixture was slowly warmed to 22°C and after 2 h, extracted with CH_2Cl_2 (3 x 50 mL). The combined organics were washed once with a 1:1 mixture of 1N NaOH/sat aq $NaHSO_3$ (50 mL), once with brine and dried over anhydrous Na_2SO_3. The crude material was purified by silica gel flash chomatography on SiO_2 eluting with 5 – 10 – 20 – 40% acetone in chloroform to give compound **800B** (0.344 g) as a white foam. NMR spectroscopy confirmed assignment and no other isomers were present. HPLC: 94% at 2.460 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 mincontaining 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm), MS (ES): m/z 367.22 $[M+H]^+$.

C. [3a*S*-(3aα,4β,6β,7β,7aα)]-4-(Octahydro-6-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile & [3a*R*-(3aα,4β,6β,7β,7aα)]-4-(Octahydro-6-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (800Ci & 800Cii)

The individual enantiomers of compound **800B** were separated by preparative chiral HPLC using a Chiralcel OD column (50 x 500 mm) eluting with 17% EtOH/hexanes at 50 mL/min monitoring at 220 nm. Compound **800Ci** has a retention time of 69.4 min and compound **800Cii** has a retention time of 84.1 min. Absolute stereochemistry was not determined. Compound **800Ci**: HPLC: 100% at 2.460 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 mincontaining 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). Compound **800Cii**: HPLC: 100% at 2.460 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 mincontaining 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). The absolute stereochemistry of compounds **800Ci** & **800Cii** has not been established. Although each compound represents a single antipode, the nomenclature and structure shown does not reflect the absolute stereochemistry of the compound.

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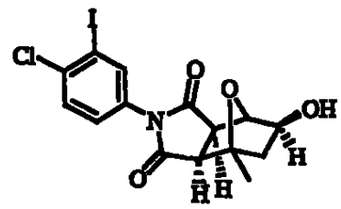
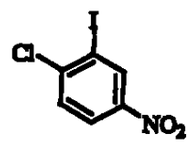
Example 801

[3a*R*-(3aα,4β,5β,7β,7aα)]-2-(4-Chloro-3-iodophenyl)hexahydro-5-hydroxy-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione (801C)

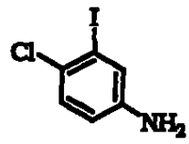


A. 1-Chloro-2-iodo-4-nitro-benzene (801A)



2-amino-5-nitro-iodobenzene (10.00 g, 37.9 mmol) was suspended in 12 N HCl (25 mL) and water (40 mL) and stirred for 30 min at 22°C. The mixture was then cooled to 0°C and $NaNO_2$ (5.23 g, 75.8 mmol in 18 mL of H_2O) was added over a 10 min period. After 1 h, this solution was transferred to a solution of CuCl (3.75 g, 37.9 mmol) in water (50 mL) at 60°C. After 2 h, the mixture was cooled to 22°C and extracted with EtOAc (3 x 150 mL) and the organics were dried over anhydrous $MgSO_4$. The crude product was purified by silica gel flash chomatography eluting with 10 – 20 % CH_2Cl_2 in hexanes to give compound 801A (4.20 g) as a yellow solid. HPLC: 100% at 3.447 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 mincontaining 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm).

B. 4-Chloro-3-iodo-phenylamine (801B)

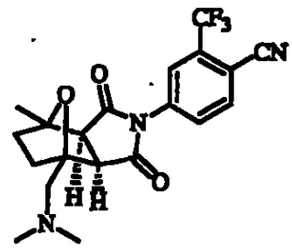


1-Chloro-2-iodo-4-nitro-benzene (2.00 g, 7.09 mmol) was dissolved in THF (30 mL) at 60°C and EtOH (35 mL) was added followed by NH_4Cl (0.569 g, 10.6 mmol in 30 mL of water) and iron powder (1.58 g, 28.4 mmol). This mixture was stirred vigorously for 3 h and then cooled in 22°C and filtered though celite rinsing with EtOAc. The solution was then concentrated to ~ 30 mL *in vacuo* and then poured into a 1:1 solution of 1N NaOH/brine (100 mL). This mixture was then extracted with EtOAc (3 x 50 mL) and the organics were dried over anhydrous $MgSO_4$. Filtration and concentration gave compound **801B** as a yellow solid. No purification was necessary: HPLC: 100% at 2.310 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 mincontaining 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm), MS (ES): m/z 517.6 $[M+Na]^+$.

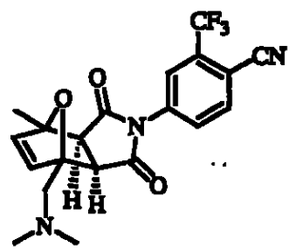
C. [3a*R*-(3aα,4β,5β,7β,7aα)]-2-(4-Chloro-3-iodophenyl)hexahydro-5-hydroxy-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione (801C)

Compound **801B** (0.300 g, 1.19 mmol) and compound **752** (0.229 g, 1.08 mmol) were added to DMA (1.2 mL) in a high pressure reaction vessel. 4Å molecular seives (0.300 g) were then added and the vessel sealed and heated to 190°C. After 45 min, the reaction was cooled to rt and poured into EtOAc (50 mL). The solution was then washed once with water (20 mL), three times with sat aq NH_4Cl (20 mL) and dried over anhydrous $MgSO_4$. The crude material was purified by flash chromatography on silica eluting with 10 – 20 – 30% acetone in chloroform to give compound **801C** (0.217 g) as a tan solid. HPLC: 100% at 3.000 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 mincontaining 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm), MS (ES): m/z 448.18 $[M+H]^+$. The absolute stereochemistry of compound **801C** is established by the known stereochemistry of the intermediate compound **752** and the retention of configuration therein. The absolute stereochemistry is as drawn in the above figure and rendered by the nomenclature.

Example 802



A. (802A)

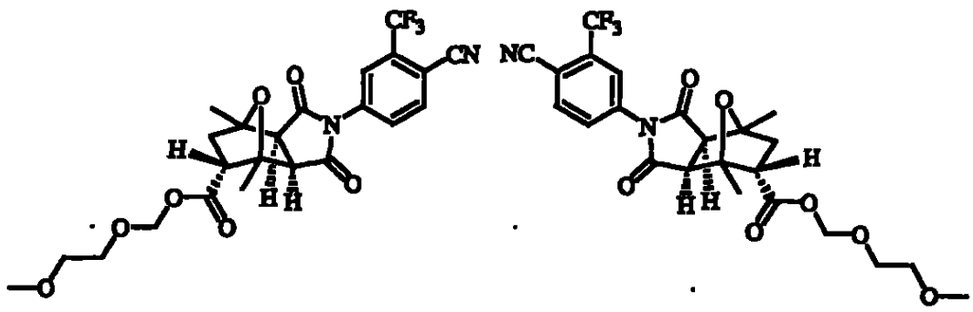


4-(2,5-Dioxo-2,5-dihydro-pyrrol-1-yl)-2-trifluoromethyl-benzonitrile (0.200 g, 0.79 mmol) and 2-(N,N-dimethylaminomethyl)-5-methylfuran (0.548 g, 3.94 mmol) were dissolved in THF (0.5 mL) and heated to 60°C for 3 h. The mixture was then concentrated *in vacuo* to give compound **802A** as a brown oil. The crude material was used without purification.

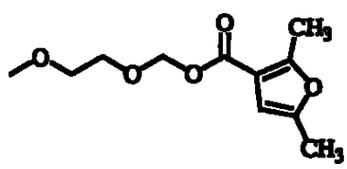
B. (802B)

Compound **802A** (~ 0.4 mmol) was dissolved in EtOAc (5.0 mL) and Pd/C (10% Pd, 0.020 g) was added followed by introduction of H_2 via a balloon. After 3 h, the reaction was purged with N_2 and filtered through celite rinsing with EtOAc. The crude material was purified by silica gel flash chromatography eluting with 10 – 20 – 30% acetone in chloroform to give compound **802B** (0.080 g) as a tan oil. HPLC: 95% at 2.040 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 mincontaining 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm), MS (ES): m/z 408.31 $[M+H]^+$. Compound **802B** represents a racemic mixture of antipodes. The nomenclature and structure shown does not reflect the absolute stereochemistry of the compound.

Example 803

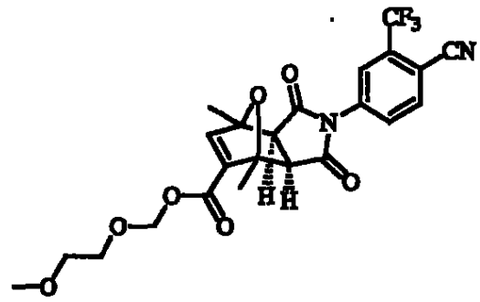


A. 2,5-Dimethylfuran-3-carboxylic Acid 2-Methoxyethoxymethyl Ester (803A)



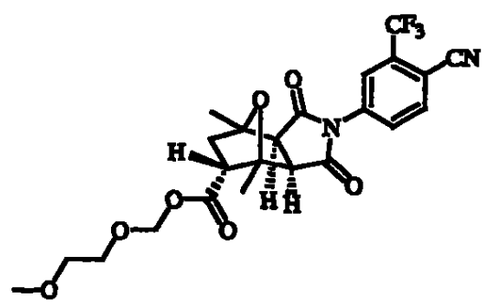
A 2 L round-bottomed flask equipped with a mechanical stirrer was charged with 2,5-dimethyl-3-furoic acid (81.0 g, 0.58 mol) and potassium carbonate (95.9 g, 0.69 mol) in DMF (500 mL). An ice bath was used to cool the reaction as 2-methoxyethoxymethyl chloride (72.2 g, 0.58 mol) was added portionwise. The reaction was stirred for 5 h at rt. The mixture was then diluted with water (1.5 L) and extracted with EtOAc (2 x 600 mL). The combined organics were washed with water (2 x 900 mL) and saturated sodium chloride solution (1 L), dried over $MgSO_4$, filtered and concentrated to afford compound 803A (103 g, 82%) as a yellow oil. ^1H NMR($CDCl_3$): δ = 6.23 (s, 1H), 5.47 (s, 1H), 3.84 (m, 2H), 3.56 (m, 2H), 3.38 (s, 3H), 2.51 (s, 3H) and 2.20 ppm (s, 3H).

B. (803B)



A 250 mL round-bottomed flask was charged with 4-(2,5-dioxo-2,5-dihydropyrrol-1-yl)-2-trifluoromethylbenzonitrile (15.0 g, 0.056 mol) and 2,5-dimethylfuran-3-carboxylic acid 2-methoxyethoxymethyl ester (22.8 g, 0.10 mol). The mixture was heated to 125 °C for 1.5 h then stirred at rt overnight. The crude product was dissolved in EtOAc and adsorbed onto silica gel. Purification by silica gel chomatography, eluting with 30% EtOAc in hexanes, afforded compound **803B** (8.21 g, 30%) as a viscous oil. ^{1}H NMR($CDCl_3$): δ = 7.95 (d, J = 8.3 Hz, 1H), 7.86 (d, J = 1.9 Hz, 1H), 7.75 (m, 1H), 7.13 (s, 1H), 5.44 (m, 2H), 3.83 (m, 2H), 3.57 (m, 2H), 3.39 (s, 3H), 3.19 (d, J = 6.5 Hz, 1H), 3.09 (d, J = 6.5 Hz, 1H), 2.04 (s, 3H) and 1.91 ppm (s, 3H).

C. (803C)



A 250 mL Parr hydrogenation bottle was charged with compound **803B** (7.75 g, 0.015 mol), EtOAc (80 mL) and palladium on carbon (0.40 g, 10% Pd, 50% wet). The bottle was placed on a Parr hydrogenation apparatus, pressurized with hydrogen to 5 psi, and shook until the uptake of hydrogen ceased. Filtration of the contents over celite and concentration afforded a yellow oil. Purification by silica gel chomatography, eluting with 30% EtOAc in hexanes, afforded compound **803C** (3.92 g, 50%) as a white solid. HPLC: 100% at 14.5 min (retention time) (Hypersil C18 BDS column, 250 x 4.6 mm, 5 μm, a detection wavelength of 254 nm, and a flow rate

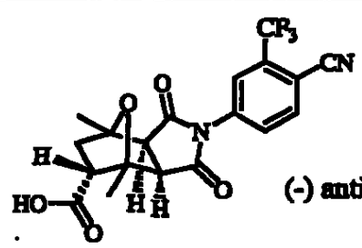
of 1 mL/min. A linear gradient of 90% of 0.1% trifluoroacetic acid in water, 10% acetonitrile (start) to 100% acetonitrile over 15 min, then 100% acetonitrile for 5 min was used). R_f = 0.61 (SiO_2, 60% EtOAc in hexanes). Mpt >300 °C. ^{1}H NMR($CDCl_3$): δ = 7.94 (d, J = 8.3 Hz, 1H), 7.84 (d, J = 1.9 Hz, 1H), 7.74 (m, 1H), 5.46 (d, J = 6.1 Hz, 1H), 5.34 (d, J = 6.1 Hz, 2H), 3.85 (m, 2H), 3.57 (t, J = 4.5 Hz, 2H), 3.38 (s, 3H), 3.33 (d, J = 7.2 Hz, 1H), 3.19 (d, J = 7.2 Hz, 1H), 3.04 (m, 1H), 2.28 (m, 1H), 2.05 (t, J = 12.2 Hz, 1H), 1.78 (s, 3H) and 1.64 ppm (s, 3H). m/z = 496 $[M+H]^+$.

D. (803Di and 803Dii).

Racemic compound 803C was separated into its two enantiomers by preparative chiral HPLC using a Chiracel OD column (50x500 mm) eluting with 50 EtOH in Heptane at 100 mL/min and 290 nm detection. Compound 803Di had a retention time of 6.68 min and $[\alpha]_{25}^{D}$ = +28.7° (c = 1.0, MeOH). Compound 803Dii had a retention time of 13.9 min and $[\alpha]_{25}^{D}$ = -29.2° (c = 1.0, MeOH). The absolute stereochemistry of compounds 803Di & 803Dii has not been established. Although each compound represents a single antipode, the nomenclature and structure shown does not reflect the absolute stereochemistry of the compound.

Example 804

[3a*R*-(3aα,4β,5α,7β,7aα)]-2-(4-Cyano-3-(trifluoromethyl)phenyl)hexahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-1H-isoindole-5-carboxylic acid (804)



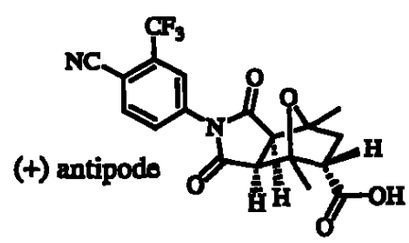
(-) antipode

A 250 mL round-bottomed flask was charged with compound 803Di (9.85 g, 19.8 mmol) and THF (60 mL). A solution of 3N hydrochloric acid (50 mL) was added and the reaction mixture stirred for 16 h at rt. Water (60 mL) was then added and the aqueous layer extracted with EtOAc (3 x 120 mL). The combined organics

were dried over sodium sulfate, filtered and concentrated to afford compound **804** (8.00 g, 98%) which was shown to be identical to compound **791**. HPLC: 100% at 13.3 min (retention time) (Hypersil C18 BDS column, 250 x 4.6 mm, 5 μm, a detection wavelength of 254 nm, and a flow rate of 1 mL/min. A linear gradient of 90% of 0.1% trifluoroacetic acid in water, 10% acetonitrile (start) to 100 acetonitrile over 15 min, then 100% acetonitrile for 5 min was used), MS (ES): m/z 409 $[M+H]^+$. R_f = 0.41 (SiO_2, 10% MeOH in CH_2Cl_2). Mpt >300 °C. $[\alpha]_{25}^{D}$ = -28.5° (c = 1.0, MeOH). ^{1}H NMR (CD_3OD): δ = 8.12 (d, *J* = 8.3 Hz, 1H), 7.92 (s, 1H), 7.82 (dd, *J* = 8.3 and 2.0 Hz, 1H), 3.39 (t, *J* = 6.7 Hz, 1H), 3.30 (d, *J* = 6.7 Hz, 1H), 3.00 (dd, *J* = 12.0 and 5.2 Hz, 1H), 2.23 (dd, *J* = 12.0 and 5.2 Hz, 1H), 2.01 (t, *J* = 12.0 Hz, 1H), 1.70 (s, 3H) and 1.57 ppm (s, 3H). The absolute stereochemistry of compound **804** has not been established. Although the compound represent a single antipode the nomenclature and structure shown does not reflect the absolute stereochemistry of the compound.

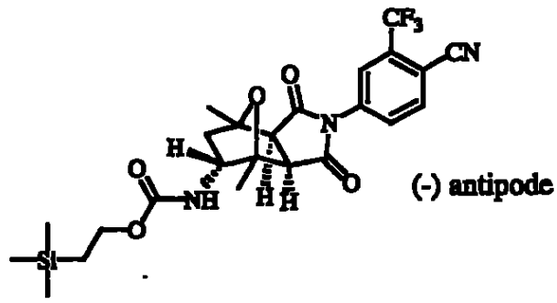
Example 805

[3*S*-(3aα,4β,5α,7β,7aα)]-2-(4-Cyano-3-(trifluoromethyl)phenyl)hexahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-1H-isoindole-5-carboxylic acid (805)



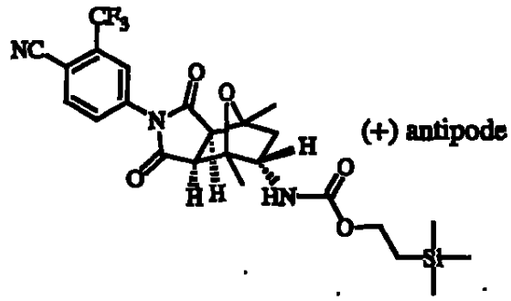
Compound **805** was prepared in identical fashion as described in example **804** with the exception that compound **803Dii** was the starting material in place of compound **803Di**. Compound **805** was obtained in 98% yield. $[\alpha]^{25}_{D}$ = +28.0° (c = 1.0, MeOH). The absolute stereochemistry of compound **805** has not been established. Although the compound represent a single antipode the nomenclature and structure shown does not reflect the absolute stereochemistry of the compound.

Example 806



A 50 mL round-bottomed flask was charged with dioxane (6 mL), compound **804** (400 mg, 0.984 mmol), diphenylphosphoryl azide (334 mg, 1.21 mmol), triethylamine (123 mg, 1.22 mmol) and powdered 4Å molecular sieves (400 mg). The resulting suspension was heated at 50 °C for 1.5 h, the temperature was then raised to 75 °C and 2-(trimethylsilyl)ethanol (590 mg, 5.02 mmol) was added. Heating was continued for an additional 1.5 h. The reaction mixture was then cooled, filtered though a celite pad and the filtrate concentrated under reduced pressure. Purification of the residue by silica gel chomatography, eluting with 20% then 40% EtOAc in hexanes, afforded compound **806** (400 mg, 78%) as a white solid. HPLC: 100% at 15.3 min (retention time) (Hypersil C18 BDS column, 250 x 4.6 mm, 5 μm, a detection wavelength of 254 nm, and a flow rate of 1 mL/min. A linear gradient of 90% of 0.1% trifluoroacetic acid in water, 10% acetonitrile (start) to 100 acetonitrile over 15 min, then 100% acetonitrile for 5 min was used), MS (ES): m/z 524 $[M+H]^+$. $R_f = 0.79$ (SiO_2, 50% EtOAc in hexanes). Mpt >300 °C. $[\alpha]_{25}^{D} = -1.8°$ (c = 1.0, MeOH). ^{1}H NMR($CDCl_3$): δ = 7.96 (d, *J* = 8.3 Hz, 1H), 7.83 (s, 1H), 7.73 (dd, *J* = 8.3 and 2.0 Hz, 1H), 4.72 (bs, 1H), 4.19 (t, *J* = 12.0 Hz, 2H), 4.05 (m, 1H), 3.45 (d, *J* = 8.3 Hz, 1H), 3.12 (d, *J* = 8.3 Hz, 1H), 2.36 (t, *J* = 12.0 Hz, 1H), 1.61 (s, 6H), 1.04 (t, *J* = 12.0 Hz, 2H) and 0.05 ppm (s, 6H). The absolute stereochemistry of compound **806** has not been established. Although the compound represents a single antipode, the nomenclature and structure shown does not reflect the absolute stereochemistry of the compound.

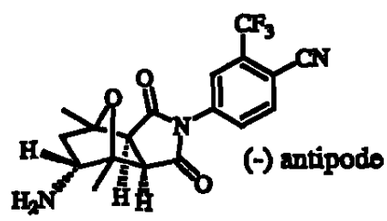
Example 807



Compound **807** was prepared in identical fashion as described in example **806** with the exception that compound **805** was the starting material in place of compound **804**. Compound **807** was obtained in 80% yield. $[\alpha]^{25}_{D} = +1.1°$ (c = 1.0, MeOH). The absolute stereochemistry of compound **807** has not been established. Although the compound represents a single antipode, the nomenclature and structure shown does not reflect the absolute stereochemistry of the compound.

Example 808

[3a*R*-(3aα,4β,5α,7β,7aα)]-4-(Octahydro-5-amino-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (808)

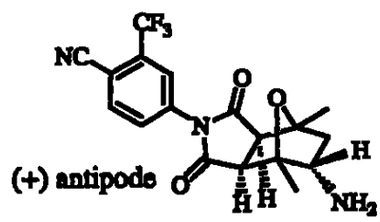


A solution of compound **806** (400 mg, 0.76 mmol) in methylene chloride (10 mL) was treated with trifluoroacetic acid (2 mL) and the mixture stirred at rt for 2 h. After this time the reaction was rendered basic (pH = 9) by the addition of saturated aqueous sodium carbonate solution (20 mL) and solid potassium carbonate. The organic phase was then separated and the aqueous layer extracted with methylene chloride (3 x 40 mL). The combined organics were dried over sodium sulfate, filtered, and concentrated to afford compound **808** (283 mg, 99%) as a white solid. HPLC: 100% at 10.5 min (retention time) (Hypersil C18 BDS column, 250 x 4.6 mm, 5 μm, a detection wavelength of 254 nm, and a flow rate of 1 mL/min. A linear gradient of 90% of 0.1% trifluoroacetic acid in water, 10% acetonitrile (start) to 100% acetonitrile over 15 min, then 100% acetonitrile for 5 min was used), MS (ES): m/z

380 $[M+H]^+$. R_f = 0.59 (SiO_2, 5% MeOH in CH_2Cl_2). $[\alpha]_{25}^{D}$ = -26.7° (c = 1.0, MeOH). Mpt = 150-152 °C. ^{1}H NMR (CD_3OD): δ = 8.12 (d, *J* = 8.3 Hz, 1H), 7.94 (s, 1H), 7.83 (dd, *J* = 8.3 and 2.0 Hz, 1H), 3.66 (d, *J* = 7.2 Hz, 1H), 3.21 (m, 4H), 2.16 (t, *J* = 12.0 Hz, 1H), 1.51 (s, 3H), 1.49 (s, 3H) and 1.42 ppm (dd, *J* = 12.0 and 5.0 Hz, 1H). The absolute stereochemistry of compound **808** has not been established. Although the compound represents a single antipode, the nomenclature and structure shown does not reflect the absolute stereochemistry of the compound.

Example 809

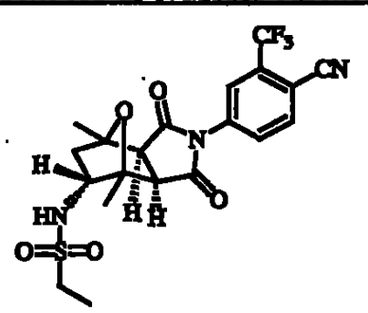
[3a*S*-(3aα,4β,5α,7β,7aα)]-4-(Octahydro-5-amino-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (809)



Compound **809** was prepared in identical fashion as described in example **808** with the exception that compound **807** was the starting material in place of compound **806**. Compound **809** was isolated in 94% overall yield. $[\alpha]^{25}_{D}$ = +27.3° (c = 1.0, MeOH). The absolute stereochemistry of compound **809** has not been established. Although the compound represents a single antipode, the nomenclature and structure shown does not reflect the absolute stereochemistry of the compound.

Example 810

(3aα,4β,5α,7β,7aα)-4-(Octahydro-5-ethylsulfonamido-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (810)

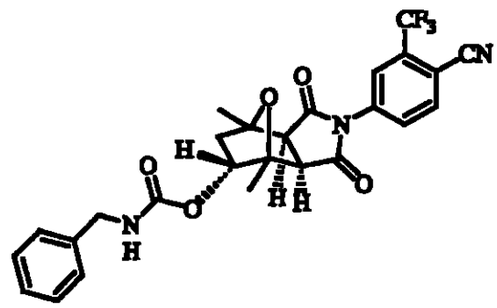


319

A 25 mL round-bottomed flask was charged with a racemic mixture of compounds **808** & **809** (102 mg, 0.27 mmol) and methylene chloride (10 mL). Ethanesulfonyl chloride (54.3 mg, 0.42 mmol) and triethylamine (43.6 mg, 0.43 mmol) were added and the resulting mixture stirred at rt overnight. Analysis of the reaction mixture by TLC (SiO_2, EtOAc) indicated the presence of starting material so an additional equivalent of ethanesulfonyl chloride (54.3 mg, 0.42 mmol) was added and stirring continued at rt for 4 h. The reaction mixture was then diluted with CH_2Cl_2 (25 mL) and washed with water (10 mL). Drying over magnesium sulfate, filtration, and concentration afforded a yellow oil. Purification of this oil by silica gel chomatography, eluting with 25% EtOAc in hexanes, then 50% EtOAc in hexanes and finally EtOAc, afforded compound **810** (55.9 mg, 44%) as a white solid. HPLC: 100% at 13.8 min (retention time) (Hypersil C18 BDS column, 250 x 4.6 mm, 5 μm, a detection wavelength of 254 nm, and a flow rate of 1 mL/min. A linear gradient of 90% of 0.1% trifluoroacetic acid in water, 10% acetonitrile (start) to 100% acetonitrile over 15 min, then 100% acetonitrile for 5 min was used), MS (ES): m/z 472 $[M+H]^+$. R_f = 0.72 (EtOAc). Mpt = 189-192 °C. ^{1}H NMR($CDCl_3$): δ = 7.94 (d, J = 8.3 Hz, 1H), 7.85 (s, 1H), 7.74 (dd, J = 8.3 and 2.0 Hz, 1H), 5.72 (d, J = 8.3 Hz, 1H), 3.71 (m, 1H), 3.51 (d, J = 7.2 Hz, 1H), 3.18 (d, J = 7.2 Hz, 1H), 3.11 (q, J = 7.2 Hz, 2H), 2.37 (t, J = 12.0 Hz, 1H), 1.67 (m, 1H), 1.62 (s, 3H), 1.61 (s, 3H) and 1.40 ppm (t, J = 7.2 Hz, 3H). The absolute stereochemistry of compound **810** has not been established. Although the compound represents a single antipode, the nomenclature and structure shown does not reflect the absolute stereochemistry of the compound.

Example 811

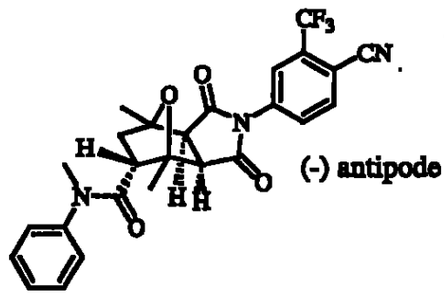
(3aα,4β,5α,7β,7aα)-4-(Octahydro-5-[[((phenylmethyl)amino)carbonyl]oxy]-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (811)



A 25 mL round-bottomed flask was charged with compound 222D (102 mg, 0.27 mmol) and THF (2 mL). Benzyl isocyanate (37.7 mg, 0.28 mmol) was added and the resulting mixture stirred at rt for 1.5 h then heated at 60 °C for an additional 1.5 h. Sodium hydride (50 mg, 60% dispersion in mineral oil) was then added followed by additional benzyl isocyanate (37.7 mg, 0.28 mmol). Heating was continued at 60 °C overnight. Benzyl isocyanate (75.4 mg, 0.56 mmol) and THF (2 mL) were then added and the reaction re-heated to 60 °C for an additional 3 h. The reaction mixture was then cooled to rt and concentrated under reduced pressure to afford an off white solid. Ether (20 mL) was then added and a precipitate formed. The mixture was filtered and the filtrate concentrated to a white solid, which was further purified by preparative HPLC. Fractions containing the desired product were concentrated and a solution of saturated sodium bicarbonate (15 mL) added. The aqueous layer was extracted with methylene chloride (3 x 25 mL), dried over magnesium sulfate, filtered, and concentrated to afford compound 811 (119 mg, 80%) as a white solid. HPLC: 100% at 15.3 min (retention time) (Hypersil C18 BDS column, 250 x 4.6 mm, 5 μm, a detection wavelength of 254 nm, and a flow rate of 1 mL/min. A linear gradient of 90% of 0.1% trifluoroacetic acid in water, 10% acetonitrile (start) to 100% acetonitrile over 15 min, then 100% acetonitrile for 5 min was used), MS (ES): m/z 514 $[M+H]^+$. R_f = 0.58 (SiO_2, 50% EtOAc in hexanes). Mpt >300 °C. ^{1}H NMR($CDCl_3$): δ = 7.94 (d, J = 8.1 Hz, 1H), 7.85 (s, 1H), 7.74 (m, 1H), 7.36-7.34 (m, 5H), 5.07 (bs, 1H), 4.92 (m, 1H), 4.39 (bs, 2H), 3.59 (m, 1H), 3.11 (m, 1H), 2.35 (t, J = 12.0 Hz, 1H) and 1.61 ppm (s, 6H). The absolute stereochemistry of compound 811 has not been established. Although the compound represents a single antipode, the nomenclature and structure shown does not reflect the absolute stereochemistry of the compound.

Example 812

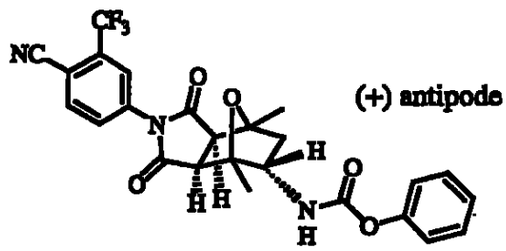
[3a*R*-(3aα,4β,5α,7β,7aα)]-2-(4-Cyano-3-(trifluoromethyl)phenyl)hexahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-*N*-methyl-*N*-phenyl-1H-isoindole-5-carboxamide (812)



To a dry, nitrogen purged 100 mL round-bottomed flask was added compound **804** (100 mg, 0.245 mmol) and CH_2Cl_2 (10 mL). The solution was stirred at rt and oxalyl chloride (311 mg, 2.45 mmol) and *N,N*-dimethylformamide (28.0 mg, 0.387 mmol) were added. Gas evolution was observed and the reaction was stirred at rt for 1 h. The resulting solution was then concentrated to dryness under reduced pressure and CH_2Cl_2 (10 mL) was added. *N*-Methylaniline (262 mg, 2.45 mmol) was added and the reaction stirred for 15 h at rt. After concentrating the resulting solution under reduced pressure, the resulting oil was chomatographed on silica gel, using 50% EtOAc in hexanes as the eluant, to give an orange oil that was contaminated with *N*-methylaniline. The material was re-chomatographed on silica gel, using 40% EtOAc in hexanes as eluant, to afford compound **812** (115 mg, 94%) as a white foam. HPLC: 100% at 18.7 min (retention time) (Hypersil C18 BDS column, 250 x 4.6 mm, 5 μm, a detection wavelength of 254 nm, and a flow rate of 1 mL/min. A linear gradient of 90% of 0.1% trifluoroacetic acid in water, 10% acetonitrile (start) to 100% acetonitrile over 15 min, then 100% acetonitrile for 5 min was used), MS (ES): m/z 498 $[M+H]^+$. R_f = 0.37 (SiO_2, 40% EtOAc in hexanes). Mpt >300 °C. $[\alpha]^{25}_D$ = -30.0° (c = 1.0, MeOH). ^{1}H NMR($CDCl_3$): δ = 7.92 (d, *J* = 8.4 Hz, 1H), 7.84 (d, *J* = 1.5 Hz, 1H), 7.73 (dd, *J* = 8.3 and 2.0 Hz, 1H), 7.52-7.35 (m, 3H), 7.17 (d, *J* = 7.1 Hz, 2H), 4.24 (d, *J* = 7.3 Hz, 1H), 3.30 (s, 3H), 3.28 (d, *J* = 7.3 Hz, 1H), 3.09-2.96 (m, 1H), 2.10-1.99 (m, 1H), 1.81 (t, *J* = 12.0 Hz, 1H), 1.56 (s, 3H) and 1.41 ppm (s, 3H). The absolute stereochemistry of compound **812** has not been established. Although

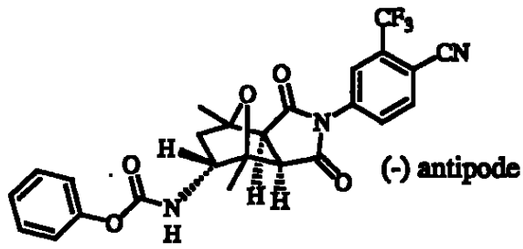
the compound represents a single antipode, the nomenclature and structure shown does not reflect the absolute stereochemistry of the compound.

Example 813



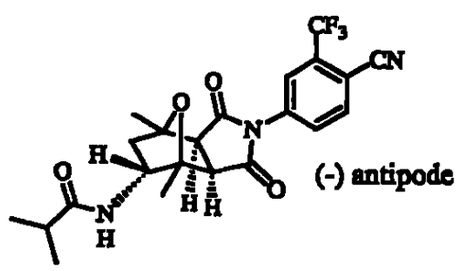
A 25 mL round-bottomed flask was charged with dioxane (3 mL), compound **805** (76.3 mg, 0.187 mmol), diphenylphosphoryl azide (62.6 mg, 0.227 mmol), triethylamine (23.2 mg, 0.230 mmol) and powdered 4Å molecular sieves (200 mg) and the resulting suspension heated at 50 °C for 1.5 h. The temperature was then raised to 75 °C and phenol (93.0 mg, 0.988 mmol) added. Heating was continued for an additional 1.5 h. The reaction mixture was then cooled, filtered though a celite pad and the filtrate concentrated under reduced pressure. Purification of the residue by silica gel chomatography, eluting with 10%-50% EtOAc in hexanes, afforded compound **813** (71.5 mg, 77%) as a white solid. HPLC: 100% at 15.9 min (retention time) (Hypersil C18 BDS column, 250 x 4.6 mm, 5 μm, a detection wavelength of 254 nm, and a flow rate of 1 mL/min. A linear gradient of 90% of 0.1 trifluoroacetic acid in water, 10% acetonitrile (start) to 100% acetonitrile over 15 min, then 100% acetonitrile for 5 min was used), $R_f = 0.70$ (SiO_2, 50% EtOAc in hexanes). $[\alpha]_{25}^{D} = +13.0°$ (c = 1.0, MeOH). Mpt >300 °C. HPLC: $R_t = 15.9$ min. ^{1}H NMR (CD_3OD): $\delta = 8.14$ (d, $J = 8.3$ Hz, 1H), 7.95 (s, 1H), 7.85 (dd, $J = 8.3$ and 2.0 Hz, 1H), 7.41-7.12 (m, 5H), 4.06 (dd, $J = 12.0$ and 5.0 Hz, 1H), 3.55 (d, $J = 7.2$ Hz, 1H), 3.29 (d, $J = 7.2$ Hz, 1H), 2.29 (t, $J = 12.0$ Hz, 1H), 1.71 (dd, $J = 12.0$ and 5.0 Hz, 1H), 1.56 (s, 3H) and 1.54 ppm (s, 3H). The absolute stereochemistry of compound **813** has not been established. Although the compound represents a single antipode, the nomenclature and structure shown does not reflect the absolute stereochemistry of the compound.

Example 814



Compound **814** was prepared in identical fashion as described in example **813** with the exception that compound **804** was the starting material in place of compound **805**. Compound **814** was isolated in 62% overall yield. $[\alpha]^{25}_{D}$ = -11.7° (c = 1.0, MeOH). The absolute stereochemistry of compound **814** has not been established. Although the compound represents a single antipode, the nomenclature and structure shown does not reflect the absolute stereochemistry of the compound.

Example 815

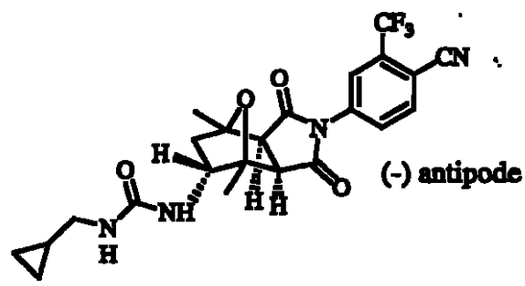


Compound **807** (0.060 g, 0.15 mmol) was dissolved in 2 mL of CH_2Cl_2 and triethylamine (0.020 g, 0.16 mmol) and a catalytic amount of DMAP were added followed by isobutyryl chloride (0.02g, 0.16 mmol). The reaction was stirred for 1 h at 23°C when HPLC showed complete consumption of starting material. The reaction was diluted with CH_2Cl_2, washed successively with 1N HCl, saturated sodium bicarbonate, brine, dried ($MgSO_4$), filtered and concentrated *in vacuo* to give compound **815** (0.06 g, 83%), as a white solid. No was purification necessary. HPLC: 100% at 3.12 min(YMC S5 ODS column) eluting with 10-90% aqueous methanol containing 0.2% phosphoric acid over a 4 min gradient monitoring at 220 nm. LC/MS – [M+H] = 450.12. The absolute stereochemistry of compound **815** has

not been established. Although the compound represents a single antipode, the nomenclature and structure shown does not reflect the absolute stereochemistry of the compound.

Example 816

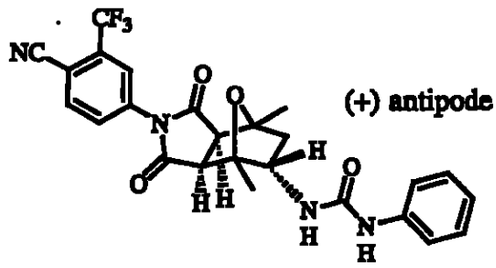
[3a*R*-(3aα,4β,5α,7β,7aα)]-4-(Octahydro-5-[[(cyclopropylmethyl)aminolcarbonyl]amino]-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (816)



A 50 mL round-bottomed was charged with compound **815** (0.052 g, 0.10 mmol), methyl sulfoxide (2 mL) and aminomethylcyclopropane (10 μL, 8.2 mg, 0.11 mmol). The reaction was stirred for 4 h after which time the reaction mixture was diluted with water (9 mL) and saturated $NaHCO_3$ solution (1 mL). Extraction with CH_2Cl_2 (1 x 20 mL then 1 x 10 mL), drying over $MgSO_4$, filtration and concentration afforded the crude product as a yellow oil. Purification by silica gel chomatography, eluting with 20% to 50% EtOAc in hexanes afforded compound **816** (33.6 mg, 67). HPLC: 100% at 12.9 min (retention time) (Hypersil C18 BDS column, 250 x 4.6 mm, 5 μm, a detection wavelength of 254 nm, and a flow rate of 1 mL/min. A linear gradient of 90% of 0.1% trifluoroacetic acid in water, 10% acetonitrile (start) to 100% acetonitrile over 15 min, then 100% acetonitrile for 5 min was used), MS (ES): m/z 477 $[M+H]^+$. R_f = 0.42 (SiO_2, 50% EtOAc in hexanes). Mpt > 300 °C. $[\alpha]^{25}_D$ = -31.5° (c =1.0, MeOH). ^{1}H NMR($CDCl_3$): δ = 8.12 (d, *J* = 8.3 Hz, 1H), 7.94 (s, 1H), 7.84 (d, *J* = 8.3 Hz, 1H) 4.12-4.06 (m, 1H), 3.46 (d, *J* = 8.3 Hz, 1H), 3.34 (bs, 1H), 3.22 (d, *J* = 8.3 Hz, 1H), 1.41 (t, *J* = 12.3 Hz, 1H), 1.54 (s, 3H), 1.50 (s, 3H), 1.01-0.92 (m, 1H), 0.51-0.45 (m, 2H) and 0.21-0.17 ppm (m, 2H). The absolute stereochemistry of compound **816** has not been established. Although the compound

represents a single antipode, the nomenclature and structure shown does not reflect the absolute stereochemistry of the compound.

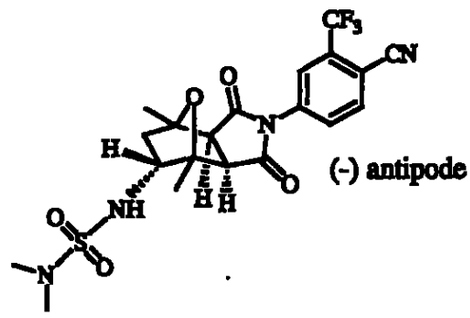
Example 817



A 50 mL round-bottomed was charged with compound **809** (0.057 g, 0.15 mmol) and phenyl isocyanate (0.1 mL, 0.9 mmol). After heating for 3 h at 65-70 °C, analysis of the reaction by HPLC indicated complete consumption of starting material. Dilution with EtOAc (0.5 mL) and purification by silica gel chomatography, eluting with 60% EtOAc in hexanes afforded compound **817** (39 mg, 52%) as a white solid. HPLC: 100% at 14.2 min (retention time) (Hypersil C18 BDS column, 250 x 4.6 mm, 5 μm, a detection wavelength of 254 nm, and a flow rate of 1 mL/min. A linear gradient of 90% of 0.1% trifluoroacetic acid in water, 10% acetonitrile (start) to 100% acetonitrile over 15 min, then 100% acetonitrile for 5 min was used), MS (ES): m/z 499 $[M+H]^+$. R_f = 0.17 (50% EtOAc in hexanes). Mpt > 300 °C. $[\alpha]^{25}_D$ = +30.7° (c = 1.0, MeOH). ^{1}H NMR($CDCl_3$): δ = 8.12 (d, *J* = 8.3 Hz, 1H), 7.94 (s, 1H), 7.84 (d, *J* = 8.3 Hz, 1H), 7.35 (d, *J* = 7.8 Hz, 2H), 7.26 (t, *J* = 7.7 Hz, 2H), 6.99 (t, *J* = 7.1 Hz, 1H), 4.19-4.14 (m, 1H), 3.51 (d, *J* = 7.1 Hz, 1H), 3.27-3.25 (m, 2H), 2.31 (t, *J* = 12.3 Hz, 1H), 1.63-1.61 (m, 1H), 1.56 (s, 3H) and 1.55 ppm (s, 3H). The absolute stereochemistry of compound **817** has not been established. Although the compound represents a single antipode, the nomenclature and structure shown does not reflect the absolute stereochemistry of the compound.

Example 818

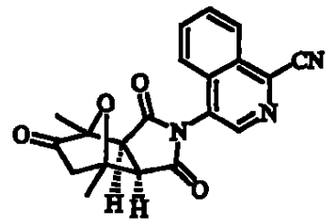
[3a*R*-(3aα,4β,5α,7β,7aα)]-4-(Octahydro-5-[[(dimethylamino)sulfonyl]amino]-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (817)



A 50 mL round-bottomed flask was charged with compound **808** (100 mg, 0.28 mmol), methylene chloride (2 mL), triethylamine (28.3 mg, 0.28 mmol) and dimethylsulfamoyl chloride (40.2 mg, 0.28 mmol). The reaction was then stirred at rt for 3 h, after which time it was quenched with water (10 mL) and extracted with CH_2Cl_2 (2 x 20 mL). The organic layer was washed once more with water (10 mL), dried over $MgSO_4$, filtered and concentrated to a yellow oil. Purification by silica gel chomatography, eluting with 20% EtOAc in hexanes to 100% EtOAc afforded compound **818** (64.2 mg, 47%). HPLC: 100% at 14.2 min (retention time) (Hypersil C18 BDS column, 250 x 4.6 mm, 5 μm, a detection wavelength of 254 nm, and a flow rate of 1 mL/min. A linear gradient of 90% of 0.1% trifluoroacetic acid in water, 10% acetonitrile (start) to 100% acetonitrile over 15 min, then 100% acetonitrile for 5 min was used), MS (ES): m/z 487 $[M+H]^+$. R_f = 0.19 (SiO_2, 50% EtOAc in hexanes). $[\alpha]^{25}_D$ = -22.8° (c = 1.0, MeOH). Mpt = 262-269 °C. ^{1}H NMR($CDCl_3$): δ = 8.12 (d, *J* = 8.3 Hz, 1H), 7.94 (s, 1H), 7.84 (d, *J* = 8.2 Hz, 1H), 3.61 (m, 1H), 3.54 (d, *J* = 7.2 Hz, 1H), 3.35 (s, 1H), 3.22 (d, *J* = 7.2 Hz, 1H), 2.79 (s, 6H), 2.27 (t, *J* = 12.4 Hz, 1H), 1.68 (m, 1H), 1.54 (s, 3H) and 1.53 ppm (s, 3H). The absolute stereochemistry of compound **818** has not been established. Although the compound represents a single antipode, the nomenclature and structure shown does not reflect the absolute stereochemistry of the compound.

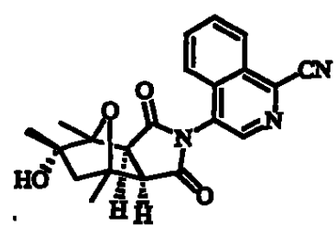
Example 819

323



A mixture of 4-(2,5-dioxo-2,5-dihydro-pyrrol-1-yl)-isoquinoline-1-carbonitrile (1 g, 4 mmol), 2,5-dimethyl-2,3-dihydrofuran-3-one (0.45 g, 4 mmol), DMAP (20 mg, 0.16 mmol), anhydrous methylene chloride (10 mL), and THF (20mL) was stirred at 80°C overnight, and then concentrated under reduced pressure. Purification by silica gel flash chomatography on SiO_2 eluting with EtOAc/heptane (gradient from 1:4 to 1:0 ratio) gave a solid that was crystalized in a mixture of EtOAc and heptane to give 0.4 g (28%) of compound **819** as a yellowish solid. HPLC: 90% at 3.37 min (retention time) (YMC S5 ODS-A column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 mincontaining 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 362 $[M+H]^+$. Compound **819** represents a racemic mixture of antipodes. The nomenclature and structure shown does not reflect the absolute stereochemistry of the compound.

Example 820

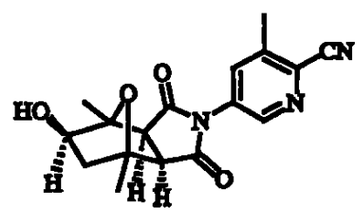


To a stirred solution of compound **819** (36 mg, 0.1 mmol) in anhydrous THF (1 mL) cooled at 0°C under argon was added MeMgBr (1.4 M THF solution, 0.3 mL, 0.4 mmol) dropwise. After the mixture was stirred at 0°C for 1 h and at rt for 10 min, saturated aqueous solution of NH_4Cl was added with stirring. The mixture was extracted with EtOAc (3X). The combined extracts were dried over Na_2SO_4, and

concentrated under reduced pressure. Purification by silica gel flash chomatography eluting with EtOAc/heptane (gradient from 1:2 to 1:0 ratio) gave a solid that was crystallized in a mixture of EtOH and H_2O to give compound **820** (8 mg, 21%) as a white solid. HPLC: 97% at 3.36 min (retention time) (YMC S5 ODS-A column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 mincontaining 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 378 $[M+H]^+$. Compound **820** represents a racemic mixture of antipodes. The nomenclature and structure shown does not reflect the absolute stereochemistry of the compound.

Example 821

[3aS-(3aα,4β,5β,7β,7aα)]-5-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-3-methyl-2-pyridinecarbonitrile (821)



A mixture of compound **772B** (20 mg, 0.14 mmol), compound **751** (48 mg, 0.20 mmol) and 4 Å molecular sieves (100 mg) in DMA (0.2 mL) was heated at 70 °C in a sealed tube for 5 h. The reaction mixture was filtered and the residue was washed with EtOAc. The filtrates were combined and washed with H_2O (2 x 5 mL) and brine (1 x 5 mL). The combined aqueous layers were extracted with EtOAc (2 x 5 mL) and the combined organic layers were dried over Na_2SO_4 and concentrated under reduced pressure. Purification by silica gel flash chomatography eluting with 30 acetone/$CHCl_3$ gave 55 mg of product contaminated with compound **751**. Further purification by silica gel flash chomatography on SiO_2 eluting with 90% EtOAc/hexanes gave compound **821** (46 mg, 62%) as a white solid. HPLC: 100% at 2.27 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90 aqueous methanol over 4 mincontaining 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 328.2 $[M+H]^+$. The absolute stereochemistry of compound **821** is established by the known stereochemistry of the intermediate compound **751** and the retention of configuration therein. The absolute stereochemistry is as drawn in the above figure and rendered by the nomenclature.

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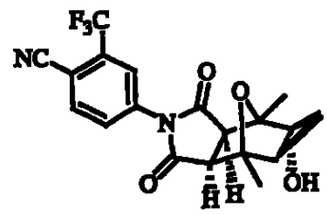
Example 822

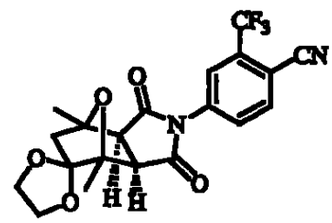
[3a*R*-(3aα,4β,4aα,5aα,6β,7aα)]-4-(Octahydro-4a-hydroxy-4,6-dimethyl-1,3-dioxo-4,6-epoxycycloprop[f]isoindol-2(1H)-yl)-2-(trifluoromethyl)benzonitrile (822)



A solution of compound **222B** (114 mg, 0.231 mmol) in 1,2-dichloroethane (2.30 mL), in a dry flask under argon, was cooled to 0 °C with an ice bath. To this solution was added Et_2Zn solution (0.460 mL, 0.462 mmol, 1 M in hexanes), followed by dropwise addition of chloroiodomethane (70.0 μL, 0.926 mmol). The reaction mixture was stirred at 0 °C for 1 h then at rt for 18 h. After judging the reaction to be only 50% complete by TLC and HPLC methods, more Et_2Zn (0.469 mL) and chloroiodomethane (70 μL) were added and the mixture was stirred at rt for 2.5 h. The reaction mixture was quenched with saturated NH_4Cl, extracted with *t*-butyl methyl ether (2 X 10 mL) and the combined organic layers were dried over $MgSO_4$ and *in vacuo*. The crude material (174 mg) was dissolved in a mixture of EtOH (5 mL) and conc. HCl (2 mL) and stirred at rt for 1 h. The mixture was then diluted with H_2O and extracted with EtOAc (1 X 25 mL). The organic layer was washed with brine (1 X 25 mL), dried and concentrated under reduced pressure. Purification by preparative TLC (SiO_2) eluting with 30% acetone/$CHCl_3$ gave compound **822** (9.1 mg, 10%) as a tan solid. HPLC: 90% at 3.15 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 393.03 $[M+H]^+$. Compound **822** represents a racemic mixture of antipodes. The nomenclature and structure shown does not reflect the absolute stereochemistry of the compound.

Example 823

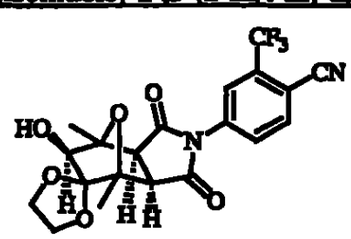
[3'a*R*-(3'aα,4'β,7'β,7'aα)]-Tetrahydro-4',7'-dimethyl-2'-[4-cyano-3(trifluoromethyl)phenyl]-spiro[1,3-dioxolane-2,5'-4,7-epoxy(5H)isoindole]-1',3'(2'H,4'H)-dione (823)



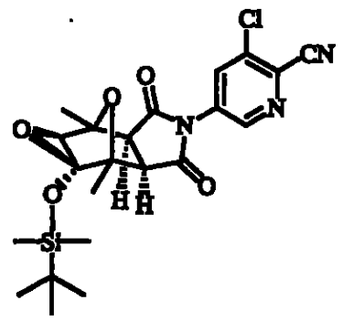
A mixture of compound 796 (44.3 mg, 0.117 mmol), ethylene glycol (0.065 mL, 1.17 mmol) and *p*-toluenesulphonic acid (2.2 mg, 0.012 mmol) in benzene (3 mL) was refluxed for 18 h. The reaction mixture was then diluted with benzene, washed with 5% Na_2CO_3 (1 X 10 mL), H_2O (1 X 10 mL), dried (Na_2SO_4) and concentrated *in vacuo*. Purification by silica gel flash chomatography on silica gel eluting with 10% acetone/$CHCl_3$ gave compound 823 (44.5 mg, 90%) as a white solid. HPLC: 99% at 3.11 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ESI): m/z 423.01 $[M+H]^+$. Compound 823 represents a racemic mixture of antipodes. The nomenclature and structure shown does not reflect the absolute stereochemistry of the compound.

Example 824

[3'a*R*-(3'aα,4'β,6'β,7'β,7'aα)]-Tetrahydro-6'-hydroxy-4',7'-dimethyl-2'-[4-cyano-3(trifluoromethyl)phenyl]-spiro[1,3-dioxolane-2,5'-4,7-epoxy(5H)isoindole]-1',3'(2'H,4'H)-dione (824B)



A. (824A)



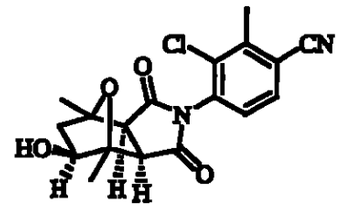
A solution of dimethyldioxirane (32 mL, 1.588 mmol, 0.05 M) was added to a solution of compound **222B** (521.6 mg, 1.059 mmol) in acetone (1 mL) at rt. After 2.5 h the reaction was shown to be complete by HPLC and was concentrated under reduced pressure to give 559 mg (quant.) of crude compound **824A** as a yellow solid.

B. [3'a*R*-(3'aα,4'β,6'β,7'β,7'aα)]-Tetrahydro-6'-hydroxy-4',7'-dimethyl-2'-[4-cyano-3(trifluoromethyl)phenyl]-spiro[1,3-dioxolane-2,5'-4,7-epoxy(5H)isoindole]-1',3'(2'H,4'H)-dione (824B)

A mixture of compound **824A** (57.5 mg, 0.113 mmol), ethylene glycol (0.100 mL, 1.13 mmol) and *p*-toluenesulphonic acid (11.0 mg, 0.057 mmol) in benzene (5 mL) was refluxed for 18 h. The reaction mixture was concentrated *in vacuo*. Purification by silica gel flash chomatography eluting with 30% acetone/$CHCl_3$ gave compound **824B** (43 mg, 88%) as a white solid. HPLC: 98% at 2.87 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ESI): m/z 439.07 $[M+H]^+$. Compound **824B** represents a racemic mixture of antipodes. The nomenclature and structure shown does not reflect the absolute stereochemistry of the compound.

Example 825

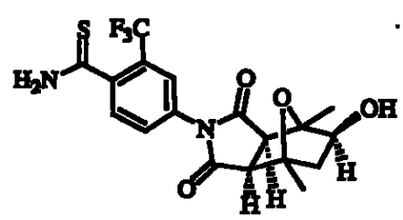
[3a*R*-(3aα,4β,5β,7β,7aα)]-4-[Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-3-chloro-2-methylbenzonitrile (825)



A mixture of 4-amino-3-chloro-2-methyl-benzonitrile (23 mg, 0.14 mmol), compound 752 (44 mg, 0.21 mmol) and 4 Å molecular sieves (100 mg) in DMA (0.2 mL) was heated at 135 °C in a sealed tube for 18 h. Purification by preparative TLC (SiO_2) eluting with 30% acetone/$CHCl_3$ gave compound 825 (5.0 mg, 10%) as a yellow film. HPLC: 90% at 2.37 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 mincontaining 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 360.97 $[M+H]^+$. The absolute stereochemistry of compound 825 is established by the known stereochemistry of the intermediate compound 752 and the retention of configuration therein. The absolute stereochemistry is as drawn in the above figure and rendered by the nomenclature.

Example 826

[3a*R*-(3aα,4β,5β,7β,7aα)]-4-[Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-(trifluoromethyl)benzenecarbothioamide (826)

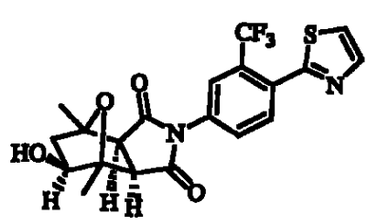


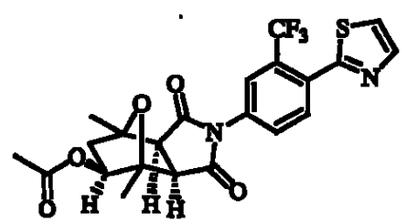
H_2S gas was condensed into a pyrex tube at –78 °C until there was 5 mL of liquid. Compound 471Di (108 mg, 0.284 mmol), Et_3N (50.0 µL, 0.341 mmol) and DMF (1 mL) were added at –78 °C and the tube was sealed. The reaction mixture was allowed to warm to rt with stirring behind a blast shield then heated at 90 °C for 50 mins at which time the color changed to green. The reaction mixture was re-cooled to –78 °C to check the progress by HPLC. All the starting material was consumed, so the mixture was allowed to warm to rt to remove H_2S, diluted with

EtOAc and washed with H_2O (4 X 10 mL). Purification by silica gel flash chomatography eluting with 50% acetone/$CHCl_3$ gave compound **826** (116 mg, 98%) as a white solid. HPLC: 98% at 1.90 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 mincontaining 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 415.23 $[M+H]^+$. The absolute stereochemistry of compound **826** is established by the known stereochemistry of the intermediate compound **471Di** and the retention of configuration therein. The absolute stereochemistry is as drawn in the above figure and rendered by the nomenclature.

Example 827

[3a*R*-(3aα,4β,5β,7β,7aα)]-2-[3-(trifluoromethyl)-4-(2-thiazolyl)phenyl]-5-(acetoxy)hexahydro-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione (827I) & [3a*R*-(3aα,4β,5β,7β,7aα)]-2-[3-(trifluoromethyl)-4-(2-thiazolyl)phenyl]hexahydro-5-hydroxy-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione (827II)



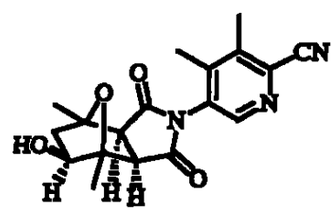


A solution of compound **826** (61.6 mg, 0.149 mmol), bromoacetaldehyde diethyl acetal (30.0 µL, 0.186 mmol) and *p*-toluene sulphonic acid (1 mg, cat.) in AcOH (1 mL) was heated at 100 °C for 1 h. The reaction mixture was cooled to rt and diluted with H_2O. The mixture was extracted with EtOAc (1 X 10 mL) and the resulting organic layer was washed with H_2O (1 X 10 mL), saturated $NaHCO_3$ (1 X 10 mL) and brine (1 X 10 mL), then dried over $MgSO_4$ and concentrated *in vacuo*. Purification by preparative TLC (SiO_2) eluting with 30% acetone/$CHCl_3$ gave two products both of which were subjected to further purification. The less polar product was purified further by silica gel flash chomatography eluting with 50% EtOAc/hexanes to give compound **827I** (30.0 mg, 42%) as a white solid. The more

polar product was purified further by silica gel flash chomatography eluting with 10% acetone/$CHCl_3$ to give compound **827li** (4.6 mg, 7%) as a white solid. Compound **827l**: HPLC: 99% at 3.12 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 mincontaining 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 481.04 $[M+H]^+$. Compound **827li**: HPLC: 99% at 2.62 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 mincontaining 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 439.02 $[M+H]^+$. The absolute stereochemistry of compounds **827l** & **827li** is established by the known stereochemistry of the intermediate compound **471Di** and the retention of configuration there in. The absolute stereochemistry is as drawn in the above figure and rendered by the nomenclature.

Example 828

[3a*R*-(3aα,4β,5β,7β,7aα)]-5-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-3,4-dimethyl-2-pyridinecarbonitrile (828)

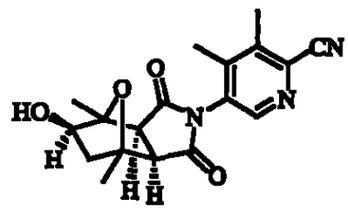


A mixture of 5-amino-3,4-dimethylpyridine-2-carbonitrile (30 mg, 0.20 mmol), compound **752** (65 mg, 0.31 mmol) and 4 Å molecular sieves (200 mg) in DMA (1 mL) was heated at 160 °C in a sealed tube for 18 h. The reaction mixture was filtered, the residue was washed with EtOAc and the combined filtrates were concentrated under reduced pressure. Purification by preparative TLC (SiO_2) eluting with 90% EtOAc/hexanes gave compound **828** (42 mg, 40%) as a light pink solid. HPLC: 94% at 1.92 & 2.00 min (retention time-atropisomers) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 mincontaining 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 342.21 $[M+H]^+$. The absolute stereochemistry of compound **828** is established by the known stereochemistry of the intermediate compound **752** and the retention of configuration

therein. The absolute stereochemistry is as drawn in the above figure and rendered by the nomenclature.

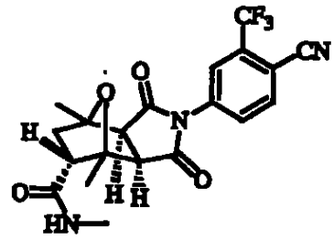
Example 829

[3aS-(3aα,4β,5β,7β,7aα)]-5-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-3,4-dimethyl-2-pyridinecarbonitrile (829)



A mixture of 5-amino-3,4-dimethylpyridine-2-carbonitrile (30 mg, 0.20 mmol), compound **751** (65 mg, 0.31 mmol) and 4 Å molecular sieves (200 mg) in DMA (0.25 mL) was heated at 160 °C in a sealed tube for 18 h. The reaction mixture was filtered, the residue was washed with EtOAc and the combined filtrates were washed with H_2O (2 X 10 mL), brine (1 X 10 mL), dried (Na_2SO_4) and concentrated under reduced pressure. Purification by silica gel flash chomatography on silica gel eluting with 90% EtOAc/hexanes followed by preparative TLC (SiO_2) eluting with 90% EtOAc/hexanes gave compound **829** (35 mg, 33%) as a light pink solid. HPLC: 98% at 1.92 & 2.00 min (retention time-atropisomers) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 mincontaining 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 342.21 $[M+H]^+$. The absolute stereochemistry of compound **829** is established by the known stereochemistry of the intermediate compound **751** and the retention of configuration therein. The absolute stereochemistry is as drawn in the above figure and rendered by the nomenclature.

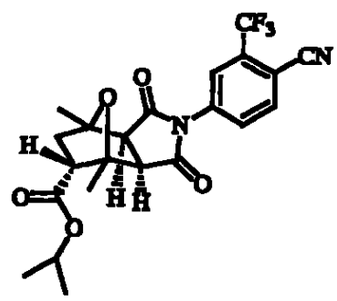
Example 830



A solution of compound **791B** (41 mg; 0.1 mmol), 2.0M methylamine in THF (0.2 mL; 0.4 mmol), 1-hydroxy-7-azabenzotriazole (17 mg; 0.12 mmol), EDCI (40 mg; 0.2 mmol) and diisopropylethylamine (0.075 mL; 0.4 mmol) in 0.5 mL of DMF was heated to 55°C for 3 hs. After partitioning the reaction mixture between EtOAc (20 mL) and water (20 mL), the organic layer was washed with 1N NaOH (2 x 20 mL), saturated potassium bisulfate solution (2 x 20 mL) and brine (20 mL). Drying ($MgSO_4$) and concentration *in vacuo* gave an residue that was crystallized from ethyl ether to afford compound **830** (30 mg, 71%) as a white solid. HPLC: 97.5% at 1.48 min (retention time) (Phenominex S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 2 mincontaining 0.1% TFA, 4 mL/min, monitoring at 254 nm); MS (ES): m/z 422.30 $[M+H]^+$. Compound **830** represents a racemic mixture of antipodes. The nomenclature and structure shown does not reflect the absolute stereochemistry of the compound.

Example 831

Name 831

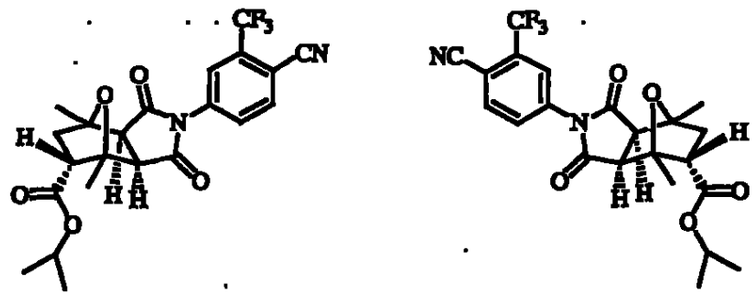


One drop of DMF was added to a solution of compound **792B** (60 mg; 0.15 mmol) and oxalyl chloride (0.026 mL; 0.3 mmol) in methylene chloride (1 mL) at rt. After stirring 2 h at rt, the volatiles were removed *in vacuo*. The residue was dissolved in ~2 mL of isopropanol. After standing 30 minat rt, the volatiles were removed *in vacuo* and the residue was dissolved in EtOAc:isopropanol, 9:1 (20 mL). The solution was allowed to stand 15 min over decolorizing carbon. Filtration though celite and concentration of the filtrate afforded compound **831** (56 mg, 83%) as a light yellow foam. HPLC: 96.9% at 1.52 min (retention time) (Phenominex S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 2 mincontaining 0.1% TFA, 4 mL/min, monitoring at 254 nm); MS (ES): m/z 451.08 $[M+H]^+$.

Compound 831 represents a racemic mixture of antipodes. The nomenclature and structure shown does not reflect the absolute stereochemistry of the compound.

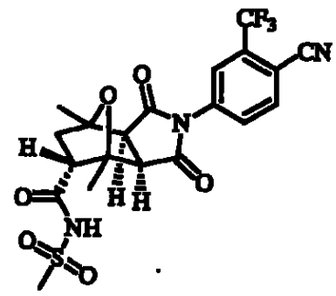
Example 832

Name 832i & 832ii



Racemic compound 831 (0.4 g) was separated into its enantiomers by normal phase preparative chiral HPLC (CHIRALPAK OJ 5 x 50 cm column; eluting with 25% MeOH/EtOH (1:1) in hexane (isocratic) at 50 mL/min) to give 170 mg of faster eluting enantiomer, compound 832i (Chiral HPLC: 8.97 min; CHIRALPAK OJ 4.6 x 250 mm column; eluting with 20% MeOH/EtOH (1:1) in hexane at 1 mL/min); HPLC: 99% at 1.84 min (retention time) (Phenominex S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 2 mincontaining 0.1% TFA, 4 mL/min, monitoring at 254 nm); MS (ES): m/z 451.06 $[M+H]^+$and 190 mg of the slower eluting enantiomer, compound 832ii (Chiral HPLC: 14.79 min; CHIRALPAK OJ 4.6 x 250 mm column; eluting with 20% MeOH/EtOH (1:1) in hexane at 1 mL/min); HPLC: 99% at 1.85 min (retention time) (Phenominex S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 2 mincontaining 0.1% TFA, 4 mL/min, monitoring at 254 nm); MS (ES): m/z 451.03 $[M+H]^+$. The absolute stereochemistry of compounds 832i & 832ii has not been established. Although each compound represents a single antipode, the nomenclature and structure shown does not reflect the absolute stereochemistry of the compound.

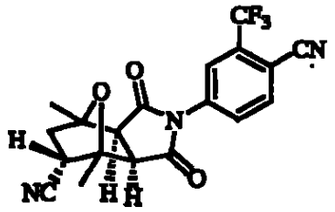
Example 833



A solution of compound 792B (45 mg; 0.11 mmol), methane sulfonamide (27 mg; 0.28 mmol), 4-dimethylaminopyridine (34 mg; 0.28 mmol) and EDCI (24 mg; 0.12 mmol) in 1 mL of dichloromethane was stirred at rt for 18 hs. After partitioning the reaction mixture between EtOAc (25 mL) and water (25 mL), the organic layer was washed with saturated potassium bisulfate solution (25 mL), water (25 mL) and brine (25 mL). Drying ($MgSO_4$) and concentration gave an residue that was triturated with ethyl ether to afford compound 833 (29 mg, 55%) as an off-white powder. HPLC: 98% at 1.44 min (retention time) (Phenominex S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 2 mincontaining 0.1% TFA, 4 mL/min, monitoring at 254 nm); MS (ES): m/z 485.94 $[M+H]^+$. Compound 833 represents a racemic mixture of antipodes. The nomenclature and structure shown does not reflect the absolute stereochemistry of the compound.

Example 834

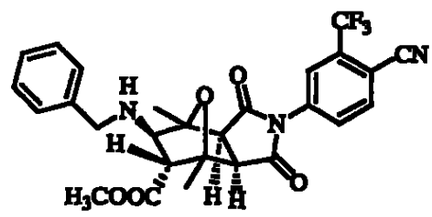
3aα,4β,5α,7β,7aα)-2-(4-Cyano-3-(trifluoromethyl)phenyl)-hexahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-1H-isoindole-5-carb (834)



A mixture of compound 792B (100 mg; 0.24 mmol), (methoxycarbonylsulfamoyl)triethylammonium hydroxide, inner salt (125 mg; 0.5 mmol) and triethylamine (0.15 mL; 1 mmol) in 2.5 mL of THF was stirred at rt for 2 hs. After partitioning the reaction mixture between ethyl ether (30 mL) and water (30

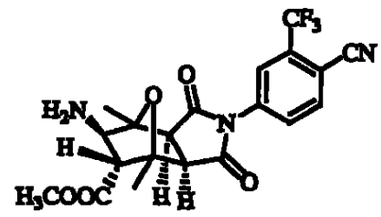
mL), the organic layer was washed with saturated potassium bisulfate solution (30 mL), saturated sodium bicarbonate solution (30 mL) and brine (30 mL). Drying ($MgSO_4$) and concentration *in vacuo* afforded compound **834** (80 mg, 97%) as a white powder. HPLC: 99% at 1.51 min (retention time) (Phenominex S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 2 mincontaining 0.1% TFA, 4 mL/min, monitoring at 254 nm); MS (ES): m/z 390.03 $[M+H]^+$. Compound **834** represents a racemic mixture of antipodes. The nomenclature and structure shown does not reflect the absolute stereochemistry of the compound.

Example 835



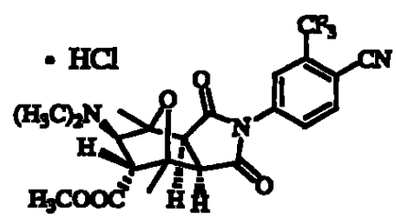
A mixture of compound **793A** (121 mg; 0.29 mmol) and benzylamine (0.032 mL; 0.29 mmol) in 0.6 mL of THF was stirred at rt for 18 hs. After adding ~5 mL of hexane, the resulting suspension was filtered and dried to afford compound **835** (135 mg, 89%) as a white powder. HPLC: 99% at 1.42 min (retention time) (Phenominex S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 2 mincontaining 0.1% TFA, 4 mL/min, monitoring at 254 nm); MS (ES): m/z 528.39 $[M+H]^+$. Compound **835** represents a racemic mixture of antipodes. The nomenclature and structure shown does not reflect the absolute stereochemistry of the compound.

Example 836



A mixture of compound 793A (190 mg; 0.45 mmol) and 2.0M ammonia in THF (0.3 mL; 0.6 mmol) in 0.7 mL of THF was stirred at rt. After 1 h, an additional amount of 2.0M ammonia in THF (0.7mL; 1.4 mmol) was added and the reaction mixture was stirred at rt for 18 hs. The volatiles were removed *in vacuo* and the residue was triturated from hexane to afford compound 835 (145 mg, 74%) as an off-white powder. HPLC: 95.1% at 1.28 min (retention time) (Phenominex S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 2 mincontaining 0.1% TFA, 4 mL/min, monitoring at 254 nm); MS (ES): m/z 438.26 $[M+H]^+$. Compound 836 represents a racemic mixture of antipodes. The nomenclature and structure shown does not reflect the absolute stereochemistry of the compound.

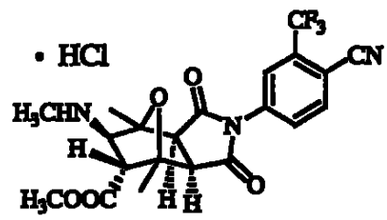
Example 837



A mixture of compound 793A (42 mg; 0.1 mmol) and 2.0M dimethylamine in MeOH (0.1mL; 0.1 mmol) in 0.5 mL of THF was stirred at rt for 18 h. The volatiles were removed *in vacuo* and the residue filtered though a 0.5 x 5 cm plug of silica gel, eluted with ~50 mL of EtOAc. After concentration of the filtrate, the light yellow residue was dissolved in ethyl ether and 0.3 mL of 1M HCl in ethyl ether was added. The volatiles were removed *in vacuo* and the solid residue was triturated from ethyl ether to afford compound 837 (25 mg, 50%) as a cream colored powder. HPLC: 99 at 1.31 min (retention time) (Phenominex S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 2 mincontaining 0.1% TFA, 4 mL/min, monitoring at

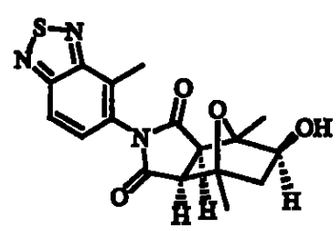
254 nm); MS (ES): m/z 466.33 $[M+H]^+$. Compound 837 represents a racemic mixture of antipodes. The nomenclature and structure shown does not reflect the absolute stereochemistry of the compound.

Example 838

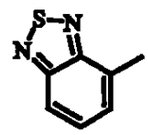


A mixture of compound 793A (42 mg; 0.1 mmol) and 2.0M dimethylamine in THF (0.1mL; 0.1 mmol) in 0.5 mL of THF was stirred at rt for 18 h. The volatiles were removed *in vacuo* and the residue filtered though a 0.5 x 5 cm plug of silica gel, eluted with ~50 mL of EtOAc. After concentration of the filtrate, the yellow residue was dissolved in ethyl ether and 0.3 mL of 1M HCl in ethyl ether was added. The volatiles were removed *in vacuo* and the solid residue was triturated from ethyl ether to afford compound 838 (22 mg, 46%) as a yellow powder. HPLC: 99% at 1.28 min (retention time) (Phenominex S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 2 mincontaining 0.1% TFA, 4 mL/min, monitoring at 254 nm); MS (ES): m/z 452.31 $[M+H]^+$. Compound 838 represents a racemic mixture of antipodes. The nomenclature and structure shown does not reflect the absolute stereochemistry of the compound.

Example 839

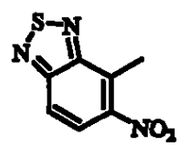


A. 4-Methyl-benzo[1,2,5]thiadiazole (839A)



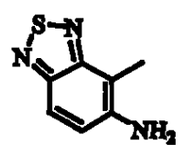
To a solution of 2,3-diaminotoluene (5.0g, 40.9 mmol) in pyridine (40 mL) at 0°C was added thionyl chloride (7.0 mL, 98.2 mmol) dropwise. The reaction mixture was stirred at 0°C for 30 mins, then water (200 mL) was added. The solution was extracted with dicholomethane (2 x 250 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to give compound 839A (5.57g) as a dark brown liquid.

B. 4-Methyl-5-nitro-benzo[1,2,5]thiadiazole (839B)



To a solution of 4-methyl-benzo[1,2,5]thiadiazole (5.57 g, 37.1 mmol) in conc. H_2SO_4 (14.5 mL) at 0°C was slowly added HNO_3/H_2SO_4 (3.25 mL/4.25 mL). The reaction mixture was stirred at 0°C for 20 min and then at rt for 30 min and then was poured into iced water (200 mL). The resulting precipitate was isolated by filtration, rinsed with water and purified by silica gel flash chomatography, eluting with $CHCl_3$ to give compound 839B (1.5 g) as a yellow solid and 4-methyl-7-nitro-benzo[1,2,5]thiadiazole (2.0 g) as a yellow solid.

C. 4-Methyl-benzo[1,2,5]thiadiazol-5-ylamine (839C)



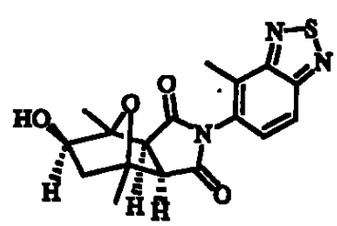
4-Methyl-5-nitro-benzo[1,2,5]thiadiazole (1.4 g, 7.18 mmol) was dissolved in THF (10 mL), acetic acid (1 mL) and water (21 mL) and iron powder (1.4 g, 25.0

mmol, 325 Mesh) was added. The reaction mixture was heated at 80°C for 1.5 h, cooled to rt and filtered though celite to remove the iron powder. The solution was extracted with $CHCl_3$ (2 x 250 mL). The combined organic layers were washed with brine, dried over Na_2SO_4 and concentrated *in vacuo* to give compound **839C** (1.1 g) as a light brown solid.

D. (839D)

4-Methyl-benzo[1,2,5]thiadiazol-5-ylamine (0.10 g, 0.610 mmol), 4Å molecular sieve (0.46 g) and compound **752** (0.128 g, 0.610 mmol) were dissolved in DMA (0.60 mL) in a sealed tube. The reaction mixture was heated at 190°C for 1 h and then was cooled to rt. The solution was filtered though celite to remove the sieves and then the filtrate was washed with saturated NH_4Cl (10 mL) followed by brine (10 mL). The organic layer was then dried over Na_2SO_4 and concentrated *in vacuo* to yield a yellow oil. The resulting material was purified by preparative TLC (SiO_2), eluting with 20% acetone in $CHCl_3$ to give compound **839D** (70 mg) as a light yellow solid. HPLC: 98% at 2.87 min (retention time) (YMC S-5 ODS-A column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2 phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ESI): m/z 360.19 [M+H]. The absolute stereochemistry of compound **752** is established by the known stereochemistry of the intermediate compound **839D** and the retention of configuration therein. The absolute stereochemistry is as drawn in the above figure and rendered by the nomenclature.

Example 840

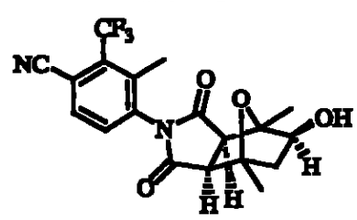


4-Methyl-benzo[1,2,5]thiadiazol-5-ylamine (0.078g, 0.47 mmol), 4Å molecular sieve (0.46 g) and compound **751** (0.100 g, 0.47 mmol) were dissolved in

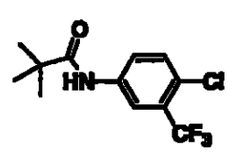
DMA (0.50 mL) in a sealed tube. The reaction mixture was heated at 190°C for 1 h and then was cooled to rt. The solution was filtered though celite to remove the sieves and then the filtrate was washed with saturated NH_4Cl (10 mL), followed by brine (10 mL). The organic layer was then dried over Na_2SO_4 and concentrated *in vacuo* to yield a yellow oil. The resulting material was purified by preparative TLC (SiO_2), eluting with 20% acetone in $CHCl_3$ to give compound **840** (20 mg) as a light yellow solid. HPLC: 97% at 2.87 min (retention time) (YMC S-5 ODS-A column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2 phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ESI): m/z 360.30 [M+H]. The absolute stereochemistry of compound **840** is established by the known stereochemistry of the intermediate compound **751** and the retention of configuration therein. The absolute stereochemistry is as drawn in the above figure and rendered by the nomenclature.

Example 841

[3a*R*-(3aα,4β,5β,7β,7aα)]-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-3-methyl-2-(trifluoromethyl)benzonitrile (841E)



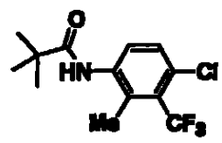
A. *N*-(4-Chloro-3-trifluoromethylphenyl)-2,2-dimethylpropionamide (841A)



To a solution of commercially available 4-chloro-3-(trifluoromethyl)aniline (15.0 g, 76.7 mmol) in anhydrous THF (200 mL) cooled to 0-5 °C was added triethylamine (11.7 mL, 84.4 mmol) followed by pivaloyl chloride (10.4 mL, 84.4

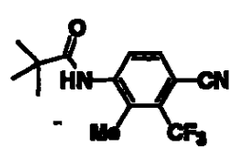
mmol) over 30 min. The ice bath was removed and the mixture stirred at rt for 1 h. The mixture was diluted with ether and filtered. The filtrate was washed with water (2X) and brine, dried over $MgSO_4$, filtered and concentrated. The residue was triturated with hexanes and the solid was filtered and dried *in vacuo* to afford compound **841A** (20.4 g, 95%). MS (ES): m/z = 280 $[M+1]^+$.

B. *N*-(4-Chloro-2-methyl-3-trifluoromethylphenyl)-2,2-dimethyl-propionamide (841B)



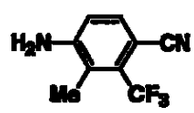
To a solution of *N*-(4-chloro-3-trifluoromethylphenyl)-2,2-dimethylpropionamide (2.29 g, 8.19 mmol) in anhydrous THF (25 mL) cooled to 0-5 °C was added a solution of 1.6 M *n*-butyllithium in hexanes (12.3 mL, 19.7 mmol), added slowly so that the reaction temperature was maintained below 5 °C. The solution was stirred at 0-5 °C for 1.5 h. A solution of iodomethane (0.56 mL, 9.01 mmol) in petroleum ether (2 mL) was added over 20 min while maintaining the temperature below 5 °C. The suspension was stirred at 0-5 °C for 1 h and diluted with water and ether. The aqueous layer was extracted with ether and the combined organic layers were washed with brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was chomatographed (silica gel), eluting with CH_2Cl_2 to afford compound **841B** (1.60 g, 67%). MS (ES): m/z = 294 $[M+1]^+$.

C. *N*-(4-Cyano-2-methyl-3-trifluoromethylphenyl)-2,2-dimethyl-propionamide (841C)



A suspension of *N*-(4-chloro-2-methyl-3-trifluoromethylphenyl)-2,2-dimethylpropionamide (8.36 g, 28.5 mmol) and CuCN (4.33 g, 65.5 mmol) in anhydrous *N*-methylpyrrolidinone (85 mL) was refluxed for 38 h. After cooling to rt, the suspension was poured into ice water with stirring. The resulting solid was filtered, washed with water and dried to yield an 85:15 mixture (7.55 g) of compound **841C** and **841D**. The resulting mixture was used in the next step.

D. 4-Amino-3-methyl-2-trifluoromethylbenzonitrile (841D)



A solution of the mixed product from example **841C** (7.53 g, 26.5 mmol) was dissolved in 120 mL of concentrated HCl/EtOH (1:1) and was refluxed for 14 h. After cooling to rt, the solution was concentrated *in vacuo*. The resulting residue was dissolved in EtOAc, washed with saturated aqueous $NaHCO_3$ (2X) and brine (1X), dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was chomatographed (silica gel), eluting with chloroform/methanol (98:2) to furnish compound **841D** (4.62 g, 87%). MS (ES): m/z = 201 $[M+1]^+$.

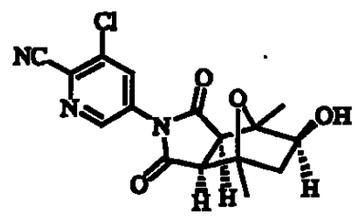
E. [3a*R*-(3aα,4β,5β,7β,7aα)]-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-3-methyl-2-(trifluoromethyl)benzonitrile (841E)

4-Amino-3-methyl-2-trifluoromethylbenzonitrile (0.051 g, 0.25 mmol), 4Å molecular sieve (0.20 g) and compound **752** (0.059 g, 0.28 mmol) were dissolved in DMA (0.30 mL) in a sealed tube. The reaction mixture was heated at 175°C for 30 min and then was cooled to rt. The solution was filtered though celite to remove the sieves and then the filtrate was washed with saturated NH_4Cl (10 mL), followed by brine (10 mL). The organic layer was then dried over Na_2SO_4 and concentrated *in vacuo* to yield a yellow oil. The resulting material was purified by preparative TLC (SiO_2), eluting with 25 acetone in $CHCl_3$ to give compound **841E** (40 mg) as a light

brown solid. HPLC: 97% at 3.18 min (retention time) (YMC S-5 ODS-A column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ESI): m/z 393.18 $[M-H]^-$. The absolute stereochemistry of compound 841E is established by the known stereochemistry of the intermediate compound 752 and the retention of configuration therein. The absolute stereochemistry is as drawn in the above figure and rendered by the nomenclature.

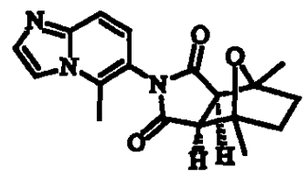
Example 842

[3aS-(3aα,4β,5β,7β,7aα)]-5-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-3-chloro-2-pyridinecarbonitrile (842)

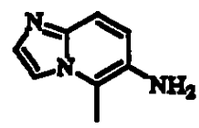


Compound 752 (500 mg, 2.36 mmol), 4 Å mol sieves (1.5 g), 5-amino-3-chloro-2-cyanopyridine (357 mg, 2.34 mmol) and DMA (2 mL) were combined in a sealed tube. The mixture was heated in a pre-heated oil-bath at 170°C for 25 min, cooled and the sieve was removed by filtration, eluting with EtOAc. The organics were washed 3x with water, followed by brine. The resulting organics were dried over $MgSO_4$ and concentrated *in vacuo*. The residue was pre-adsorbed on Celite and purified by silica gel flash chomatography with 0 to 40% acetone in CH_2Cl_2 to give Compound 842 (480 mg, 63%) as a tan solid. HPLC: 97% at 2.66 min (retention time) (YMC S5 ODS-A column 4.6 x 50 mm Ballistic, 10-90% aqueous methanol over 4 mincontaining 0.2% H_3PO_4, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 348.30 $[M+H]^+$. The absolute stereochemistry of compound 842 is established by the known stereochemistry of the intermediate compound 752 and the retention of configuration ther in. The absolute stereochemistry is as drawn in the above figure and rendered by the nomenclature.

Example 843



A. 5-Methyl-imidazo[1,2-a]pyridin-6-ylamine (843A)



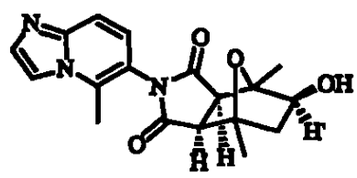
2-Methyl-3-nitro-6-amino pyridine (63 mg, 0.41 mmol) was suspended in 1.3 mL EtOH containing 0.3 mL conc. HCl. 2-Bromo-1,1-dimethoxy-ethane (73 μL, 0.62 mmol) was added and the resulting mixture was refluxed for 8 h, at which point additional 2-bromo-1,1-dimethoxy-ethane (0.1 mL, 0.85 mmol) was added. The mixture was stirred at reflux overnight, cooled and diluted with CH_2Cl_2. The organics were washed with sat. $NaHCO_3$ solution, dried over $MgSO_4$ and concentrated *in vacuo*. The residue was dissolved in 4 mL AcOH/EtOAc (1:1) and the resulting solution was heated to 75 °C. Iron powder (46 mg, 0.82 mmol, 325 Mesh) was added and the mixture was stirred for 20 min. Additional iron powder (46 mg, 0.82 mmol, 325 Mesh) was added and stirring was continued for 30 min. The mixture was cooled to room tempearture and concentrated. The resulting residue was purified by silica gel silica gel flash chomatography with 20% MeOH in CH_2Cl_2 to give compound 843A (51 mg, 85%) as a yellow-brown solid. HPLC: 72% at 0.18 min and 28% at 0.27 min (retention time) (YMC S5 ODS-A column 4.6 x 50 mm Ballistic, 10-90% aqueous methanol over 4 mincontaining 0.2% H_3PO_4, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 147.85 $[M+H]^+$.

C. (843B)

In a sealed tube was placed 5-methyl-imidazo[1,2-a]pyridin-6-ylamine (46 mg, 0.31 mmol), compound 20A (92 mg, 0.47 mmol), 250 mg 4 Å mol sieves and 0.3 mL DMA. The tube was sealed and heated in a pre-heated oil-bath to 170 °C for 30

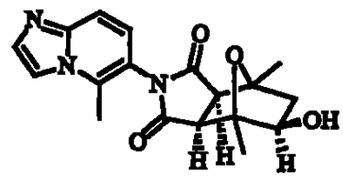
min. The mixture was cooled and filtered eluting with EtOAc. The filtrate was washed 3x with water followed by brine. The organic layer was dried over $MgSO_4$, concentrated *in vacuo* and purified by preparative TLC (SiO_2) with 50% acetone in $CHCl_3$ to give Compound **843B** (32 mg, 32%) as a pale yellow solid. HPLC: 99% at 1.47 min (retention time) (YMC S5 ODS-A column 4.6 x 50 mm Ballistic, 10-90% aqueous methanol over 4 mincontaining 0.2% H_3PO_4, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 326.39 $[M+H]^+$.

Example 844



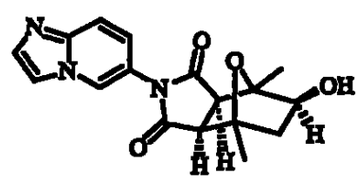
In a sealed tube were combined 5-methyl-imidazo[1,2-a]pyridin-6-ylamine (50 mg, 0.34 mmol), compound **752** (108 mg, 0.51 mmol), $MgSO_4$ (102 mg, 0.85 mmol), Et_3N (0.24 mL, 1.7 mmol) and 0.3 mL 1,2-dimethoxy-ethane. The tube was sealed and heated to 135°C for 14 h. The mixture was cooled to rt, filtered to remove the sieve, eluting with MeOH, and concentrated *in vacuo*. Purification of the resulting residue by silica gel flash chomatography with 0 to 10% MeOH in CH_2Cl_2 afforded compound **844** (86 mg, 74%) as a tan solid. HPLC: 100% at 0.85 min (retention time) (YMC S5 ODS-A column 4.6 x 50 mm Ballistic, 10-90% aqueous methanol over 4 mincontaining 0.2% H_3PO_4, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 342.20 $[M+H]^+$. The absolute stereochemistry of compound **844** is established by the known stereochemistry of the intermediate compound **752** and the retention of configuration therein. The absolute stereochemistry is as drawn in the above figure and rendered by the nomenclature.

Example 845

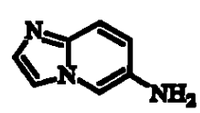


According to the procedure of Example 843, 5-methyl-imidazo[1,2-a]pyridin-6-ylamine (50 mg, 0.34 mmol), compound 751 (108 mg, 0.51 mmol), $MgSO_4$ (102 mg, 0.85 mmol), Et_3N (0.24 mL, 1.7 mmol) were reacted in 0.3 mL 1,2-dimethoxy-ethane. Purification gave compound 845 (79 mg, 68%) as a tan solid. HPLC: 100% at 0.85 min (retention time) (YMC S5 ODS-A column 4.6 x 50 mm Ballistic, 10-90% aqueous methanol over 4 mincontaining 0.2% H_3PO_4, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 342.20 $[M+H]^+$. The absolute stereochemistry of compound 845 is established by the known stereochemistry of the intermediate compound 751 and the retention of configuration therein. The absolute stereochemistry is as drawn in the above figure and rendered by the nomenclature.

Example 846



A. Imidazo[1,2-a]pyridin-6-ylamine (846A)



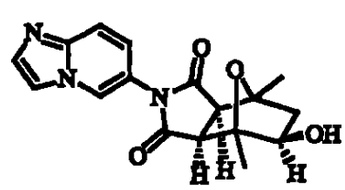
2-Amino-5-nitro pyridine was suspended in a 40 mL solution of EtOH/conc. HCl (3:1). To this suspension was added 2-bromo-1,1-dimethoxy-ethane (6.37 mL, 53.91 mmol) and the resulting mixture was heated to reflux for 8 h, after which additional 2-bromo-1,1-dimethoxy-ethane (6.37 mL, 53.91 mmol) was added. The mixture was heated at reflux overnight, cooled to rt and placed in a refrigerator for 24

h. The precipitates were collected, washed with ice-cold EtOH, air-dried and converted to the free-based using standard procedures to afford a yellow solid. The resulting crude yellow solid, (404 mg) was dissolved in 150 mL THF/MeOH (1:1) and the resulting solution was hydrogenated for 4 h over Pd/C (250 mg, 10%) using a hydrogen balloon. The mixture was filtered though Celite eluting with THF/MeOH (1:1) and the filtrate was concentrated. Purification was achieved using silica gel flash chomatography with 20% MeOH in CH_2Cl_2 to give Compound **846A** (241 mg, 75%) as a colorless oil which turns dark upon standing.

B. (**846B**)

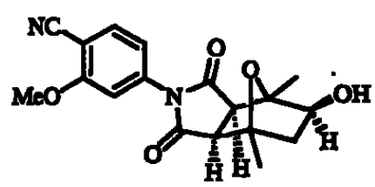
In a sealed tube were combined imidazo[1,2-a]pyridin-6-ylamine (64 mg, 0.48 mmol), compound **752** (148 mg, 0.71 mmol), $MgSO_4$ (146 mg, 1.21 mmol), Et_3N (0.34 mL, 2.40 mmol) and 0.4 mL 1,2-dimethoxy-ethane. The tube was sealed and heated to 135°C for 14 h. The mixture was cooled, filtered though Celite eluting with MeOH and concentrated. Purification was achieved by silica gel flash chomatography with 10% MeOH in CH_2Cl_2 to give compound **846B** (107 mg, 64%) as a pale yellow solid. HPLC: 40% at 0.19 min and 60% at 0.38 min (retention time) (YMC S5 ODS-A column 4.6 x 50 mm Ballistic, 10-90% aqueous methanol over 4 minutes containing 0.2% H_3PO_4, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 328.16 $[M+H]^+$. The absolute stereochemistry of compound **846B** is established by the known stereochemistry of the intermediate compound **752** and the retention of configuration therein. The absolute stereochemistry is as drawn in the above figure and rendered by the nomenclature.

Example 847

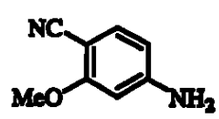


According to the procedure given in Example **846**, imidazo[1,2-a]pyridin-6-ylamine (50 mg, 0.38 mmol), compound **751** (119 mg, 0.56 mmol), $MgSO_4$ (114 mg, 0.95 mmol), Et_3N (0.26 mL, 1.9 mmol) were reacted in 0.35 mL 1,2-dimethoxy-ethane. Purification gave compound **847** (87 mg, 70%) as a white solid. HPLC: 32% at 0.20 min and 68% at 0.37 min (retention time) (YMC S5 ODS-A column 4.6 x 50 mm Ballistic, 10-90% aqueous methanol over 4 mincontaining 0.2% H_3PO_4, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 328.12 $[M+H]^+$. The absolute stereochemistry of compound **847** is established by the known stereochemistry of the intermediate compound **751** and the retention of configuration therein. The absolute stereochemistry is as drawn in the above figure and rendered by the nomenclature.

Example 848



A. 4-Amino-2-methoxy-benzonitrile (848A)



2-Methoxy-4-nitro-benzonitrile (500 mg, 2.81 mmol) was suspended into 4 mL AcOH/EtOAc (1:1) and the resulting mixture was heated to 75°C to give a clear solution. Fe powder (313 mg, 5.61 mmol, 325 Mesh) was added and the mixture was stirred for 30 min, after which additional Fe powder (313 mg, 5.61 mmol, 325 Mesh) was introduced. The mixture was stirred at 75°C for an additonal 30 min, and then cooled to rt and filtered, eluting with EtOAc. The filtrate was concentrated *in vacuo*, re-dissolved in EtOAc, filtered (eluting with EtOAc) and concentrated. Purification

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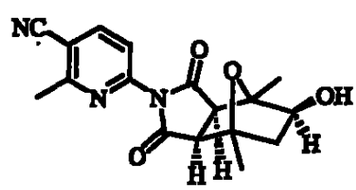
was achieved by silica gel flash chromatography with 0 to 10% MeOH in CH_2Cl_2 to give compound **848A** as a tan solid.

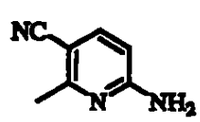
B. (848B)

In a sealed tube were combined 4-amino-2-methoxy-benzonitrile (40 mg, 0.27 mmol), compound **752** (86 mg, 0.41 mmol), $MgSO_4$ (81 mg, 0.68 mmol), Et_3N (0.19 mL, 1.4 mmol) and 0.25 mL 1,2-dimethoxy-ethane. The tube was closed and heated to 135°C for 14 h. The mixture was cooled to rt, filtered (eluting with MeOH) and concentrated *in vacuo*. Purification of the resulting residue by silica gel flash chromatography using 0 to 100% EtOAc in CH_2Cl_2 to afforded compound **848B** (36 mg, 39%) as an off-white solid. HPLC: 100% at 2.36 min (retention time) (YMC S5 ODS-A column 4.6 x 50 mm Ballistic, 10-90% aqueous methanol over 4 mincontaining 0.2% H_3PO_4, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 341.23 $[M-H]^-$. The absolute stereochemistry of compound **848B** is established by the known stereochemistry of the intermediate compound **752** and the retention of configuration therein. The absolute stereochemistry is as drawn in the above figure and rendered by the nomenclature.

Example 849



A. 6-Amino-2-methyl-nicotinonitrile (849A)

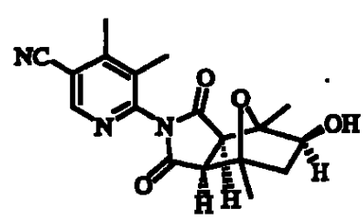


A mixture of 6-amino-2-methyl-nicotinonitrile (500 mg, 2.67 mmol), CuCN (478 mg, 5.34 mmol) and DMA (2 mL) was stirred under nitrogen for 20 h at 170°C. The reaction mixture was cooled and added to 50 mL of a 20% aqueous solution of ethane-1,2-diamine. The layers were separated and the aqueous layer was extracted 3x with EtOAc. The combined organics were washed with water followed by brine, dried over $MgSO_4$ and concentrated *in vacuo*. Purification by silica gel flash chomatography with 0 to 100% EtOAc in CH_2Cl_2 gave compound **849A** (199 mg, 56%) as a white solid.

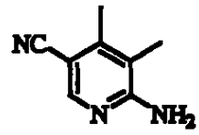
B. (**849B**)

In a sealed tube was placed 6-amino-2-methyl-nicotinonitrile (50 mg, 0.38 mmol), compound **752** (119 mg, 0.56 mmol), $MgSO_4$ (114 mg, 0.95 mmol), Et_3N (0.26 mL, 1.9 mmol) and 0.3 mL 1,2-dimethoxy-ethane. The tube was sealed and heated to 135°C for 14 h. The mixture was cooled to rt, filtered (eluting with MeOH) and concentrated *in vacuo*. The filtrate was concentrated and purified by silica gel flash chomatography with 0 to 100% EtOAc in CH_2Cl_2 to give compound **849B** (36 mg, 29%) as a white solid. HPLC: 100% at 1.99 min (retention time) (YMC S5 ODS-A column 4.6 x 50 mm Ballistic, 10-90% aqueous methanol over 4 min containing 0.2% H_3PO_4, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 328.04 $[M+H]^+$. The absolute stereochemistry of compound **849B** is established by the known stereochemistry of the intermediate compound **752** and the retention of configuration therein. The absolute stereochemistry is as drawn in the above figure and rendered by the nomenclature.

Example 850



A. 6-Amino-4,5-dimethyl-nicotinonitrile (850A)

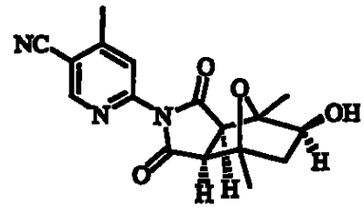


A mixture of 5-bromo-3,4-dimethyl-pyridin-2-ylamine (500 mg, 2.49 mmol), CuCN (445 mg, 4.97 mmol) and DMA (3.5 mL) was stirred under nitrogen for 20 h at 170°C. The reaction mixture was cooled and added to 50 mL of a 20% aqueous solution of ethane-1,2-diamine. The layers were separated and the aqueous layer was extracted 3x with EtOAc. The combined organics were washed with water, followed by brine and dried over $MgSO_4$. Concentration *in vacuo* afforded compound **850A** (362 mg, 99%) as a white solid.

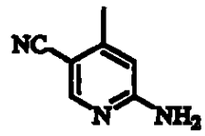
B. (850B)

In a sealed tube were combined 6-amino-4,5-dimethyl-nicotinonitrile (50 mg, 0.34 mmol), compound **752** (108 mg, 0.50 mmol), $MgSO_4$ (102 mg, 0.85 mmol), Et_3N (0.24 mL, 1.7 mmol) and 0.3 mL 1,2-dimethoxy-ethane. The tube was closed and heated to 135 °C for 14 h. The mixture was cooled to rt, filtered (eluting with MeOH) and concentrated *in vacuo*. Purification of the resulting residue by silica gel flash chomatography with 0 to 100% EtOAc in CH_2Cl_2 afforded compound **850B** (68 mg, 59%) as an off-white solid. HPLC: 10% at 2.15 min and 82% at 2.31 min (retention time) (YMC S5 ODS-A column 4.6 x 50 mm Ballistic, 10-90% aqueous methanol over 4 mincontaining 0.2% H_3PO_4, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 342.06 $[M+H]^+$. The absolute stereochemistry of compound **850B** is established by the known stereochemistry of the intermediate compound **752** and the retention of configuration therein. The absolute stereochemistry is as drawn in the above figure and rendered by the nomenclature.

Example 851



A. 6-Amino-4-methyl-nicotinonitrile (851A)



A mixture of 5-bromo-4-methyl-pyridin-2-ylamine (500 mg, 2.67 mmol), CuCN (478 mg, 5.34 mmol) and DMA (2 mL) was stirred under nitrogen for 20 h at 170°C. The reaction mixture was cooled and added to 50 mL of a 20% aqueous solution of ethane-1,2-diamine. The layers were separated and the aqueous layer was extracted 3x with EtOAc. The combined organics were washed with water followed by brine and dried over $MgSO_4$. Concentration *in vacuo* afforded compound 851A (309 mg, 87%) as a white solid.

B. (851B)

In a sealed tube was placed 6-amino-4-methyl-nicotinonitrile (50 mg, 0.38 mmol), compound 752 (119 mg, 0.56 mmol), $MgSO_4$ (114 mg, 0.95 mmol), Et_3N (0.26 mL, 1.9 mmol) and 0.3 mL 1,2-dimethoxy-ethane. The tube was sealed and heated to 135°C for 14 h. The mixture was allowed to cool to rt and filtered, eluting with MeOH. The filtrate was concentrated *in vacuo* and purified by silica gel flash chomatography with 0 to 100% EtOAc in CH_2Cl_2 to give compound 851B (67 mg, 54%) as a white solid. HPLC: 100% at 1.95 min (retention time) (YMC S5 ODS-A column 4.6 x 50 mm Ballistic, 10-90% aqueous methanol over 4 mincontaining 0.2% H_3PO_4, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 328.04 $[M+H]^+$. The absolute stereochemistry of compound 851B is established by the known stereochemistry of the intermediate compound 752 and the retention of configuration therein. The absolute stereochemistry is as drawn in the above figure and rendered by the nomenclature.

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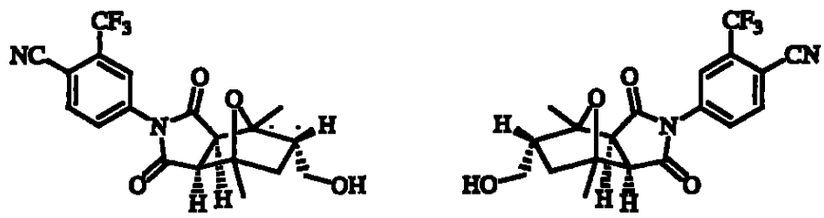
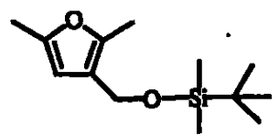
Example 852

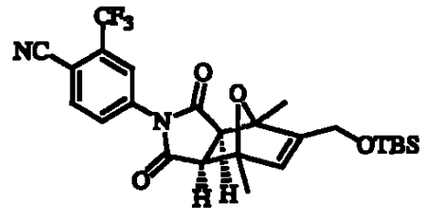


A. *tert*-Butyl-(2,5-dimethyl-furan-3-ylmethoxy)-dimethyl-silane (852A)



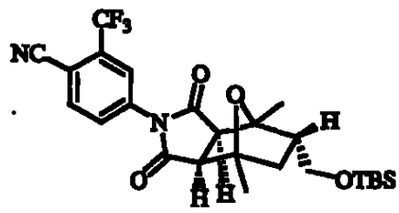
In a dry 100 mL round-bottom flask was prepared a solution of methyl 2,5-dimethyl-3-furoate (2.00 g, 13.0 mmol) in anhydrous Et_2O (10 mL) under an inert atmosphere. To this solution was added dropwise a 1.0 M solution of $LiAlH_4$ in Et_2O (13 mL, 13 mmol) at 0°C. The resulting suspension was stirred at 0°C for 30 min and was then allowed to warm to rt, where it was kept for 4 h. The reaction was quenched by the careful addition of solid $Na_2SO_4 \cdot 10\ H_2O$ (excess) and Celite (excess). To facilitate stirring, Et_2O was added as necessary. The resulting mixture was stirred overnight, filtered and carefully concentrated *in vacuo* to yield the volatile alcohol which was dissolved in anhydrous DMF (5 mL) under an inert atmosphere. To this solution was added imidazole (1.32 g, 19.5 mmol) and TBSCl (2.05 g, 13.6 mmol) and the mixture was stirred for 6 h. The reaction mixture was diluted with EtOAc and water was added. The layers were separated and the organic layer was washed several times with water. The organics were dried over $MgSO_4$, concentrated *in vacuo* and purified by silica gel flash chomatography with 0 to 50% EtOAc in hexanes yielding compound 852A (3.08 g, 99 %) as a colorless oil.

B. (852B)



In a sealed-tube were combined *tert*-butyl-(2,5-dimethyl-furan-3-ylmethoxy)-dimethyl-silane (2.60 g, 10.8 mmol), 4-(2,5-dihydro-2,5-2,5-dioxo-1H-pyrrol-1-yl)-2-trifluoromethylbenzonitrile (1.44 g,5.41 g) and THF (1 mL). The tube was sealed and quickly heated to 95 °C to yield an almost clear solution. The mixture was then allowed to cool to rt and was stirred at rt overnight. Purification was achieved by silica gel flash chomatography with 0 to 100 % EtOAc in hexanes to give compound **852B** (2.37 g, 86 %) as a white solid.

C. (852C)



A solution Compound **852B** of (1.4 g, 2.8 mmol) in EtOAc (50 mL) was hydrogenated over Pd/C (10 %, 800 mg) for 6 h using a hydrogen balloon. The mixture was filtered, eluting with EtOAc, and concentrated *in vacuo*. Purification was achieved using silica gel flash chomatography with 0 to 100 % EtOAc in hexanes to afford Compound **852C** (0.9 g, 64%) as a white foam.

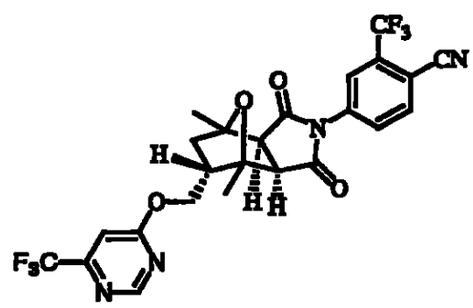
D.

Compound **852C** (0.9 g, 1.8 mmol) was dissolved in 7 mL EtOH containing 2 % conc. HCl at rt and the resulting mixture was stirred for 2 h. The reaction mixture was carefully poured into sat. $NaHCO_3$ solution and the aqueous layer was extracted twice with EtOAc. The combined organics were dried over $MgSO_4$, concentrated *in vacuo* and purified by silica gel flash chomatography with 0 to 100 % EtOAc in CH_2Cl_2 to afford a racemic mixture of compound **852DI** & **852DII** (0.7 g, 100 %) as a

white solid. The racemic material was separated into its enantiomers by normal phase preparative chiral HPLC (CHIRALPAK OJ 5 x 50 cm column; eluting with 30% MeOH/EtOH (1:1) in heptane (isocratic) at 50 mL/min) to give the faster eluting enantiomer compound **852Di** (Chiral HPLC: 5.56 min; CHIRALPAK OJ 4.6 x 250 mm column; eluting with 30% MeOH/EtOH (1:1) in heptane containing 0.1% DEA at 1 mL/min) and the slower eluting anantiomer compound **852Dii** (Chiral HPLC: 7.01 min; CHIRALPAK OJ 4.6 x 250 mm column; eluting with 30% MeOH/EtOH (1:1) in heptane containingat 1 mL/min). The absolute stereochemistry of compounds **852Di** & **852Dii** has not been established. Although each compound represents a single antipode, the nomenclature and structure shown does not reflect the absolute stereochemistry of the compound.

Example 853

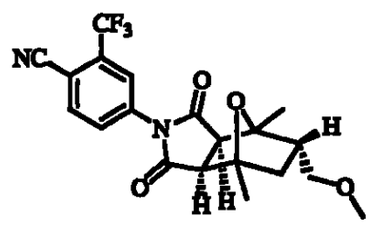
(3aα,4β,5α,7β,7aα)-4-(Octahydro-5-[[6-(trifluoromethyl)-4-pyrimidinyl]oxy]methyl]-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (853)



Triphenylphosphine (0.066g, 0.254 mmol) and di-*tert*-butyl-azodicarboxylate (0.058g, 0.254 mmol) in THF (0.5 mL) were stirred at rt under N_2 for 10 min, then 6-trifluoromethyl-4-pyrimidinol (0.042g, 0.254 mmol) was added. The reaction mixture was stirred under N_2 for another 15 min, followed by the addition of a racemic mixture of compounds **852Di** & **852Dii** (0.050g, 0.127 mmol). The reaction was allowed to proceed for 2 h, at which point CH_2Cl_2 (15 mL) was added. The organic layer was isloated and then washed consecutively with 1N NaOH (15 mL), brine (15 mL) and dried over $MgSO_4$ and concentrated *in vacuo*. The resulting solid was purified by silica gel chomatograph, eluting with EtOAc in Hexane from 0% to 100%,

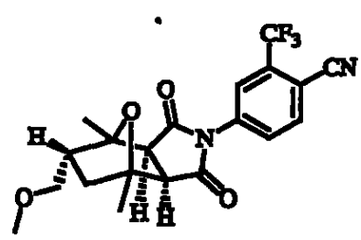
to give compound 853 (60 mg) as a white solid. HPLC: 99% at 4.083 min (retention time) (YMC S-5 ODS-A column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ESI): m/z 541.06 [M+H]. Compound 853 represents a racemic mixture of antipodes. The nomenclature and structure shown does not reflect the absolute stereochemistry of the compound.

Example 854



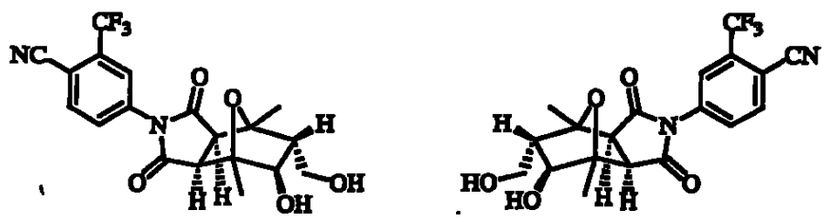
In a sealed tube was prepared a mixture of compound 852Di (150 mg, 0.38 mmol), MeI (0.24 mL, 3.8 mmol) and Ag_2O (881 mg, 3.8 mmol) in 2 mL CH_3CN. The tube was sealed and heated to 80°C overnight. The mixture was cooled to rt, filtered, eluting with EtOAc, and concentrated. Purification was achieved by silica gel flash chromatography with 0 to 100% EtOAc in hexanes to give compound 854(49 mg, 32%) as a colorless oil. HPLC: 97% at 3.58 min (retention time) (YMC S5 ODS-A column 4.6 x 50 mm Ballistic, 10-90% aqueous methanol over 4 mincontaining 0.2% H_3PO_4, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 407.20 $[M+H]^+$. The absolute stereochemistry of compound 854 has not been established. Although the compound represents a single antipode, the nomenclature and structure shown does not reflect the absolute stereochemistry of the compound.

Example 855



Compound 852Dii (150 mg, 0.38 mmol), MeI (0.24 mL, 3.8 mmol) and Ag_2O (881 mg, 3.8 mmol) were reacted in 2 mL CH_3CN and the reaction mixture purified as described for Example 854 to afford compound 855 (45 mg, 29%) as a colorless oil. HPLC: 98% at 3.58 min (retention time) (YMC S5 ODS-A column 4.6 x 50 mm Ballistic, 10-90% aqueous methanol over 4 mincontaining 0.2% H_3PO_4, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 407.19 $[M-H]^-$. The absolute stereochemistry of compound 855 has not been established. Although the compound represents a single antipode, the nomenclature and structure shown does not reflect the absolute stereochemistry of the compound.

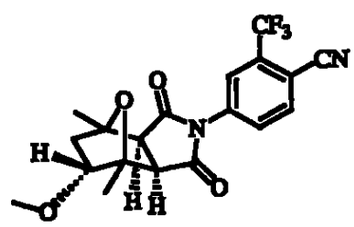
Example 856



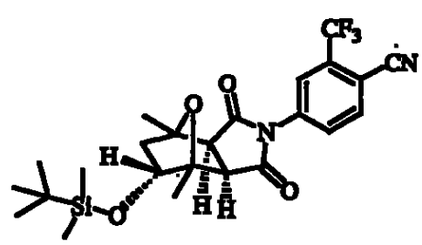
To a solution of compound 852B (835 mg, 1.65 mmol) in 10 mL THF was added a 1.0M solution of BH_3•THF (3.3 mL, 3.30 mmol) dropwise at 0 °C. The resulting mixture was stirred at 0°C for 2 h, after which 15 mL EtOH, 5 mL THF, 30 mL pH 7 phosphate buffer and 2.1 mL 30% H_2O_2 were added. The resulting mixture was stirred for 2 h at 0°C after which water and EtOAc were added. The layers were separated and the aqueous layer was extracted again with EtOAc. The combined organic phases were washed with 10% $Na_2S_2O_3$-solution followed by brine. The organics were dried over $MgSO_4$, concentrated and purified by flash chromatography with 0 to 25% EtOAc in CH_2Cl_2. The material was dissolved in 8 mL EtOH containing 2% conc. HCl and the resulting mixture was stirred for 2 h. The reaction mixture was diluted with EtOAc and carefully poured into sat. $NaHCO_3$-solution. The layers were separated and the aqueous layer was extracted again with EtOAc. The combined organic layers were dried over $MgSO_4$ and concentrated *in vacuo*. The resulting racemic material was separated into its enantiomers by normal phase preparative chiral HPLC (CHIRALPAK OD 5 x 50 cm column; eluting with 15% MeOH/EtOH (1:1) in heptane (isocratic) at 50 mL/min) to give the faster eluting

compound **856l** (128 mg) (Chiral HPLC: 13.64 min; CHIRALPAK OD 4.6 x 250 mm column; eluting with 15% MeOH/EtOH (1:1) in heptane containing at 1 mL/min) and the slower eluting compound **856li** (137 mg, 39% combined yield) (Chiral HPLC: 16.31 min; CHIRALPAK OD 4.6 x 250 mm column; eluting with 15% MeOH/EtOH (1:1) in heptane at 1 mL/min).). MS (ES): m/z 411.01 $[M+H]^+$. The absolute stereochemistry of compounds **856l** & **856li** has not been established. Although each compound represents a single antipode, the nomenclature and structure shown does not reflect the absolute stereochemistry of the compound.

Example 857



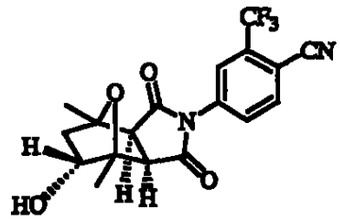
A. (857A)



Compound **798i** was converted to compound **857A** by the procedure described in Example **774**. HPLC: 95% at 4.307 min (retention time) (YMC S5 ODS-A column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 mincontaining 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm).

B. (857B)

342

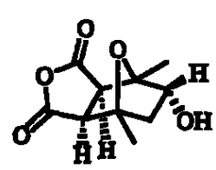


Compound 857A was converted to compound 857B by the procedure described in Example 774. HPLC: 100% at 2.89 min (retention time) (YMC S5 ODS-A column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 mincontaining 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 381.16 $[M+H]^+$.

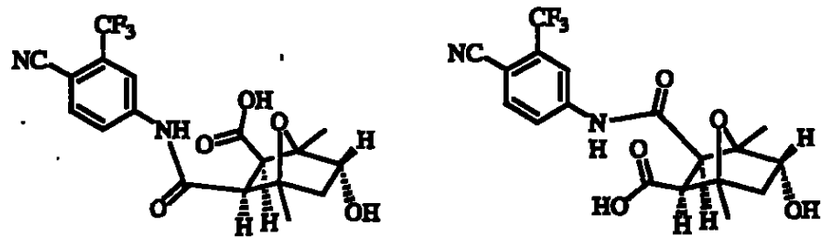
C. (857C)

Compound 857B (0.100 g, 0.26 mmol), MeI (0.163 mL, 2.6 mmol), Ag_2O (0.603 g, 2.60 mmol) and acetonitrile (2.5 mL) were added to a high pressure reaction vessel. The vessel was sealed and heated to 75°C. After 16 h, the reaction was cooled to rt, diluted with EtOAc and filtered through celite, rinsing with EtOAc. The crude material was purified by flash chromatography on silica eluting with 0 – 5 – 8% acetone in chloroform to give compound 857C as a white solid. HPLC: 90% at 2.887 min (retention time) (YMC S5 ODS-A column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 mincontaining 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 395.07 $[M+H]^+$. The absolute stereochemistry of compound 857C has not been established. Although the compound represents a single antipode, the nomenclature and structure shown does not reflect the absolute stereochemistry of the compound.

Example 858



A. (858Ai & 858Aii)



Compound 857B (2.50 g, 6.57 mmol) was dissolved in THF (10.0 mL) at 22°C and 1 N NaOH (10.0 mL) was added. After 1 h, THF (10.0 mL), 1 N HCl (1.10 mL) and brine (10.0 mL) were added. The mixture was then extracted once with EtOAc (20.0 mL) and twice with 1:1 THF/EtOAc (20.0 mL). The combined organics were dried over anhydrous $MgSO_4$, filtered and concentrated *in vacuo* to give compounds 858Ai and 858Aii (1:1 by HPLC) as a white solid. No was purification necessary. HPLC: 100% at 2.383 and 2.573 min (retention time) (YMC S5 ODS-A column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 mincontaining 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm).

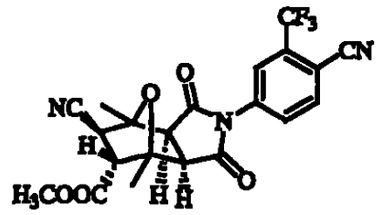
B. (858B)

Compounds 858Ai and 858Aii were suspended in a mixture of THF (50.0 mL) and AcOH (20.0 mL) and heated to 60°C for 16 h. The reaction became homogenous after 4 h. The reaction was cooled to 22°C and concentrated *in vacuo*. Toluene (20.0 mL) was then added and mixture heated to 90°C for 4 h until all product was dissolved. The mixture was then cooled to 22°C and left standing for 20 h. Compound 858B precipitates from solution over the 20 h period. The product was filtered and rinsed with toluene followed by drying *in vacuo*. Compound 858B (1.10 g) was isolated as an off-white solid and used without further purification. ^{1}H NMR(DMSO-d^6): δ = 4.91 (d, 1H, J = 6.2 Hz), 3.97 (dd, 1H, J = 3.9, 6.2 Hz), 3.82 (d, 1 H, J = 7.6 Hz), 3.31 (d, 1 H, J = 7.6 Hz), 2.27 (dd, 1H, J = 10.2, 12.8 Hz), 1.77 (s, 3H), 1.49 (m, 1 H) and 1.47 ppm (s, 3H). The absolute stereochemistry of compound 858B has not been established. Although the compound represents a single antipode,

the nomenclature and structure shown does not reflect the absolute stereochemistry of the compound.

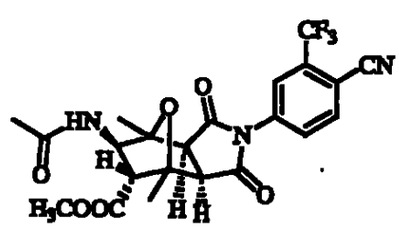
Example 859

(3aα,4β,5α,6β,7β,7aα)-2-(4-Cyano-3-(trifluoromethyl)phenyl)hexahydro-6-cyano-4,7-dimethyl-1,3-dioxo-4,7-epoxy-1H-isoindole-5-carboxylic acid, methyl ester (859)



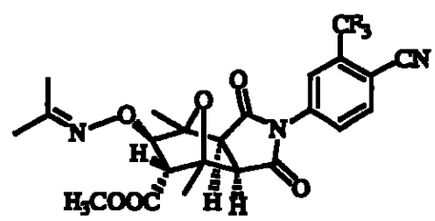
A mixture of compound 792A (84 mg; 0.2 mmol), KCN (15 mg; 0.22 mmol) and ammonium chloride (12 mg; 0.22 mmol) in 1 ml of DMF and 0.25 ml of water was stirred at rt for 18 hr. A precipitant formed on standing overnight. After adding an additional 10 ml of water, the suspension was filtered and the filter cake was washed with water. Drying and trituration with hexane afforded compound 859 (25 mg, 28%) as a tan powder. HPLC: 95% at 1.67 min (retention time) (Phenominex S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 2 mincontaining 0.1% TFA, 4 mL/min, monitoring at 254 nm); MS (ES): m/z 448.29 $[M+H]^+$. Compound 859 represents a racemic mixture of antipodes. The nomenclature and structure shown does not reflect the absolute stereochemistry of the compound.

Example 860



A mixture of compound **792A** (44 mg; 0.1 mmol) and acetic anhydride (0.25 ml) was heated to 60°C for 2hr. The volatiles were removed *in vacuo* and the residue was co-evaporated from heptane (3 x 2 ml) to afford compound **860** (47 mg, 99%) as a white powder. HPLC: 95.8% at 1.49 min (retention time) (Phenominex S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 2 mincontaining 0.1% TFA, 4 mL/min, monitoring at 254 nm); MS (ES): m/z 480.35 $[M+H]^+$. Compound **860** represents a racemic mixture of antipodes. The nomenclature and structure shown does not reflect the absolute stereochemistry of the compound.

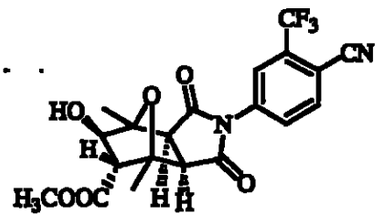
Example 861



Sodium hydride, 60% in mineral oil (120 mg; 3 mmol) was added in portions over 10 minto a solution of compound **792A** (1.9 g; 4.5 mmol) and acetone oxime (667 mg; 9 mmol) in THF at rt. After stirring 45 min, the reaction mixture was partitioned between brine (100 ml) and EtOAc (150 ml). The organic layer was washed with brine (50 ml), dried ($MgSO_4$) and concentrated *in vacuo*. The residue was chromatographed on a 5 x 20 cm silica gel column, eluting with 1000 ml of 25 EtOAc/hexane and 500 ml of 40% EtOAc/hexane. Concentration of the pure fractions *in vacuo* afforded compound **861** (1.75 g, 80%) as a white powder. HPLC: 98% at 1.82 min (retention time) (Phenominex S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 2 mincontaining 0.1% TFA, 4 mL/min, monitoring at 254 nm); MS (ES): m/z 494.05 $[M+H]^+$. Compound **861** represents a racemic mixture of antipodes. The nomenclature and structure shown does not reflect the absolute stereochemistry of the compound.

Example 862

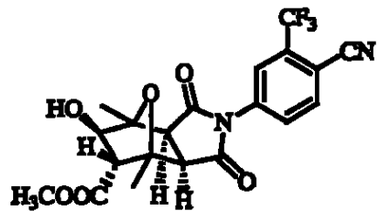
(3aα,4β,5α,6β,7β,7aα)]-2-(4-Cyano-3-(trifluoromethyl)phenyl)-hexahydro-6-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-1H-isoindole-5-carboxylic acid, methyl ester (862)

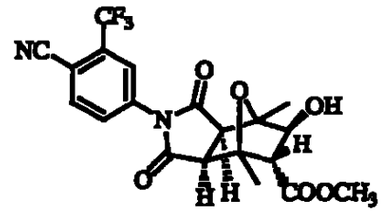


A mixture of compound **861** (1.75 g; 3.5 mmol) and zinc dust (6.07 g, 87.50 mA) in 19 ml of formic acid was refluxed for 20 min. After cooling to rt, the reaction mixture was diluted with ~50 ml of EtOAc and filtered though celite. The filtrate was diluted with ~200 ml of EtOAc and the organic layer was washed with water (200 ml), 0.5M NaOH (2 x 200 ml), water (200 ml) and brine (100 ml). Drying over $MgSO_4$ and concentration *in vacuo* gave a residue that was chromatographed on a 2.5 x 20 cm silica gel column, eluting with 1000 ml of 40% EtOAc/hexane and 500 ml of 50% EtOAc/hexane. Concentration of the pure fractions *in vacuo* afforded compound **862** (820 g, 54%) as a colorless foam. HPLC: 99% at 1.47 min (retention time) (Phenominex S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 2 mincontaining 0.1% TFA, 4 mL/min, monitoring at 254 nm); MS (ES): m/z 438.99 $[M+H]^+$. Compound **862** represents a racemic mixture of antipodes. The nomenclature and structure shown does not reflect the absolute stereochemistry of the compound.

Example 863

[3aS-(3aα,4β,5α,6β,7β,7aα)]-2-(4-Cyano-3-(trifluoromethyl)phenyl)-hexahydro-6-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-1H-isoindole-5-carboxylic acid, methyl ester (863i) & [3aS-(3aα,4β,5α,6β,7β,7aα)]-2-(4-Cyano-3-(trifluoromethyl)phenyl)-hexahydro-6-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-1H-isoindole-5-carboxylic acid, methyl ester (863ii)

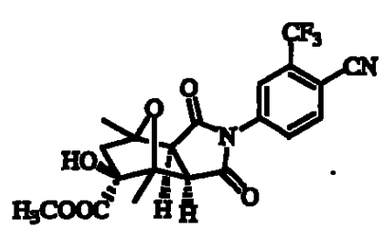




Racemic compound 862 (0.8 g) was separated into its enantiomers by normal phase preparative chiral HPLC (CHIRALPAK OD 5 x 50 cm column; eluting with 15% EtOH in hexanes (isocratic) at 50 mL/min) to give 355 mg of faster eluting compound 863i (Chiral HPLC: 8.89 min; CHIRALPAK OD 4.6 x 250 mm column; eluting with 15% EtOH in hexanes at 2 mL/min); HPLC: 99% at 2.91 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 2 mincontaining 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm); MS (ES): m/z 471.00 $[M+MeOH]^+$and 330 mg of the slower eluting compound 863ii (Chiral HPLC: 12.30 min; CHIRALPAK OD 4.6 x 250 mm column; eluting with 15% EtOH in hexanes at 2 mL/min); HPLC: 99% at 2.89 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 2 mincontaining 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm); MS (ES): m/z 471.99 $[M+MeOH]^+$. The absolute stereochemistry of compounds 863i & 863ii has not been established. Although each compound represents a single antipode, the nomenclature and structure shown does not reflect the absolute stereochemistry of the compound.

Example 864

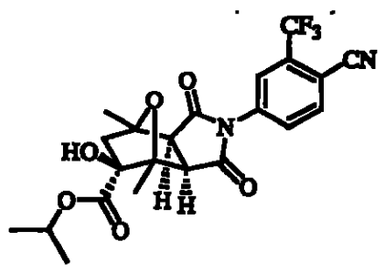
(3aα,4β,5α,7β,7aα)-2-(4-Cyano-3-(trifluoromethyl)phenyl)-hexahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-1H-isoindole-5-carboxylic acid, methyl ester (864)



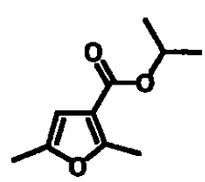
A mixture of compound 792A (210 mg; 0.5 mmol), phenylsilane (0.13 ml, 1 mmol) and $Mn(acac)_2$ (5mg; 0.01 mmol) in 2.5 ml isopropanol and 0.25 ml of THF was stirred 3 days at rt in open air. After adding 5% sodium bisulfite solution (5 ml) and stirring 30 min, the reaction mixture was partitioned between EtOAc (30 ml) and water (30 ml). Washing the organic layer with brine (20 ml), followed by drying over $MgSO_4$ and concentration *in vacuo*, afforded a residue that was chromatographed on a 2.5 x 15 cm silica gel column, eluting with 50%EtOAc/hexane. Concentration of the pure fractions *in vacuo*, afforded compound 864 (109 mg, 50%) as a white powder. HPLC: 98.6% at 1.18 min (retention time) (Phenominex S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 2 mincontaining 0.1% TFA, 4 mL/min, monitoring at 254 nm); MS (ES): m/z 438.98 $[M+H]^+$. Compound 864 represents a racemic mixture of antipodes. The nomenclature and structure shown does not reflect the absolute stereochemistry of the compound.

Example 865

(3aα,4β,5a,7β,7aα)-2-(4-Cyano-3-(trifluoromethyl)phenyl)hexahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-1H-isoindole-5-carboxylic acid, (1-methylethyl) ester (865C)



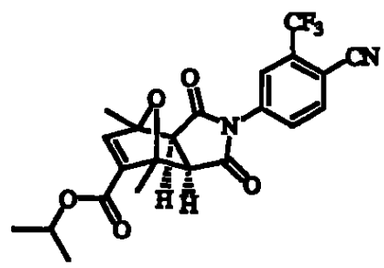
A. **2,5-Dimethyl-furan-3-carboxylic acid isopropyl ester (865A)**



Isopropanol (5 ml) was added to a solution of 2,5-dimethylfuran-3-carbonylchloride (1.64 g; 10.3 mmol) in 15 ml of methylene chloride at rt. After

allowing the reaction mixture to stand at rt for 30 mins, the volatiles were removed *in vacuo* and the residue was co-evaporated from isopropanol to afford compound **865A** (1.8 g, 96%) as a light amber liquid. ^{1}HNMR ($CDCl_3$): δ 1.30 (d, j= 6.5 Hz, 6H), 2.23 (s, 3H), 2.52 (s, 3H), 5.14 (m, 1H), 6.21 (s, 1H).

B. (3aα,4β,7β,7aα)-2-(4-Cyano-3-(trifluoromethyl)phenyl)tetrahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-1H-isoindole-5-carboxylic acid, (1-methylethyl) ester (865B)



A mixture of 4-(2,5-dihydro-2,5-2,5-dioxo-1H-pyrrol-1-yl)-2-trifluoromethyl-benzonitrile (851 mg; 3.2 mmol) and compound **865A** (1.7 g; 9.4 mmol) was heated to 140°C for 4 h. After allowing the mixture to cool to rt and stand 4 days, the reaction mixture was chromatographed on a 5 x 25 cm silica gel column, eluting with 25% EtOAc/hexane. Concentration of the pure fractions *in vacuo* afforded compound **865B** (869 mg, 60%) as thick yellow oil. Due to the instability of this compound, it was stored at –20C and used promptly.

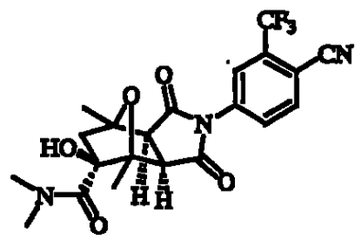
C. (3aα,4β,5α,7β,7aα)-2-(4-Cyano-3-(trifluoromethyl)phenyl)hexahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-1H-isoindole-5-carboxylic acid, (1-methylethyl) ester (865C)

Compound **865B** (224; 0.5 mmol) was converted to compound **865C** using the procedure described in Example **791B** to afford compound **865C** (82 mg, 35%) as a white powder. HPLC: 98.4% at 1.18 min (retention time) (Phenominex S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 2 mincontaining 0.1% TFA, 4 mL/min, monitoring at 254 nm); MS (ES): m/z 466.98 $[M+H]^+$.

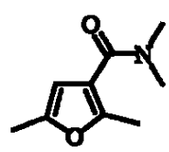
Compound 865C represents a racemic mixture of antipodes. The nomenclature and structure shown does not reflect the absolute stereochemistry of the compound.

Example 866

(3aα,4β,5α,7β,7aα)-2-(4-Cyano-3-(trifluoromethyl)phenyl)hexahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-*N,N*-dimethyl-1H-isoindole-5-carboxamide (866C)

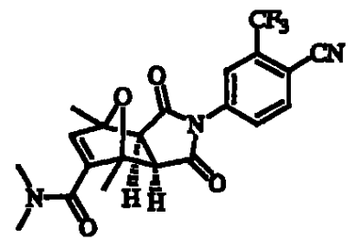


A. 2,5-Dimethyl-furan-3-carboxylic acid dimethylamide (866A)



A solution of 2,5-dimethylfuran-3-carbonylchloride (2.19 g; 13.8 mmol) in 10 ml of THF was added to a 2M solution of dimethylamine in dioxane (21 ml; 42 mmol) in 80 ml of THF at rt. After stirring for 1 hr, the volatiles were removed *in vacuo* and the residue was partitioned between EtOAc (100 ml) and water (100 ml). The organic layer was washed with saturated potassium bisulfate solution (100 ml), 1N NaOH (50 ml) and brine (50 ml). Drying over $MgSO_4$ and concentration *in vacuo* afforded compound 866A (1.84 g, 80%) as an amber liquid. ^{1}HNMR ($CDCl_3$): δ 2.23 (s, 3H), 2.33 (s, 3H), 3.04 (s, 6H), 5.96 (s, 1H).

B. (866B)

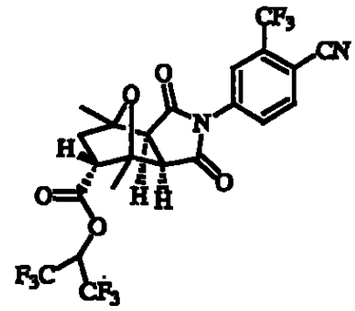


A mixture of 4-(2,5-dihydro-2,5-2,5-dioxo-1H-pyrrol-1-yl)-2-trifluoromethyl-benzonitrile (1.45 mg; 5.4 mmol) and compound **866A** (1.82 g; 10.9 mmol) was heated neat to 125°C for 1 hr. After allowing the mixture to cool to rt overnight, the reaction mixture was dissolved in ~75 ml of EtOAc. Treatment with decolorizing carbon, filtration through celite and concentration *in vacuo* of the filtrate gave a residue that was dissolved in ~ 20 ml of ethyl ether. Addition of ~30 ml of hexane, followed by filtration and drying afforded compound **866B** (1.89 g, 81%) as light pink solid.

C. (3aα,4β,5α,7β,7aα)-2-(4-Cyano-3-(trifluoromethyl)phenyl)hexahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-*N,N*-dimethyl-1H-isoindole-5-carboxamide (866C)

Compound **866B** (433; 1 mmol) was converted to compound **866C** using the procedure described in Example **792B** to afford compound **866C** (85 mg, 18) as a white powder. HPLC: 97.9% at 1.39 min (retention time) (Phenominex S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 2 mincontaining 0.1% TFA, 4 mL/min, monitoring at 254 nm); MS (ES): m/z 452.00 $[M+H]^+$. Compound **866C** represents a racemic mixture of antipodes. The nomenclature and structure shown does not reflect the absolute stereochemistry of the compound.

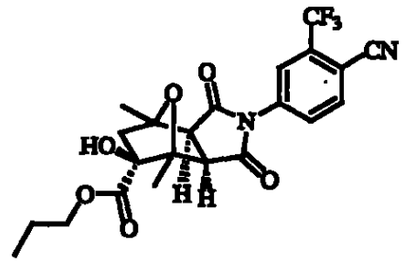
Example 867



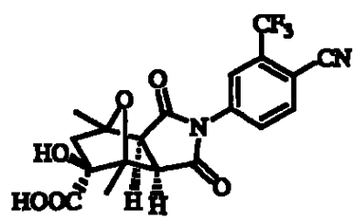
One drop of DMF was added to a solution of compound 792B (50 mg; 0.125 mmol) and oxalyl chloride (0.03 ml; 0.36 mmol) in methylene chloride (1 ml) at rt. After stirring 1.5 h at rt, the volatiles were removed *in vacuo*. The residue was treated with 1 ml of 1,3-hexafluoro-2-propanol, followed by 0.04 ml of pyridine and 2 mg of 4-dimethylpyridine. After stirring 18 h. at rt the reaction mixture was partitioned between EtOAc (20 ml) and saturated sodium bicarbonate solution (20 ml). The organic layer was washed with saturated potassium bisulfate solution (20 ml) and brine (20 ml). Drying over $MgSO_4$ and concentration *in vacuo* afforded a residue that was chromatographed on a 2.5 x 15 cm silica gel column, eluting with 25%EtOAc/hexane. Concentration of the pure fractions *in vacuo* afforded compound 867 (36 mg, 52%) as a white solid. HPLC: 99% at 1.96 min (retention time) (Phenominex S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 2 mincontaining 0.1% TFA, 4 mL/min, monitoring at 254 nm); MS (ES): m/z 558.00 $[M+H]^+$. Compound 867 represents a racemic mixture of antipodes. The nomenclature and structure shown does not reflect the absolute stereochemistry of the compound.

Example 868

(3aα,4β,5α,7β,7aα)-2-(4-Cyano-3-(trifluoromethyl)phenyl)hexahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-1H-isoindole-5-carboxylic acid, propyl ester (868B)



A (3aα,4β,5α,7β,7aα)-2-(4-Cyano-3-(trifluoromethyl)phenyl)hexahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-1H-isoindole-5-carboxylic acid (868A)



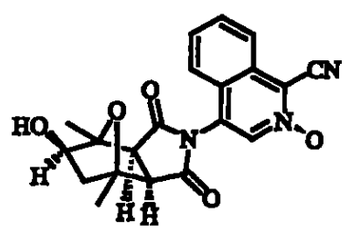
1N NaOH (2.2 ml; 2.2 mmol) was added to a solution of compound 867 (238 mg; 0.54 mmol) in 5 ml of methanol at rt. After stirring 5 h at rt, the volatiles were removed *in vacuo* and the residue was treated with 2 ml of trifluoroacetic acid for 18 hr. Concentration of the reaction mixture *in vacuo*, followed by co-evaporation from toluene (3 x 8 ml) gave a residue that was partitioned between EtOAc (40 ml) and brine (20 ml). Drying over $MgSO_4$ and concentration *in vacuo* afforded a solid that was triturated with hexane to afford compound 868A (120 mg, 53%) as a cream colored solid. HPLC: 93% at 1.35 min (retention time) (Phenominex S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 2 mincontaining 0.1% TFA, 4 mL/min, monitoring at 254 nm); MS (ES): m/z 425.08 $[M+H]^+$.

B. (3aα,4β,5α,7β,7aα)-2-(4-Cyano-3-(trifluoromethyl)phenyl)hexahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-1H-isoindole-5-carboxylic acid, propyl ester (868B)

Oxalylchloride (0.18 ml, 2 mmol) was added to a solution of compound 868A (135 mg; 0.32 mmol) in 4 ml of THF at room rt. Bubbling was observed

immediately. One drop of DMF was added and the reaction mixture was stirred 4 hrs. After adding 2 ml of n-propanol and stirring 18 h at rt, the reaction mixture was partitioned between EtOAc (30 ml) and water (30 ml). The organic layer was washed with saturated sodium bicarbonate solution (30 ml), dried over $MgSO_4$ and concentrated *in vacuo*. The residue was chromatographed on a 2.5 x 15 cm silica gel column, eluting with 25% EtOAc/hexane. The pure fractions were concentrated *in vacuo* to afford compound **868B** (78 mg, 52%) as a white powder. HPLC: 95.4% at 1.63 min (retention time) (Phenominex S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 2 mincontaining 0.1% TFA, 4 mL/min, monitoring at 254 nm); MS (ES): m/z 467.10 $[M+H]^+$. Compound **868B** represents a racemic mixture of antipodes. The nomenclature and structure shown does not reflect the absolute stereochemistry of the compound.

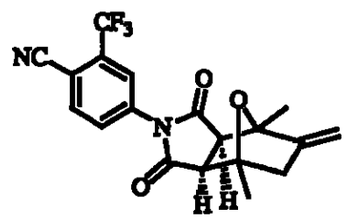
Example 869



30% Hydrogen peroxide (0.1 ml) was added to a solution of compound **748** (36 mg; 0.1 mmol) in 1 ml of AcOH at 100 C. Four additional 0.1 ml aliquots of 30 hydrogen peroxide were added at 30 min intervals to the reaction mixture. Water (8 ml) was added to the reaction mixture 30 minutes after the last addition of 30 hydrogen peroxide. After cooling to rt and standing 2 days, the resulting suspension was filtered and the filter cake was washed with water. After drying, the solid was dissolved in ~2 ml of acetone and the solution was applied to a SiO_2 preparative thin layer chromatography plate. Elution with 30% acetone/chloroform, extraction of the more polar band, filtration and concentration afforded compound **869** (6 mg, 16%) as an off-white solid. HPLC: 99% at 1.06 min (retention time) (Phenominex S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 2 mincontaining 0.1% TFA, 4 mL/min, monitoring at 254 nm); MS (ES): m/z 380.43 $[M+H]^+$.

Compound **869** represents a racemic mixture of antipodes. The nomenclature and structure shown does not reflect the absolute stereochemistry of the compound.

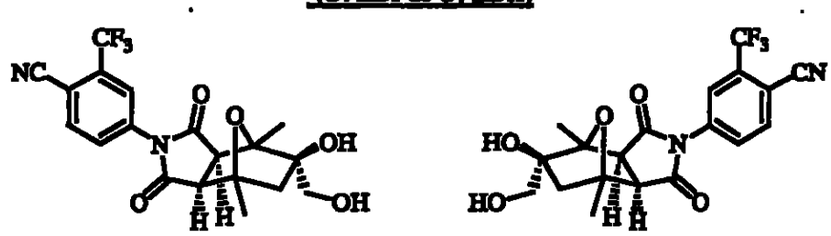
Example 870



A racemic mixture of compound **852DI** & **852DII** (150 mg, 0.38 mmol) was dissolved in THF (2 mL) under nitrogen and 2-nitrophenyl selenocyanate (202 mg, 0.89 mmol) followed by PBu_3 (0.22 mL, 0.89 mmol) was added. The resulting mixture was stirred for 20 h, concentrated and purified by flash chromatography with 0 to 100% EtOAc in hexanes. The resulting product was dissolved in THF (11 mL) and treated with 2 mL 30% H_2O_2 at 0°C. The reaction mixture was stirred for 10 min, then warmed to rt and stirred overnight. The reaction was quenched by the addition of 5% $Na_2S_2O_3$-solution and brine. The layers were separated and the aqueous layer was extracted 2X with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, concentrated *in vacuo* and purified by flash chromatography with 0 to 100% EtOAc in hexanes to give compound **870** (114 mg, 80%) as a yellow solid. HPLC: 100% at 3.67 min (retention time) (YMC S5 ODS-A column 4.6 x 50 mm Ballistic, 10-90% aqueous methanol over 4 mincontaining 0.2% H_3PO_4, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 375.23 $[M-H]^-$. Compound **870** represents a racemic mixture of antipodes. The nomenclature and structure shown does not reflect the absolute stereochemistry of the compound.

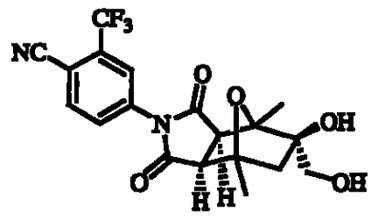
Example 871

(871BI & 871BII)



349

A. (871A)



To a solution of a racemic mixture of compounds **852Di & 852Dii** (33 mg, 0.09 mmol) in 0.5 mL acetone/0.4 mL water was added a 50% wt. solution of NMO in water (22 μL, 0.11 mmol) followed by a 4% wt. solution of OsO_4 in water (54 μL, 8.7 μmol). The resulting mixture was stirred for 12 h and the reaction was quenched by the addition of 5% $Na_2S_2O_3$-solution. CH_2Cl_2 was added, the layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic layers were dried over $MgSO_4$, concentrated *in vacuo* and purified by SiO_2 preparative TLC with 40% acetone in CH_2Cl_2 to give racemic compound **871A** (30 mg, 83%) as a white solid. HPLC: 100% at 2.91 min (retention time) (YMC S5 ODS-A column 4.6 x 50 mm Ballistic, 10-90% aqueous methanol over 4 mincontaining 0.2% H_3PO_4, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 469.26 $[M+OAc]^-$. Compound **871A** represents a racemic mixture of antipodes. The nomenclature and structure shown does not reflect the absolute stereochemistry of the compound.

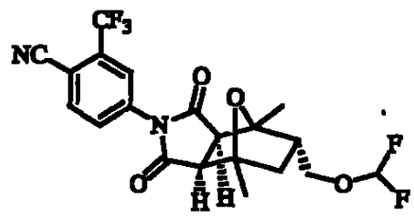
B. (**871Bi & 871Bii**)

Racemic compound **871A** was separated into its enantiomers by normal phase preparative chiral HPLC (CHIRALPAK OJ 5 x 50 cm column; eluting with 30% MeOH/EtOH (1:1) in heptane (isocratic) at 50 mL/min) to give the faster eluting antipode compound **871Bi** (Chiral HPLC: 7.35 min; CHIRALPAK OJ 4.6 x 250 mm column; eluting with 30% MeOH/EtOH (1:1) in heptane at 1 mL/min) and the slower eluting antipode compound **871Bii** (Chiral HPLC: 11.49 min; CHIRALPAK OJ 4.6 x 250 mm column; eluting with 30% MeOH/EtOH (1:1) in heptane at 1 mL/min). The absolute stereochemistry of compounds **871Bi & 871Bii** has not been established.

Although each compound represents a single antipode, the nomenclature and structure shown does not reflect the absolute stereochemistry of the compound.

Example 872

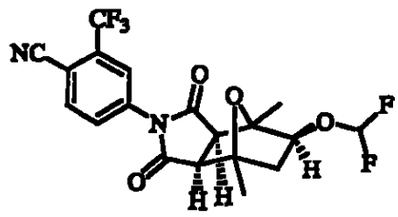
(3aα,4β,5α,7β,7aα)-4-(Octahydro-5-[[difluoromethyl]oxy]methyl]-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (872)

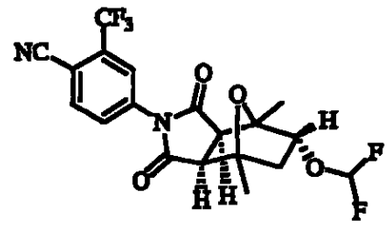


A racemic mixture of compounds 852Di & 852Dii (50 mg, 0.13 mmol) was dissolved under nitrogen in 1 mL CH_3CN and CuI (2 mg, 8.9 μmol) was added. This mixture was heated to 45°C and 2-(fluorosulfonyl)difluoroacetic acid (27 mg, 0.15 mmol) was added via syringe. The reaction mixture was stirred for 1.5 h at 45°C and then allowed to cool to rt. The reaction was quenched by the addition of water and CH_2Cl_2. The layers were separated and the aqueous layer was extracted with CH_2Cl_2. The combined organic phases were dried over $MgSO_4$, concentrated *in vacuo* and purified twice by SiO_2 flash chromatography with 0 to 100% EtOAc in hexanes to afford compound 872 (10 mg, 18%) as a white foam. HPLC: 92% at 3.72 min (retention time) (YMC S5 ODS-A column 4.6 x 50 mm Ballistic, 10-90% aqueous methanol over 4 mincontaining 0.2% H_3PO_4, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 443.22 $[M-H]^-$. Compound 872 represents a racemic mixture of antipodes. The nomenclature and structure shown does not reflect the absolute stereochemistry of the compound.

Example 873

(873i & 873ii)

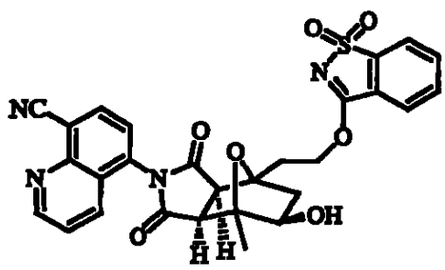


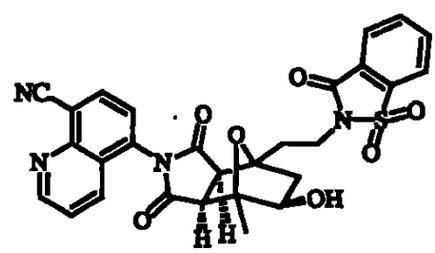


Compound 471Di (50 mg, 0.13 mmol), CuI (2 mg, 8.9 μmol) and 2-(fluorosulfonyl)difluoroacetic acid (28 mg, 0.16 mmol) were reacted in 1 mL CH_3CN and purified as described in Example 872. Compounds 873i & 873ii (15 mg, 0.03 mmol) were obtained as a inseparable 6:1 mixture as determined by ^{1}H-NMR. HPLC: 91% at 3.64 min (retention time) (YMC S5 ODS-A column 4.6 x 50 mm Ballistic, 10-90% aqueous methanol over 4 mincontaining 0.2% H_3PO_4, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 489.22 $[M+OAc]^-$. Compounds 873i & 873ii each represent a racemic mixture of antipodes. The nomenclature and structure shown does not reflect the absolute stereochemistry of the compound.

Example 874

(874i & 874ii)



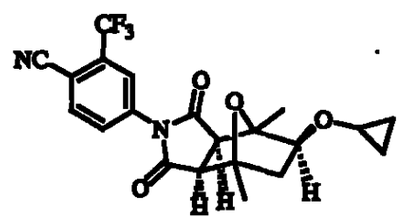


Triphenylphosphine (0.067g, 0.254 mmol) and di-*tert*-butyl-azodicarboxylate (0.059g, 0.254 mmol) in THF (1 mL) were stirred at rt under N_2 for 10 min, then saccharin (0.047g, 0.254 mmol) was added. The reaction mixture was stirred under N_2 for another 15 min, followed by the addition of compound 429i (0.050g, 0.127 mmol). The reaction was allowed to proceed for 24 h, at which point CH_2Cl_2 (15 mL) was added. The organic layer was isloated and then washed consecutively with 1N NaOH (15 mL), brine (15 mL) and dried over $MgSO_4$ and concentrated *in vacuo*. The resulting solid was purified by SiO_2 preparative TLC eluting with 25% acetone in $CHCl_3$, to give compound 874i (18 mg, 25%) as a white solid (HPLC: 91% at 2.96 min (retention time) (YMC S-5 ODS-A column, 4.6 x 50 mm, eluting with 10-90

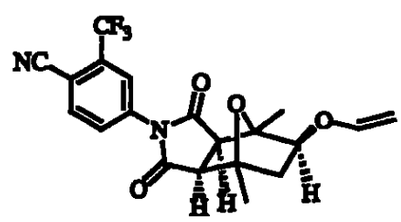
aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ESI): m/z 559.42 $[M+H]^+$) and compound **874ii** (18 mg, 25%) as a white solid (HPLC: 93% at 2.85 min (retention time) (YMC S-5 ODS-A column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ESI): m/z 557.12 $[M-H]^-$). The absolute stereochemistry of compounds **874i** & **874ii** has not been established. Although each compound represents a single antipode, the nomenclature and structure shown does not reflect the absolute stereochemistry of the compound.

Example 875

[3a*R*-(3aα,4β,5β,7β,7aα)]-4-(Octahydro-5-cyclopropyloxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (875B)



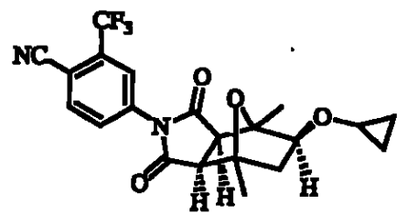
A. (875A)



A solution of compound **471Di** (300 mg, 0.79 mmol), mercuric trifluoroacetate (17 mg, 0.04 mmol) in tetrahydrofuran (THF, 1.5 mL) and ethyl vinyl ether (3 mL) in a thick-walled sealed tube was heated to 45°C for 48 h. The tube was cooled, opened and the reaction mixture was concentrated *in vacuo* to give an oil. The crude material was purified by silica gel flash chomatography eluting with 1:4:4 EtOAc/methylene chloride/heptane to give compound **875A** (115 mg, 36%) as a white solid. HPLC: 99% at 3.80 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm,

eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 407.09 $[M+H]^+$. The absolute stereochemistry of compound **875A** is established by the known stereochemistry of the intermediate compound **471Di** and the retention of configuration therein. The absolute stereochemistry is as drawn in the above figure and rendered by the nomenclature.

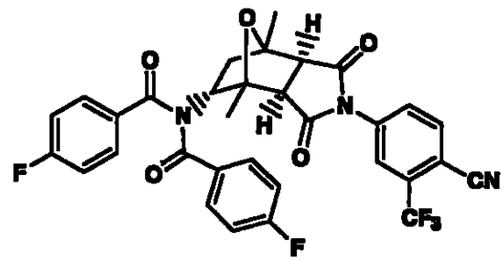
B. [3a*R*-(3aα,4β,5β,7β,7aα)]-4-(Octahydro-5-cyclopropyloxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (875B)



To a solution of compound **875A** (100 mg, 0.25 mmol) in dry methylene chloride (5 mL) cooled to 5°C was aded, dropwise, diethylzinc solution (1.0M in hexanes, 1.4 mL, 1.4 mmol). The reaction mixture was warmed to rt, then diiodomethane (80 mL, 1.0 mmol) was introduced. After 3 h, HPLC indicated the reaction was 2/3 complete. Two additional portions of diethylzinc and diiodomethane were successively added then the reaction mixture cooled in an ice-bath, quenched with water, and partitioned between 1 M HCl solution (20 mL) and EtOAc (20 mL). The organic phase was separated, dried over sodium sulfate, concentrated *in vacuo* and purified by silica gel flash chomatography eluting with 2:3 EtOAc/heptane to give compound **875B** as a white solid. HPLC: 100% at 3.72 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 421.08 $[M+H]^+$. The absolute stereochemistry of compound **875B** is established by the known stereochemistry of the intermediate compound **471Di** and the retention of configuration therein. The absolute stereochemistry is as drawn in the above figure and rendered by the nomenclature.

Example 876

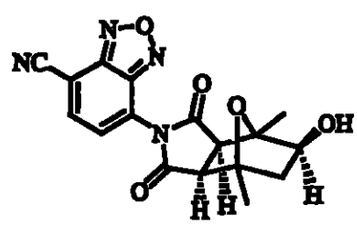
(876)



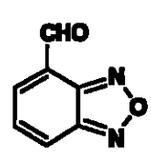
A racemic mixture of compounds **808**& **809** (0.057g, 0.15 mmol) was dissolved in 2 mL of CH_2Cl_2. Triethylamine (0.018g, 0.18 mmol), a catalytic amount of DMAP, and 4-fluorobenzoyl chloride (0.075g, 0.48 mmol) were added and the reaction was stirred for 6 h. The reaction mixture was diluted with CH_2Cl_2 and washed sequentially with 1N HCl, 10% K_2CO_3, and brine, dried over $MgSO_4$, filtered and concentrated *in vacuo*. The residue was purified by preparative TLC on silica gel using 2:1 EtOAc/hexanes as eluent. Removal of solvent gave compound **876** (0.066g, 70%) as a white solid. HPLC: 100% at 3.94 min(YMC S5 ODS column) eluting with 10-90% aqueous methanol containing 0.2% phosphoric acid over a 4 min gradient monitoring at 220 nm. MS (ES): m/z 552.11 $[M+H]^+$.

Example 877

(877)

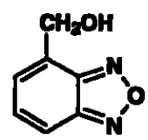


A. (877A)



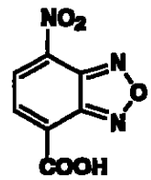
A 1.6 M solution of *n*-BuLi (54.6 mL, 87.4 mL) was added dropwise to a solution of diisopropylamine (12.8 mL, 91.6 mmol) in THF (40 mL) at –20 °C. The reaction mixture was cooled to –78 °C and a solution of benzofurazan (10.0 g, 83.3 mmol) in THF (34 mL) was added dropwise. After stirring for 35 mins, the mixture was poured into a solution of DMF (10.3 mL, 133.2 mmol) in THF (34 mL) at –78 °C and a solution of 3:1 H_2O:AcOH (80 mL) was added. After stirring at rt for 12 h, toluene (150 mL) was added and the layers were separated. The organic layer was concentrated to ~30 mL and triturated with hexanes (150 mL). The resulting solid was filtered and rinsed with hexanes. Purification by flash chromatography on silica gel eluting with 50% EtOAc/hexanes gave compound **877A** (7.77 g, 63%) as a tan solid. HPLC: 99% at 1.22 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 149.08 $[M+H]^+$.

B. (877B)



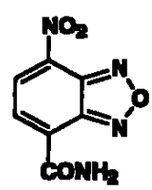
$NaBH_4$ (2.00 g, 52.5 mmol) was added portionwise to a solution of compound **877A** (7.77 g, 52.5 mmol) in MeOH (100 mL) at 0 °C. After 5 mins, the mixture was partitioned between H_2O (100 mL) and CH_2Cl_2 (100 mL). The aqueous layer was extracted with EtOAc (2 X 100 mL) and the combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to give crude compound **877B** (7.55 g, 96%) which was taken on without purification. HPLC: 99% at 1.63 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 133.05 $[M+H-H_2O]^+$.

C. (877C)



Fuming HNO_3 (4.25 mL, 100.58 mmol) was added dropwise to a solution of crude compound 877B (7.55 g, 50.29 mmol) in H_2SO_4 (50 mL) at 0 °C. The mixture was, stirred at rt for 20 mins, poured onto ice (1 L), warmed to rt and then extracted with EtOAc (3 X 250 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure. The resulting solid was washed with H_2O and air-dried to give compound 877C (6.0 g) as an orange solid. An additional 2.7 g was recovered from the aqueous wash by extraction with EtOAc for a total yield of 8.7 g (83%). HPLC: 99% at 1.63 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 210.18 $[M+H]^+$.

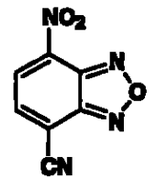
D. (877D)



Urea (29.3 mg, 0.488 mmol) was added portionwise to a solution of compound 877C (100 mg, 0.488 mmol) in fuming H_2SO_4 (2 mL) at 50 °C with vigorous stirring. The mixture was then heated to 100 °C for 30 mins, cooled to rt and poured onto ice (100 mL). The resulting aqueous mixture was extracted with EtOAc (3 X 50 mL) and the combined organic layers were washed with H_2O (1 X 100 mL), dried ($MgSO_4$) and concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with 50% EtOAc/hexanes gave compound 877D (76.3 mg, 77%) as a yellow-orange solid. HPLC: 96% at 1.39 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4

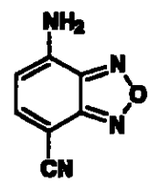
min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 209.17 $[M+H]^+$.

E. (877E)



A mixture of compound 877D (1.01 mg, 4.85 mmol) and P_2O_5 (2.75 g, 9.70 mmol) in toluene (24 mL) was refluxed for 30 mins. H_2O (50 mL) was added and the resulting mixture was extracted with EtOAc (3 X 100 mL). The combined organic layers were dried ($MgSO_4$) and concentrated under reduced pressure to give compound 877E (0.90 g, 98%) as a brown solid which was taken on without purification. HPLC: 90% at 1.78 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm).

F. (877F)



Iron powder (0.53 g, 9.47 mmol, 325 Mesh) was added in one portion to a solution of compound 877E (0.90 g, 4.73 mmol) in AcOH (24 mL) at 70 °C. The reaction was complete after 30 mins, as judged by HPLC. The mixture was concentrated under reduced pressure, dissolved in EtOAC (50 mL) and washed with sat. $NaHCO_3$ (2 X 50 mL). The aqueous layer was extracted with EtOAc (4 X 20 mL) and the combined organic layers were dried (Na_2SO_4) and concentrated under reduced pressure. Purification by flash chromatography on silica gel eluting with

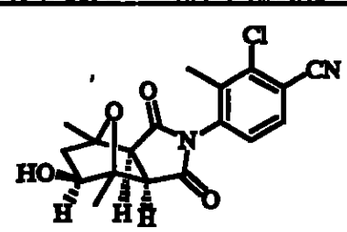
50% EtOAc/hexanes gave compound **877F** (0.62 g, 82%) as a dark orange solid. HPLC: 94% at 1.94 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 161.00 $[M+H]^+$.

G. (**877G**)

A small vial was charged with compound **752** (22.1 mg, 0.104 mmol compound **877F** (11.1 mg, 0.069 mmol) and $MgSO_4$ (21 mg, 0.173 mmol). DME (0.07 mL) was added then Et_3N (0.05 mL) and the vial was sealed with Teflon tape and heated at 135 °C for 18 h. Purification by preparative TLC (SiO_2) eluting with 30% acetone/$CHCl_3$ gave compound **877G** (6.3 mg, 17%) as a brown solid. HPLC: 98% at 2.15 min (retention time) (YMC S5 ODS column, 4.6 x 50 mm, eluting with 10-90% aqueous methanol over 4 min containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 337.16 $[M+H-H_2O]^+$. The absolute stereochemistry of compound **877G** is established by the known stereochemistry of the intermediate compound **752** and the retention of configuration therein. The absolute stereochemistry is as drawn in the above figure and rendered by the nomenclature.

Example 878

[3a*R*-(3aα,4β,5β,7β,7aα)]-4-[Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2-chloro-3-methylbenzonitrile (878)



A mixture of 4-amino-2-chloro-3-methyl-benzonitrile (54.5 mg, 0.327 mmol), compound **752**(104 mg, 0.491 mmol), $MgSO_4$ (98 mg, 0.818 mmol) and diisopropylethyl amine (0.28 mL, 1.64 mmol) in DME (0.33 mL) was heated at 150 °C in a sealed tube for 18 h. Purification by preparative TLC (SiO_2) eluting with 30%

acetone/$CHCl_3$ gave 53.0 mg (45%) of compound **878** as a tan solid. HPLC: 95% at 2.63 min (retention time) (YMC S5 ODS column 4.6 x 50 mm eluting with 10-90% aqueous methanol over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm). MS (ES): m/z 361.03 $[M+H]^+$. The absolute stereochemistry of compound **878** is established by the known stereochemistry of the intermediate compound **752** and the retention of configuration therein. The absolute stereochemistry is as drawn in the above figure and rendered by the nomenclature.

Examples 879 to 1020

Additional compounds of the present invention were prepared by procedures analogous to those described above. The compounds of Examples 879 to 1020 have the following structure (L is a bond):

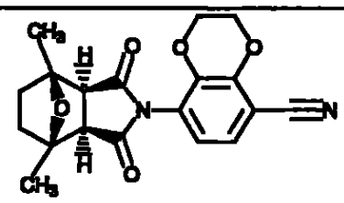
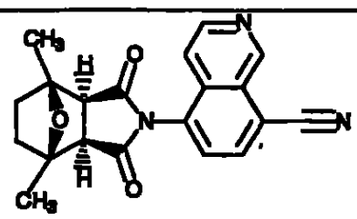
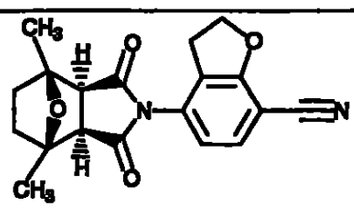
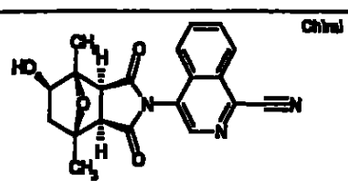
where the structure, the compound name, retention time, molecular mass, and the procedure employed, are set forth in **Table 18**. The absolute configuration for designated compounds was not determined. Compounds having one or more optical centers are designated as being racemic or chiral. Racemic compounds represent a mixture of both possible antipodes. Chiral refers to a compound, which represents a single antipode of a possible pair. For compounds that are chiral but the absolute stereochemistry is not known, the structure does not reflect the absolute stereochemistry. For compounds which are chrial and the absolute stereochemistry is known by reference to a starting material, then the structure drawn reflects the absolute stereochemistry of the compound. .

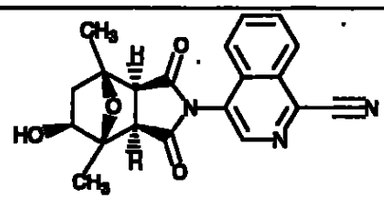
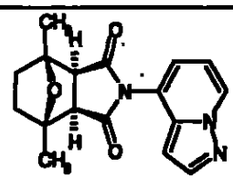
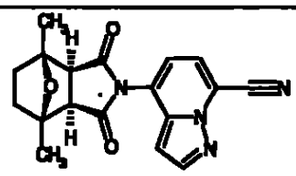
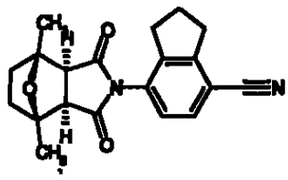
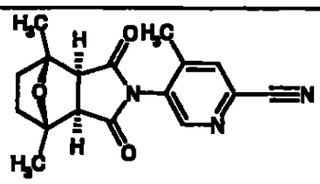
The chromatography techniques used to determine the compound retention times of **Table 18** are as follows: LCMS = YMC S5 ODS column, 4.6 X 50 mm eluting with 10-90% $MeOH/H_2O$ over 4 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm. LCMS* = YMC S5 ODS column, 4.6 X 50 mm eluting with 10-90% $MeOH/H_2O$ over 2 minutes containing 0.1% TFA; 4 mL/min, monitoring at 220 nm. LC* = Hypersil C18 BDS column, 250 x 4.6 mm, 5 μm, a detection wavelength of 254 nm, and a flow rate of 1 mL/min. A linear gradient of 90% of 0.1% trifluoroacetic acid in water, 10% acetonitrile (start) to 100% acetonitrile over 15 min, then 100% acetonitrile for 5 min was used. LC = YMC S5 ODS column 4.6

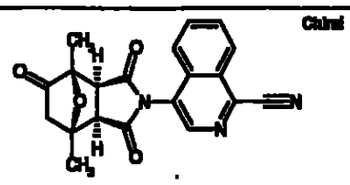
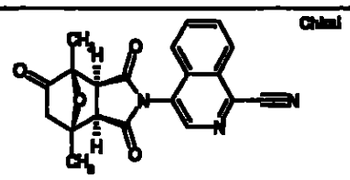
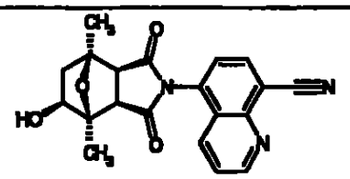
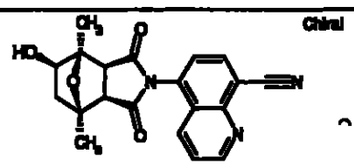
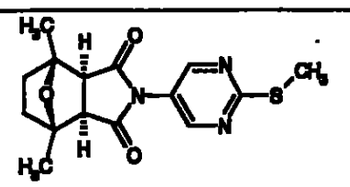
x 50 mm eluting with 10-90% MeOH/H_2O over 4 minutes containing 0.2% phosphoric acid, 4 mL/min, monitoring at 220 nm.

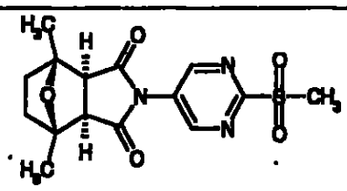
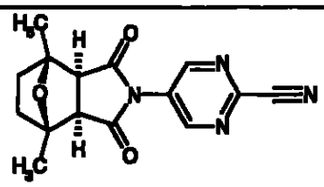
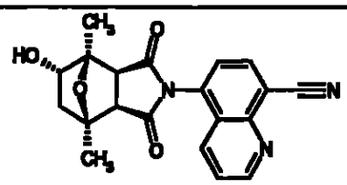
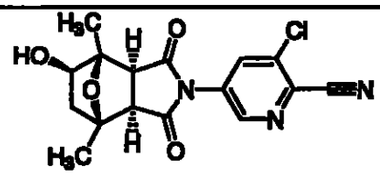
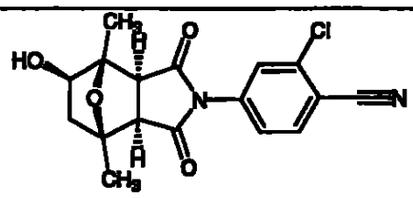
The molecular mass of the compounds listed in Table 18 were determined by MS (ES) by the formula m/z.

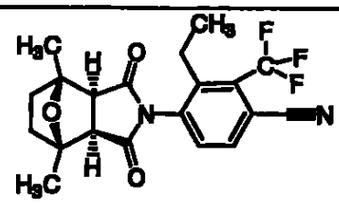
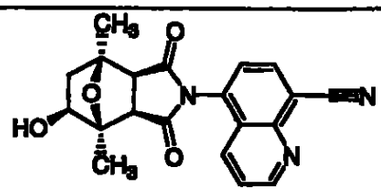
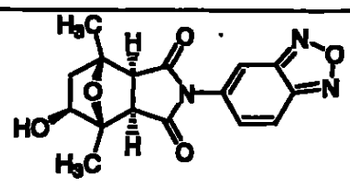
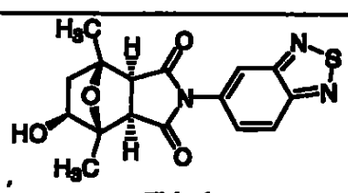
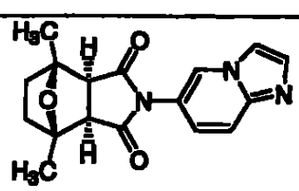
Table 18.

Ex. No	Structure	Compound Name/Comments	Retention Time Min./ Molecular Mass	Proc. of Ex.
879			2.34 LCMS $[M+H]^+$= 355.23	470E
880			2.44 LCMS $[M+H]^+$= 348.24	470E
881			3.21 LCMS $[M+H]^+$= 339.24	470E
882		Chiral, absolute stereochemistry not known	1.2 LCMS $[M+H]^+$= 364.15	754

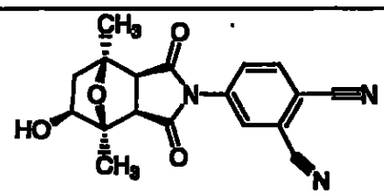
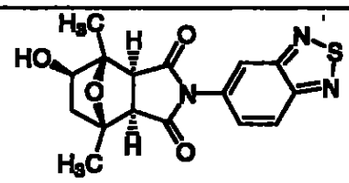
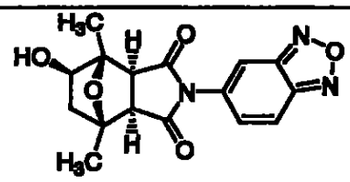
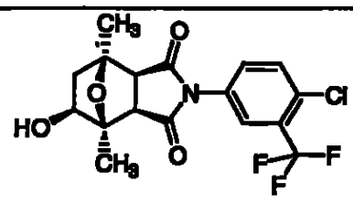
Ex. No	Structure	Compound Name/Comments	Retention Time Min./ Molecular Mass	Proc. of Ex.
883	 Chiral, absolute stereochem not known	Chiral, absolute stereochemistry not known	1.20 LCMS $[M+H]^+$= 364.15	761
884			2.72 LCMS $[M+H]^+$= 312.18	470E
885			2.95 LCMS $[M+H]^+$= 337.09	470E, 777F
886			2.93 LCMS $[M+H]^+$= 337.23	470E
887			2.69 LCMS $[M+H]^+$= 312.06	470E

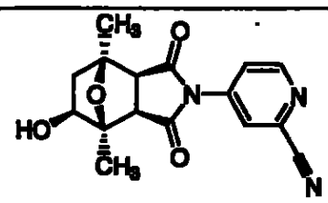
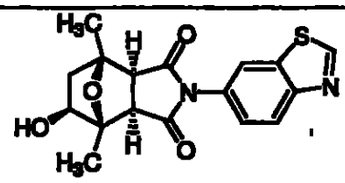
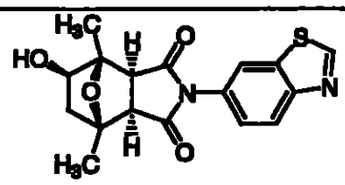
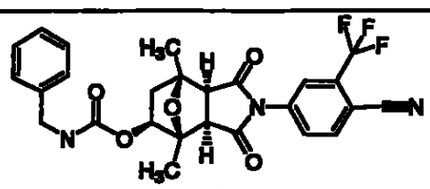
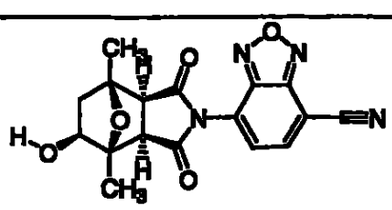
Ex. No	Structure	Compound Name/Comments	Retention Time Min./ Molecular Mass	Proc. of Ex.
888		Chiral, absolute stereochemistry not known	1.46 LCMS $[M+H]^+$= 362.15	795, 818
889		Chiral, absolute stereochemistry not known	1.48 LCMS $[M+H]^+$= 362.15	795, 818
890		Chiral, absolute stereochemistry as shown	1.833 LCMS $[M+H]^+$= 364.16	761
891		Chiral, absolute stereochemistry as shown	1.827 LCMS $[M+H]^+$= 364.17	754
892			3.09 LCMS $[M+H]^+$= 319.93	470E

Ex. No	Structure	Compound Name/Comments	Retention Time Min./ Molecular Mass	Proc. of Ex.
893			2.30 LCMS $[M+H]^+$= 351.96	470E
894			2.88 LCMS $[M+H]^+$= 299.02	470E
895		Chiral, absolute stereochemistry as shown	2.16 LCMS $[M+H]^+$= 364.20	799
896	 Chiral	Chiral, absolute stereochemistry as shown	2.66 LCMS $[M+H]^+$= 348.30	754
897		Chiral, absolute stereochemistry as shown	2.32 LCMS $[M+H]^+$= 347.18	754

Ex. No	Structure	Compound Name/Comments	Retention Time Min./ Molecular Mass	Proc. of Ex.
898			3.47 LCMS $[M+H]^+$= 393.19	470E
899		Chiral, absolute stereochemistry as shown	1.83 LCMS $[M+H]^+$= 364.17	761
900	 Chiral	Chiral, absolute stereochemistry as shown	2.56 LCMS $[M+H]^+$= 330.20	480A, 761
901	 Chiral	Chiral, absolute stereochemistry as shown	2.54 LCMS $[M+H]^+$= 346.12	424A, 761
902			1.48 LCMS $[M+H]^+$= 312.14	470E, 844A

357

Ex. No	Structure	Compound Name/Comments	Retention Time Min./ Molecular Mass	Proc. of Ex.
903	 Chiral	Chiral, absolute stereochemistry as shown	1.89 LCMS $[M+H]^+$= 336.17	761
904	 Chiral	Chiral, absolute stereochemistry as shown	2.52 LCMS $[M+H]^+$= 346.06	424A, 754
905	 Chiral	Chiral, absolute stereochemistry as shown [3aS-(3aα,4β,5β,7β,7aα)]-2-(2,1,3-Benzoxadiazol-5-yl)hexahydro-5-hydroxy-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione	2.55 LCMS $[M-H]^-$= 328.10	480A, 754
906	 Chiral	Chiral, absolute stereochemistry as shown [3aR-(3aα,4β,5β,7β,7aα)]-2-(4-Chloro-3-(trifluoromethyl)phenyl)hexahydro-5-hydroxy-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione	3.06 LCMS $[M+H]^+$= 390.20	761

Ex. No	Structure	Compound Name/Comments	Retention Time Min./ Molecular Mass	Proc. of Ex.
907	 Chiral	Chiral, absolute stereochemistry as shown	1.567 LCMS $[M+H]^+$= 314.16	761
908	 Chiral	Chiral, absolute stereochemistry as shown	2.10 LCMS $[M+H]^+$= 345.14	761
909	 Chiral	Chiral, absolute stereochemistry as shown [3aS-(3aα,4β,5β,7β,7aα)]-2-(6-Benzothiazolyl)hexahydro-5-hydroxy-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione	2.10 LCMS $[M+H]^+$= 345.14	754
910	 Chiral	Chiral, absolute stereochemistry as shown	3.90 LCMS $[M+H]^+$= 514.36	756
911	 Chiral	Chiral, absolute stereochemistry as shown	2.15 LCMS $[M+H]^+$= 337.16	761

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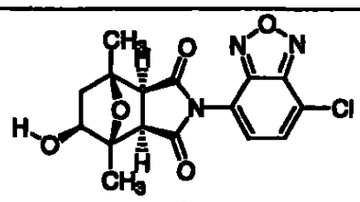
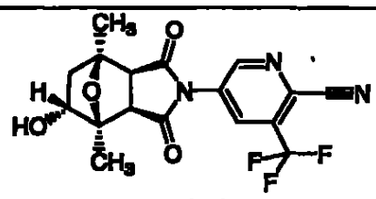
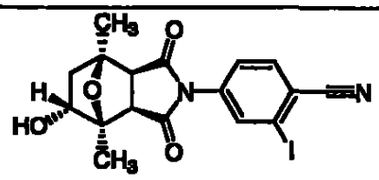
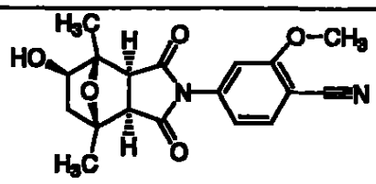
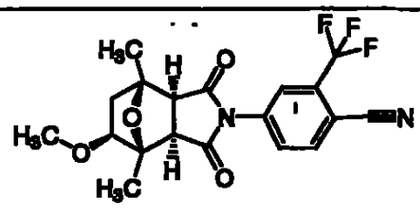
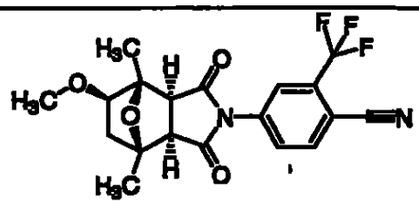
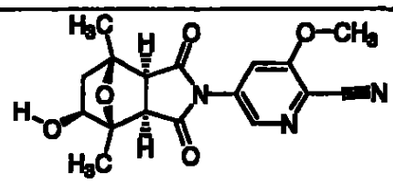
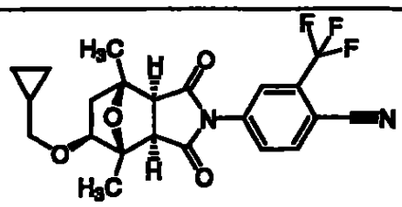
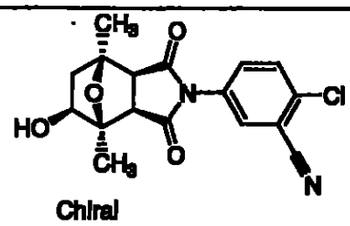
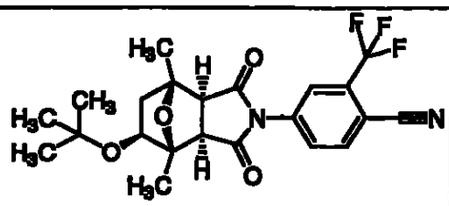
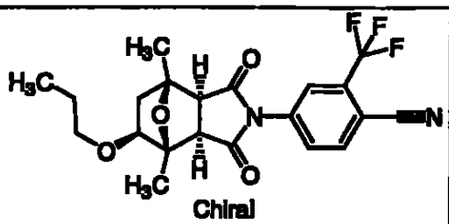
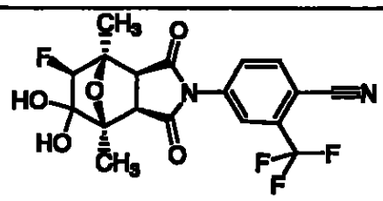
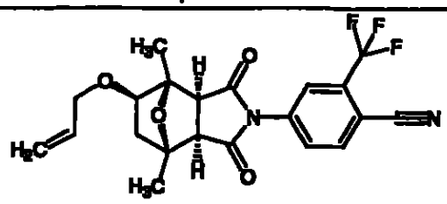
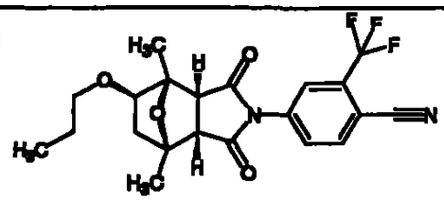
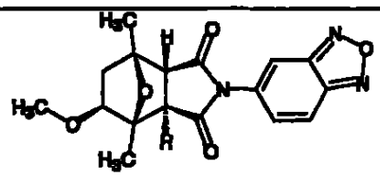
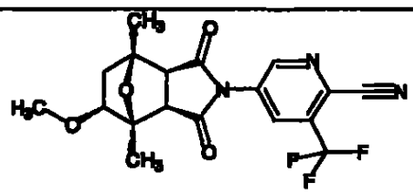
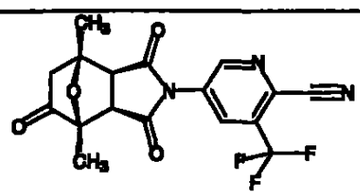
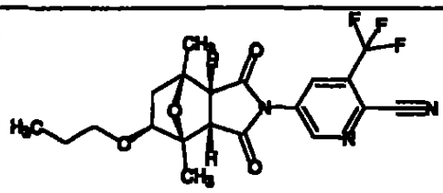
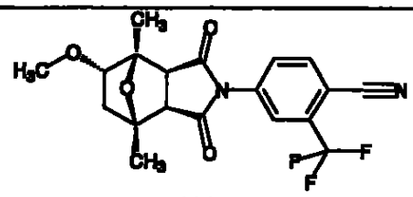
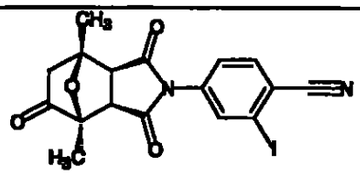
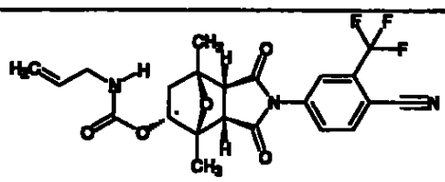
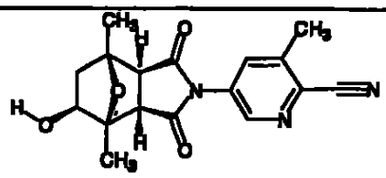
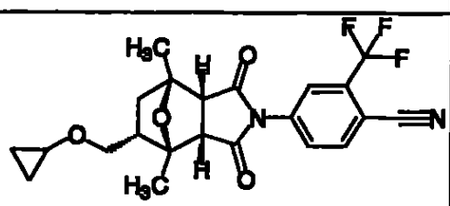
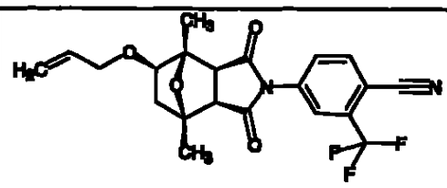
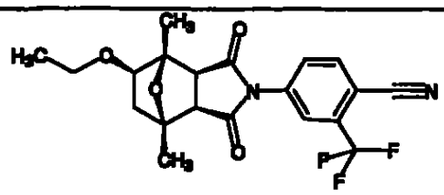
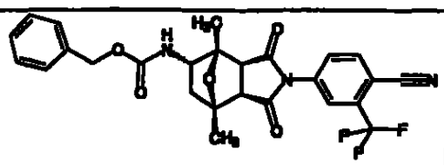
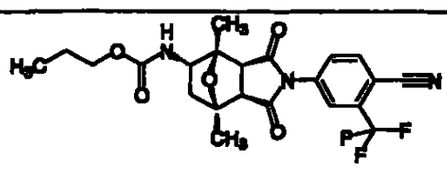
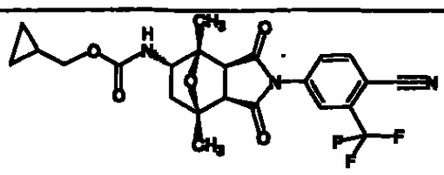
Ex. No	Structure	Compound Name/Comments	Retention Time Min./ Molecular Mass	Proc. of Ex.
912	 Chiral	Chiral, absolute stereochemistry as shown [3aR-(3aα,4β,5β,7β,7aα)]-2-(7-Chloro-2,1,3-benzoxadiazol-4-yl)hexahydro-5-hydroxy-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione	2.55 LCMS $[M+H]^+$= 364.18	761
913	 Chiral	Chiral, absolute stereochemistry not known [3aR-(3aα,4β,5α,7β,7aα)]-5-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-3-(trifluoromethyl)-2-pyridinecarbonitrile	2.933 LCMS $[M+H]^+$= 382.26	763E, 799
914	 Chiral	Chiral, absolute stereochemistry not known [3aR-(3aα,4β,5α,7β,7aα)]-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-iodobenzonitrile	2.73 LCMS $[M+H]^+$= 439.30	753F, 799
915	 Chiral	Chiral, absolute stereochemistry as shown	2.34 LCMS $[M+H]^+$= 341.26	846

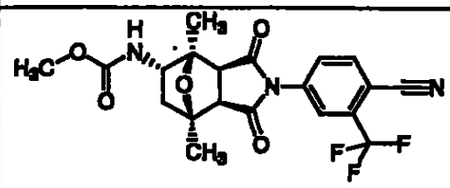
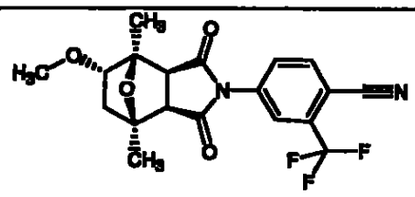
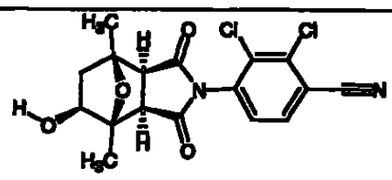
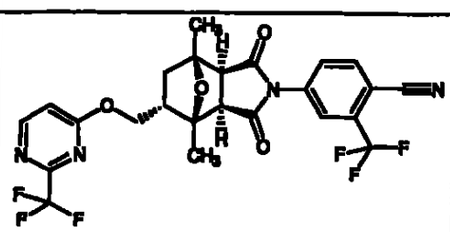
Ex. No	Structure	Compound Name/Comments	Retention Time Min./ Molecular Mass	Proc. of Ex.
916	 Chiral	Chiral, absolute stereochemistry as shown [3a*R*-(3aα,4β,5β,7β,7aα)]-4-(Octahydro-5-methoxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile	3.44 LCMS $[M+H]^+$= 395.43	757A
917	 Chiral	Chiral, absolute stereochemistry as shown [3a*S*-(3aα,4β,5β,7β,7aα)]-4-(Octahydro-5-methoxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile	$[M+H]^+$= 395.07	757A
918	 Chiral	Chiral, absolute stereochemistry as shown	1.83 LCMS $[M+H]^+$= 344.03	761
919	 Chiral	Chiral, absolute stereochemistry as shown [3a*R*-(3aα,4β,5β,7β,7aα)]-4-(Octahydro-5-cyclopropylmethoxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile	3.84 LCMS $[M+H]^+$= 435.10	757A

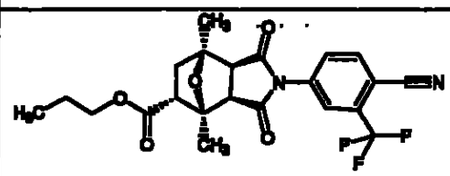
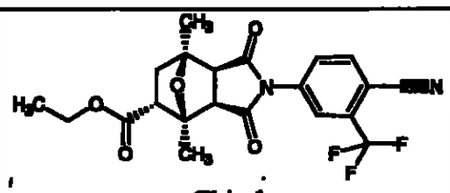
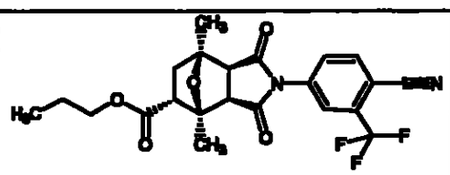
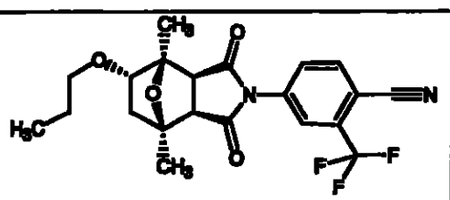
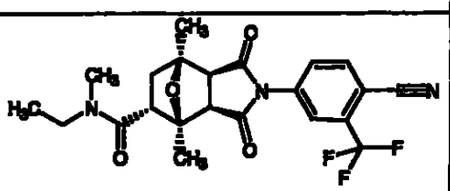
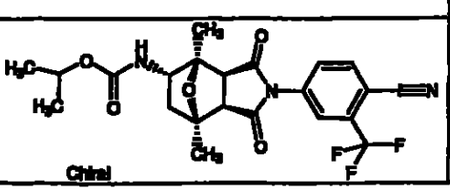
Ex. No	Structure	Compound Name/Comments	Retention Time Min./ Molecular Mass	Proc. of Ex.
920	 Chiral	Chiral, absolute stereochemistry as shown	2.373 LCMS $[M+H]^+$= 347.01	761
921	 Chiral	Chiral, absolute stereochemistry as shown	3.91 LCMS $[M+H]^+$= 436	757A
922	 Chiral	Chiral, absolute stereochemistry as shown	3.88 LCMS $[M+H]^+$= 422.99	757A
923	 Chiral	Chiral, absolute stereochemistry as shown [3a*R*-(3aα,4β,6β,7β,7aα)]-4-(Octahydro-6-fluoro-5,5-dihydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile	2.663 LCMS $[M+H]^+$= 413.19	798
924	 Chiral	Chiral, absolute stereochemistry as shown	3.74 LCMS $[M+H]^+$= 421.06	757A

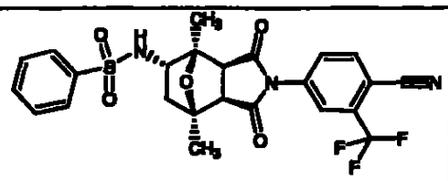
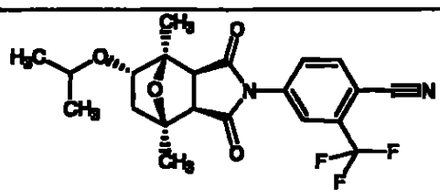
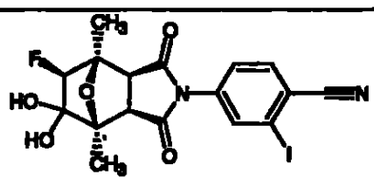
Ex. No	Structure	Compound Name/Comments	Retention Time Min./ Molecular Mass	Proc. of Ex.
925	 Chiral	Chiral, absolute stereochemistry as shown	3.89 LCMS $[M+H]^+$= 423.07	757A
926	 Chiral	Chiral, absolute stereochemistry as shown	3.027 LCMS $[M+H]^+$= 344.01	480A, 757A, 761
927	 Chiral	Chiral, absolute stereochemistry as shown	2.993 LCMS $[M+H]^+$= 396.00	757A, 763F
928	 Chiral	Chiral, absolute stereochemistry as shown [3aR-(3aα,4β,7β,7aα)]-5-(Octahydro-4,7-dimethyl-1,3,5-trioxo-4,7-epoxy-2H-isoindol-2-yl)-3-(trifluoromethyl)-2-pyridinecarbonitrile	3.153 LCMS $[M+H]^+$= 411.04	763E, 795
929	 Chiral	Chiral, absolute stereochemistry as shown	3.50 LCMS $[M+H]^+$= 424.07	757A

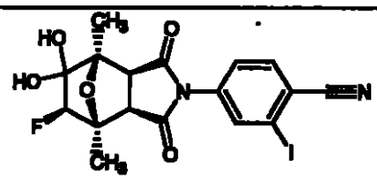
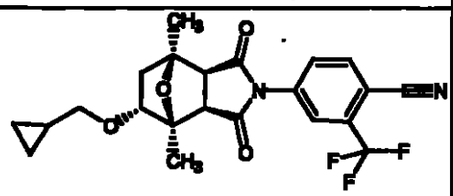
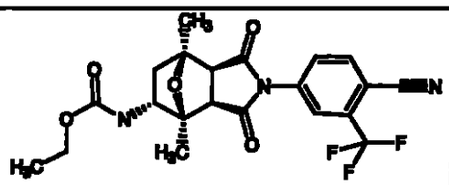
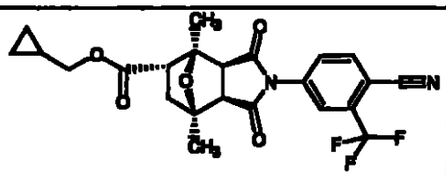
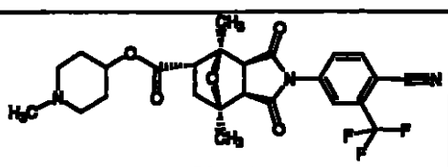
Ex. No	Structure	Compound Name/Comments	Retention Time Min./ Molecular Mass	Proc. of Ex.
930	 Chiral	Chiral, absolute stereochemistry as shown	2.887 LCMS $[M+H]^+$= 395.07	757A
931	 Chiral	Chiral, absolute stereochemistry as shown (3aα,4β,7β,7aα)-4-(Octahydro-4,7-dimethyl-1,3,5-trioxo-4,7-epoxy-2H-isoindol-2-yl)-2-iodobenzonitrile	2.963 LCMS $[M+H]^+$= 469.0	753F, 795
932		Chiral, absolute stereochemistry not known	14.30 LC** $[M+H]^+$= 464	810
933		Chiral, absolute stereochemistry as shown	1.83 LCMS $[M+H]^+$= 328.37	761
934		Chiral, absolute stereochemistry not know	3.85 LCMS $[M+H]^+$= 433.27	852

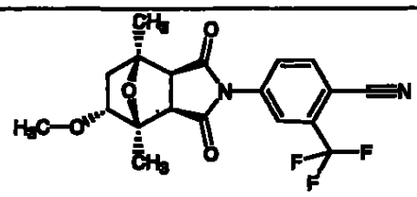
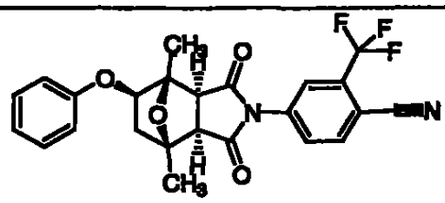
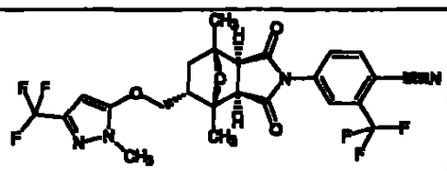
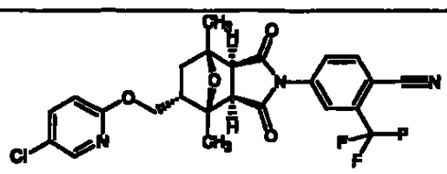
Ex. No	Structure	Compound Name/Comments	Retention Time Min./ Molecular Mass	Proc. of Ex.
935		Chiral, absolute stereochemistry as shown	16.070 LC* $[M+H]^+$= 421	*757A*
936		Chiral, absolute stereochemistry as shown	15.812 LC* $[M+H]^+$= 409	*757A*
937		Chiral, absolute stereochemistry not known (3aα,4β,5α,7β,7aα)-4-(Octahydro-5-[[phenylmethoxycarbonyl]amino]-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile	15.627 LC* $[M+H]^+$= 514	812
938		Chiral, absolute stereochemistry not known (3aα,4β,5α,7β,7aα)-4-(Octahydro-5-[[propyloxycarbonyl]amino]-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile	14.842 LC* $[M+H]^+$= 416	812
939		Chiral, absolute stereochemistry not know (3aα,4β,5α,7β,7aα)-4-(Octahydro-5-[[cyclopropylmethylo	14.852 LC* $[M+H]^+$=	812

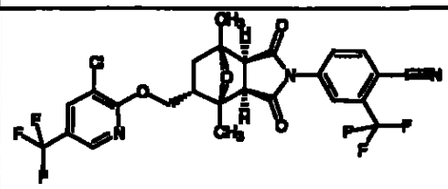
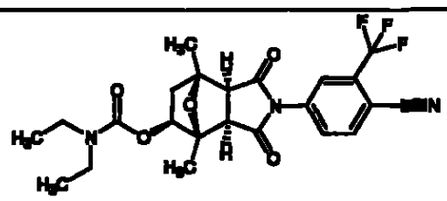
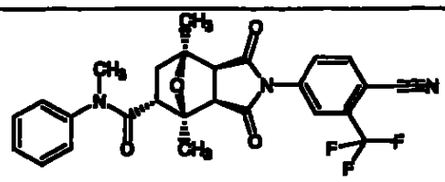
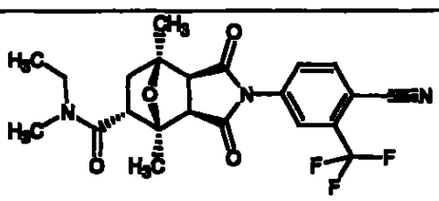
Ex. No	Structure	Compound Name/Comments	Retention Time Min./ Molecular Mass	Proc. of Ex.
		xy]carbonyl]amino]-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile	478	
940		Chiral, absolute stereochemistry not known (3aα,4β,5α,7β,7aα)-4-(Octahydro-5-[[methoxycarbonyl]amino]-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile	13.241 LC* $[M+H]^+$= 438	812
941		Chiral, absolute stereochemistry not known	14.671 LC* $[M+H]^+$= 395.3	855
942	 Chiral	Chiral, absolute stereochemistry as shown [3aR-(3aα,4β,5β,7β,7aα)]-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2,3-dichlorobenzonitrile	2.63 LCMS $[M+H]^+$= 382.95	761
943		Chiral, absolute stereochemistry not known	3.987 LCMS $[M+H]^+$= 541.07	851

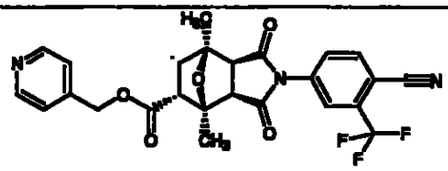
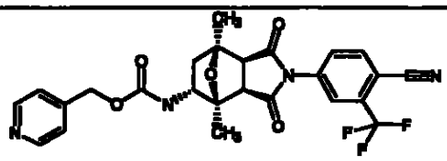
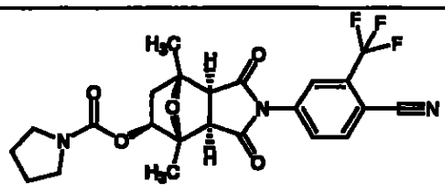
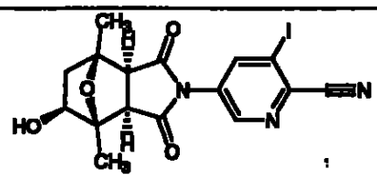
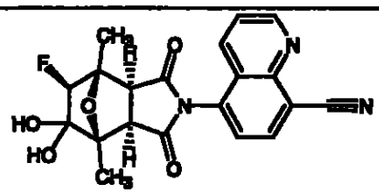
Ex. No	Structure	Compound Name/Comments	Retention Time Min./ Molecular Mass	Proc. of Ex.
944	 Chiral	Chiral, absolute stereochemistry not known	16.595 LC* $[M+H]^+$= 451.3	830
945	 Chiral	Chiral, absolute stereochemistry not known	16.294 LC* $[M+H]^+$= 437.3	830
946		Chiral, absolute stereochemistry not known	17.077 LC* $[M+H]^+$= 451.2	830
947		Chiral, absolute stereochemistry not known	16.970 LC* $[M+H]^+$= 423.7	757A
948		Chiral, absolute stereochemistry not known	14.750 LC* $[M+H]^+$= 450.4	811
949	 Chiral	Chiral, absolute stereochemistry not known [3a*S*-(3aα,4β,5α,7β,7aα)]-	15.314 LC* $[M+H]^+$=	812

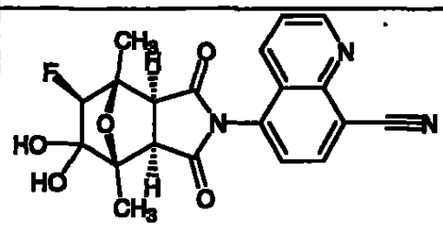
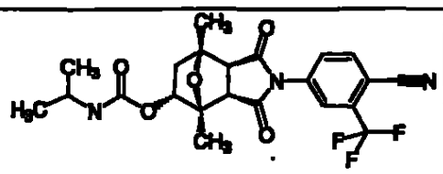
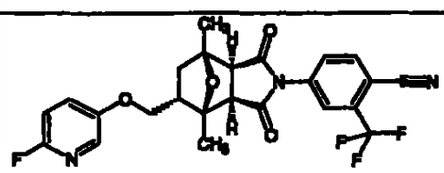
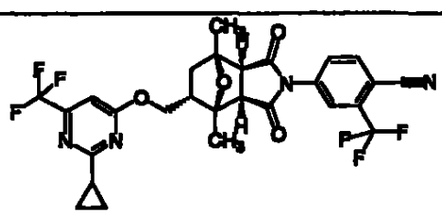
Ex. No	Structure	Compound Name/Comments	Retention Time Min./ Molecular Mass	Proc. of Ex.
		4-(Octahydro-5-[[(1-methylethoxy)carbonyl]amino]-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile	465	
950		Chiral, absolute stereochemistry not known (3aα,4β,5α,7β,7aα)-4-(Octahydro-5-benzenesulfonamido-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile	15.394 LC* $[M+H]^+$= 519	809
951		Chiral, absolute stereochemistry not known	16.902 LC* $[M+H]^+$= 423	757A
952	 Chiral	Chiral, absolute stereochemistry as shown [3a*R*-(3aα,4β,6β,7β,7aα)]-4-(Octahydro-6-fluoro-5,5-dihydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-iodobenzonitrile	2.497 LCMS $[M-H]^+$= 471.07	753F, 798

Ex. No	Structure	Compound Name/Comments	Retention Time Min./ Molecular Mass	Proc. of Ex.
953	 Chiral	Chiral, absolute stereochemistry as shown [3a*S*-(3aα,4β,6β,7β,7aα)]-4-(Octahydro-6-fluoro-5,5-dihydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-iodobenzonitrile	2.497 LCMS $[M-H]^+$= 471.07	753F, 798
954		Chiral, absolute stereochemistry not known	17.119** MS $[M+H]^+$= 435	A. 757 A
955	 Chiral	Chiral, absolute stereochemistry not known [3a*R*-(3aα,4β,5α,7β,7aα)]-4-(Octahydro-5-[[ethoxycarbonyl]amino]-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile	14.536 LC* $[M+H]^+$= 452	812
956	 Chiral	Chiral, absolute stereochemistry not known	18.043 LC* $[M+H]^+$= 436.2	830
957	 Chiral	Chiral, absolute stereochemistry not known	13.764 LC* $[M+H]^+$=	830

Ex. No	Structure	Compound Name/Comments	Retention Time Min./ Molecular Mass	Proc. of Ex.
			506.2	
958	 Chiral	Chiral, absolute stereochemistry not known [3aR-(3aα,4β,5α,7β,7aα)]-4-(Octahydro-5-methoxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile	3.243 LCMS $[M+H]^+$= 395.07	855
959	 Chiral	Chiral, absolute stereochemistry as shown	4.15 LCMS $[M+H]^+$= 455.00	757
960		Chiral, absolute stereochemistry as shown (3aα,4β,5α,7β,7aα)-4-(Octahydro-5-[[[2-methyl-5-(trifluoromethyl)-2H-pyrazol-3-yl]oxy]methyl]-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile	3.933 LCMS $[M+H]^+$= 543.00	851
961		Chiral, absolute stereochemistry as shown (3aα,4β,5α,7β,7aα)-4-(Octahydro-5-[[[5-chloro-2-pyridinyl]oxy]methyl]-4,7-dimethyl-1,3-	4.46 LCMS $[M+H]^+$= 505.92	851

Ex. No	Structure	Compound Name/Comments	Retention Time Min./ Molecular Mass	Proc. of Ex.
		dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile		
962		Chiral, absolute stereochemistry as shown	4.46 LCMS $[M+H]^+$= 573.93	851
963	 Chiral	Chiral, absolute stereochemistry as shown	4.00 LCMS $[M+H]^+$= 480.03	756
964	 Chiral	Chiral, absolute stereochemistry not known [3a*R*-(3aα,4β,5α,7β,7aα)]-2-(4-Cyano-3-(trifluoromethyl)phenyl)hexahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-*N*-methyl-*N*-phenyl-1H-isoindole-5-carboxamide	18.695 LC* $[M+H]^+$= 498.0	811
965	 Chiral	Chiral, absolute stereochemistry not known	17.025 LC* $[M+H]^+$= 450.2	811

Ex. No	Structure	Compound Name/Comments	Retention Time Min./ Molecular Mass	Proc. of Ex.
966	 Chiral	Chiral, absolute stereochemistry not known	15.425 LC* $[M+H]^+$= 500.2	830
967	 Chiral	Chiral, absolute stereochemistry not known	14.375 LC* $[M+H]^+$= 498	812
968	 Chiral	Chiral, absolute stereochemistry as shown	3.90 LCMS $[M+H]^+$= 478.09	756
969	 Chiral	Chiral, absolute stereochemistry as shown	2.32 LCMS $[M+H]^+$= 439.92	761
970		Chiral, absolute stereochemistry as shown	1.95 LCMS $[M+H]^+$= 398.25	798

Ex. No	Structure	Compound Name/Comments	Retention Time Min./ Molecular Mass	Proc. of Ex.
971	 Chiral	Chiral, absolute stereochemistry as shown [3a*R*-(3aα,4β,5α,7β,7aα)]-4-(Octahydro-5-[[(4-fluorophenylamino)carbonyl]oxy]-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile	3.757 LCMS $[M+H]^+$= 516.31	798
972	 Chiral	Chiral, absolute stereochemistry not known [3a*R*-(3aα,4β,5α,7β,7aα)]-4-(Octahydro-5-[[(1-methylethylamino)carbonyl]oxy]-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile	3.367 LCMS $[M+H]^+$= 464.32	810
973		Chiral, absolute stereochemistry not known	3.80 LCMS $[M+H]^+$= 490.04	851
974		Chiral, absolute stereochemistry not known	4.383 LCMS $[M+H]^+$= 581.10	851

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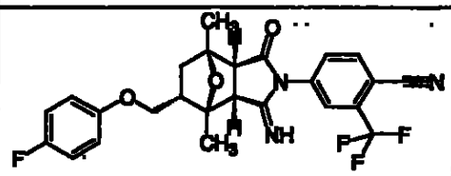
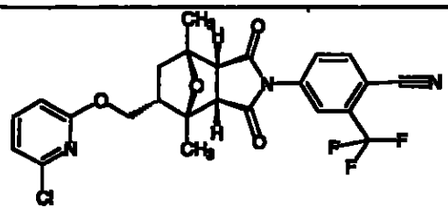
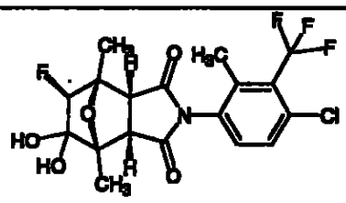
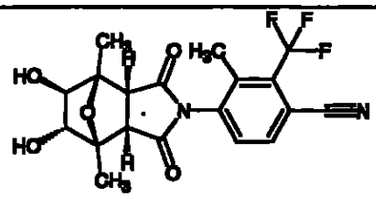
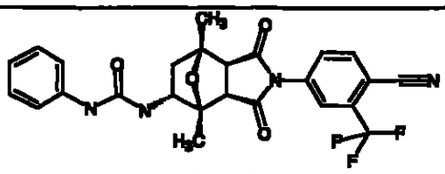
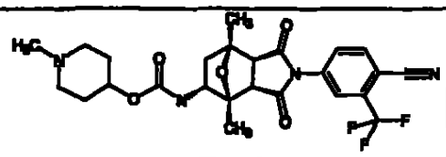
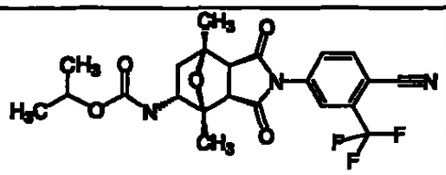
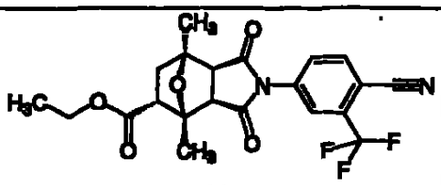
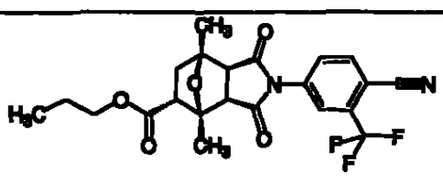
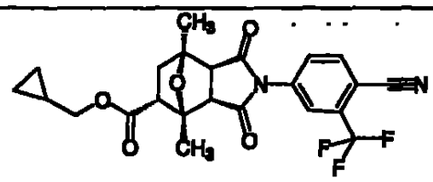
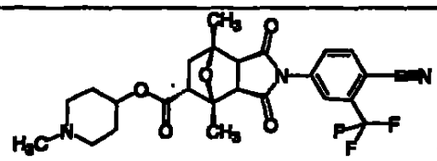
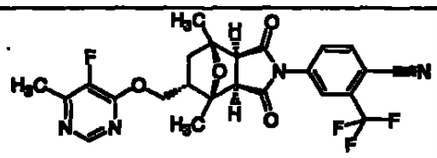
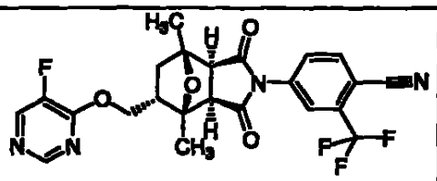
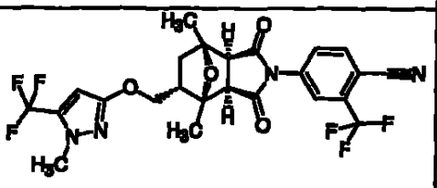
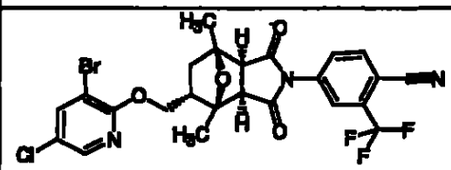
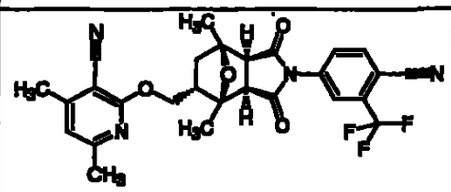
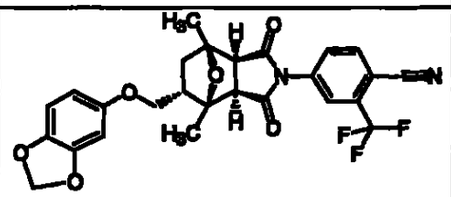
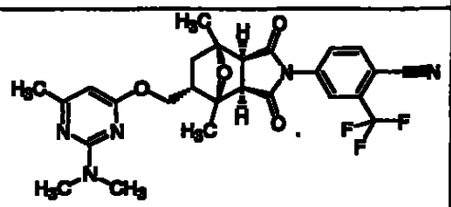
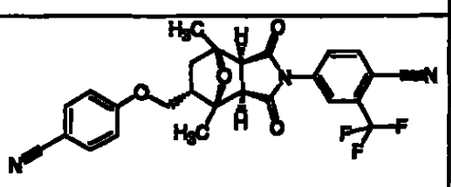
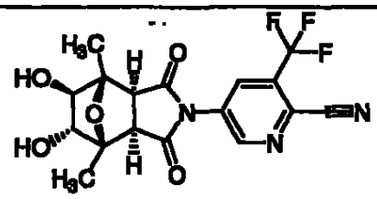
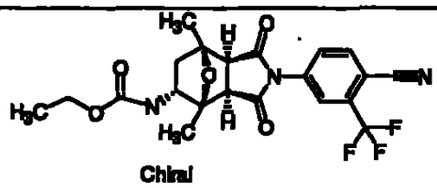
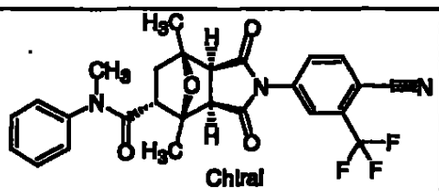
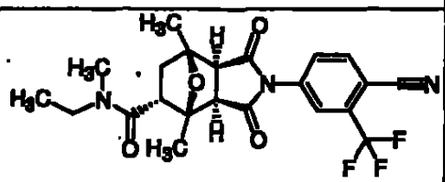
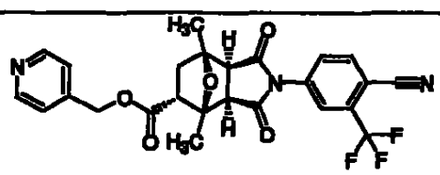
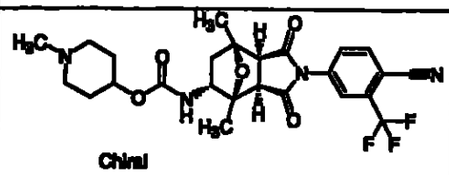
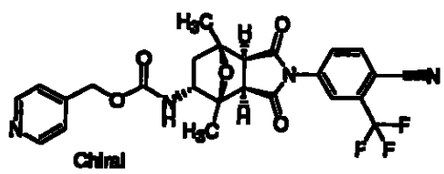
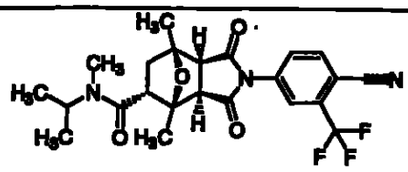
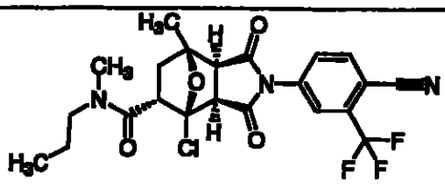
Ex. No	Structure	Compound Name/Comments	Retention Time Min./ Molecular Mass	Proc. of Ex.
975		Chiral, absolute stereochemistry not known	4.147 LCMS $[M+H]^+$= 489.01	851
976		Chiral, absolute stereochemistry not known	4.173 LCMS $[M+H]^+$= 507.99	851
977		Chiral, absolute stereochemistry as shown	3.34 LCMS $[M+H]^+$= 436.26	798
978	 Chiral	Chiral, absolute stereochemistry not known [3a*R*-(3aα,4β,5β,6α,7β,7aα)]-4-(Octahydro-5,6-dihydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-3-methyl-2-(trifluoromethyl)benzonitrile	3.28 LCMS $[M+H]^+$= 411.0	787
979	 Chiral	Chiral, absolute stereochemistry not known [3a*R*-(3aα,4β,5α,7β,7aα)]-4-(Octahydro-5-[[[phenylamino]carbonyl]amino]-4,7-	14.736 LC* $[M+H]^+$= 499.3	815

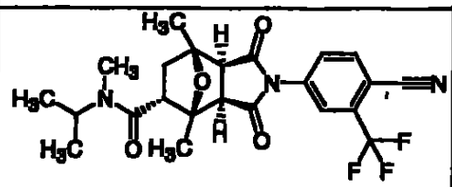
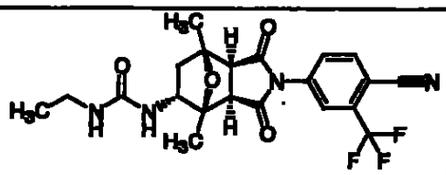
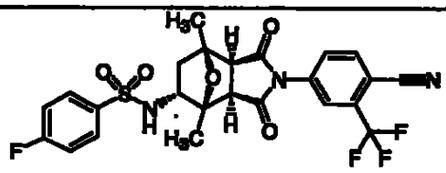
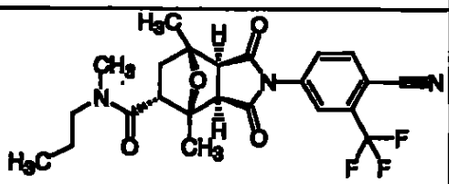
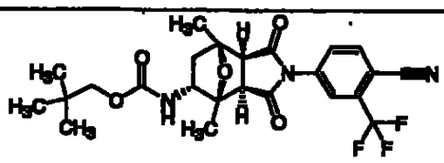
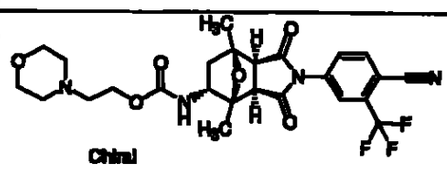
Ex. No	Structure	Compound Name/Comments	Retention Time Min./ Molecular Mass	Proc. of Ex.
		dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile		
980	 Chiral	Chiral, absolute stereochemistry not known	15.370 LC* $[M+H]^+$= 521.4	812
981	 Chiral	Chiral, absolute stereochemistry not known [3a*R*-(3aα,4β,5α,7β,7aα)]-4-(Octahydro-5-[[(1-methylethyloxy)carbonyl]amino]-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile	15.108 LC* $[M+H]^+$= 466	812
982	 Chiral	Chiral, absolute stereochemistry not known	16.235 LC* $[M+H]^+$= 437.0	830
983	 Chiral	Chiral, absolute stereochemistry not known	17.195 LC* $[M+H]^+$= 451.20	830

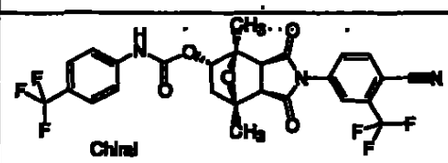
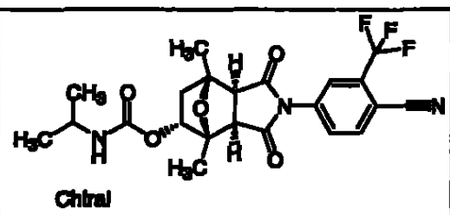
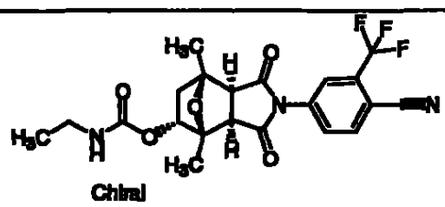
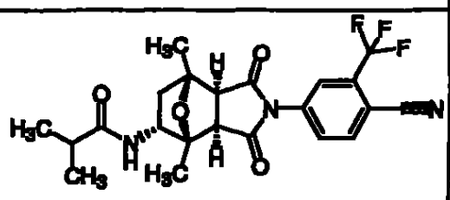
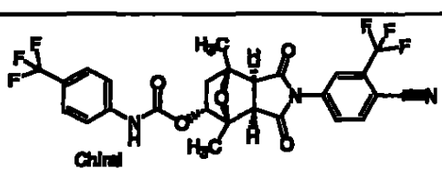
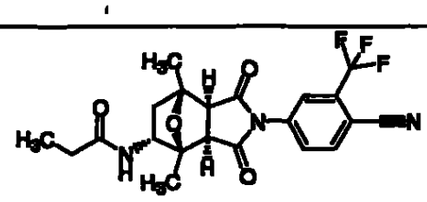
Ex. No.	Structure	Compound Name/Comments	Retention Time Min./ Molecular Mass	Proc. of Ex.
984	 Chiral	Chiral, absolute stereochemistry not known	16.851 LC* $[M+H]^+$= 463.25	830
985	 Chiral	Chiral, absolute stereochemistry not known	12.530 LC* $[M+H]^+$= 506.30	830
986		Chiral, absolute stereochemistry not known	3.947 LCMS $[M+H]^+$= 505.27	851
987		Chiral, absolute stereochemistry not known (3aα,4β,5α,7β,7aα)-4-(Octahydro-5-[[[5-fluoro-4-pyrimidinyl]oxy]methyl]-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile	3.80 LCMS $[M+H]^+$= 491.08	851
988		Chiral, absolute stereochemistry not known	3.80 LCMS $[M+H]^+$= 543.07	851

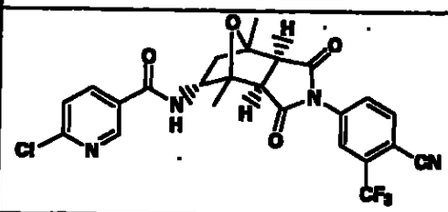
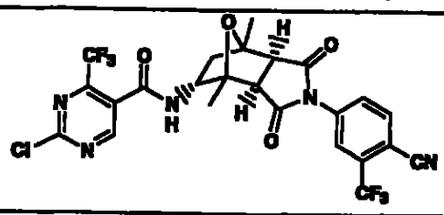
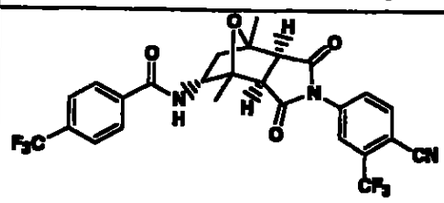
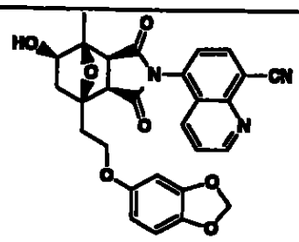
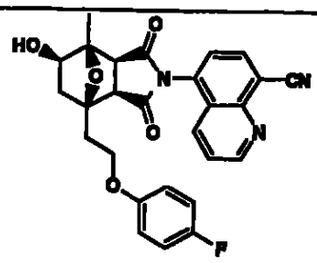
Ex. No	Structure	Compound Name/Comments	Retention Time Min./ Molecular Mass	Proc. of Ex.
989		Chiral, absolute stereochemistry not known	4.50 LCMS $[M+H]^+$= 585.96	851
990		Chiral, absolute stereochemistry not known	4.09 LCMS $[M+H]^+$= 525.12	851
991		Chiral, absolute stereochemistry not known	4.12 LCMS $[M+H]^+$= 515.05	851
992		Chiral, absolute stereochemistry not known	3.10 LCMS $[M+H]^+$= 530.13	851
993		Chiral, absolute stereochemistry not known	3.95 LCMS $[M+H]^+$= 496.05	851

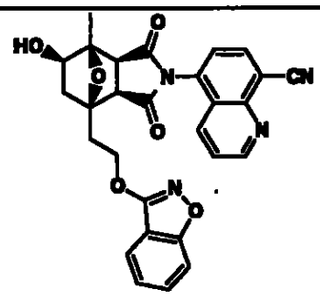
Ex. No	Structure	Compound Name/Comments	Retention Time Min./ Molecular Mass	Proc. of Ex.
994	 Chiral	Chiral, absolute stereochemistry not known	XXX LCMS $[M+H]^+$= XXX	797
995	 Chiral	Chiral, absolute stereochemistry not known [3a*R*-(3aα,4β,5α,7β,7aα)]-4-(Octahydro-5-[[ethyloxycarbonyl]amino]-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile	14.522 LC* $[M+H]^+$= 452	812
996	 Chiral	Chiral, absolute stereochemistry not known	16.068 LC* $[M+H]^+$= 498.25	811
997	 Chiral	Chiral, absolute stereochemistry not known	14.076 LC* $[M+H]^+$= 450.20	811
998	 Chiral	Chiral, absolute stereochemistry not known [3a*R*-(3aα,4β,5α,7β,7aα)]-2-(4-Cyano-3-(trifluoromethyl)phenyl)-hexahydro-4,7-	12.008 LC* $[M+H]^+$= 500.2	830

Ex. No	Structure	Compound Name/Comments	Retention Time Min./ Molecular Mass	Proc. of Ex.
		-dimethyl-1,3-dioxo-4,7-epoxy-1H-isoindole-5-carboxylic acid, 4-pyridinylmethyl ester		
999	 Chiral	Chiral, absolute stereochemistry not known	11.196 LC* $[M+H]^+$= 521.3	812
1000	 Chiral	Chiral, absolute stereochemistry not known [3a*R*-(3aα,4β,5α,7β,7aα)]-4-(Octahydro-5-[[4-pyridinylmethoxycarbonyl]amino]-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile	11.342 LC* $[M+H]^+$= 515.4	812
1001	 Chiral	Chiral, absolute stereochemistry not known	14.897 LC* $[M+H]^+$= 464.25	811
1002	 Chiral	Chiral, absolute stereochemistry not known	14.905 LC* $[M+H]^+$= 464.25	811

Ex. No	Structure	Compound Name/Comments	Retention Time Min./ Molecular Mass	Proc. of Ex.
1003	 Chiral	Chiral, absolute stereochemistry not known	14.692 LC* $[M+H]^+$= 464.25	815
1004	 Chiral	Chiral, absolute stereochemistry not known	11.93 LC* $[M+H]^+$= 451.50	809
1005		Chiral, absolute stereochemistry not known	15.325 LC* $[M+H]^+$= 538.40	811
1006	 Chiral	Chiral, absolute stereochemistry not known	14.724 LC* $[M+H]^+$= 464.25	812
1007	 Chiral	Chiral, absolute stereochemistry not known	16.123 LC* $[M+H]^+$= 494.0	812
1008	 Chiral	Chiral, absolute stereochemistry not known	11.187 LC* $[M+H]^+$= 537.3	812

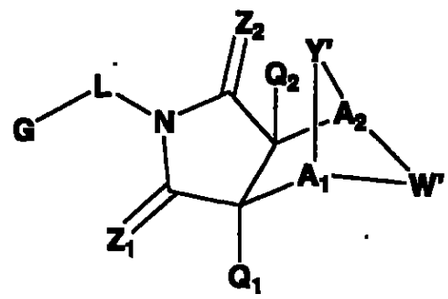
Ex. No	Structure	Compound Name/Comments	Retention Time Min./ Molecular Mass	Proc. of Ex.
1009		Chiral, absolute stereochemistry not known	4.02 LCMS $[M-H]^-$= 566.18	812
1010		Chiral, absolute stereochemistry not known	3.35 LCMS $[M-H]^-$= 464.19	810
1011		Chiral, absolute stereochemistry not known	3.23 LCMS	814
1012		Chiral, absolute stereochemistry not known	3.12 LCMS $[M+H]^+$= 450.12	812
1013		Chiral, absolute stereochemistry not known	4.04 LCMS	810
1014		Chiral, absolute stereochemistry not known	3.02 LCMS $[M-H]^-$= 436.1	814

Ex. No	Structure	Compound Name/Comments	Retention Time Min./ Molecular Mass	Proc. of Ex.
1015		Racemic	3.32 LCMS $[M+H]^+$= 519.05	812
1016		Racemic	3.56 LCMS $[M+H]^+$= 587.97	812
1017		Racemic	3.65 LCMS $[M-H]^-$= 552.11	812
1018		[3a*S*-(3aα,4β,5β,7β,7aα)]-5-[7-[2-(1,3-Benzodioxol-5-yloxy)ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile	2.86 LCMS $[M + H]^+$= 514.16	485, 486, 487 & 488
1019		[3a*S*-(3aα,4β,5β,7β,7aα)]-5-[7-[2-(4-Fluorophenoxy)ethyl]octahydro-5-hydroxy-4-methyl-	3.02 LCMS $[M + H]^+$= 488.2	485, 486, 487 & 488

Ex. No	Structure	Compound Name/Comments	Retention Time Min./ Molecular Mass	Proc. of Ex.
		1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile		
1020		[3aS-(3aα,4β,5β,7β,7aα)]-5-[7-[2-(1,2-Benzisoxazol-3-yloxy)ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile	2.94 LCMS $[M + H]^+$= 511.2	485, 486, 487 & 488

What We Claim Is:

1. A compound of the following formula:



(Ia)

wherein the symbols have the following meanings and are, for each occurrence, independently selected:

G is an aryl or heterocyclo group, where said group is mono- or polycyclic, and which is optionally substituted at one or more positions;

Z_1 is O, S, NH, or NR^6;

Z_2 is O, S, NH, or NR^6;

A_1 is CR^7 or N;

A_2 is CR^7 or N;

Y' is J-J'-J" where J is $(CR^7R^{7'})n$ and n = 0-3, J' is a bond or O, S, S=O, SO_2, NH, NR^7, $CR^7R^{7'}$, $R^2P{=}O$, $R^2P{=}S$, $R^2OP{=}O$, $R^2NHP{=}O$, $OP{=}OOR^2$, $OP{=}ONHR^2$, OSO_2, NHNH, $NHNR^6$, NR^6NH, N=N, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, or heterocyclo or substituted heterocyclo, and J" is $(CR^7R^{7'})n$ and n = 0-3, where Y is not a bond; and

W' is $CR^7R^{7'}$—$CR^7R^{7'}$, $CR^7R^{7'}$—C=O, C=O—C=O, $CR^7R^{7'}$—$C{=}CH_2$, $C{=}CH_2$—$C{=}CH_2$, $CR^7R^{7'}$—$C{=}NR^1$, $C{=}NR^1$—$C{=}NR^1$, NR^9—$CR^7R^{7'}$, $N{=}CR^8$, N=N, NR^9—$NR^{9'}$, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, or aryl or substituted aryl, wherein when W' is not NR^9—$CR^7R^{7'}$, $N{=}CR^8$, N=N, NR^9—$NR^{9'}$, or

heterocyclo or substituted heterocyclo, then J' must be O, S, S=O, SO_2, NH, NR^7, $OP{=}OOR^2$, $OP{=}ONHR^2$, OSO_2, NHNH, $NHNR^6$, NR^6NH, or N=N; or when W' is $CR^7R^{7'}$—$CR^7R^{7'}$, the R^7 and $R^{7'}$ substituents in each occurrence may be taken together to form a substituted or unsubstituted carbocyclic or substituted or unsubstituted heterocyclic ring system which can be formed by any combination of R^7 and $R^{7'}$ attached to the same carbon atom;

Q_1 is H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocycloalkyl or substituted heterocycloalkyl, arylalkyl or substituted arylalkyl, alkynyl or substituted alkynyl, aryl or substituted aryl, heterocyclo (e.g., heteroaryl) or substituted heterocyclo (e.g., substituted heteroaryl), halo, CN, $R^1OC{=}O$, $R^4C{=}O$, $R^5R^6NC{=}O$, $HOCR^7R^{7'}$, nitro, R^1OCH_2, R^1O, NH_2, $C{=}OSR^1$, SO_2R^1 or NR^4R^5;

Q_2 is H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocycloalkyl or substituted heterocycloalkyl, arylalkyl or substituted arylalkyl, alkynyl or substituted alkynyl, aryl or substituted aryl, heterocyclo (e.g., heteroaryl) or substituted heterocyclo (e.g., substituted heteroaryl), halo, CN, $R^1OC{=}O$, $R^4C{=}O$, $R^5R^6NC{=}O$, $HOCR^7R^{7'}$, nitro, R^1OCH_2, R^1O, NH_2, $C{=}OSR^1$, SO_2R^1 or NR^4R^5;

L is a bond, $(CR^7R^{7'})n$, NH, NR^5, NH $(CR^7R^{7'})n$, or $NR^5(CR^7R^{7'})n$, where n = 0-3;

R^1 and $R^{1'}$ are each independently H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkyalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl;

R^2 is alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl,

heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl;

R^3 and $R^{3'}$ are each independently H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, halo, CN, hydroxylamine, hydroxamide, alkoxy or substituted alkoxy, amino, NR^1R^2, thiol, alkylthio or substituted alkylthio;

R^4 is H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, $R^1C{=}O$, $R^1OC{=}O$, $R^1NHC{=}O$, SO_2OR^1, SO_2R^1 or $SO_2NR^1R^{1'}$;

R^5 is alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, $R^1C{=}O$, $R^1NHC{=}O$, SO_2R^1, SO_2OR^1, or $SO_2NR^1R^{1'}$;

R^6 is alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, CN, OH, OR^1, $R^1C{=}O$, $R^1NHC{=}O$, SO_2R^1, SO_2OR^1, or $SO_2NR^1R^{1'}$;

R^7 and $R^{7'}$ are each independently H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, halo, CN, OR^4, nitro, hydroxylamine, hydroxylamide, amino, NHR^4, NR^2R^5, NR^5R^5, NOR^1, thiol, alkylthio or substituted alkylthio, HOC=O, R^1C=O, R^1(C=O)O, R^1OC=O, R^1NHC=O, NH_2C=O, SO_2R^1, SOR^1, $PO_3R^1R^{1'}$, $R^1R^{1'}NC$=O, C=OSR^1, SO_2R^1, SO_2OR^1, or $SO_2NR^1R^{1'}$, or, wherein A_1 or A_2 contains a group R^7 and W contains a group R^7, said R^7 groups of A_1 or A_2 and W together form a heterocyclic ring;

R^8 and $R^{8'}$ are each independently H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkyalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, nitro, halo, CN, OR^1, amino, NHR^4, NR^2R^5, NOR^1, alkylthio or substituted alkylthio, C=OSR^1, R^1OC=O, R^1C=O, R^1NHC=O, $R^1R^{1'}NC$=O, SO_2OR^1, S=OR^1, SO_2R^1, $PO_3R^1R^{1'}$, or $SO_2NR^1R^{1'}$; and

R^9 and $R^{9'}$ are each independently H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, CN, OH, OR^1, R^1C=O, R^1OC=O, R^1NHC=O, SO_2R^1, SO_2OR^1, or $SO_2NR^1R^{1'}$;

with the provisos that:

(1) when Y' is -O-, Q_1 and Q_2 are hydrogen, Z_1 and Z_2 are O, W' is $-CH_2-CH_2-$, and A_1 and A_2 are CH, then G-L is not phenyl, monosubstituted phenyl or

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phenyl which is substituted with two or more of the following groups: methoxy, halo, NO_2, methyl, CH_3-S-, OH, CO_2H, trifluoromethyl, -C(O)-C_6H_5, NH_2, 4-7-epoxy, hexahydro-1H-isoindole-1,3(2H)dione, or -C(O)-CH_3;

(2) when Y' is -O-, Q_1 and Q_2 are hydrogen, Z_1 and Z_2 are O, W' is CH_2-CH_2, and one of A_1 and A_2 is CH and the other is CR^7, then G-L is not unsubstituted phenyl;

(3) when Y' is -O-, Q_1 and Q_2 are hydrogen, Z_1 and Z_2 are O, W' is CH_2-CH_2, and one of A_1 and A_2 is CH and the other is C-CH_3, then G-L is not phenyl substituted with chloro and/or methyl;

(4) when Y' is -O- or -S-, Q_1 and Q_2 are hydrogen, Z_1 and Z_2 are O, W' is CH_2-CH_2, and one of A_1 and A_2 is CH and the other is CH or C-alkyl, then G-L is not N-substituted piperazine-alkyl- or N-substituted imidazolidine-alkyl-;

(5) when Y' is -O-; Q_1 and Q_2 are hydrogen, Z_1 and Z_2 are O, W' is CH_2-CH_2, and A_1 and A_2 are CH, then G-L is not oxazole or triazole;

(6) when Y' is -O-; Q_1 and Q_2 are hydrogen or methyl, Z_1 and Z_2 are O, W' is CH_2-CH_2, and A_1 and A_2 are CH or C-CH_3, then G-L is not thiazole or substituted thiazole;

(7) when Y' contains a group J' selected from S, S=O, SO_2, NH, NR^7, R^2P=O, R^2P=S, R^2OP=O, R^2NHP=O, OP=OOR^2, OP=$ONHR^2$, OSO_2, NHNH, NHR^6, NR^6NH or N=N, W' is $CR^7R^{7'}$- $CR^7R^{7'}$, and Z_1 and Z_2 are O, then G-L is not unsubstituted phenyl;

(8) when Y is NR^7, W' is unsubstituted or substituted phenyl, and Q_1 and Q_2 are hydrogen, then Z_1 and Z_2 are not O;

(9) when Y' is —O—, Q_1 and Q_2 are hydrogen, Z_1 and Z_2 are O, W' is dihydroisoxazole bearing an optionally substituted phenyl group, and A_1 and A_2 are CH, then G-L is not unsubstituted phenyl or dichlorophenyl;

(10) when Y' is O, Q_1 and Q_2 are hydrogen, Z_1 and Z_2 are O, W' is ethylene oxide, and A_1 and A_2 are CH, then G-L is not methylphenyl or chlorophenyl;

(11) when Y' is NR^7—$CR^7R^{7'}$, W' is CR^8=$CR^{8'}$, Q_1 and Q_2 are hydrogen, A_1 and A_2 are CH, C-CH_3, C-CH_2-C_6H_5 or C-CH_2-CH_3, and Z_1 and Z_2 are O, then G-L is not unsubstituted phenyl, monosubstituted phenyl or methylpyridinyl;

(12) when Y' is $CR^7R^{7'}$—C=O, , W' is NR^9—$CR^7R^{7'}$, Q_1 and Q_2 are hydrogen, A_1 and A_2 are CH, and Z_1 and Z_2 are O, then G-L is not unsubstituted phenyl;
(13) when Y' is $CHR^{7'}$—NR^7 where $R^{7'}$ is unsubstituted phenyl, methoxy or ethoxy and R^7 is unsubstituted phenyl, methyl or -C(O)-C_6H_5, W' is dimethoxyphenylene or unsubstituted phenylene, Z_1 and Z_2 are O, Q_1 and Q_2 are hydrogen, A_1 and A_2 are CH, C-CN, C-C(O)-C_6H_5, or -C(O)-dimethoxyphenyl, then G-L is not unsubstituted phenyl;
(14) the compound of formula Ia is not 6,10-epithio-4H-thieno-[3',4':5,6]cyclooct[1,2-*f*]isoindole-7,9(5H,8H)dione, 8-(3,5-dichlorophenyl)-6,6a,9a,10,11,12,-hexahydro-1,3,6,10-tetramethyl-2,2,13-trioxide, (6R,6aR,9aS,10S);
(15) when Y' is O, W' is –CH_2-CH_2-, Q_1 and Q_2 are methyl, Z_1 and Z_2 are O, and A_1 and A_2 are CH, then G-L is not unsubstituted phenyl, phenyl substituted with methoxy, phenyl-alkyl-, or morpholine-alkyl, nor is the compound bridged to itself through a group L which is alkylene to form a bis compound;
(16) when Y' is –O-, Q_1 and Q_2 are hydrogen, Z_1 and Z_2 are O, W' is $CR^7R^{7'}$-$CR^7R^{7'}$, and A_1 and A_2 are CH, then G-L is not an unsubstituted phenyl group; and
(17) when Y' is –O-, Q_1 and Q_2 are hydrogen, Z_1 and Z_2 are O, W' is cyclopentyl, cyclohexyl, 3-phenyl-2-isoxazoline or $CR^7R^{7'}$-$CR^7R^{7'}$ where R^7 and $R^{7'}$ are each independently defined as Cl, Br, H and 4-butyrolactone and R^7 and $R^{7'}$ are not all simultaneously H, and A_1 and A_2 are CH, then G-L is not an unsubstituted naphthyl ring or a monosubstituted phenyl ring, where said substituent is methoxy, Br, Cl, NO_2, methyl, ethyl, CH_2-phenyl, S-phenyl, or O-phenyl;
or a pharmaceutically acceptable salt, solvate, prodrug or stereoisomer thereof.

2. The compound of Claim 1 wherein
G is an aryl or heterocyclo group, where said group is mono- or polycyclic, and which is optionally substituted at one or more positions;

Z_1 is O, S, NH, or NR^6;

Z_2 is O, S, NH, or NR^6;

A_1 is CR^7 or N;

A_2 is CR^7 or N;

Y' is J-J'-J" where J is $(CR^7R^{7'})n$ and n = 0-3, J' is a bond or O, S, S=O, SO_2, NH, NR^7, $CR^7R^{7'}$, R^2P=O, R^2P=S, R^2OP=O, R^2NHP=O, OP=OOR^2, OP=$ONHR^2$, OSO_2, NHNH, $NHNR^6$, NR^6NH, N=N, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, or heterocyclo or substituted heterocyclo, and J" is $(CR^7R^{7'})n$ and n = 0-3, where Y' is not a bond;

W' is $CR^7R^{7'}$—$CR^7R^{7'}$, $CR^7R^{7'}$—C=O, C=O—C=O, $CR^7R^{7'}$—C=CH_2, C=CH_2—C=CH_2, $CR^7R^{7'}$—C=NR^1, C=NR^1—C=NR^1, NR^9—$CR^7R^{7'}$, N=CR^8, N=N, NR^9—$NR^{9'}$, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, or aryl or substituted aryl, wherein when W' is not NR^9—$CR^7R^{7'}$, N=CR^8, N=N, NR^9—$NR^{9'}$, or heterocyclo or substituted heterocyclo, then J' must be O, S, S=O, SO_2, NH, NR^7, OP=OOR^2, OP=$ONHR^2$, OSO_2, NHNH, $NHNR^6$, NR^6NH, or N=N; or when W' is $CR^7R^{7'}$—$CR^7R^{7'}$, the R^7 and $R^{7'}$ substituents in each occurrence may be taken together to form a substituted or unsubstituted carbocyclic or substituted or unsubstituted heterocyclic ring system which can be formed by any combination of R^7 and $R^{7'}$ attached to the same carbon atom;

Q_1 is H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocycloalkyl or substituted heterocycloalkyl, arylalkyl or substituted arylalkyl, alkynyl or substituted alkynyl, aryl or substituted aryl, heterocyclo or substituted heterocyclo, halo, CN, R^1OC=O, R^4C=O, R^5R^6NC=O, $HOCR^7R^{7'}$, nitro, R^1OCH_2, R^1O, NH_2, or NR^4R^5;

Q_2 is H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocycloalkyl or substituted heterocycloalkyl, arylalkyl or substituted arylalkyl, alkynyl or substituted alkynyl, aryl or substituted aryl, heterocyclo or

substituted heterocyclo, halo, CN, $R^1OC{=}O$, $R^4C{=}O$, $R^5R^6NC{=}O$, $HOCR^7R^{7'}$, nitro, R^1OCH_2, R^1O, NH_2, or NR^4R^5;

L is a bond, $(CR^7R^{7'})n$, NH, NR^5 or $NR^5(CR^7R^{7'})n$, where n = 0-3;

R^1 and $R^{1'}$ are each independently H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkyalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl;

R^2 is alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl;

R^3 and $R^{3'}$ are each independently H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, halo, CN, hydroxylamine, hydroxamide, alkoxy or substituted alkoxy, amino, NR^1R^2, thiol, alkylthio or substituted alkylthio;

R^4 is H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, $R^1C{=}O$, $R^1NHC{=}O$, or $SO_2NR^1R^{1'}$;

R^5 is alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, $R^1C{=}O$, $R^1NHC{=}O$, SO_2R^1, or $SO_2NR^1R^{1'}$;

R^6 is alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, CN, OH, OR^1, $R^1C{=}O$, $R^1NHC{=}O$, SO_2R^1, or $SO_2NR^1R^{1'}$;

R^7 and $R^{7'}$ are each independently H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, halo, CN, OR^4, nitro, hydroxylamine, hydroxylamide, amino, NHR^4, NR^2R^5, NOR^1, thiol, alkylthio or substituted alkylthio, $R^1C{=}O$, $R^1(C{=}O)O$, $R^1OC{=}O$, $R^1NHC{=}O$, SOR^1, $PO_3R^1R^{1'}$, $R^1R^{1'}NC{=}O$, $C{=}OSR^1$, SO_2R^1, or $SO_2NR^1R^{1'}$;

R^8 and $R^{8'}$ are each independently H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkyalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, nitro, halo, CN, OR^1, amino, NHR^4, NR^2R^5, NOR^1, alkylthio or substituted alkylthio, $C{=}OSR^1$, $R^1OC{=}O$, $R^1C{=}O$, $R^1NHC{=}O$, $R^1R^{1'}NC{=}O$, $S{=}OR^1$, SO_2R^1, $PO_3R^1R^{1'}$, or $SO_2NR^1R^{1'}$;

R^9 and $R^{9'}$ are each independently H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, CN, OH, OR^1, $R^1C{=}O$, $R^1OC{=}O$, $R^1NHC{=}O$, or $SO_2NR^1R^{1'}$;

with the provisos (1) to (17) of said formula Ia, and further where (i) when Y' is -O- and W' is $CR^7R^{7'}$—$CR^7R^{7'}$, A_1 and A_2 are not simultaneously CH; and (ii) when L is a bond, G is not an unsubstituted phenyl group;

or a pharmaceutically acceptable salt, solvate, prodrug or stereoisomer thereof.

3. The compound of Claim 1, wherein

G is an aryl or heterocyclo group, where said group is mono- or polycyclic, and which is optionally substituted at one or more positions;

Z_1 is O;

Z_2 is O;

A_1 is CR^7;

A_2 is CR^7;

Y' is J-J'-J'' where J is $(CR^7R^{7'})n$ and n = 0-3, J' is a bond or O, S, S=O, SO_2, NH, NR^7, $CR^7R^{7'}$, $R^2P{=}O$, $R^2P{=}S$, $R^2OP{=}O$, $R^2NHP{=}O$, $OP{=}OOR^2$, $OP{=}ONHR^2$, OSO_2, NHNH, $NHNR^6$, NR^6NH, N=N, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, or heterocyclo or substituted heterocyclo, and J'' is $(CR^7R^{7'})n$ and n = 0-3, where Y' is not a bond;

W' is $CR^7R^{7'}$—$CR^7R^{7'}$, $CR^7R^{7'}$—C=O, C=O—C=O, $CR^7R^{7'}$—$C{=}CH_2$, $C{=}CH_2$—$C{=}CH_2$, $CR^7R^{7'}$—$C{=}NR^1$, $C{=}NR^1$—$C{=}NR^1$, NR^9—$CR^7R^{7'}$, $N{=}CR^8$, N=N, NR^9—$NR^{9'}$, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, or aryl or substituted aryl, wherein when W' is not NR^9—$CR^7R^{7'}$, $N{=}CR^8$, N=N, NR^9—$NR^{9'}$, or heterocyclo or substituted heterocyclo, then J' must be O, S, S=O, SO_2, NH, NR^7, $OP{=}OOR^2$, $OP{=}ONHR^2$, OSO_2, NHNH, $NHNR^6$, NR^6NH, or N=N; or

when W' is $CR^7R^{7'}$—$CR^7R^{7'}$, the R^7 and $R^{7'}$ substituents in each occurrence may be taken together to form a substituted or unsubstituted carbocyclic or substituted or unsubstituted heterocyclic ring system which can be formed by any combination of R^7 and $R^{7'}$ attached to the same carbon atom;

Q_1 is H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocycloalkyl or substituted heterocycloalkyl, arylalkyl or substituted arylalkyl, alkynyl or substituted alkynyl, aryl or substituted aryl, heterocyclo or substituted heterocyclo, halo, CN, $R^4C{=}O$, $R^5R^6NC{=}O$, $HOCR^7R^{7'}$, nitro, R^1OCH_2, R^1O, NH_2, or NR^4R^5;

Q_2 is H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocycloalkyl or substituted heterocycloalkyl, arylalkyl or substituted arylalkyl, alkynyl or substituted alkynyl, aryl or substituted aryl, heterocyclo or substituted heterocyclo, halo, CN, $R^4C{=}O$, $R^5R^6NC{=}O$, $HOCR^7R^{7'}$, nitro, R^1OCH_2, R^1O, NH_2, or NR^4R^5;

L is a bond;

R^1 and $R^{1'}$ are each independently H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkyalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl;

R^2 is alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl;

R^3 and $R^{3'}$ are each independently H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl,

cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, halo, CN, alkoxy or substituted alkoxy, amino, NR^1R^2, alkylthio or substituted alkylthio;

R^4 is H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, $R^1C{=}O$, $R^1NHC{=}O$, or $SO_2NR^1R^{1'}$;

R^5 is alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, $R^1C{=}O$, $R^1NHC{=}O$, SO_2R^1, or $SO_2NR^1R^{1'}$;

R^6 is alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, CN, OH, OR^1, $R^1C{=}O$, $R^1NHC{=}O$, SO_2R^1, or $SO_2NR^1R^{1'}$;

R^7 and $R^{7'}$ are each independently H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted

heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, halo, CN, OR^4, nitro, amino, NHR^4, NR^2R^5, alkylthio or substituted alkylthio, $R^1C{=}O$, $R^1(C{=}O)O$, $R^1NHC{=}O$, SO_2R^1, $R^1R^{1'}NC{=}O$, or $SO_2NR^1R^{1'}$;

R^8 and $R^{8'}$ are each independently H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkyalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, nitro, halo, CN, OR^1, amino, NHR^4, NR^2R^5, alkylthio or substituted alkylthio, $R^1C{=}O$, $R^1NHC{=}O$, $R^1R^{1'}NC{=}O$, SO_2R^1, or $SO_2NR^1R^{1'}$; and

R^9 and $R^{9'}$ are each independently H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, CN, OH, OR^1, $R^1C{=}O$, $R^1NHC{=}O$, or $SO_2NR^1R^{1'}$;

with the provisos (1) to (17) of said formula Ia, and further where (i) when Y' is -O- and W' is $CR^7R^{7'}$—$CR^7R^{7'}$, A_1 and A_2 are not simultaneously CH; and (ii) when L is a bond, G is not an unsubstituted phenyl group;

or a pharmaceutically acceptable salt, solvate, prodrug or stereoisomer thereof.

4. A compound selected from the group consisting of:

(3aα,4β,5β,7β,7aα)-4-[Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-1-isoquinolinecarbonitrile (748D);

[3a*S*-(3aα,4β,5β,7β,7aα)]-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (471Di) or [3a*R*-(3aα,4β,5β,7β,7aα)]-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile (471Dii);

[3a*S*-(3aα,4β,5β,7β,7aα)]-5-[7-[2-[[3-Chloro-5-(trifluoromethyl)-2-pyridinyl]oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile (744);

[3a*S*-(3aα,4β,5β,7β,7aα)]-5-[7-[2-(3-Fluorophenoxy)ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile (745);

[3a*S*-(3aα,4β,5β,7β,7aα)]-5-[7-[2-(1,3-Benzodioxol-5-yloxy)ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile;

[3a*S*-(3aα,4β,5β,7β,7aα)]-5-[7-[2-(4-Fluorophenoxy)ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile;

[3a*S*-(3aα,4β,5β,7β,7aα)]-5-[7-[2-(1,2-Benzisoxazol-3-yloxy)ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile;

[3a*S*-(3aα,4β,5β,7β,7aα)]-5-[7-[2-[(5-Chloro-1,2-benzisoxazol-3-yl)oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile (737);

[3a*S*-(3aα,4β,7β,7aα)]-5-[4-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile (577);

[3a*S*-(3aα,4β,7β,7aα)]-5-[Octahydro-4-methyl-1,3-dioxo-7-[2-[[6-(trifluoromethyl)-4-pyrimidinyl]oxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile (579);

[3a*S*-(3aα,4β,7β,7aα)]-5-[4-[2-[(5-Chloro-1,2-benzisoxazol-3-yl)oxy]ethyl]octahydro-7-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile (581);

[3a*S*-(3aα,4β,7β,7aα)]-5-[Octahydro-4-methyl-7-[2-(5-methyl-2H-1,2,3-benzotriazol-2-yl)ethyl]-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile (589);

[3a*S*-(3aα,4β,5β,7β,7aα)]-5-[Octahydro-5-hydroxy-4-methyl-1,3-dioxo-7-[2-[[6-(trifluoromethyl)-4-pyrimidinyl]oxy]ethyl]-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile (689);

[3a*R*-(3aα,4β,7β,7aα)]-5-[7-[2-[(5-Chloro-2-pyridinyl)oxy]ethyl]octahydro-5-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-8-quinolinecarbonitrile (487);

[3a*R*-(3aα,4β,5β,7β,7aα)]-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-iodobenzonitrile (489Gi);

[3a*S*-(3aα,4β,5β,7β,7aα)]-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-iodobenzonitrile (489Gii);

(3aα,4β,7β,7aα)-4-(Octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-1,2-benzenedicarbonitrile (313);

(3aα,4β,7β,7aα)-2-Methoxy-4-(octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)benzonitrile (328);

(3aα,4β,7β,7aα)-5-(Octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-8-quinolinecarbonitrile (345);

(3aα,4β,7β,7aα)-2-(Methylthio)-4-(octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)benzonitrile (224);

(3aα,4β,7β,7aα)-2-(6-Benzothiazolyl)hexahydro-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione (368);

(3aα,4β,7β,7aα)-7-[Octahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl]-2,1,3-benzoxadiazole-4-carbonitrile (423); and

(3aα,4β,7β,7aα)-2-(2,1,3-Benzoxadiazol-5-yl)hexahydro-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione (480B);

or a pharmaceutically acceptable salt, solvate or prodrug thereof.

5. A compound selected from the group consisting of:

[3a*S*-(3aα,4β,6β,7β,7aα)]-4-(Octahydro-6-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

[3a*R*-(3aα,4β,6β,7β,7aα)]-4-(Octahydro-6-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

[3a*S*-(3aα,4β,5β,6α,7β,7aα)]-4-(Octahydro-5,6-dihydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

[3a*S*-(3aα,4β,5β,7β,7aα)]-5-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-3methyl-2-pyridinecarbonitrile;

[3a*S*-(3aα,4β,5β,7β,7aα)]-2-(2,1,3-Benzoxadiazol-5-yl)hexahydro-5-hydroxy-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione;

[3a*S*-(3aα,4β,5β,7β,7aα)]-5-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-3,4-dimethyl-2-pyridinecarbonitrile;

[3a*R*-(3aα,4β,5β,7β,7aα)]-5-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-3,4-dimethyl-2-pyridinecarbonitrile;

[3a*S*-(3aα,4β,5β,7β,7aα)]-2-(6-Benzothiazolyl)hexahydro-5-hydroxy-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione;

[3a*R*-(3aα,4β,5β,7β,7aα)]-2-(7-Chloro-2,1,3-benzoxadiazol-4-yl)hexahydro-5-hydroxy-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione;

[3a*R*-(3aα,4β,5α,7β,7aα)]-5-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-3-(trifluoromethyl)-2-pyridinecarbonitrile;

[3a*R*-(3aα,4β,5α,7β,7aα)]-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-iodobenzonitrile;

(3aα,4β,5α,6β,7β,7aα)-2-(4-Cyano-3-(trifluoromethyl)phenyl)hexahydro-6-cyano-4,7-dimethyl-1,3-dioxo-4,7-epoxy-1H-isoindole-5-carboxylic acid, methyl ester;

(3aα,4β,7β,7aα)-4-(Octahydro-4,7,8-trimethyl-1,3-dioxo-4,7-imino-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

[3a*R*-(3aα,4β,5β,6α,7β,7aα)]-4-(Octahydro-5,6-dichloro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

[3a*S*-(3aα,4β,5β,6α,7β,7aα)]-4-(Octahydro-5,6-dichloro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

(3aα,4β,7β,7aα)-4-(Octahydro-4,7-dimethyl-1,3,5-trioxo-4,7-epoxy-2H-isoindol-2-yl)-2-iodobenzonitrile;

(3aα,4β,5α,7β,7aα)-4-(Octahydro-5-[[difluoromethyl]oxy]methyl]-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

(3aα,4β,5α,7β,7aα)-4-(Octahydro-5-[[phenylmethoxycarbonyl]amino]-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

(3aα,4β,5α,7β,7aα)-4-(Octahydro-5-[[propyloxycarbonyl]amino]-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

(3aα,4β,5α,7β,7aα)-4-(Octahydro-5-[[[cyclopropylmethyloxy]carbonyl]amino]-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

(3aα,4β,5α,7β,7aα)-4-(Octahydro-5-[[methoxycarbonyl]amino]-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

[3a*R*-(3aα,4β,5β,7β,7aα)]-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2,3-dichlorobenzonitrile;

[3a*R*-(3aα,4β,4aα,5aα,6β,7aα)]-4-(Octahydro-4a-hydroxy-4,6-dimethyl-1,3-dioxo-4,6-epoxycycloprop[f]isoindol-2(1H)-yl)-2-(trifluoromethyl)benzonitrile;

(3aα,4β,5α,7β,7aα)-2-(4-Cyano-3-(trifluoromethyl)phenyl)hexahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-*N*,*N*-dimethyl-1H-isoindole-5-carboxamide;

[3a*R*-(3aα,4β,5β,6β,7β,7aα)]-4-(Octahydro-5-chloro-6-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

[3a*S*-(3aα,4β,5β,6β,7β,7aα)]-4-(Octahydro-5-chloro-6-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

(3aα,4β,5α,7β,7aα)-4-(Octahydro-5-[[[6-(trifluoromethyl)-4-pyrimidinyl]oxy]methyl]-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

(3aα,4β,5α,7β,7aα)-4-(Octahydro-5-[[[5-chloro-2-pyridinyl]oxy]methyl]-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

[3a*R*-(3aα,4β,5α,7β,7aα)]-4-(Octahydro-5-[[[phenylamino]carbonyl]amino]-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

[3a*R*-(3aα,4β,5α,7β,7aα)]-4-(Octahydro-5-[[(1-methylethyloxy)carbonyl]amino]-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-Isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

(3aα,4β,5α,7β,7aα)-4-(Octahydro-5-[[[5-fluoro-4-pyrimidinyl]oxy]methyl]-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-Isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

[3a*R*-(3aα,4β,5α,7β,7aα)]-4-(Octahydro-5-[[ethyloxycarbonyl]amino]-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-Isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

[3a*R*-(3aα,4β,5α,7β,7aα)]-2-(4-Cyano-3-(trifluoromethyl)phenyl)-hexahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-1H-Isoindole-5-carboxylic acid, 4-pyridinylmethyl ester;

[3a*R*-(3aα,4β,5α,7β,7aα)]-4-(Octahydro-5-[[4-pyridinylmethoxycarbonyl]amino]-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-Isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

3aα,4β,5β,7β,7aα)-4-(Octahydro-5-[[[2-methyl-5-(trifluoromethyl)-2H-pyrazol-3-yl]oxy]methyl]-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-Isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

(3aα,4β,5α,7β,7aα)-2-(4-Cyano-3-(trifluoromethyl)phenyl)hexahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-1H-Isoindole-5-carboxylic acid, methyl ester;

[3a*R*-(3aα,4β,5β,7β,7aα)]-4-(Octahydro-5-cyclopropylmethoxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-Isoindol-2-yl)-2-(trifluoromethyl)benzonitril ;

(3aα,4β,5α,7β,7aα)-4-(Octahydro-5-[[((phenylmethyl)amino)carbonyl]oxy]-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-Isoindol-2-yl)-2-(trifluoromethyl)benzonitrile; and

[3a*R*-(3aα,4β,5β,7β,7aα)]-4-(Octahydro-5-cyclopropyloxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-Isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

or a pharmaceutically acceptable salt, solvate or prodrug thereof.

6. A compound selected from the group consisting of:

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[3a*R*-(3aα,4β,5β,7β,7aα)]-5-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-3-(trifluoromethyl)-2-pyridinecarbonitrile;

[3a*S*-(3aα,4β,5β,7β,7aα)]-5-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-3-(trifluoromethyl)-2-pyridinecarbonitrile;

[3a*R*-(3aα,4β,5β,7β,7aα)]-2-(4-Chloro-3-iodophenyl)hexahydro-5-hydroxy-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione;

[3a*S*-(3aα,4β,5β,6α,7β,7aα)]-4-(Octahydro-5,6-dihydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

[3a*R*-(3aα,4β,7β,7aα)]-4-(Octahydro-4,7-dimethyl-1,3,5-trioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

[3a*R*-(3aα,4β,5α,7β,7aα)]-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

[3a*S*-(3aα,4β,5α,7β,7aα)]-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

[3a*S*-(3aα,4β,6β,7β,7aα)]-4-(Octahydro-6-hydroxy-4-methyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

[3a*R*-(3aα,4β,5β,7β,7aα)]-2-(4-Chloro-3-(trifluoromethyl)phenyl)hexahydro-5-hydroxy-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione;

[3a*S*-(3aα,4β,5β,7β,7aα)]-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-iodobenzonitrile;

[3a*R*-(3aα,4β,5β,7β,7aα)]-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-iodobenzonitrile;

[3a*S*-(3aα,4β,5β,7β,7aα)]-2-(4-Chloro-3-(trifluoromethyl)pyridinyl)hexahydro-5-hydroxy-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione;

[3a*R*-(3aα,4β,5β,7β,7aα)]-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-3-methyl-2-(trifluoromethyl)benzonitrile;

[3a*R*-(3aα,4β,5β,7β,7aα)]-4-(Octahydro-5-methoxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

[3a*R*-(3aα,4β,5α,7β,7aα)]-5-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-3-(trifluoromethyl)-2-pyridinecarbonitrile;

[3a*S*-(3aα,4β,5β,7β,7aα)]-4-(Octahydro-5-methoxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

[3a*S*-(3aα,4β,6β,7β,7aα)]-4-(Octahydro-6-fluoro-5,5-dihydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

[3a*R*-(3aα,4β,7β,7aα)]-5-(Octahydro-4,7-dimethyl-1,3,5-trioxo-4,7-epoxy-2H-isoindol-2-yl)-3-(trifluoromethyl)-2-pyridinecarbonitrile;

[3a*S*-(3aα,4β,5β,7β,7aα)]-2-(4-Chloro-2-methyl-3-(trifluoromethyl)phenyl)hexahydro-5-hydroxy-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione;

[3a*R*-(3aα,4β,5β,7β,7aα)]-2-(4-Chloro-2-methyl-3-(trifluoromethyl)phenyl)hexahydro-5-hydroxy-4,7-dimethyl-4,7-epoxy-1H-isoindole-1,3(2H)-dione;

(3aα,4β,6β,7β,7aα)-4-(Octahydro-6-fluoro-5,5-dihydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-iodobenzonitrile;

(3aα,4β,5α,7β,7aα)-2-(4-Cyano-3-(trifluoromethyl)phenyl)-hexahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-1H-isoindole-5-carboxylic acid, methyl ester;

[3a*S*-(3aα,4β,6β,7β,7aα)]-4-(Octahydro-6-fluoro-5,5-dihydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-iodobenzonitrile;

(3aα,4β,5α,7β,7aα)-4-(Octahydro-5-ethylsulfonamido-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

[3a*R*-(3aα,4β,5α,7β,7aα)]-4-(Octahydro-5-[[(4-fluorophenylamino)carbonyl]oxy]-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

[3a*R*-(3aα,4β,5α,7β,7aα)]-4-(Octahydro-5-[[(1-methylethylamino)carbonyl]oxy]-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

[3a*S*-(3aα,4β,5α,7β,7aα)]-4-(Octahydro-5-[[(1-methylethoxy)carbonyl]amino]-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

[3a*R*-(3aα,4β,6β,7β,7aα)]-4-(Octahydro-6-fluoro-5,5-dihydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-iodobenzonitrile;

[3a*R*-(3aα,4β,5α,7β,7aα)]-2-(4-Cyano-3-(trifluoromethyl)phenyl)hexahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-*N*-methyl-*N*-phenyl-1H-isoindole-5-carboxamide;

[3a*R*-(3aα,4β,5β,7β,7aα)]-4-(Octahydro-5-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-chloro-3-methylbenzonitrile;

[3a*R*-(3aα,4β,5α,7β,7aα)]-4-(Octahydro-5-[[ethoxycarbonyl]amino]-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

(3aα,4β,5α,7β,7aα)-4-(Octahydro-5-[[[2-methyl-5-(trifluoromethyl)-2H-pyrazol-3-yl]oxy]methyl]-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

[3a*S*-(3aα,4β,5α,6β,7β,7aα)]-2-(4-Cyano-3-(trifluoromethyl)phenyl)-hexahydro-6-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-1H-isoindole-5-carboxylic acid, methyl ester;

(3aα,4β,5α,7β,7aα)-4-(Octahydro-5-[[[6-(trifluoromethyl)-4-pyrimidinyl]oxy]methyl]-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

[3a*R*-(3aα,4β,5α,7β,7aα)]-4-(Octahydro-5-methoxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

(3aα,4β,5α,7β,7aα)-2-(4-Cyano-3-(trifluoromethyl)phenyl)-hexahydro-4,7-dimethyl-1,3-dioxo-4,7-epoxy-1H-isoindole-5-carbonitrile;

[3a*R*-(3aα,4β,5β,6α,7β,7aα)]-4-(Octahydro-5,6-dihydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-3-methyl-2-(trifluoromethyl)benzonitrile;

[3a*R*-(3aα,4β,5α,7β,7aα)]-4-(Octahydro-5-[[[(cyclopropylmethyl)amino]carbonyl]amino]-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

[3a*R*-(3aα,4β,5α,7β,7aα)]-4-(Octahydro-5-[[(dimethylamino)sulfonyl]amino]-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

(3aα,4β,5α,7β,7aα)-4-(Octahydro-5-benzenesulfonamido-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

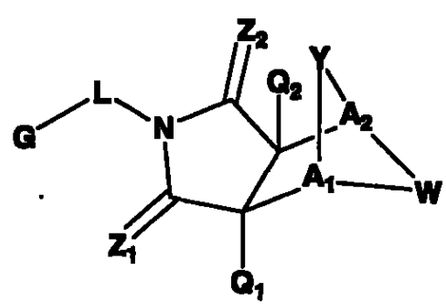
[3a*R*-(3aα,4β,6β,7β,7aα)]-4-(Octahydro-6-fluoro-5,5-dihydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

[3a*R*-(3aα,4β,5α,6β,7β,7aα)]-2-(4-Cyano-3-(trifluoromethyl)phenyl)-hexahydro-6-hydroxy-4,7-dimethyl-1,3-dioxo-4,7-epoxy-1H-isoindole-5-carboxylic acid, methyl ester; and

[3a*R*-(3aα,4β,5α,7β,7aα)]-4-(Octahydro-5-[[(dimethylamino)sulfonyl]amino]-4,7-dimethyl-1,3-dioxo-4,7-epoxy-2H-isoindol-2-yl)-2-(trifluoromethyl)benzonitrile;

or a pharmaceutically acceptable salt, solvate or prodrug thereof.

7. A pharmaceutical composition capable of treating a NHR - associated condition, comprising at least one compound of the following formula I or a pharmaceutically acceptable salt, solvateor prodrug thereof, and a pharmaceutically acceptable carrier:



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wherein the symbols have the following meanings and are, for each occurrence, independently selected:

G is an aryl or heterocyclo group, where said group is mono- or polycyclic, and which is optionally substituted at one or more positions;

Z_1 is O, S, NH, or NR^6;

Z_2 is O, S, NH, or NR^6;

A_1 is CR^7 or N;

A_2 is CR^7 or N;

Y is J-J'-J" where J is $(CR^7R^{7'})n$ and n = 0-3, J' is a bond or O, S, S=O, SO_2, NH, NR^7, C=O, OC=O, NR^1C=O, $CR^7R^{7'}$, $C=CR^8R^{8'}$, R^2P=O, R^2P=S, R^2OP=O, R^2NHP=O, OP=OOR^2, OP=$ONHR^2$, OP=OR^2, OSO_2, $C=NR^7$, NHNH, $NHNR^6$, NR^6NH, N=N, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo or aryl or substituted aryl, and J" is $(CR^7R^{7'})n$ and n = 0-3, where Y is not a bond;

W is $CR^7R^{7'}$—$CR^7R^{7'}$, CR^8=$CR^{8'}$, $CR^7R^{7'}$—C=O, C=O—C=O, $CR^7R^{7'}$—$C=CH_2$, $C=CH_2$—$C=CH_2$, $CR^7R^{7'}$—$C=NR^1$, $C=NR^1$—$C=NR^1$, NR^9—$CR^7R^{7'}$, N=CR^8, N=N, NR^9—$NR^{9'}$, S—$CR^7R^{7'}$, SO—$CR^7R^{7'}$, SO_2—$CR^7R^{7'}$, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, or aryl or substituted aryl, wherein when W is not NR^9—$CR^7R^{7'}$, N=CR^8, N=N, NR^9—$NR^{9'}$, S—$CR^7R^{7'}$, SO—$CR^7R^{7'}$, SO_2—$CR^7R^{7'}$, or heterocyclo or substituted heterocyclo, then J' must be O, S, S=O, SO_2, NH, NR^7, OC=O, NR^1C=O, OP=OOR^2, OP=$ONHR^2$, OSO_2, NHNH, $NHNR^6$, NR^6NH, or N=N; or

when W is $CR^7R^{7'}$—$CR^7R^{7'}$, the R^7 and $R^{7'}$ substituents in each occurrence may be taken together to form a substituted or unsubstituted carbocyclic or substituted or unsubstituted heterocyclic ring system which can be formed by any combination of R^7 and $R^{7'}$ attached to the same carbon atom;

Q_1 is H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocycloalkyl or substituted heterocycloalkyl, arylalkyl or substituted arylalkyl, alkynyl or substituted alkynyl, aryl or substituted aryl, heterocyclo (e.g., heteroaryl) or substituted heterocyclo (e.g., substituted heteroaryl), halo,

CN, $R^1OC{=}O$, $R^4C{=}O$, $R^5R^6NC{=}O$, $HOCR^7R^{7'}$, nitro, R^1OCH_2, R^1O, NH_2, $C{=}OSR^1$, SO_2R^1 or NR^4R^5;

Q_2 is H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocycloalkyl or substituted heterocycloalkyl, arylalkyl or substituted arylalkyl, alkynyl or substituted alkynyl, aryl or substituted aryl, heterocyclo (e.g., heteroaryl) or substituted heterocyclo (e.g., substituted heteroaryl), halo, CN, $R^1OC{=}O$, $R^4C{=}O$, $R^5R^6NC{=}O$, $HOCR^7R^{7'}$, nitro, R^1OCH_2, R^1O, NH_2, $C{=}OSR^1$, SO_2R^1 or NR^4R^5;

L is a bond, $(CR^7R^{7'})n$, NH, NR^5, NH $(CR^7R^{7'})n$, or $NR^5(CR^7R^{7'})n$, where n = 0-3;

R^1 and $R^{1'}$ are each independently H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkyalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl;

R^2 is alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl;

R^3 and $R^{3'}$ are each independently H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, halo, CN, hydroxylamine, hydroxamide, alkoxy or substituted alkoxy, amino, NR^1R^2, thiol, alkylthio or substituted alkylthio;

R^4 is H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, $R^1C{=}O$, $R^1OC{=}O$, $R^1NHC{=}O$, SO_2OR^1, SO_2R^1or $SO_2NR^1R^{1'}$;

R^5 is alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, $R^1C{=}O$, $R^1NHC{=}O$, SO_2R^1, SO_2OR^1, or $SO_2NR^1R^{1'}$;

R^6 is alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, CN, OH, OR^1, $R^1C{=}O$, $R^1NHC{=}O$, SO_2R^1, SO_2OR^1, or $SO_2NR^1R^{1'}$;

R^7 and $R^{7'}$ are each independently H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, halo, CN, OR^4, nitro, hydroxylamine, hydroxylamide, amino, NHR^4, NR^2R^5, NR^5R^5, NOR^1, thiol, alkylthio or substituted alkylthio, $HOC{=}O$, $R^1C{=}O$, $R^1(C{=}O)O$, $R^1OC{=}O$, $R^1NHC{=}O$, $NH_2C{=}O$, SO_2R^1, SOR^1, $PO_3R^1R^{1'}$, $R^1R^{1'}NC{=}O$, $C{=}OSR^1$, SO_2R^1, SO_2OR^1,

or $SO_2NR^1R^{1'}$, or, wherein A_1 or A_2 contains a group R^7 and W contains a group R^7, said R^7 groups of A_1 or A_2 and W together form a heterocyclic ring;

R^8 and $R^{8'}$ are each independently H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkyalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, nitro, halo, CN, OR^1, amino, NHR^4, NR^2R^5, NOR^1, alkylthio or substituted alkylthio, $C{=}OSR^1$, $R^1OC{=}O$, $R^1C{=}O$, $R^1NHC{=}O$, $R^1R^{1'}NC{=}O$, SO_2OR^1, $S{=}OR^1$, SO_2R^1, $PO_3R^1R^{1'}$, or $SO_2NR^1R^{1'}$; and

R^9 and $R^{9'}$ are each independently H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, CN, OH, OR^1, $R^1C{=}O$, $R^1OC{=}O$, $R^1NHC{=}O$, SO_2R^1, SO_2OR^1, or $SO_2NR^1R^{1'}$.

8. A pharmaceutical composition of Claim 7 further comprising another anti-cancer agent.

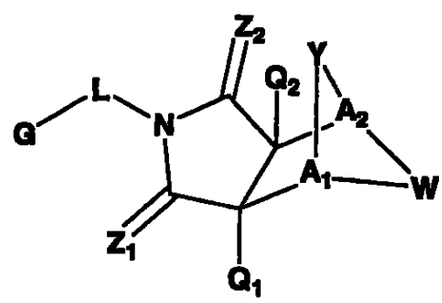
9. A pharmaceutical composition capable of treating a NHR - associated condition, comprising at least one compound as defined in Claim 2 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

10. A pharmaceutical composition of Claim 9 further comprising another anti-cancer agent.

11. A pharmaceutical composition capable of treating a NHR - associated condition, comprising at least one compound as defined in Claim 3 or a pharmaceutically acceptable salt thereof, and a pharmaceutically acceptable carrier.

12. A pharmaceutical composition of Claim 11 further comprising another anti-cancer agent.

13. A method of modulating the function of a nuclear hormone receptor which comprises administering to a mammalian species in need thereof an effective nuclear hormone receptor modulating amount of at least one compound of the following formula I:



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wherein the symbols have the following meanings and are, for each occurrence, independently selected:

G is an aryl or heterocyclo group, where said group is mono- or polycyclic, and which is optionally substituted at one or more positions;

Z_1 is O, S, NH, or NR^6;

Z_2 is O, S, NH, or NR^6;

A_1 is CR^7 or N;

A_2 is CR^7 or N;

Y is J-J'-J" where J is $(CR^7R^{7'})n$ and n = 0-3, J' is a bond or O, S, S=O, SO_2, NH, NR^7, C=O, OC=O, NR^1C=O, $CR^7R^{7'}$, $C=CR^8R^{8'}$, R^2P=O, R^2P=S, R^2OP=O, R^2NHP=O, $OP=OOR^2$, $OP=ONHR^2$, $OP=OR^2$, OSO_2, $C=NR^7$, NHNH,

$NHNR^6$, NR^6NH, N=N, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo or aryl or substituted aryl, and J" is $(CR^7R^{7'})n$ and n = 0-3, where Y is not a bond;

W is $CR^7R^{7'}$—$CR^7R^{7'}$, CR^8=$CR^{8'}$, $CR^7R^{7'}$—C=O, C=O—C=O, $CR^7R^{7'}$—$C=CH_2$, $C=CH_2$—$C=CH_2$, $CR^7R^{7'}$—$C=NR^1$, $C=NR^1$—$C=NR^1$, NR^9—$CR^7R^{7'}$, $N=CR^8$, N=N, NR^9—$NR^{9'}$, S—$CR^7R^{7'}$, SO—$CR^7R^{7'}$, SO_2—$CR^7R^{7'}$, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, or aryl or substituted aryl, wherein when W is not NR^9—$CR^7R^{7'}$, $N=CR^8$, N=N, NR^9—$NR^{9'}$, S—$CR^7R^{7'}$, SO—$CR^7R^{7'}$, SO_2—$CR^7R^{7'}$, or heterocyclo or substituted heterocyclo, then J' must be O, S, S=O, SO_2, NH, NR^7, OC=O, NR^1C=O, $OP=OOR^2$, $OP=ONHR^2$, OSO_2, NHNH, $NHNR^6$, NR^6NH, or N=N; or

when W is $CR^7R^{7'}$—$CR^7R^{7'}$, the R^7 and $R^{7'}$ substituents in each occurrence may be taken together to form a substituted or unsubstituted carbocyclic or substituted or unsubstituted heterocyclic ring system which can be formed by any combination of R^7 and $R^{7'}$ attached to the same carbon atom;

Q_1 is H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocycloalkyl or substituted heterocycloalkyl, arylalkyl or substituted arylalkyl, alkynyl or substituted alkynyl, aryl or substituted aryl, heterocyclo (e.g., heteroaryl) or substituted heterocyclo (e.g., substituted heteroaryl), halo, CN, R^1OC=O, R^4C=O, R^5R^6NC=O, $HOCR^7R^{7'}$, nitro, R^1OCH_2, R^1O, NH_2, $C=OSR^1$, SO_2R^1 or NR^4R^5;

Q_2 is H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocycloalkyl or substituted heterocycloalkyl, arylalkyl or substituted arylalkyl, alkynyl or substituted alkynyl, aryl or substituted aryl, heterocyclo (e.g., heteroaryl) or substituted heterocyclo (e.g., substituted heteroaryl), halo, CN, R^1OC=O, R^4C=O, R^5R^6NC=O, $HOCR^7R^{7'}$, nitro, R^1OCH_2, R^1O, NH_2, $C=OSR^1$, SO_2R^1 or NR^4R^5;

L is a bond, $(CR^7R^{7'})n$, NH, NR^5, NH $(CR^7R^{7'})n$, or $NR^5(CR^7R^{7'})n$, where n = 0-3;

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R^1 and $R^{1'}$ are each independently H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkyalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl;

R^2 is alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl;

R^3 and $R^{3'}$ are each independently H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, halo, CN, hydroxylamine, hydroxamide, alkoxy or substituted alkoxy, amino, NR^1R^2, thiol, alkylthio or substituted alkylthio;

R^4 is H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, $R^1C{=}O$, $R^1OC{=}O$, $R^1NHC{=}O$, SO_2OR^1, SO_2R^1 or $SO_2NR^1R^{1'}$;

R^5 is alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl,

heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, $R^1C{=}O$, $R^1NHC{=}O$, SO_2R^1, SO_2OR^1, or $SO_2NR^1R^{1'}$;

R^6 is alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, CN, OH, OR^1, $R^1C{=}O$, $R^1NHC{=}O$, SO_2R^1, SO_2OR^1, or $SO_2NR^1R^{1'}$;

R^7 and $R^{7'}$ are each independently H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, halo, CN, OR^4, nitro, hydroxylamine, hydroxylamide, amino, NHR^4, NR^2R^5, NR^5R^5, NOR^1, thiol, alkylthio or substituted alkylthio, $HOC{=}O$, $R^1C{=}O$, $R^1(C{=}O)O$, $R^1OC{=}O$, $R^1NHC{=}O$, $NH_2C{=}O$, SO_2R^1, SOR^1, $PO_3R^1R^{1'}$, $R^1R^{1'}NC{=}O$, $C{=}OSR^1$, SO_2R^1, SO_2OR^1, or $SO_2NR^1R^{1'}$, or, wherein A_1 or A_2 contains a group R^7 and W contains a group R^7, said R^7 groups of A_1 or A_2 and W together form a heterocyclic ring;

R^8 and $R^{8'}$ are each independently H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkyalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, nitro, halo, CN, OR^1, amino, NHR^4, NR^2R^5, NOR^1, alkylthio or substituted alkylthio, $C{=}OSR^1$, $R^1OC{=}O$, $R^1C{=}O$, $R^1NHC{=}O$, $R^1R^{1'}NC{=}O$, SO_2OR^1, $S{=}OR^1$, SO_2R^1, $PO_3R^1R^{1'}$, or $SO_2NR^1R^{1'}$; and

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R^9 and $R^{9'}$ are each independently H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, CN, OH, OR^1, $R^1C{=}O$, $R^1OC{=}O$, $R^1NHC{=}O$, SO_2R^1, SO_2OR^1, or $SO_2NR^1R^{1'}$; or a pharmaceutically acceptable salt, solvate, prodrug or stereoisomer thereof.

14. The method of Claim 13 wherein said nuclear hormone receptor is a steroid binding nuclear hormone receptor.

15. The method of Claim 13 wherein said nuclear hormone receptor is the androgen receptor.

16. The method of Claim 13 wherein said nuclear hormone receptor is the estrogen receptor.

17. The method of Claim 13 wherein said nuclear hormone receptor is the progesterone receptor.

18. The method of Claim 13 wherein said nuclear hormone receptor is the glucocorticoid receptor.

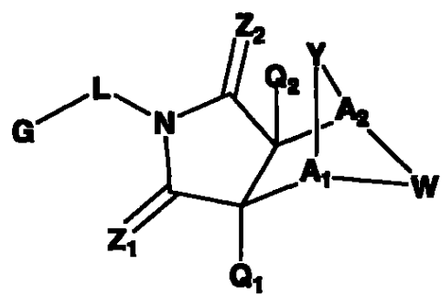
19. The method of Claim 13 wherein said nuclear hormone receptor is the mineralocorticoid receptor.

20. The method of Claim 13 wherein said nuclear hormone receptor is the aldosterone receptor.

21. The method of Claim 13 wherein said nuclear hormone receptor is the RORbeta receptor.

22. The method of Claim 13 wherein said nuclear hormone receptor is the COUP-TF2 receptor.

23. A method for treating a condition or disorder comprising administering to a mammalian species in need thereof a therapeutically effective amount of at least one compound of the following formula:



(I)

or a pharmceutically acceptable salt, solvate, prodrug or stereoisomer thereof, wherein the symbols have the following meanings and are, for each occurrence, independently selected:

G is an aryl or heterocyclo group; where said group is mono- or polycyclic, and which is optionally substituted at one or more positions;

Z_1 is O, S, NH, or NR^6;

Z_2 is O, S, NH, or NR^6;

A_1 is CR^7 or N;

A_2 is CR^7 or N;

Y is J-J'-J" where J is $(CR^7R^{7'})n$ and n = 0-3, J' is a bond or O, S, S=O, SO_2, NH, NR^7, C=O, OC=O, NR^1C=O, $CR^7R^{7'}$, $C=CR^8R^{8'}$, R^2P=O, R^2P=S, R^2OP=O, R^2NHP=O, OP=OOR^2, OP=$ONHR^2$, OP=OR^2, OSO_2, C=NR^7, NHNH, $NHNR^6$, NR^6NH, N=N, cycloalkyl or substituted cycloalkyl, cycloalkenyl or

substituted cycloalkenyl, heterocyclo or substituted heterocyclo or aryl or substituted aryl, and J'' is $(CR^7R^{7'})n$ and n = 0-3, where Y is not a bond;

W is $CR^7R^{7'}$—$CR^7R^{7'}$, CR^8=$CR^{8'}$, $CR^7R^{7'}$—C=O, C=O—C=O, $CR^7R^{7'}$—C=CH_2, C=CH_2—C=CH_2, $CR^7R^{7'}$—C=NR^1, C=NR^1—C=NR^1, NR^9—$CR^7R^{7'}$, N=CR^8, N=N, NR^9—$NR^{9'}$, S—$CR^7R^{7'}$, SO—$CR^7R^{7'}$, SO_2—$CR^7R^{7'}$, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, or aryl or substituted aryl, wherein when W is not NR^9—$CR^7R^{7'}$, N=CR^8, N=N, NR^9—$NR^{9'}$, S—$CR^7R^{7'}$, SO—$CR^7R^{7'}$, SO_2—$CR^7R^{7'}$, or heterocyclo or substituted heterocyclo, then J' must be O, S, S=O, SO_2, NH, NR^7, OC=O, NR^1C=O, OP=OOR^2, OP=ONHR^2, OSO_2, NHNH, $NHNR^6$, NR^6NH, or N=N; or

when W is $CR^7R^{7'}$—$CR^7R^{7'}$, the R^7 and $R^{7'}$ substituents in each occurrence may be taken together to form a substituted or unsubstituted carbocyclic or substituted or unsubstituted heterocyclic ring system which can be formed by any combination of R^7 and $R^{7'}$ attached to the same carbon atom;

Q_1 is H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocycloalkyl or substituted heterocycloalkyl, arylalkyl or substituted arylalkyl, alkynyl or substituted alkynyl, aryl or substituted aryl, heterocyclo (e.g., heteroaryl) or substituted heterocyclo (e.g., substituted heteroaryl), halo, CN, R^1OC=O, R^4C=O, R^5R^6NC=O, HO$CR^7R^{7'}$, nitro, R^1OCH_2, R^1O, NH_2, C=OSR^1, SO_2R^1 or NR^4R^5;

Q_2 is H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocycloalkyl or substituted heterocycloalkyl, arylalkyl or substituted arylalkyl, alkynyl or substituted alkynyl, aryl or substituted aryl, heterocyclo (e.g., heteroaryl) or substituted heterocyclo (e.g., substituted heteroaryl), halo, CN, R^1OC=O, R^4C=O, R^5R^6NC=O, HO$CR^7R^{7'}$, nitro, R^1OCH_2, R^1O, NH_2, C=OSR^1, SO_2R^1 or NR^4R^5;

L is a bond, $(CR^7R^{7'})n$, NH, NR^5, NH $(CR^7R^{7'})n$, or $NR^5(CR^7R^{7'})n$, where n = 0-3;

R^1 and $R^{1'}$ are each independently H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkyalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl;

R^2 is alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl;

R^3 and $R^{3'}$ are each independently H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, halo, CN, hydroxylamine, hydroxamide, alkoxy or substituted alkoxy, amino, NR^1R^2, thiol, alkylthio or substituted alkylthio;

R^4 is H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, $R^1C{=}O$, $R^1OC{=}O$, $R^1NHC{=}O$, SO_2OR^1, SO_2R^1 or $SO_2NR^1R^{1'}$;

R^5 is alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl,

heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, $R^1C{=}O$, $R^1NHC{=}O$, SO_2R^1, SO_2OR^1, or $SO_2NR^1R^{1'}$;

R^6 is alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, CN, OH, OR^1, $R^1C{=}O$, $R^1NHC{=}O$, SO_2R^1, SO_2OR^1, or $SO_2NR^1R^{1'}$;

R^7 and $R^{7'}$ are each independently H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, halo, CN, OR^4, nitro, hydroxylamine, hydroxylamide, amino, NHR^4, NR^2R^5, NR^5R^5, NOR^1, thiol, alkylthio or substituted alkylthio, $HOC{=}O$, $R^1C{=}O$, $R^1(C{=}O)O$, $R^1OC{=}O$, $R^1NHC{=}O$, $NH_2C{=}O$, SO_2R^1, SOR^1, $PO_3R^1R^{1'}$, $R^1R^{1'}NC{=}O$, $C{=}OSR^1$, SO_2R^1, SO_2OR^1, or $SO_2NR^1R^{1'}$, or, wherein A_1 or A_2 contains a group R^7 and W contains a group R^7, said R^7 groups of A_1 or A_2 and W together form a heterocyclic ring;

R^8 and $R^{8'}$ are each independently H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkyalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, nitro, halo, CN, OR^1, amino, NHR^4, NR^2R^5, NOR^1, alkylthio or substituted alkylthio, $C{=}OSR^1$, $R^1OC{=}O$, $R^1C{=}O$, $R^1NHC{=}O$, $R^1R^{1'}NC{=}O$, SO_2OR^1, $S{=}OR^1$, SO_2R^1, $PO_3R^1R^{1'}$, or $SO_2NR^1R^{1'}$; and

R^9 and $R^{9'}$ are each independently H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, CN, OH, OR^1, $R^1C{=}O$, $R^1OC{=}O$, $R^1NHC{=}O$, SO_2R^1, SO_2OR^1, or $SO_2NR^1R^{1'}$;

wherein said condition or disorder is selected from the group consisting of proliferate diseases, cancers, benign prostate hypertrophia, adenomas and neoplasies of the prostate, benign or malignant tumor cells containing the androgen receptor, heart disease, angiogenic conditions or disorders, hirsutism, acne, hyperpilosity, inflammation, immune modulation, seborrhea, endometriosis, polycystic ovary syndrome, androgenic alopecia, hypogonadism, osteoporosis, suppressing spermatogenisis, libido, cachexia, anorexia, inhibition of muscular atrophy in ambulatory patients, androgen supplementation for age related decreased testosterone levels in men, cancers expressing the estrogen receptor, prostate cancer, breast cancer, endometrial cancer, hot flushes, vaginal dryness, menopause, amennoreahea, dysmennoreahea, contraception, pregnancy termination, cancers containing the progesterone receptor, endometriosis, cachexia, menopause, cyclesynchrony, meniginoma, fibroids, labor induction, autoimmune diseases, Alzheimer's disease, psychotic disorders, drug dependence, non-insulin dependent Diabetes Mellitus, dopamine receptor mediated disorders, congestive heart failure, disregulation of cholesterol homeostasis, and attenuating the metabolism of a pharmaceutical agent.

24. A method for preparation of a compound of the following formula XVI, or salt thereof:

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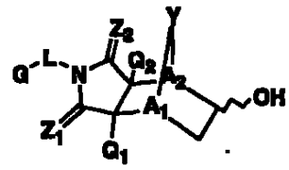


XVI

where

G is an aryl or heterocyclo group, where said group is mono- or polycyclic, and which is optionally substituted at one or more positions;

Z_1 is O, S, NH, or NR^6;

Z_2 is O, S, NH, or NR^6;

A_1 is CR^7 or N;

A_2 is CR^7 or N;

Y' is J-J'-J" where J is $(CR^7R^{7'})n$ and n = 0-3, J' is O, S, S=O, SO_2, NH, NR^7, $OP{=}OOR^2$, OC=O, $NR^1C{=}O$, $OP{=}ONHR^2$, OSO_2, NHNH, $NHNR^6$, NR^6NH, or N=N, and J" is $(CR^7R^{7'})n$ and n = 0-3;

Q_1 is H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocycloalkyl or substituted heterocycloalkyl, arylalkyl or substituted arylalkyl, alkynyl or substituted alkynyl, aryl or substituted aryl, heterocyclo or substituted heterocyclo, halo, CN, $R^1OC{=}O$, $R^4C{=}O$, $R^5R^6NC{=}O$, $HOCR^7R^{7'}$, nitro, R^1OCH_2, R^1O, NH_2, $C{=}OSR^1$, SO_2R^1 or NR^4R^5;

Q_2 is H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocycloalkyl or substituted heterocycloalkyl, arylalkyl or substituted arylalkyl, alkynyl or substituted alkynyl, aryl or substituted aryl, heterocyclo or substituted heterocyclo, halo, CN, $R^1OC{=}O$, $R^4C{=}O$, $R^5R^6NC{=}O$, $HOCR^7R^{7'}$, nitro, R^1OCH_2, R^1O, NH_2, $C{=}OSR^1$, SO_2R^1 or NR^4R^5;

L is a bond, $(CR^7R^{7'})n$, NH, NR^5 or $NR^5(CR^7R^{7'})n$, where n = 0-3;

R^1 and $R^{1'}$ are each independently H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted

heterocyclo, cycloalkylalkyl or substituted cycloalkyalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl;

R^2 is alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl;

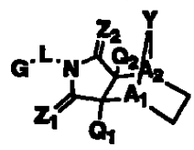
R^4 is H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, $R^1C{=}O$, $R^1NHC{=}O$, SO_2OR^1, SO_2R^1or $SO_2NR^1R^{1'}$;

R^5 is alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, $R^1C{=}O$, $R^1NHC{=}O$, SO_2R^1, SO_2OR^1, or $SO_2NR^1R^{1'}$;

R^6 is alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, CN, OH, OR^1, $R^1C{=}O$, $R^1NHC{=}O$, SO_2R^1, SO_2OR^1, or $SO_2NR^1R^{1'}$; and

R^7 and $R^{7'}$ are each independently H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, halo, CN, OR^4, nitro, hydroxylamine, hydroxylamide, amino, NHR^4, NR^2R^5, NOR^1, thiol, alkylthio or substituted alkylthio, $R^1C{=}O$, $R^1(C{=}O)O$, $R^1OC{=}O$, $R^1NHC{=}O$, SO_2R^1, SOR^1, $PO_3R^1R^{1'}$, $R^1R^{1'}NC{=}O$, $C{=}OSR^1$, SO_2R^1, SO_2OR^1, or $SO_2NR^1R^{1'}$;

comprising the steps of contacting a compound of the following formula XV, or salt thereof:

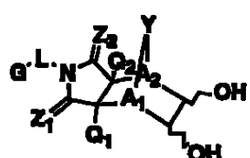


XV

where the symbols are as defined above;

with an enzyme or microorganism capable of catalyzing the hydroxylation of said compound XV to said compound XVI, and effecting said hydroxylation.

25. A method for preparation of a compound of the following formula XVIII, or salt thereof:



XVIII

where

G is an aryl or heterocyclo group, where said group is mono- or polycyclic, and which is optionally substituted at one or more positions;

Z_1 is O, S, NH, or NR^6;

Z_2 is O, S, NH, or NR^6;

A_1 is CR^7 or N;

A_2 is CR^7 or N;

Y' is J-J'-J" where J is $(CR^7R^{7'})n$ and n = 0-3, J' is O, S, S=O, SO_2, NH, NR^7, $OP{=}OOR^2$, OC=O, $NR^1C{=}O$, $OP{=}ONHR^2$, OSO_2, NHNH, $NHNR^6$, NR^6NH, or N=N, and J" is $(CR^7R^{7'})n$ and n = 0-3;

Q_1 is H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocycloalkyl or substituted heterocycloalkyl, arylalkyl or substituted arylalkyl, alkynyl or substituted alkynyl, aryl or substituted aryl, heterocyclo or substituted heterocyclo, halo, CN, $R^1OC{=}O$, $R^4C{=}O$, $R^5R^6NC{=}O$, $HOCR^7R^{7'}$, nitro, R^1OCH_2, R^1O, NH_2, $C{=}OSR^1$, SO_2R^1 or NR^4R^5;

Q_2 is H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocycloalkyl or substituted heterocycloalkyl, arylalkyl or substituted arylalkyl, alkynyl or substituted alkynyl, aryl or substituted aryl, heterocyclo or substituted heterocyclo, halo, CN, $R^1OC{=}O$, $R^4C{=}O$, $R^5R^6NC{=}O$, $HOCR^7R^{7'}$, nitro, R^1OCH_2, R^1O, NH_2, $C{=}OSR^1$, SO_2R^1 or NR^4R^5;

L is a bond, $(CR^7R^{7'})n$, NH, NR^5 or $NR^5(CR^7R^{7'})n$, where n = 0-3;

R^1 and $R^{1'}$ are each independently H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkyalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl;

R^2 is alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl;

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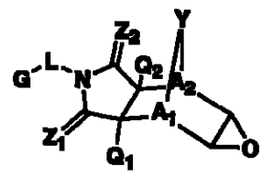
R^4 is H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, $R^1C{=}O$, $R^1NHC{=}O$, SO_2OR^1, SO_2R^1 or $SO_2NR^1R^{1'}$;

R^5 is alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, $R^1C{=}O$, $R^1NHC{=}O$, SO_2R^1, SO_2OR^1, or $SO_2NR^1R^{1'}$;

R^6 is alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, CN, OH, OR^1, $R^1C{=}O$, $R^1NHC{=}O$, SO_2R^1, SO_2OR^1, or $SO_2NR^1R^{1'}$; and

R^7 and $R^{7'}$ are each independently H, alkyl or substituted alkyl, alkenyl or substituted alkenyl, alkynyl or substituted alkynyl, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, heterocyclo or substituted heterocyclo, cycloalkylalkyl or substituted cycloalkylalkyl, cycloalkenylalkyl or substituted cycloalkenylalkyl, heterocycloalkyl or substituted heterocycloalkyl, aryl or substituted aryl, arylalkyl or substituted arylalkyl, halo, CN, OR^4, nitro, hydroxylamine, hydroxylamide, amino, NHR^4, NR^2R^5, NOR^1, thiol, alkylthio or substituted alkylthio, $R^1C{=}O$, $R^1(C{=}O)O$, $R^1OC{=}O$, $R^1NHC{=}O$, SO_2R^1, SOR^1, $PO_3R^1R^{1'}$, $R^1R^{1'}NC{=}O$, $C{=}OSR^1$, SO_2R^1, SO_2OR^1, or $SO_2NR^1R^{1'}$;

comprising the steps of contacting a compound of the following formula XVII, or salt thereof:

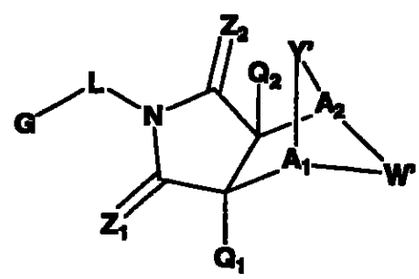


XVII

where the symbols are as defined above;

with an enzyme or microorganism capable of catalyzing the opening of the epoxide ring of compound XVII to form the diol of said compound XVIII, and effecting said ring opening and diol formation.

26. A compound of the following formula Ib:



Ib

where G, Z_1, Z_a, Q_1 and Q_2 are as defined in claim 1;

Y' is J-J'-J" where J is $(CR^7R^{7'})n$ and n = 0-3, J' is a bond or O, S, S=O, SO_2, NH, NR^7, $CR^7R^{7'}$, $R^2P{=}O$, $R^2P{=}S$, $R^2OP{=}O$, $R^2NHP{=}O$, $OP{=}OOR^2$, $OP{=}ONHR^2$, OSO_2, NHNH, $NHNR^6$, NR^6NH, N=N, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl, or heterocyclo or substituted heterocyclo, and J" is $(CR^7R^{7'})n$ and n = 0-3, where Y is not a bond; and

W' is $CR^7R^{7'}$—$CR^7R^{7'}$, $CR^7R^{7'}$—C=O, NR^9—$CR^7R^{7'}$, $N{=}CR^8$, N=N, NR^9—$NR^{9'}$, cycloalkyl or substituted cycloalkyl, cycloalkenyl or substituted cycloalkenyl,

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heterocyclo or substituted heterocyclo, or aryl or substituted aryl, wherein, when W' is not NR^9—$CR^7R^{7'}$, N=CR^8, N=N, NR^9—$NR^{9'}$, or heterocyclo or substituted

heterocyclo, then J' must be O, S, S=O, SO_2, NH, NR^7, OP=OOR^2,

OP=$ONHR^2$, OSO_2, NHNH, $NHNR^6$, NR^6NH, or N=N; or alternatively, Y' is $CR^7R^{7'}$-C=O and W' is NR^9-$CR^7R^{7'}$;

L is a bond; and

A_1 and A_2 are as defined above with the proviso that, when Y' = O and W' = -CH_2-CH_2-, then at least one of A_1 or A_2 is not CH;

with the further provisos (2), (3), (6), (7) and (8) of claim 1;

or a pharmaceutically acceptable salt, solvate, prodrug or stereoisomer thereof.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/40598

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : C07D 491/00; A61K 31/40
US CL : 548/430, 442; 514/411

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. : 548/430, 442; 514/411

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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Database HCAPLUS on STN, AN 1990:440505, WARD, et al. 'Diels-Alder reactions of 2H-thiopyrans'. Tetrahedron Letters, 1990, 31(6), 845-8.	1-26
A	US 6,090,837 A (LAVIELLE et al.) 18 July 2000 (18.07.2000), columns 1-8.	1-26
A,P	US 6,384,050 B1 (TAKEMURA et al.) 07 May 2002 (02.05.2002), columns 1-22.	1-26
A,P	US 6,448,284 B1 (BACH et al.) 10 September 2002 (10.09.2002) columns 1-5.	1-26

☐ 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

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"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 May 2003 (23.05.2003)	30 MAY 2003
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231	Authorized officer Deborah C Hamblin
Facsimile No. (703)305-3230	Telephone No. 703-308-1235

Form PCT/ISA/210 (second sheet) (July 1998)

(12) SOLICITUD INTERNACIONAL PUBLICADA BAJO EL TRATADO DE COOPERACION EN MATERIA DE PATENTES (PCT)

(19) ORGANIZACION MUNDIAL DE LA PROPIEDAD INTELECTUAL
Oficina Internacional

(código de barras)

(43) Fecha de Publicación Internacional:
31 Julio 2003 (31.07.2003)

PCT

(10) Número de Publicación Internacional:
WO 03/062241 A1

(51) Clasificación Internacional de Patentes [7]: C07D 491/00, A61K 31/40

(21) Número de Solicitud Internacional: PCT/ US 02/40598

(22) Fecha de Presentación Internacional: 18 Diciembre 2002 (18.12.2002)

(25) Lenguaje de Presentación: Inglés

(26) Lenguaje de publicación: Inglés

(30) Fecha de Prioridad:
10/025, 116 19 Diciembre 2001 (19.12.2001) US

(71) Solicitante (*todos los estados designados excepto US*): **BRISTOLS-MYERS SQUIBB COMPANY** [US/US]: P.O. Box 4000, Route 206 and Provinceline Road, Princeton, NJ 08543-4000 (US).

(72) Inventor; y
(75) Inventor/Solicitante (*para US solamente*): **SALVATI, Mark. E.** [US/US]: 9 Tracey Drive, Lawrenceville, NJ 08648 (US), **BALOG, James, Aaron** [US/US]; 17 Terrell Road, Lambertville, NJ 08530 (US). **PICKERING, Darcia, A.** [GB/US]; 507 Drexel Avenue, Lawrenceville, NJ 08648 (US). **GIESE, Soren** [DE/US]; 523 Windmere Way, New Hope, PA 18938 (US), **FURA, Aberra** [ET/US]; 15 Creshill Road, Lawrenceville, NJ 08648 (US). **LI, Wenying** [CN/US]; 6221 Town Place, Middletown. CT06457 (US), **PATEL, Ramesh N.** [US/US]; 572 Cabot Hill Road, Bridgewater, NJ 08807 (US). **HANSON, Ronald, L.** [US/US]; 54 Whitewood Drive, Morris Plains NJ 07950 (US). **MITT, Toomas** [US/US]; 1312 Aspen Drive Plainsboro, NJ 08536 (US), **ROBERGE, Jacques** [CA/US]; 57 Southern Way, Princeton, NJ 08540 (US), **CORTE, James. R.** [US/US]: 11 Abelia Court, Lawrenceville, NJ 08648 (US), **SPERGEL, Steven, H,** [US/US]; 1807 Jericho Drive, Warrington, PA 18966 (US), **RAMPULLA, Richard, A.** [US/US]; 5 Fairfax Court, Flemington, NJ 08822 (US), **MISRA, Raj** [US/US]; 12 Eaton Place, Hopewell, NJ 08525 (US), **XIAO, Hai-Yun** [CN/US]; 173 Jonathan Dayton Court, Priceton, NJ 08540 (US).

(74) Agentes: **PEIST, Kenneth et al.**; Bristol-Myers Squibb Company, P.O. Box 4000, Princeton, NJ 08543-4000 (US).

(81) Estados Designados (*nacional*): AE, AG, AL, AM, AT, AU, AZ, BA, BB, BG, BR, BY, BZ, CA, CH, CN, CO, 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, SC, SD, SE, SG, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, VC, VN, YU, ZA, ZM, ZW.

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

Publicada:

- *Con el reporte de búsqueda internacional.*
- *Antes de que expire el tiempo límite para enmendar las reivindicaciones y para republicarse en el evento de la recepción de las enmiendas.*

Para códigos de dos letras y otras abreviaciones, referirse a la "Notas Guías en Códigos y Abreviaciones" que aparece al inicio de cada publicación regular de la Gaceta PCT"

(54) Título: **COMPUESTOS DE SUCCINIMIDA HETEROCÍCLICOS FUSIONADOS Y ANÁLOGOS DE LOS MISMOS, MODULADORES DE LA FUNCIÓN DEL RECEPTOR DE LA HORMONA NUCLEAR.**

(57) Resumen: Se describen compuestos cíclicos fusionados, métodos de uso de tales compuestos en el tratamiento de condiciones asociadas con el receptor de la hormona nuclear tal como el cáncer y padecimientos inmunes, y composiciones farmacéuticas que contienen tales compuestos.

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COMPUEST S DE SUCCINIMIDA HETEROCÍCLICOS FUSIONADOS Y ANÁLOGOS DE LOS MISMOS, MODULADORES DE LA FUNCIÓN DEL RECEPTOR DE LA HORMONA NUCLEAR.

Campo de la Invención.

La presente invención se refiere a compuestos cíclicos fusionados, a métodos de uso de tales compuestos en el tratamiento de condiciones asociadas con el receptor de la hormona nuclear tal como el cáncer, y a composiciones farmacéuticas que contienen tales compuestos.

Antecedentes de la Invención.

Los receptores de la hormona nuclear (NHR's) constituyen una gran super-familia de factores de transcripción específicos de la secuencia y que dependen de los ligandos. Los miembros de esta familia, tienen influencia en la transcripción directamente, a través de enlace específico a los genes objetivo del promotor (Evans, en Science 240: 889-895 (1988)), o indirectamente, por medio de interacciones proteína-proteína con otros factores de transcripción (Jonat et al., Cell 62: 1189-1204 (1990), Schuele et al., Cell 62: 1217-1226 (1990), y Yang-Yen et al., Cell 62: 1205-1215 (1990)). La super-familia del receptor de la hormona nuclear (también conocida en la técnica como "super-familia del receptor de la hormona esteroide/tiroide"), incluye

receptores para una diversidad de ligandos hidrofóbicos, incluyendo cortisol, aldosterona, estrógeno, progesterona, testosterona, vitamina D3, hormona tiroides y ácido retinóico (Evans, 1988, supra). Además de estos receptores convencionales de la hormona nuclear, la super-familia contiene diversas proteínas que no tienen ligandos conocidos, denominados receptores huérfanos de la hormona nuclear (Mangelsdorf et al., Cell 83: 835-839 (1995), O'Malley et al., Mol. Endocrinol. 10: 1293 (1996). Enmark et al., Mol. Endocrinol. 10, 1293-1307 (1996) y Giguere, Endocrin. Rev. 20, 689-725 (1999)). Los receptores convencionales de la hormona nuclear, son generalmente transactivadores en presencia de ligando y pueden ser represores activos o transcripcionalmente inertes en ausencia de un ligando. Algunos de los receptores huérfanos, se comportan como si fueran transcripcionalmente inertes en ausencia de ligandos. Otros, sin embargo, se comportan como activadores o represores constitutivos. Estos receptores de la hormona nuclear huérfanos, están bajo el control de ligandos particulares que no se han identificado, o no necesitan enlazarse a ligandos para ejercer estas actividades.

En común con otros factores de transcripción, los receptores de la hormona nuclear tienen una estructura modular, que comprende tres diferentes dominios: un dominio en la terminal N de tamaño variable, que contiene una función

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de activación transcripcional AF-1, un dominio de enlace de ADN altamente conservado y un dominio de enlace de ligando moderadamente conservado. El dominio de enlace de ligando no solamente es responsable del enlace del ligando específico sino que también contiene una función de activación transcripcional denominada AF-2 y un dominio de dimerización (Wurtz et al., Nature Struc. Biol. 3, 87-94 (1996), Parker et al., Nature Struc. Biol. 3, 113-115 (1996) y Kumar et al., Steroids 64, 310-319 (1999)). Aunque la secuencia global de proteína de estos receptores puede variar significativamente, todos comparten una distribución estructural común, indicativa de la divergencia de un arquetipo ancestral, una homología substancial (especialmente, identidad de secuencia) en el dominio de enlace al ligando.

Los receptores esteroides de la hormona nuclear de enlace (SB-NHR's) comprenden una sub-familia de receptores de la hormona nuclear. Estos receptores se relacionan en que comparten una homología de secuencia más fuerte una con la otra, particularmente en el dominio de enlace del ligando (LBD), que los otros miembros de la super-familia NHR (Evans, 1988, supra) y utilizan todos ligandos basados en esteroides. Algunos ejemplos de esta sub-familia de NHR son el receptor de andrógeno (AR), el receptor de estrógeno (ER), el receptor de progesterona (PR), el receptor glucocorticoide (GR), el receptor mineralocorticoide (MR), el receptor de aldoesterona

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(ALDR) y el receptor esteroide y xenobiótico (SXR) (Evans et al., WO 99/35246). Con base en una homología de secuencia fuerte en el LBD, diversos receptores huérfanos también pueden ser miembros de la sub-familia SB-NHR.

Consistente con la alta homología de secuencia que se encuentra en el LBD para cada uno de los SB-NHR's, los ligandos naturales para cada uno se derivan de un núcleo esteroide común. Los ejemplos de algunos de los ligandos de base esteroide utilizados por los miembros de SB-NHR's, incluyen cortisol, aldosterona, estrógeno, progesterona, testosterona y dihidrotestosterona. La especificidad de un ligando de base esteroide particular para uno de SB-NHR contra otro, se obtiene por la substitución diferencial alrededor del núcleo esteroide. Una alta afinidad enlazada a un SB-NHR particular, acoplado con una especificidad de alto nivel para ese SB-NHR en particular, se puede alcanzar con solamente cambios estructurales menores alrededor del núcleo esteroide (por ejemplo, Waller et al., Toxicol. Appl. Pharmacol. 137, 219-227 (1996) y Mekenyan et al., Environ. Sci. Technol. 31, 3702-3711 (1997), afinidad de enlace para la progesterona hacia el receptor de andrógeno en comparación con la testosterona).

Se han descrito diversos agonistas y antagonistas esteroidales y no esteroidales sintéticamente derivados, para los miembros de la familia SB-NHR. Muchos de estos ligandos

agonistas y antagonistas se usan clínicamente en el hombre para tratar una diversidad de condiciones médicas. El RU486, es un ejemplo de un agonista sintético del PR, que se utiliza como un agente de control de la natalidad (Vegeto et al., Cell 69: 703-713 (1992)), y la flutamida, es un ejemplo de un antagonista del AR, que se utiliza para el tratamiento del cáncer de próstata (Neri et al, Endo. 91, 427-437 (1972)). El Tamoxifen es un ejemplo de un modulador específico de los tejidos de la función ER, que se utiliza en el tratamiento del cáncer de mama (Smigel, J. Natl. Cancer Inst. 90, 647-648 (1998)). El tamoxifen puede funcionar como un antagonista del ER en el tejido del pecho mientras actúa como un agonista del ER en el hueso (Grese et al., Proc. Natl. Acad. Sci. USA 94, 14105-14110 (1997)). Debido a los efectos selectivos del tejido observado en el tamoxifen, este agente y agentes similares se refieren como "agonista parcial" o "antagonista parcial". Además de los ligandos no endógenos derivados sintéticamente, se pueden obtener ligandos no endógenos para NHR de fuentes de alimentos (Regal et al., Proc. Soc. Exp. Biol. Med. 223, 372-378 (2000) y Hempstock et al., J. Med. Food 2, 267-269 (1999)). Los fitoestrógenos flavanoides, son un ejemplo de un ligando no natural para SB-NHR que se obtienen fácilmente de una fuente alimenticia tal como la soya (Quella et al., J. Clin. Oncol. 18, 1068-1074 (2000) y Banz et al., J. Med. Food 2, 271-273 (1999)). La capacidad de

modular la actividad transcripcional del NHR individual por la adición de un ligando de molécula pequeña, los hacen objetivos ideales para el desarrollo de agentes farmacéuticos para una diversidad de estados de enfermedad.

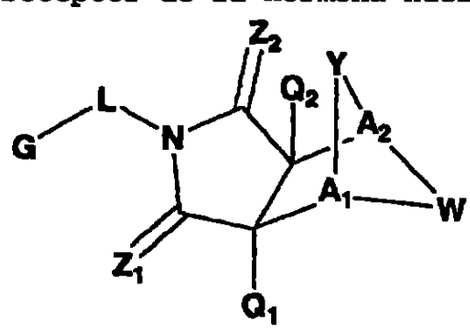
Como se menciona arriba, los ligandos no naturales se pueden preparar sintéticamente por ingeniería para servir como moduladores de la función de NHR. En el caso de SB-NHR, la ingeniería de un ligando no natural puede incluir la identificación de una estructura de núcleo que imite el sistema de núcleo esteroide natural. Esto se puede lograr por una separación por exclusión aleatoria contra diversos SB-NHR, o a través de enfoques dirigidos usando las estructuras de cristal disponibles de una variedad de dominios de enlace de ligando NHR (Bourguet et al., Nature 375, 377-382 (1995), Brzozowski, et al., Nature 389,753-758 (1997), Shiau et al., Cell 95, 927-937 (1998) y Tanenbaum et al., Proc. Natl. Acad. Sci. USA 95,5998-6003 (1998)). La substitución diferencial alrededor de tal núcleo de imitación esteroide, puede suministrar agentes con selectividad para un receptor contra otro. Además, tales modificaciones se pueden emplear para obtener agentes con actividad agonista o antagonista para un NHR-SB particular. La substitución diferencial acerca del núcleo de imitación de esteroides, puede resultar en la formación de una serie de agonistas y antagonistas de alta afinidad con especificidad para, por ejemplo, ER contra PR

contra AR contra GR contra MR. Tal enfoque de substitución diferencial se ha reportado por ejemplo, para los moduladores de base quinolina del NHR esteroide en J. Med. Chem., 41, 623 (1999); WO 9749709; US 5696133; US 5696130; US 5696127; US 5693647; US 5693646; US 5688810; US 5688808 y WO 9619458, todas se incorporan en la presente como referencia.

Los compuestos de la presente invención comprenden un núcleo que sirve como una imitación esteroide, y son útiles como moduladores de la función de los receptores de hormonas nucleares de enlace esteroide, así como otros NHR como se describen a continuación.

Breve Descripción de la Invención.

La presente invención proporciona compuestos cíclicos fusionados de la fórmula I siguiente y sales de los mismos, los compuestos son especialmente útiles como moduladores de la función del receptor de la hormona nuclear:



(I)

Como se usa en la fórmula I, y a través de la especificación, los símbolos tienen los siguientes

significados salvo que se indique lo contrario, y son, cada que se presentan, seleccionados independientemente:

G es un grupo arilo o heterociclo (por ejemplo, heteroarilo), donde el grupo es mono- o policíclico, y el cual está opcionalmente substituido en una o más posiciones, preferiblemente con hidrógeno, alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, halo, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, arilo o arilo substituido, heterociclo o heterociclo substituido, arilalquilo o arilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, CN, $R^1OC{=}O$, $R^1C{=}O$, $R^1C{=}S$, $R^1HNC{=}O$, $R^1R^2NC{=}O$, $HOCR^3R^{3'}$, nitro, R^1OCH_2, R^1O, NH_2, NR^4R^5, SR^1, $S{=}OR^1$, SO_2R^1, SO_2OR^1, $SO_2NR^1R^{1'}$, $(R^1O)(R^{1'}O)P{=}O$, oxo, $(R^1)(R^{1'})P{=}O$, o $(R^{1'})(NHR^1)P{=}O$;

Z_1 es O, S, NH, o NR^6;

Z_2 es O, S, NH, o NR^6;

A_1 es CR^7 o N;

A_2 es CR^7 o N;

Y es J-J'-J" donde J es $(CR^7R^{7'})n$ y n = 0-3, J' es un enlace u O, S, S=O, SO_2, NH, NR^7, C=O, OC=O, $NR^1C{=}O$, $CR^7R^{7'}$, $C{=}CR^8R^{8'}$, $R^2P{=}O$, $R^2P{=}S$, $R^2OP{=}O$, $R^2NHP{=}O$, $OP{=}OOR^2$, $OP{=}ONHR^2$, $OP{=}OR^2$, OSO_2, $C{=}NR^7$, NHNH, $NHNR^6$, NR^6NH, N=N, cicloalquilo o cicloalquilo substituido, cicloalquenilo o

cicloalquenilo substituido, heterociclo o heterociclo substituido o arilo o arilo substituido, y J" es $(CR^7R^{7'})n$ y n = 0-3, donde Y no es un enlace (esto es, si J' es un enlace, entonces en al menos uno de J o J" (cada uno definido como $(CR^7R^{7'})n$), n no es cero);

W es $CR^7CR^{7'}-CR^7R^{7'}$, $CR^8=CR^{8'}$, $CR^7CR^{7'}-C=O$, $C=O-C=O$, $CR^7R^{7'}-C=CH_2$, $C=CH_2-C=CH_2$, $CR^7R^{7'}-C=NR^1$, $C=NR^1-C=NR^1$, $NR^9-CR^7R^{7'}$, $N=CR^8$, $N=N$, $NR^9-NR^{9'}$, $S-CR^7R^{7'}$, $SO-CR^7R^{7'}$, $SO_2-CR^7R^{7'}$, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, o arilo o arilo substituido, en donde cuando W no es $NR^9-CR^7R^{7'}$, $N=CR^8$, $N=N$, $NR^9-NR^{9'}$, $S-CR^7R^{7'}$, $SO-CR^7R^{7'}$, $SO_2-CR^7R^{7'}$, o heterociclo o heterociclo substituido, entonces J' deberá ser O, S, S=O, SO_2, NH, NR^7, OC=O, $NR^1C=O$, $OP=OOR^2$, $OP=ONHR^2$, OSO_2, NHNH, $NHNR^6$, NR^6NH, o N=N; O

cuando W es $CR^7R^{7'}-CR^7R^{7'}$, los substituyentes R^7 y $R^{7'}$ cada que se presentan, pueden tomarse juntos para formar un sistema de anillo heterocíclico substituido o no substituido o carbocíclico substituido o no substituido que puede formarse por cualquier combinación de R^7 y $R^{7'}$ enlazado al mismo átomo de carbono;

Q_1 es H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, cicloalquilo o cicloalquilo substituido,

cicloalquenilo o cicloalquenilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilalquilo o arilalquilo substituido, alquinilo o alquinilo substituido, arilo o arilo substituido, heterociclo (por ejemplo, heteroarilo) o heterociclo substituido (por ejemplo, heteroarilo substituido), halo, CN, $R^1OC{=}O$, $R^4C{=}O$, $R^5R^6NC{=}O$, $HOCR^7R^{7'}$, nitro, R^1OCH_2, R^1O, NH_2, $C{=}OSR^1$, SO_2R^1 o NR^4R^5;

Q_2 es H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilalquilo o arilalquilo substituido, alquinilo o alquinilo substituido, arilo o arilo substituido, heterociclo (por ejemplo, heteroarilo) o heterociclo substituido (por ejemplo, heteroarilo substituido), halo, CN, $R^1OC{=}O$, $R^4C{=}O$, $R^5R^6NC{=}O$, $HOCR^7R^{7'}$, nitro, R^1OCH_2, R^1O, NH_2, $C{=}OSR^1$, SO_2R^1, o NR^4R^5;

L es un enlace, $(CR^7R^{7'})n$, NH, NR^5, $NH(CR^7R^{7'})n$, o $NR^5(CR^7R^{7'})n$, donde n = 0-3;

R^1 y $R^{1'}$ son cada uno independientemente H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo

substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido;

R^2 es alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido;

R^3 y $R^{3'}$ son cada uno independientemente H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido halo, CN, hidroxilamina,

hidroxamida, alcoxi o alcoxi substituido, amino, NR^1R^2, tiol, alquiltio o alquiltio substituido;

R^4 es H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido $R^1C{=}O$, $R^1OC{=}O$, $R^1NHC{=}O$, SO_2OR^1, SO_2R^1 o $SO_2NR^1R^{1'}$;

R^5 es alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido $R^1C{=}O$, $R^1NHC{=}O$, SO_2R^1, SO_2OR^1, o $SO_2NR^1R^{1'}$;

R^6 es alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo

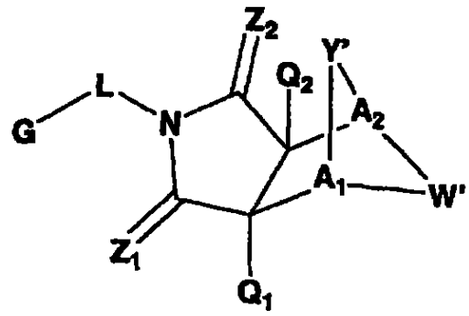
o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido, CN, OH, OR^1, $R^1C{=}O$, $R^1NHC{=}O$, SO_2R^1, SO_2OR^1, o $SO_2NR^1R^{1'}$;

R^7 y $R^{7'}$ son cada uno independientemente H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido, halo, CN, OR^4, nitro, hidroxilamina, hidroxilamida, amino, NHR^4, NR^2R^5, NR^5R^5, NOR^1, tiol, alquiltio o alquiltio substituido, $HOC{=}O$, $R^1C{=}O$, $R^1(C{=}O)O$, $R^1OC{=}O$, $R^1NHC{=}O$, $NH_2C{=}O$, SO_2R^1, SOR^1, $PO_3R^1R^{1'}$, $R^1R^{1'}NC{=}O$, $C{=}OSR^1$, SO_2R^1, SO_2OR^1, o $SO_2NR^1R^{1'}$, o, en donde A_1 o A_2 contiene un grupo R^7 y W contiene un grupo R^7, los grupos R^7 de A_1 o A_2 y W forman juntos un anillo heterocíclico;

R^8 y $R^{8'}$ son cada uno independientemente H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido, nitro, halo, CN, OR^1, amino, NHR^4, NR^2R^5, NOR^1, alquiltio o alquiltio substituido, $C{=}OSR^1$, $R^1OC{=}O$, $R^1C{=}O$, $R^1NHC{=}O$, $R^1R^{1'}NC{=}O$, SO_2OR^1, $S{=}OR^1$, SO_2R^1, $PO_3R^1R^{1'}$, o $SO_2NR^1R^{1'}$; y

R^9 y $R^{9'}$ son cada uno independientemente H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido CN, OH, OR^1, $R^1C{=}O$, $R^1OC{=}O$, $R^1NHC{=}O$, SO_2R^1, SO_2OR^1, o $SO_2NR^1R^{1'}$.

Los compuestos dentro de la fórmula I son novedosos, un subgénero preferido del cual es la siguiente fórmula Ia:



(Ia)

donde G, L, Z_1, Z_2, A_1, A_2, Q_1 y Q_2 son como se define arriba;

Y' es J-J'-J" donde J es $(CR^7R^{7'})n$ y n = 0-3, J' es un enlace u O, S, S=O, SO_2, NH, NR^7, $CR^7R^{7'}$, $R^2P=O$, $R^2P=S$, $R^2OP=O$, $R^2NHP=O$, $OP=OOR^2$, $OP=ONHR^2$, OSO_2, NHNH, $NHNR^6$, NR^6NH, N=N, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, o heterociclo o heterociclo substituido, y J" es $(CR^7R^{7'})n$ y n = 0-3, donde Y no es un enlace; y

W' es $CR^7R^{7'}$—$CR^7R^{7'}$, $CR^7R^{7'}$—C=O, C=O—C=O, $CR^7R^{7'}$—$C=CH_2$, $C=CH_2$—$C=CH_2$, $CR^7R^{7'}$—$C=NR^1$, $C=NR^1$—$C=NR^1$, NR^9—$CR^7R^{7'}$, $N=CR^8$, N=N, NR^9—$NR^{9'}$, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, o arilo o arilo substituido, en donde, cuando W' no es NR^9—$CR^7R^{7'}$, $N=CR^8$, N=N, NR^9—$NR^{9'}$, o heterociclo o heterociclo substituido,

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entonces J' deberá ser O, S, S=O, SO_2, NH, NR^7, $OP=OOR^2$, $OP=ONHR^2$, OSO_2, NHNH, $NHNR^6$, NR^6NH, o N=N; o

cuando W es $CR^7R^{7'}$—$CR^7R^{7'}$, los substituyentes cada que se presentan, pueden tomarse juntos para formar un sistema de anillo heterocíclico substituido o no substituido o carbocíclico substituido o no substituido que puede formarse por cualquier combinación de R^7 y $R^{7'}$ enlazado al mismo átomo de carbono; o alternativamente

Y' es $NR^7R^{7'}$—$CR^7R^{7'}$ y W' es $CR^8=R^{8'}$; o, alternativamente,

Y' es $CR^7R^{7'}$—C=O y W es NR^9—$CR^7R^{7'}$;

donde R^2, R^6, R^7, $R^{7'}$, R^8, R^9 y $R^{9'}$ son como se define arriba y con la condición de que

(1) cuando Y' es -O-, Q_1 y Q_2 son hidrógeno, Z_1 y Z_2 son O, W' es $-CH_2-CH_2-$, y A_1 y A_2 son CH, entonces G-L no es fenilo, fenilo monosubstituido o fenilo que está substituido con dos o más de los siguientes grupos: metoxi, halo, NO_2, metilo, CH_3-S-, OH, CO_2H, trifluorometilo, $-C(O)-C_6H_5$, NH_2, 4-7-epoxi, hexahidro-1H-isoindol-1,3(2H)diona, o $-C(O)-CH_3$;

(2) cuando Y' es -O-, Q_1 y Q_2 son hidrógeno, Z_1 y Z_2 son O, W' es CH_2-CH_2, y uno de A_1 y A_2 es CH y el otro es CR^7, entonces G-L no es fenilo insubstituido;

(3) cuando Y' es -O-, Q_1 y Q_2 son hidrógeno, Z_1 y Z_2 son O, W' es CH_2-CH_2, y uno de A_1 y A_2 es CH y el otro es C-

CH_3, entonces G-L no es fenilo substituido con cloro y/o metilo;

(4) cuando Y' es -O- o -S-, Q_1 y Q_2 son hidrógeno, Z_1 y Z_2 son O, W' es CH_2-CH_2, y uno de A_1 y A_2 es CH y el otro es CH o C-alquilo, entonces G-L no es piperazin-alquilo N-substituido o imidazolidin-alquilo N-substituido;

(5) cuando Y' es -O-; Q_1 y Q_2 son hidrógeno, Z_1 y Z_2 son O, W' es CH_2-CH_2, y A_1 y A_2 son CH, entonces G-L no es oxazol o triazol;

(6) cuando Y' es -O-; Q_1 y Q_2 son hidrógeno o metilo, Z_1 y Z_2 son O, W' es CH_2-CH_2, y A_1 y A_2 son CH o C-CH_3, entonces G-L no es tiazol o tiazol substituido (además, tales compuestos donde G-L es tiadiazol opcionalmente substituido o tiazol parcialmente saturado se remueven opcionalmente por la condición donde A_1 y A_2 ambos son CH);

(7) cuando Y' contiene un grupo J' seleccionado de S, S=O, SO_2, NH, NR^7, R^2P=O, R^2P=S, R^2OP=O, R^2NHP=O, OP=OOR^2, OP=$ONHR^2$, OSO_2, NHNH, NHR^6, NR^6NH o N=N, W' es $CR^7R^{7'}$-$CR^7R^{7'}$, y Z_1 y Z_2 son O, entonces G-L no es fenilo insubstituido;

(8) cuando Y' es NR^7, W' es fenilo insubstituido o substituido, y Q_1 y Q^2 son hidrógeno, entonces Z_1 y Z_2 no son O;

(9) cuando Y' es -O-, Q_1 y Q_2 son hidrógeno, Z_1 y Z_2 son O, W' es dihidroisoxazol que porta un grupo fenilo opcionalmente substituido, y A_1 y A_2 son CH, entonces G-L no es fenilo insubstituido o diclorofenilo;

(10) cuando Y' es O, Q_1 y Q_2 son hidrógeno, Z_1 y Z_2 son O, W' es óxido de etileno, y A_1 y A_2 son CH, entonces G-L no es metilfenilo o clorofenilo;

(11) cuando Y' es NR^7—$CR^7R^{7'}$, W' es CR^8=$CR^{8'}$, Q_1 y Q_2 son hidrógeno, A_1 y A_2 son CH, C-CH_3, C-CH_2-C_6H_5 o C-CH_2-CH_3, y Z_1 y Z_2 son O, entonces G-L no es fenilo insubstituido, fenilo monosubstituido o metilpiridinilo;

(12) cuando Y' es $CR^7R^{7'}$—C=O, W' es NR^9—$CR^7R^{7'}$, Q_1 y Q_2 son hidrógeno, A_1 y A_2 son CH, y Z_1 y Z_2 son O, entonces G-L no es fenilo insubstituido;

(13) cuando Y' es $CHR^{7'}$—NR^7 donde $R^{7'}$ es fenilo insubstituido, metoxi o etoxi y R^7 es fenilo insubstituido, metilo o -C(O)-C_6H_5, W' es dimetoxifenileno o fenileno insubstituido, Z_1 y Z_2 son O, Q_1 y Q_2 son hidrógeno, y A_1 y A_2 son CH, C-CN, C-C(O)-C_6H_5, o -C(O)-dimetoxifenilo, entonces G-L no es fenilo insubstituido;

(14) el compuesto de la fórmula Ia no es 6,10-epitio-4H-tieno-[3',4':5,6]ciclooct[1,2-f]isoindol-7,9(5H,8H)-

diona, 8-(3,5-diclorofenil)-6,6a,9a,10,11,12,-hexahidro-1,3,6,10-tetrametil-2,2,13-trióxido, (6R,6aR,9aS,10S);

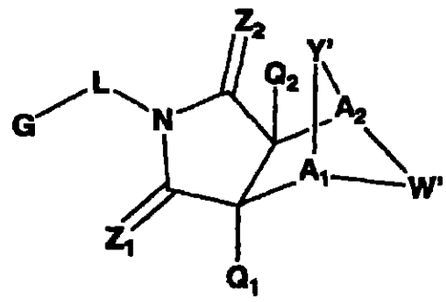
(15) cuando Y' es O, W' es $-CH_2-CH_2-$, Q_1 y Q_2 son metilo, Z_1 y Z_2 son O, y A_1 y A_2 son CH, entonces G-L no es fenilo insubstituido, fenilo substituido con metoxi, fenil-alquilo, o morfolin-alquilo, ni es el compuesto conectado a sí mismo a través de un grupo L que es alquileno para formar un compuesto bis;

(16) cuando Y' es -O-, Q_1 y Q_2 son hidrógeno, Z_1 y Z_2 son O, W' es $CR^7R^{7'}$—$CR^7R^{7'}$, y A_1 y A_2 son CH, entonces G-L no es un grupo fenilo insubstituido; y

(17) cuando Y' es -O-, Q_1 y Q_2 son hidrógeno, Z_1 y Z_2 son O, W' es ciclopentilo, ciclohexilo, 3-fenil-2-isoxazolina o $CR^7R^{7'}$—$CR^7R^{7'}$ donde R^7 y $R^{7'}$ son cada uno independientemente definidos como Cl, Br, H y 4-butirolactona y R^7 y $R^{7'}$ no son todos simultáneamente H, y A_1 y A_2 son CH, entonces G-L no es un anillo naftilo insubstituido o un anillo fenilo monosubstituido, donde el substituyente es metoxi, Br, Cl, NO_2, metilo, etilo, CH_2-fenilo, S-fenilo, u O-fenilo.

Preferiblemente, los compuestos de la fórmula I son monoméricos, y no están comprendidos dentro de otros oligómeros o polímeros.

Otro subgénero preferido novedoso es el de la siguiente fórmula Ib:



Ib

donde G, Z_1, Z_2, Q_1 y Q_2 son como se define arriba;

Y' es J-J'-J" donde J es $(CR^7R^{7'})n$ y n = 0-3, J' es un enlace u O, S, S=O, SO_2, NH, NR^7, $CR^7R^{7'}$, $R^2P=O$, $R^2P=S$, $R^2OP=O$, $R^2NHP=O$, $OP=OOR^2$, $OP=ONHR^2$, OSO_2, NHNH, $NHNR^6$, NR^6NH, N=N, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, o heterociclo o heterociclo substituido, y J" es $(CR^7R^{7'})n$ y n = 0-3, donde Y no es un enlace; y

W' es $CR^7R^{7'}$—$CR^7R^{7'}$, $CR^7R^{7'}$—C=O, C=O—C=O, $CR^7R^{7'}$—$C=CH_2$, $C=CH_2$—$C=CH_2$, $CR^7R^{7'}$—$C=NR^1$, $C=NR^1$—$C=NR^1$, NR^9—$CR^7R^{7'}$, $N=CR^8$, N=N, NR^9—$NR^{9'}$, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, o arilo o arilo substituido, en donde, cuando W' no es NR^9—$CR^7R^{7'}$, $N=CR^8$, N=N, NR^9—$NR^{9'}$, o heterociclo o heterociclo substituido,

entonces J' deberá ser O, S, S=O, SO_2, NH, NR^7, $OP=OOR^2$, $OP=ONHR^2$, OSO_2, NHNH, $NHNR^6$, NR^6NH, o N=N; o

cuando W es $CR^7R^{7'}-CR^7R^{7'}$, los substituyentes cada que se presentan, pueden tomarse juntos para formar un sistema de anillo heterocíclico substituido o no substituido o carbocíclico substituido o no substituido que puede formarse por cualquier combinación de R^7 y $R^{7'}$ enlazado al mismo átomo de carbono; o alternativamente

Y' es $CR^7R^{7'}$-C=O y W' es NR^9-$CR^7R^{7'}$;

L es un enlace; y

A_1 y A_2 son como se define arriba, especialmente donde A_1 y/o A_2 son alquilo o alquilo opcionalmente substituido (se prefiere que tales substituyentes opcionales sean uno o más grupos V^1 definidos a continuación), con la condición de que, cuando Y' = O y W' = $-CH_2-CH_2-$, entonces al menos uno de A_1 o A_2 no es CH;

con las estipulaciones adicionales (2), (3), (6), (7) y (8) de arriba.

Los compuestos de la fórmula I y sales de los mismos comprenden un núcleo que puede servir como un esteroide mimético (y no requiere la presencia de una estructura (por ejemplo análogo de ciclopentanoperhidrofenantreno) tipo esteroide).

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Descripción Adicional de la Invención

Las siguientes son definiciones de los términos usados en la presente especificación. La definición inicial proporcionada para un grupo o término en la presente, aplica a tal grupo o término a través de la presente especificación individualmente o como parte de otro grupo, salvo que se indique lo contrario.

Los términos "alquilo" y "alq" se refieren a un radical alcano de cadena recta o ramificada (hidrocarburo) que contiene desde 1 hasta 12 átomos de carbono, preferiblemente 1 hasta 6 átomos de carbono. Ejemplarmente tales grupos incluyen, pero no se limitan a, metilo, etilo, propilo, isopropilo, n-butilo, t-butilo, isobutilo, pentilo, hexilo, isohexilo, heptilo, 4,4-dimetilpentilo, octilo, 2,2,4-trimetilpentilo, nonilo, decilo, undecilo, dodecilo, y similares. "Alquilo substituido" se refiere a un grupo alquilo substituido con uno o más substituyentes, preferiblemente 1 hasta 4 substituyentes, en cualquier punto de enlace disponible. Los substituyentes ejemplares incluyen, pero no se limitan a, uno o más de los siguientes grupos: halo (por ejemplo, un substituyente halo sencillo o substituyentes halo múltiples que forman, en el último caso, grupos tales como un grupo perfluoroalquilo o un grupo alquilo que porta Cl_3 o CF_3), alcoxi, alquiltio, hidroxi, carboxi (esto es, -COOH), alcoxicarbonilo, alquilcarboniloxi,

amino (esto es, $-NH_2$), carbamoilo o carbomoilo substituido, carbamato o carbamato substituido, urea o urea substituida, amidinilo o amidinilo substituido, tiol (esto es, -SH), arilo, heterociclo, cicloalquilo, heterocicloalquilo, -S-arilo, -S-heterociclo, -S=O-arilo, -S=O-heterociclo, arilalquilo-O-, $-S(O)_2$-arilo, $-S(O)_2$-heterociclo, $-NHS(O)_2$-arilo, $-NHS(O)_2$-heterociclo, $-NHS(O)_2NH$-arilo, $-NHS(O)_2NH$-heterociclo, $-P(O)_2$-arilo, $-P(O)_2$-heterociclo, $-NHP(O)_2$-arilo, $-NHP(O)_2$-heterociclo, $-NHP(O)_2NH$-arilo, $-NHP(O)_2NH$-heterociclo, -O-arilo, -O-heterociclo, -NH-arilo, -NH-heterociclo, -NHC=O-arilo, -NHC=O-alquilo, -NHC=O-heterociclo, -OC=O-arilo, -OC=O-heterociclo, -NHC=ONH-arilo, -NHC=ONH-heterociclo, -OC=OO-arilo, -OC=OO-heterociclo, -OC=ONH-arilo, -OC=ONH-heterociclo, -NHC=OO-arilo, -NHC=OO-heterociclo, -NHC=OO-alquilo, -C=ONH-arilo, -C=ONH-heterociclo, -C=OO-arilo, -C=OO-heterociclo, -N(alquilo)$S(O)_2$-arilo, -N(alquilo)$S(O)_2$-heterociclo, -N(alquilo)$S(O)_2NH$-arilo, -N(alquilo)$S(O)_2NH$-heterociclo, -N(alquilo)$P(O)_2$-arilo, -N(alquilo)$P(O)_2$-heterociclo, -N(alquilo)$P(O)_2NH$-arilo, -N(alquilo)$P(O)_2NH$-heterociclo, -N(alquilo)-arilo, -N(alquilo)-heterociclo, -N(alquilo)C=O-arilo, -N(alquilo)C=O-heterociclo, -N(alquilo)C=ONH-arilo, -N(alquilo)C=ONH-heterociclo, -OC=ON(alquilo)-arilo, -OC=ON(alquilo)-heterociclo, -N(alquilo)C=OO-arilo, -N(alquilo)C=OO-heterociclo, -C=ON(alquilo)-arilo, -

C=ON(alquilo)-heterociclo, -NHS(O)$_2$N(alquilo)-arilo, -NHS(O)$_2$N(alquilo)-heterociclo, -NHP(O)$_2$N(alquilo)-arilo, NHP(O)$_2$N(alquilo)-heterociclo, -NHC=ON(alquilo)-arilo, -NHC=ON(alquilo)-heterociclo, -N(alquilo)S(O)$_2$N(alquilo)-arilo, -N(alquilo)S(O)$_2$N(alquilo)-heterociclo, -N(alquilo)P(O)$_2$N(alquilo)-arilo, -N(alquilo)P(O)$_2$N(alquilo)-heterociclo, -N(alquilo)C=ON(alquilo)-arilo, y -N(alquilo)C=ON(alquilo)-heterociclo. En los substituyentes ejemplares arriba mencionados, en cada caso, los grupos tales como "alquilo", "arilo" y "heterociclo" pueden por sí mismos estar opcionalmente substituidos; por ejemplo, "alquilo" en el grupo "NCH=OO-alquilo" mencionado arriba, puede estar opcionalmente substituido de tal manera que tanto "NHC=OO-alquilo" como "NHC=OO-alquilo substituido" son substituyentes ejemplares. Los substituyentes alquilo ejemplares también incluyen grupos tales como "T" y "T-R^{12}" (que se definen a continuación), especialmente para grupos alquilo substituido dentro de A_1 o A_2.

El término "alquenilo" se refiere a un radical hidrocarburo de cadena recta o ramificada que contiene desde 2 hasta 12 átomos de carbono y al menos un enlace doble carbono-carbono. Ejemplarmente, tales grupos incluyen etenilo o alilo. "Alquenilo substituido" se refiere a un grupo alquenilo substituido con uno o más substituyentes, preferiblemente 1 hasta 4 substituyentes, en cualquier punto

de enlace disponible. Los substituyentes ejemplares incluyen, pero no se limitan a, alquilo o alquilo substituido, así como aquellos grupos mencionados arriba como substituyentes alquilo ejemplares.

El término "alquinilo" se refiere a un radical hidrocarburo de cadena recta o ramificada que contiene desde 2 hasta 12 átomos de carbono y al menos un enlace triple carbono a carbono. Ejemplarmente, tales grupos incluyen etinilo. "Alquinilo substituido" se refiere a un grupo alquinilo substituido con uno o más substituyentes, preferiblemente 1 hasta 4 substituyentes, en cualquier punto de enlace disponible. Los substituyentes ejemplares incluyen, pero no se limitan a, alquilo o alquilo substituido, así como aquellos grupos mencionados arriba como substituyentes alquilo ejemplares.

El término "cicloalquilo" se refiere a un grupo hidrocarburo cíclico completamente saturado que contiene desde 1 hasta 4 anillos y 3 hasta 8 carbonos por anillo. Ejemplarmente, tales grupos incluyen ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, etc. "Cicloalquilo substituido" se refiere a un grupo cicloalquilo substituido con uno o más substituyentes, preferiblemente 1 hasta 4 substituyentes, en cualquier punto de enlace disponible. Los substituyentes ejemplares incluyen, pero no se limitan a, nitro, ciano, alquilo o alquilo substituido, así como

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aquellos grupos mencionados arriba como substituyentes alquilo ejemplares, y como se mencionó previamente como substituyentes arilo preferidos en la definición para G. Los substituyentes ejemplares también incluyen substituyentes cíclicos fusionados o enlazados a espiro, especialmente cicloalquenilo o cicloalquenilo substituido.

El término "cicloalquenilo" se refiere a un grupo hidrocarburo cíclico parcialmente insaturado que contiene 1 hasta 4 anillos y 3 hasta 8 carbonos por anillo. Ejemplarmente, tales grupos incluyen ciclobutenilo, ciclopentenilo, ciclohexenilo, etc. "Cicloalquenilo substituido" se refiere a un grupo cicloalquenilo substituido con uno o más substituyentes, preferiblemente 1 hasta 4 substituyentes, en cualquier punto de enlace disponible. Los substituyentes ejemplares incluyen, pero no se limitan a, nitro, ciano, alquilo o alquilo substituido, así como aquellos grupos mencionados arriba como substituyentes alquilo ejemplares, y como se mencionó previamente como substituyentes arilo preferidos en la definición para G. Los substituyentes ejemplares también incluyen substituyentes cíclicos enlazados o fusionados a espiro, especialmente cicloalquilo o cicloalquilo substituido.

Los términos "alcoxi" o "alquiltio" se refieren a un grupo alquilo como se describe arriba enlazado a través de un enlace oxígeno (-O-) o un enlace azufre (-S-),

respectivamente. Los términos "alcoxi substituido" o "alquiltio substituido" se refieren a un grupo alquilo substituido como se describe arriba enlazado a través de un enlace oxígeno o azufre, respectivamente.

El término "alcoxicarbonilo" se refiere a un grupo alcoxi enlazado a través de un grupo carbonilo.

El término "alquilcarbonilo" se refiere a un grupo alquilo enlazado a través de un grupo carbonilo. El término "alquilcarboniloxi" se refiere a un grupo alquilcarbonilo enlazado a través de un enlace oxígeno.

Los términos "arilalquilo", "arilalquilo substituido", "cicloalquilalquilo", "cicloalquilalquilo substituido", "cicloalquenilalquilo", "cicloalquenilalquilo substituido", "heterocicloalquilo" y "heterocicloalquilo substituido" se refieren a grupos arilo, cicloalquilo, cicloalquenilo y heterociclo enlazados a través de un grupo alquilo, substituidos en el grupo arilo, cicloalquilo, cicloalquenilo o heterociclo y/o alquilo donde se indica como "substituido".

El término "arilo" se refiere a grupos hidrocarburo cíclicos, aromáticos, que tienen 1 hasta 5 anillos aromáticos, especialmente grupos monocíclicos o bicíclicos tales como fenilo, bifenilo o naftilo. Donde contienen dos o más anillos aromáticos (bicíclico, etc.), los anillos aromáticos del grupo arilo pueden enlazarse en un punto sencillo (por ejemplo, bifenilo), o fusionarse (por ejemplo,

naftilo, fenantrenilo y similares). "Arilo substituido" se refiere a un grupo arilo substituido por uno o más substituyentes, preferiblemente 1, 2, 3, 4 ó 5 substituyentes, en cualquier punto de enlace. Los substituyentes ejemplares incluyen, pero no se limitan a, nitro, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, ciano, alquil-$S(O)_m$- (m=0, 1 ó 2), alquilo o alquilo substituido, así como aquellos grupos mencionados arriba como substituyentes alquilo ejemplares y como se mencionó previamente como substituyentes arilo preferidos en la definición para G. Los substituyentes ejemplares también incluyen substituyentes cíclicos fusionados, tales como grupos heterociclo o cicloalquenilo, o heterociclo substituido o cicloalquenilo, (por ejemplo, formando por ello un grupo fluoroenilo, tetrahidronaftalenilo, o dihidroindenilo).

"Carbamoilo" se refiere al grupo -CONH- que está enlazado en un extremo al resto de la molécula y en el otro a hidrógeno o una porción orgánica (tal como alquilo, alquilo substituido, arilo, arilo substituido, heterociclo, alquilcarbonilo, hidroxilo y nitrógeno substituido). "Carbamato" se refiere al grupo -O-CO-NH- que está enlazado en un extremo al resto de la molécula y en el otro a hidrógeno o una porción orgánica (tal como aquellas enlistadas arriba). "Urea" se refiere al grupo -NH-CO-NH- que

está enlazado en un extremo al resto de la molécula y en el otro a hidrógeno o una porción orgánica (tal como aquellas enlistadas arriba). "Amidinilo" se refiere al grupo -C(=NH)(NH_2). "Carbamoilo substituido", "carbamato substituido", "urea substituida" y "amidinilo substituido" se refiere a grupos carbamoilo, carbamato, urea o amidinilo como se describe arriba en el cual uno o más de los grupos hidrógeno son reemplazados por una porción orgánica (tal como aquellas enlistadas arriba).

Los términos "heterociclo", "heterocíclico" y "heterociclo" se refieren a grupos cíclicos completamente saturados, o parcialmente o completamente insaturados, incluyendo aromáticos (esto es, "heteroarilo") (por ejemplo, sistemas de anillo monocíclico de 3 hasta 7 miembros, bicíclico de 7 hasta 11 miembros, o tricíclico de 10 hasta 16 miembros) que tienen al menos un heteroátomo en al menos un anillo que contiene un átomo de carbono. Cada anillo del grupo heterocíclico que contiene un heteroátomo, puede tener 1, 2, 3, ó 4 heteroátomos seleccionados de átomos de nitrógeno, átomos de oxígeno y/o átomos de azufre, donde los heteroátomos de nitrógeno y azufre pueden opcionalmente oxidarse y el heteroátomo de nitrógeno puede opcionalmente cuaternizarse. (El término "heteroarilio" se refiere a un grupo heteroarilo que porta un átomo de nitrógeno cuaternario y de esta manera una carga positiva). El grupo heterocíclico

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puede enlazarse al resto de la molécula en cualquier heteroátomo o átomo de carbono del anillo o del sistema de anillo. Se entenderá que, donde W o W' son cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, o arilo o arilo substituido, que A1 y A2 pueden enlazarse separadamente a diferentes (tales como adyacentes) átomos en el anillo en tales grupos. Los grupos monocíclicos heterocíclicos ejemplares incluyen óxido de etileno, azetidinilo, pirrolidinilo, pirrolilo, pirazolilo, oxetanilo, pirazolinilo, imidazolilo, imidazolinilo, imidazolidinilo, oxazolilo, oxazolidinilo, isoxazolinilo, isoxazolilo, tiazolilo, tiadiazolilo, tiazolidinilo, isotiazolilo, isotiazolidinilo, furilo, tetrahidrofurilo, tienilo, oxadiazolilo, piperidinilo, piperazinilo, 2-oxopiperazinilo, 2-oxopiperidinilo, 2-oxopirrolodinilo, 2-oxoazepinilo, azepinilo, hexahidrodiazepinilo, 4-piperidonilo, piridilo, pirazinilo, pirimidinilo, piridazinilo, triazinilo, triazolilo, tetrazolilo, tetrahidropiranilo, morfolinilo, tiamorfolinilo, sulfóxido de tiamorfolinilo, tiamorfolinil sulfona, 1,3-dioxolano y tetrahidro-1,1-dioxotienilo, y similares. Los grupos bicíclicos heterocíclicos ejemplares incluyen indolilo, isoindolilo, benzotiazolilo, benzodioxolilo, benzoxazolilo, benzoxadiazolilo, benzotienilo, quinuclidinilo, quinolinilo,

tetrahidroisoquinolinilo, isoquinolinilo, bencimidazolilo, benzopiranilo, indolizinilo, benzofurilo, benzofurazanilo, cromonilo, cumarinilo, benzopiranilo, cinolinilo, quinoxalinilo, indazolilo, pirrolopiridilo, furopiridinilo (tales como furo[2,3-c]piridinilo, furo[3,2-b]piridinilo] o furo[2,3-b]piridinilo), dihidrobenzodioxinilo, dihidrodioxidobenzotiofenilo, dihidroisoindolilo, dihidroindolilo, dihidroquinolinilo, dihidroquinazolinilo (tales como 3,4-dihidro-4-oxo-quinazolinilo), triazinilazepinilo, tetrahidroquinolinilo y similares. Los grupos tricíclicos heterocíclicos ejemplares incluyen carbazolilo, bencidolilo, fenantrolinilo, dibenzofuranilo, acridinilo, fenantridinilo, xantenilo y similares.

"Heterociclo substituido", "heterocíclico substituido" y "heterociclo substituido" (tal como "heteroarilo substituido") se refiere a grupos heterociclo, heterocíclico o heterociclo substituidos con uno o más substituyentes, preferiblemente 1 hasta 4 substituyentes, en cualquier punto de enlace disponible. Los substituyentes ejemplares incluyen, pero no se limitan a, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, nitro, oxo (esto es, = O), ciano, alquilo-$S(O)_m$- (m = 0, 1 ó 2), alquilo o alquilo substituido, así como aquellos grupos mencionados arriba como substituyentes alquilo ejemplares, y

como se mencionó previamente como substituyentes heterociclo preferidos en la definición para G.

El término "nitrógeno cuaternario" se refiere a un átomo de nitrógeno cargado positivamente tetravalente que incluye, por ejemplo, el nitrógeno cargado positivamente en un grupo tetraalquilamonio (por ejemplo, tetrametilamonio, N-metilpiridinio), el nitrógeno positivamente cargado en especies de amonio protonadas (por ejemplo, trimetil-hidroamonio, N-hidropiridinio), el nitrógeno positivamente cargado en N-óxidos de amina (por ejemplo, N-metil-morfolin-N-óxido, piridin-N-óxido), y el nitrógeno positivamente cargado en un grupo N-amino-amonio (por ejemplo, N-aminopiridinio).

Los términos "halógeno" o "halo" se refieren a cloro, bromo, flúor o yodo.

Los términos "hidroxilamina" e "hidroxilamida" se refieren a los grupos OH-NH- y OH-NH-CO-, respectivamente.

Cuando un grupo funcional se llama "protegido", esto significa que el grupo está modificado en forma para mitigar, especialmente evitar, reacciones laterales indeseadas en el sitio protegido. Los grupos protectores apropiados para los métodos y los compuestos descritos en la presente incluyen, sin limitación, aquellos descritos en libros de texto estándar, tales como Greene T. W. et al., Protective Groups in Organic Synthesis, Wiley, N.Y. (1991).

Cuando un término tal como "(CRR)n" se usa, significa una cadena alquilo opcionalmente substituida que existe entre los dos fragmentos a los cuales está enlazada, la longitud de cuya cadena se define por el rango descrito para el término n. Un ejemplo de esto es n=0-3, que implica desde cero hasta tres unidades (CRR) que existen entre los dos fragmentos, que se enlazan a las unidades primaria y terminal (CRR). En la situación donde el término n se coloca hasta cero (n = 0) entonces existe un enlace entre los dos fragmentos enlazados a (CRR).

Salvo que se establezca lo contrario, cualquier heteroátomo con valencias insatisfactorias se asume que tiene átomos de hidrógeno suficientes para satisfacer las valencias.

Los grupos divalentes, tales como aquellos en la definición de W (por ejemplo, NR^9-$CR^7R^{7'}$), pueden enlazarse en cualquier dirección al resto de la molécula (por ejemplo, $-A_1-NR^9-CR^7R^{7'}-A_2$ ó $-A_1-CR^7R^{7'}-NR^9-A_2-$ para el grupo arriba mencionado dentro de la definición de W).

Anión carboxilato se refiere a un grupo negativamente cargado $-COO^-$.

Los compuestos de la fórmula I forman sales que también están dentro del alcance de esta invención. La referencia a

un compuesto de la fórmula I en la presente se entenderá que incluye la referencia a sales, salvo que se indique lo contrario. El término "sal(es)", como se emplea en la presente, significa sales ácidas o básicas formadas con ácidos y bases orgánicas e inorgánicas. Además, cuando un compuesto de la fórmula I contiene tanto una porción básica, tal como, pero no limitándose a piridina o imidazol, y una porción ácida tal como, pero no se limita a, ácido carboxílico, pueden formarse zwitteriones ("sales inertes") y se incluyen dentro del término "sal(es)" como se usa en la presente. Se prefieren sales farmacéuticamente aceptables (esto es, no tóxicas, fisiológicamente aceptables), no obstante que otras sales también son útiles, por ejemplo en etapas de aislado o purificación que puede emplearse durante la preparación. Las sales de los compuestos de la fórmula I pueden formarse, por ejemplo, haciendo reaccionar el compuesto I con una cantidad de ácido o base, tal como una cantidad equivalente, en un medio tal como uno en el cual la sal se precipita o en un medio acuoso seguido por liofilización.

Los compuestos de la formula I que contienen una porción básica, tal como, pero no se limita a amina o un anillo piridina o imidazol, pueden formar sales con una variedad de ácidos orgánicos e inorgánicos. Las sales de adición ácidas ejemplares incluye acetatos (tales como aquellos formados con

ácido acético o ácido trihaloacético, por ejemplo, ácido trifluoroacético), adipatos, alginatos, ascorbatos, aspartatos, benzoatos, bencenesulfonatos, bisulfatos, boratos, butiratos, citratos, canforatos, canforsulfonatos, ciclopentanpropionatos, digluconatos, dodecilsulfatos, etansulfonatos, fumaratos, glucoheptanoatos, glicerofosfatos, hemisulfatos, heptanoatos, hexanoatos, clorohidratos, bromohidratos, yodohidratos, hidroxietansulfonatos (por ejemplo, 2-hidroxietansulfonatos), lactatos, maleatos, metansulfonatos, naftalensulfonatos (por ejemplo, 2-naftalensulfonatos), nicotinatos, nitratos, oxalatos, pectinatos, persulfatos, fenilpropionatos (por ejemplo, 3-fenilpropionatos), fosfatos, picratos, pivalatos, propionatos, salicilatos, succinatos, sulfatos (tales como aquellos formados con ácido sulfúrico), sulfonatos (tales como aquellos mencionados en la presente), tartratos, tiocianatos, toluensulfonatos tales como tosilatos, undecanoatos, y similares.

Los compuestos de la fórmula I que contienen una porción ácida, tales como, pero no limitándose a, ácido carboxílico, pueden formar sales con una variedad de bases orgánicas e inorgánicas. Las sales básicas ejemplares incluyen sales de amonio, sales de metal alcalino tales como sales de sodio, litio y potasio, sales de metales alcalinotérreos tales como sales de calcio y magnesio, sales con bases orgánicas (por

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ejemplo, aminas orgánicas) tales como benzatinas, diciclohexilaminas, hidrabaminas (formadas con N,N-bis(dehidroabietil)etilendiamina), N-metil-D-glucaminas, N-metil-D-glicamidas, t-butil aminas, y sales con aminoácidos tales como arginina, lisina y similares. Los grupos que contienen nitrógeno básicos pueden cuaternizarse con agentes tales como haluros de alquilo inferior (por ejemplo cloruros, bromuros y yoduros de metilo, etilo, propilo, y butilo), sulfatos dialquilo (por ejemplo sulfatos de dimetilo, dietilo, dibutilo, y diamilo), haluros de cadena larga (por ejemplo cloruros, bromuros y yoduros de decilo, laurilo, mirestilo y estearilo), haluros de aralquilo (por ejemplo bromuros de bencilo y fenetilo), y otros.

Los profármacos y solvatos de los compuestos de la invención también se contemplan en la presente. El término "profármaco" como se emplea en la presente, significa un compuesto que, durante la administración a un sujeto, experimenta la conversión química por procesos metabólicos o químicos para producir un compuesto de la fórmula I, o una sal y/o solvato del mismo. Los solvatos de los compuestos de la fórmula I incluyen, por ejemplo, hidratos.

Los compuestos de la fórmula I y sales de los mismos, pueden existir en su forma tautomérica (por ejemplo, como una amida o éter imino). Todas la formas tautoméricas están

contempladas en la presente como parte de la presente invención.

Todos los estereoisómeros de los presentes compuestos (por ejemplo, aquellos que pueden existir debido a los carbonos asimétricos en varios substituyentes), incluyendo formas enantioméricas y formas diaestereoméricas, están contemplados dentro del alcance de esta invención. Los estereoisómeros individuales de los compuestos de la invención pueden, por ejemplo, estar substancialmente libres de otros isómeros (por ejemplo, como un isómero óptico puro o substancialmente puro que tiene una actividad específica), o pueden mezclarse, por ejemplo, como racematos o con todos los otros, u otros estereoisómeros seleccionados. Los centros quirales de la presente invención pueden tener la configuración S o R como se define por las recomendaciones IUPAC 1974. Las formas racémicas pueden resolverse por los métodos físicos, tales como, por ejemplo, cristalización fraccional, separación o cristalización de derivados diaestereoméricos o separación por cromatografía de columna quiral. Los isómeros ópticos individuales pueden obtenerse de los racematos por cualquier método apropiado, que incluyen sin limitación, métodos convencionales, tales como, por ejemplo, formación de sal con un ácido ópticamente activo seguido por la cristalización.

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Todos los isómeros configuracionales de los compuestos de la presente invención están contemplados, ya sea en mezcla o en forma pura o substancialmente pura. La definición de los compuestos de la presente invención abarca isómeros de alqueno tanto cis (Z) como trans (E), así como isómeros cis y trans de hidrocarburo cíclico o anillos heterociclos. En ciertos casos, por ejemplo, la conformación exo o endo puede preferirse para el sistema de anillo fusionado enlazado a G-L en la fórmula I. Por ejemplo, para antagonistas del receptor andrógeno (o moduladores del receptor andrógeno selectivo), donde Y es O ó NR^7, la configuración exo puede preferirse, aunque para la mayoría de las otras definiciones de Y, la configuración endo puede preferirse. Como puede apreciarse, la configuración preferida puede estar en función del compuesto particular y su actividad preferida. La separación de los isómeros configuracionales puede realizarse por cualquier método apropiado, tal como cromatografía de columna.

A través de las especificaciones, los grupos y substituyentes de los mismos pueden elegirse para proporcionar porciones y compuestos estables.

Las modalidades indicadas en la presente como ejemplares o preferidas, se pretende que sean ilustrativas y no limitantes.

Mét dos de Preparación.

Los compuestos de la presente invención pueden prepararse por métodos tales como aquellos ilustrados en los siguientes Esquemas de Reacción I hasta XI. Los solventes, temperaturas, presiones, y otras condiciones de reacción pueden seleccionarse fácilmente por alguien de experiencia ordinaria en la técnica. Los materiales de partida están comercialmente disponibles o se preparan fácilmente por alguien de experiencia ordinaria en la técnica. Pueden emplearse técnicas de combinación en la preparación de los compuestos, por ejemplo, donde los grupos poseen intermediarios apropiados para estas técnicas. Ver lo siguiente que describe otros métodos que pueden emplearse en la preparación de los compuestos de la presente invención: Li, et al., Eur. J. Org. Chem. 9, 1841-1850 (1998); Li, Y-Q, Synlett. 5,461-464 (1996); Thiemann, et al., Bull. Chem. Soc. Jpn. 67, 1886-1893 (1994); Tsuge et al., Heterocycles 14, 423-428 (1980); Ward et al., Can J. Chem. 75,681-693 (1997); Ward et al., Can J. Chem. 69, 1487-1497 (1991); Ward et al., Tetrahedron Lett. 31, 845-848 (1990); Fleming et al., J. Org. Chem. 44, 2280-2282 (1979); Jankowski et al., J. Organomet. Chem. 595, 109-113 (2000); Keglevich et al., J. Organomet. Chem. 579, 182-189 (1999); Keglevich et al., J. Organomet. Chem. 570, 49-539 (1998); Jankowski et al., Hetroat. Chem. 7, 369-374 (1996); Jankowski et al., J. Am. Chem. Soc. 113,

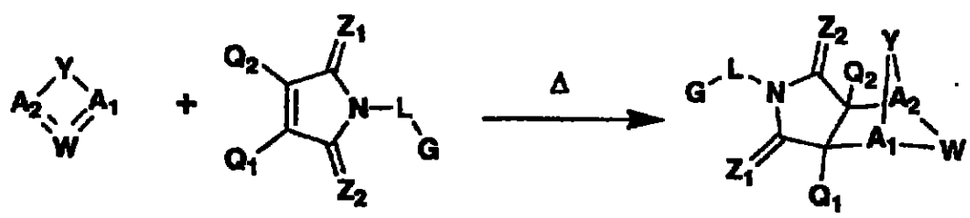
7011-7017 (1991); Quin et al., Tetrahedron Lett. 31, 6478-6476 (1990); Quin et al., J. Org. Chem. 59, 120-129 (1994); Quin et al., J. Org. Chem. 58, 6212-6216 (1993); Quin et al., Phosphorous, Sulfur Silicon Relat. Elem. 63, 349-362 (1991); Quin et al., Hetroat. Chem. 2, 359-367 (1991); Hussong et al., Phosphorus, Sulfur. 25,201-212 (1985); Quin et al., J. Org. Chem. 51, 3341-3347 (1986); Myers et al., J. Am. Chem. Soc. 114, 5684-5692 (1992); Myers et al., J. Am. Chem. Soc. 113, 6682-6683 (1991); Shen et al., Patente E.U.A. No. 5817679; Cordone et al., J. Am. Chem. Soc. 111, 5969-5970 (1989); Jung et al., J. Chem. Soc. Commun. 630-632 (1984); Lay et al., J. Am. Chem. Soc. 104, 7658-7659 (1982); Gonzalez et al., J. Am. Chem. Soc. 117, 3405-3421 (1995); Kreher et al., Chem Ber. 125, 183-189 (1992); Simig et al., Synlett. 7,425-426 (1990); Sha et al., J. Org. Chem. 55, 2446-2450 (1990); Drew et al., J. Chem. Soc., Perkin Trans. 1 7, 1277-1284 (1985); Kreher et al., Anorg. Chem., Org Chem. 31B, 599-604 (1976); Avalos et al., Tetrahedron Lett. 39,9301-9304 (1998); Gousse et al., Macromolecules 31, 314-321 (1998); Mikhailyuchenko et al., Khim. Geterotsikl. Soedin. 6, 751-758 (1993); Lubowitz et al., patente E.U.A No. 4476184; Padwa et al., J. Org. Chem. 61, 3706-3714 (1996); Schlessinger et al., J. Org. Chem. 59, 3246-3247 (1994); Buchmeiser et al., publicación WO No. 9827423; Tanabe et al., Documento de Patente Japonesa JP 07144477; Mochizucki et al., Documento de

Patente Japonesa JP 63170383; Hosoda et al., Documento de Patente Japonesa JP 62053963; Onaka et al., Documento de Patente Japonesa JP 62053964; Kato et al., Documento de Patente Japonesa JP 53086035; Kato et al., Documento de Patente Japonesa JP 51088631; Tottori et al., Documento de Patente Japonesa JP 49124225; Augustin et al., Documento de Patente Alemana DD101271; Title et al., documento de Patente Francesa FR 2031538; Gousse et al., Polym. Int. 48, 723-731 (1999); Padwa et al., J. Org. Chem. 62, 4088-4096 (1997); Theurillat-Moritz et al., Tetrahedron: Asymmetry 7, 3163-3168 (1996); Mathews et al., J. Carbohydr. Chem. 14, 287-97 (1995); Srivastava et al., Natl. Acad. Sci. Lett. (India) 15, 41-44 (1992); Mayorga et al., Rev. Cubana Quim. 4, 1-6 (1988); Kondoli et al., J. Chem. Res., Synop. 3,76 (1987); Primelles et al., Cent. Azucar 7-14 (1985); Solov'eva et al., Khim. Geterotsikl. Soedin. 5, 613-15 (1984); Liu et al., Yaoxue Xuebao 18, 752-759 (1983); Joshi et al., Indian J. Chem, Sect.B. 22B, 131-135(1983); Amos et al., publicación WO No. 9829495; Odagiri et al., Patente E.U.A. No. 4670536; Gallucci et al., documento de Patente Europea EP 355435; Redmore, D. Patente E.U.A. No. 3821232; Nakano et al., Heterocycles 35,37-40 (1993); Tomisawa et al., Chem. Pharm. Bull. 36, 1692-1697 (1988); Krow et al., J. Heterocycl. Chem. 22, 131-135 (1985); Krow et al., J. Org. Chem. 47, 1989-1993 (1982); Liu et al., Yaoxue Xuebao 18, 752-759 (1983);

Nishikawa et al., Yaoxue Xuebao JP 01061457; y/o Rice et al., J. Med. Chem. 11, 183-185 (1968).

Todos los documentos citados en la presente especificación, tales como aquellos citados en estos "Métodos de Preparación" así como otras secciones en la presente, se incorporan en la presente para referencia en su totalidad. La referencia a cualquier documento en la presente no deberá constituirse como una admisión de que tal documento es el arte previo

Esquema de Reacción I



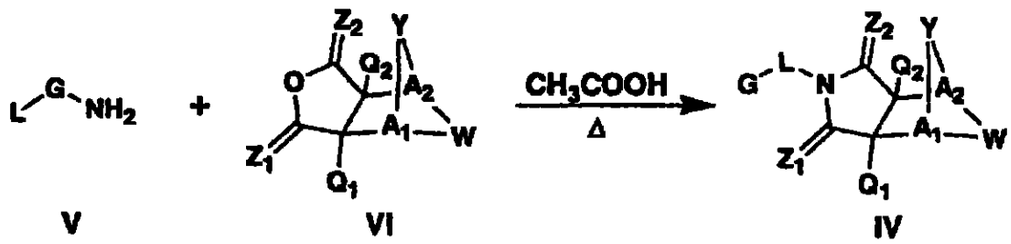
II III IV

Como se ilustra en Esquema de Reacción I, un dieno de la fórmula II puede reaccionar con un dienófilo de la fórmula III, bajo condiciones fácilmente seleccionadas por alguien experto en la técnica (tal como por la adición de calor ("Δ")), para obtener un compuesto de la fórmula IV, el cual es un compuesto de la fórmula I. Un dieno intermediario de la fórmula II puede obtenerse de proveedores comerciales o hacerse fácilmente por alguien experto en la técnica, por ejemplo, de conformidad con los siguientes documentos y referencias de la literatura encontrados en la presente:

Hofman et al., J. Agric. Food Chem. 45, 898-906 (1997); Baciocchi et al., J. Chem. Soc., Perkin Trans. 2 8, 821-824 (1975); Wu et al., J. Heterocycles 38, 1507-1518 (1994); Yin et al., Tetrahedron Lett. 38, 5953-5954 (1997); Mic'ovic' et al., Tetrahedron 20, 2279-2287 (1964); Gorbunova et al., J. Org. Chem.. 35, 1557-1566 (1999); Rassu et al., Chem. Soc. Rev. 29, 109-118 (2000); Kaberdin et al., Russ. Chem. Rev., 68,765-779 (1999); Barluenga et al., Aldrichimica Acta 32,4-15 (1999); Bogdanowicz-Szwed et al., Pol. Wiad. Chem. 52, 821-842 (1998); Casiraghi et al., Adv. Asymmetric Synth. 3, 113-189 (1998); y/o Baeckvall et al; Chem. Rev. 98, 2291-2312 (1998). Un dienófilo intermediario de la fórmula III puede obtenerse de proveedores comerciales o hacerse fácilmente por alguien experto en la técnica, por ejemplo, de conformidad con las siguientes referencias de la literatura y las referencias encontradas en la presente: Deshpande et al., Heterocycles 51, 2159-2162 (1999); Seijas et al., J. Chem. Res., Synop. 7, 420-421 (1999); Langer et al., Eur. J. Org. Chem. 7, 1467-1470 (1998); Kita et al., Documento de Patente Japonesa JP 09194458; Lopez-Alvarado et al., J. Org. Chem. 61, 5865-5870 (1996); Condon et al., Patente E.U.A. No. 5523277; Sasakihara et al., Documento de Patente Japonesa JP 04290868; Igarashi et al., Documento de Patente Japonesa JP 04149173; Aoyama et al., Documento de Patente Japonesa JP 04134063; Aoyama et al., Documento de Patente Japonesa JP

04134062; Pastor et al., J. Org. Chem. 53, 5776-5779 (1988); y/o Takahashi et al., Chem. Lett. 6, 1229-1232 (1987).

Esquema de Reacción II



Como se ilustra en el Esquema de Reacción II, los compuestos de la fórmula I puede obtenerse por la reacción de una amina primaria de la fórmula V con un intermediario tipo anhidro substituido de la fórmula VI, por ejemplo, en un solvente tal como ácido acético con o sin calor, para producir un compuesto de la fórmula IV, el cual es un compuesto de la fórmula I. Las aminas primarias de la fórmula V pueden obtenerse de proveedores comerciales o sintetizarse fácilmente por alguien experto en la técnica. Los agentes tipo anhídridos de la fórmula VI pueden obtenerse de proveedores comerciales o sintetizarse fácilmente por alguien experto en la técnica. Los documentos listados a continuación describen enfoques ejemplares para la síntesis de intermediarios de la fórmula VI así como enfoques sintéticos que pueden aplicarse a la síntesis de los compuestos de la

fórmula IV (todos incorporados en la presente para referencia en su totalidad): Kohler, E. P.; Tishler, M.; Potter, H.; Thompson, H. T. J. Am. Chem. Soc. 1939, 1057-1061; Yur'ev, Y. K.; Zefirov, N. S. J. Gen. Chem. U.S.S.R. (Engl. Transl.) 1961, 31, 772-5; Norman G. Gaylod Patente E.U.A. No. 3,995,099; Schueler, P. E.; Rhodes, Y. E. J. Org. Chem. 1974, 39, 2063-9; Ishitobi, H.; Tanida, H; Tsuji, T. Bull. Chem. Soc. Japan 1971, 44, 2993-3000; Stájer, G.; Virág, M.; Szabó. A. E.; Bernáth, G.; Sohár, P.; Sillanpää, R. Acta. Chem. Scand. 1996, 50, 922-30; Hart, H.; Ghosh, T. Tetrahedron Lett. 1988,29,881-884; Kato, M.; Yamamoto, S.; Yoshihara, T.; Furuichi, K; Miwa. T. Chem. Lett. 1987, 1823-1826; Kottwitz, J.; Vorbrüggen, H. Synthesis 1995,636-637; Creary, X. J. Org. Chem. 1975,40, 3326-3331; Alder, K.; Ache, H.-J.; Flock, F. H. Chem. Ber. 1960,93. 1888-1895; Toder. B. H.; Branca, S. J.; Dieter, R. K.; Smith, A. B. III Synth. Commun. 1975, 5, 435-439; Sprague, P. W.; Heikes, J. E.; Gougoutas, J. Z.; Malley, M. F.; Harris, D. N.; y/o Greenberg, R. J. Med. Chem. 1985,28, 1580-1590.

Los enfoques arriba mencionados pueden aplicarse en una manera en combinación, por ejemplo, al utilizar un bloque de reacción de pozos múltiples tal como el descrito en Waldemar Ruediger, Wen-Jeng Li, John W., Allen Jr., y Harold N. Weller III, Patente E.U.A. No. 5,961,925, Apparatus for Synthesis of Multiple Oganic Compounds With Pinch Valve Block (incorporado

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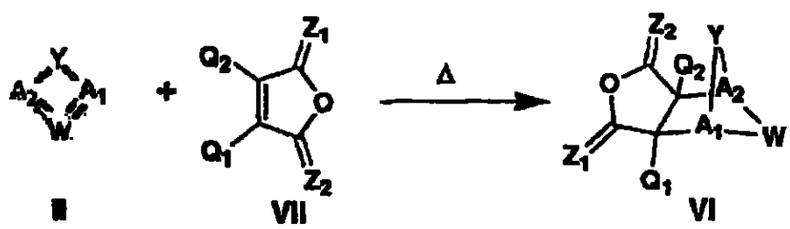
en la presente para referencia en su totalidad). Al utilizar el bloque de reacción de pozos múltiples antes mencionado, se pueden, por ejemplo, realizar múltiplos de 96 reacciones al mismo tiempo. El solvente puede removerse después de los tubos de reacción sin removerlo del bloque de reacción, y los productos crudos pueden precipitarse con el uso de una base tal como bicarbonato de sodio. Los precipitados pueden colectarse por filtración del bloque de reacción y después los productos deseados pueden transferirse directamente a las placas de 96 pozos para separación. De esta manera, puede sintetizarse una configuración grande de compuesto de la fórmula I, y las pruebas conducirse como se desea por un enfoque automatizado.

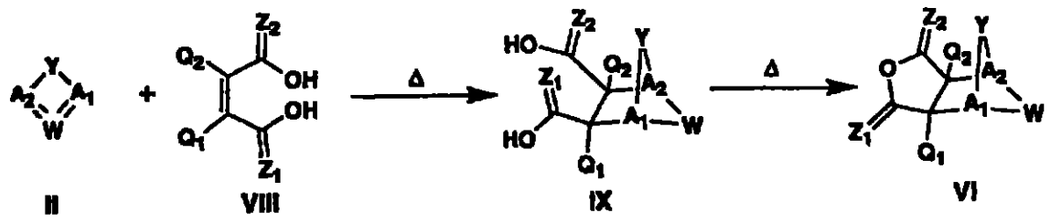
Esquema de Reacción III



El Esquema de Reacción III describe un método para preparar un compuesto intermediario de la fórmula VI el cual puede usarse para sintetizar un compuesto de la fórmula I, como se describe en el Esquema de Reacción II. Como se describe en el Esquema de Reacción III, un dieno de la

fórmula II puede hacerse reaccionar con un dienófilo de la fórmula VII para producir el intermediario de la fórmula VI. Los métodos aplicados para obtener tal transformación son análogos a aquellos descritos en el Esquema de Reacción I.

Esquema de Reacción IV

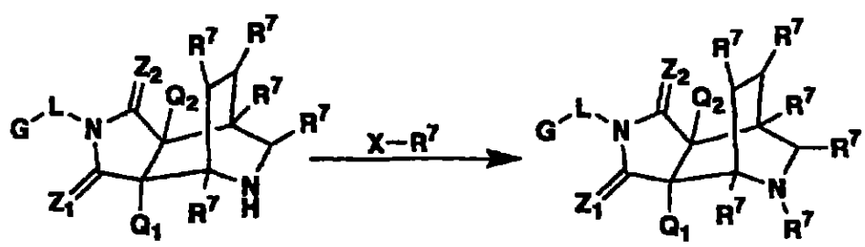


El Esquema de Reacción IV describe un método para preparar un compuesto intermediario de la fórmula VI el cual puede usarse para sintetizar un compuesto de la fórmula I, como se describe en el Esquema de Reacción II. Como se muestra en el Esquema de Reacción IV, un dieno de la fórmula II puede hacerse reaccionar con un dienófilo de la fórmula VIII para producir el intermediario de la fórmula IX. El intermediario de la fórmula IX puede deshidratarse hasta un intermediario tipo anhídrido de la fórmula VI. La deshidratación del intermediario bis-ácido de la fórmula IX puede realizarse por una variedad de métodos, tal como aquellos conocidos por alguien experto en la técnica y descritos en los siguientes documentos y las referencias abarcadas en la presente: Sprague et al., J. Med. Chem. 28,

1580-1590 (1985); y/o Retemi et al., J. Org. Chem. 61, 6296-6301 (1996).

Los Esquemas de Reacción I a IV describen métodos generales para la síntesis de los compuestos de la fórmula I, e intermediarios de los mismos, en cuya substitución alrededor del sistema de anillo se incorpora directamente, por ejemplo, al nivel del dieno intermediario, dienófilo, intermediario tipo anhídrido y grupos amina. Además de estos enfoques, la substitución adicional puede incorporarse en un compuesto ya preparado de la fórmula I por una variedad de enfoques para preparar otros compuestos de la fórmula I. Los métodos ejemplares para la substitución adicional se describen en los Esquemas de Reacción V a XI.

Esquema de Reacción V

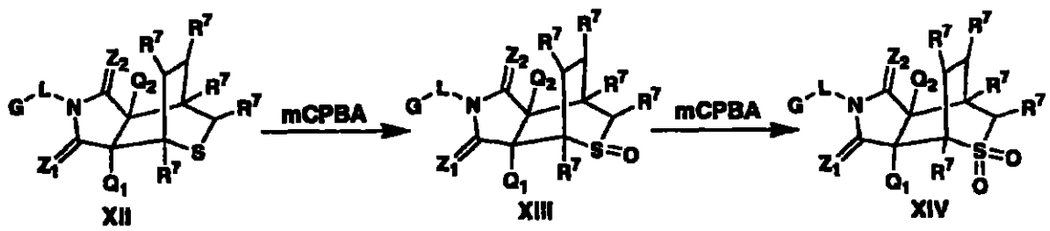


X XI

El Esquema de Reacción V describe uno de tales enfoques para incorporar una substitución adicional en una estructura de la fórmula I. Como se ilustra en el Esquema de Reacción V, un compuesto de la fórmula X, el cual es un compuesto de la fórmula I donde A_1 y A_2 son CR^7, W es NH—CHR^7 e Y es

CHR^7—CHR^7, puede funcionalizarse en la amina libre del grupo W por la reacción con cualesquiera de una variedad de agentes electrofílicos tales como haluros ácidos o haluro de alquilo en presencia de una base, por ejemplo, por métodos conocidos por alguien experto en la técnica. En el Esquema de Reacción V, X es un grupo de partida, y un compuesto de la fórmula XI es un compuesto de la fórmula I donde A_1 y A_2 son CR^7, W es NR^7—CHR^7 e Y es CHR^7—CHR^7.

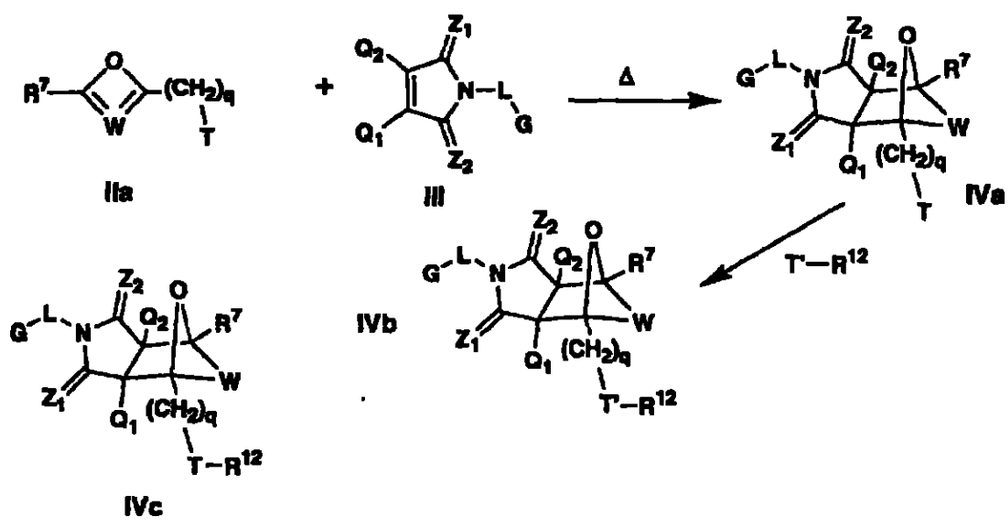
Esquema de Reacción VI



El Esquema de Reacción VI describe un enfoque adicional para la substitución incorporada adicional en el compuesto de la fórmula I. Como se ilustra en el Esquema de Reacción VI, un compuesto de la fórmula XII, el cual es un compuesto de la fórmula I donde A_1 y A_2 son CR^7, W es S—CHR^7 e Y es CHR^7—CHR^7, puede oxidarse parcialmente con un agente oxidante tal como mCPBA u otros agentes tales como aquellos conocidos por alguien experto en la técnica, para dar el análogo sulfóxido de la fórmula XIII, el cual es un compuesto de la fórmula I donde A_1 y A_2 son CR^7, W es SO—CHR^7 e Y es CHR^7—CHR^7. El

tratamiento adicional de un compuesto de la fórmula XIII con un agente oxidante tal como mCPBA u otros agentes tales como aquellos conocidos por alguien experto en la técnica, puede producir el análogo de sulfona de la fórmula XIV, el cual es un compuesto de la fórmula I donde A_1 y A_2 son CR^7, W es SO_2—CHR^7 e Y es CHR^7—CHR^7. Alternativamente, un compuesto de la fórmula XII puede convertirse directamente a un compuesto de la fórmula XIV por el tratamiento prolongado con un agente oxidante, tal como mCPBA, o con otros agentes tales como aquellos conocidos por alguien experto en la técnica.

Esquema de Reacción VII



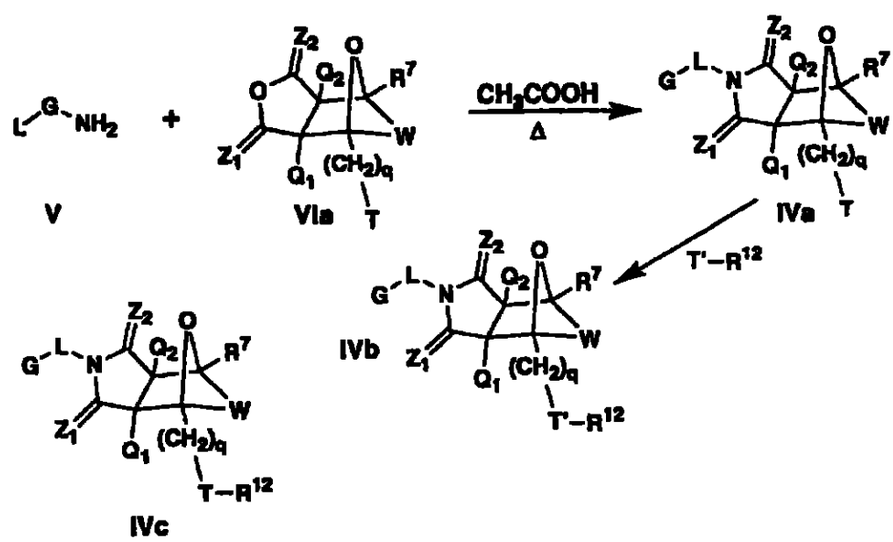
El Esquema de Reacción VII describe otro enfoque para incorporar una substitución adicional en un compuesto de la fórmula I. Como se ilustra en el Esquema de Reacción VII, un dieno de la fórmula IIa puede hacerse reaccionar con un dienófilo de la fórmula III, como se describe en el Esquema

de Reacción I, para producir un compuesto de la fórmula IVa, el cual es un compuesto de la fórmula I donde Y es O, A_2 es CR^7 y A^1 es $C—(CH_2)_q—T$. El compuesto de la fórmula IVa puede hacerse reaccionar con un reactivo de la fórmula $R^{12}—T'$ para obtener un compuesto de la fórmula IVb o IVc los cuales son compuestos de la fórmula I donde Y es O, A_2 es CR^7 y A_1 es $C—(CH_2)_q—T'—R^{12}$ o $C—(CH_2)_q—T—R^{12}$, respectivamente. El reactivo $R^{12}—T'$ puede obtenerse de proveedores comerciales o puede prepararse fácilmente por alguien experto en la técnica.

En el Esquema de Reacción anterior, R^{12} tiene la misma definición como R^7 definido previamente, q es cero o un entero desde 0-8, y T es como se define previamente como (1) un centro nucleofílico tal como, pero no limitándose a, un grupo que contiene nitrógeno, oxígeno o azufre, capaz de experimentar una reacción de substitución nucleofílica con el grupo de partida T' o (2) un grupo de partida capaz de experimentar una reacción de substitución nucleofílica con el grupo nucleofílico T' (tal como, pero no limitándose a, un grupo nucleofílico que contiene nitrógeno, oxígeno o azufre). T' tiene la misma definición como T. En el presente caso, por ejemplo, una reacción de substitución nucleofílica ocurre cuando el reactivo de ataque (el nucleófilo) enlaza un electrón par al substrato, usando este par para formar el enlace nuevo, y el grupo de partida (el nucleófugo) se retira

con el par electrón, quedando como un intermediario aniónico. Para una discusión detallada del mecanismo de substituciones nucleofílicas alifáticas y una revisión de reacciones de substitución nucleofílicas alifáticas específicas, ver Advanced Organic Chemestry, Reactions, Mechanisms, and Structure, 4th Addition. Jerry March (Ed.), John Wiley & Sons, New York (1992) 293-500 y las referencias en la presente. Los compuestos de las fórmulas IVa, IVb, o IVc pueden, por supuesto, emplearse en los métodos descritos en la presente (especialmente, en el tratamiento de condiciones asociadas con el receptor de hormona nuclear) sin experimentar una reacción adicional de T o T'.

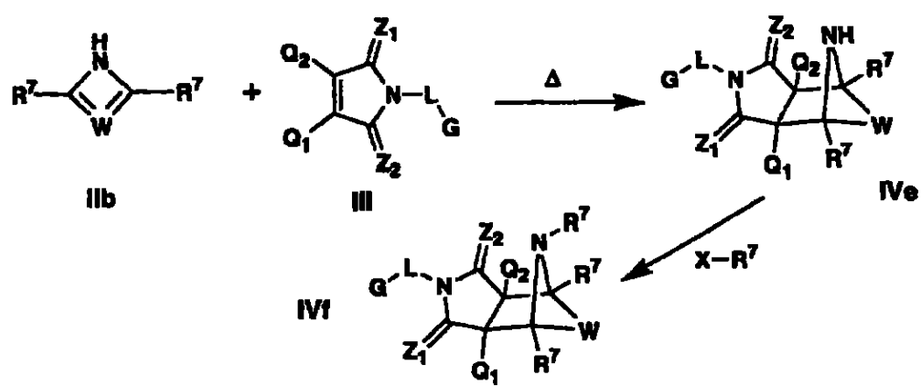
Esquema de Reacción VIII



Un enfoque alternativo a los compuestos de la fórmula IVa, IVb y IVc se ilustra en el Esquema de Reacción VIII.

Para este enfoque, las técnicas tales como aquellas descritas en los Esquemas de Reacción II, III y IV pueden aplicarse para la preparación de un intermediario de la fórmula VIa, donde T y q son como se define en el Esquema de Reacción VII. El intermediario de la fórmula VIa puede hacerse reaccionar con una amina substituida de la fórmula V, como se describe en el Esquema de Reacción II, para producir el compuesto de la fórmula IVa, el cual es un compuesto de la fórmula I donde Y es O, A_2 es CR^7 y A_1 es $C-(CH_2)_q-T$. El compuesto de la fórmula IVa puede tratarse en la manera descrita en el Esquema VII para obtener compuestos de la fórmula IVb o IVc los cuales son compuestos de la fórmula I donde Y es O, A_2 es CR^7 y A_1 es $C-(CH_2)_q-T'-R^{12}$ o $C-(CH_2)_q-T-R^{12}$, respectivamente.

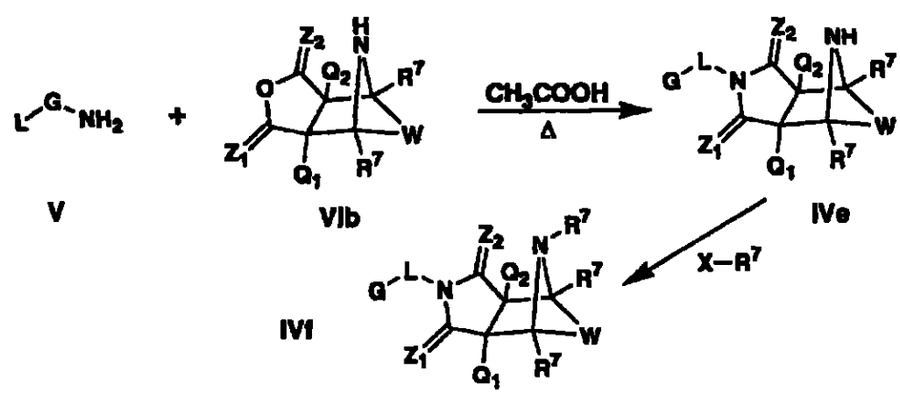
Esquema de Reacción IX



El Esquema de Reacción IX describe otro enfoque para incorporar una substitución adicional en un compuesto de la fórmula I. Como se ilustra en el Esquema de Reacción IX

(donde X es un grupo de partida), un dieno de la fórmula IIb puede hacerse reaccionar con un dienófilo de la fórmula III, como se describe en el Esquema de Reacción I, para producir un compuesto de la fórmula IVe, el cual es un compuesto de la fórmula I donde Y es NH, y A_1 y A_2 son CR^7. El compuesto de la fórmula IVe puede funcionalizarse en la amina libre al hacerlo reaccionar con una variedad de agentes electrofílicos tales como haluros ácidos o haluros de alquilo en presencia de una base, por ejemplo por métodos conocidos por alguien experto en la técnica y descritos en el Esquema de Reacción V, para producir un compuesto de la fórmula IVf, el cual es un compuesto de la fórmula I donde Y es NR^7 y A_1 y A_2 son CR^7.

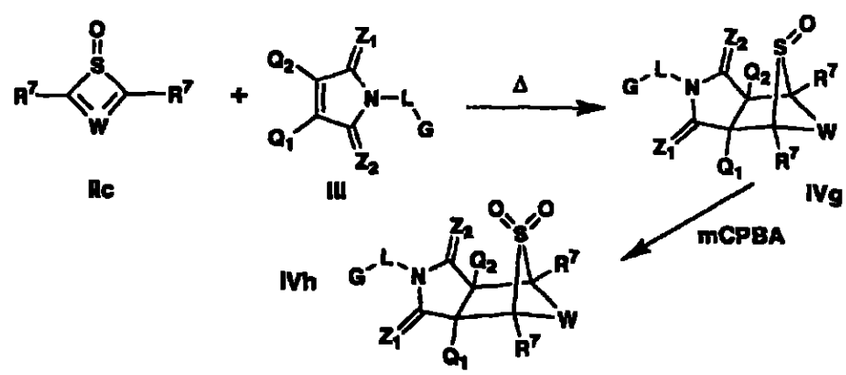
Esquema de Reacción X



Un enfoque alternativo a los compuestos de la fórmula IVe y IVf se ilustra en el Esquema de Reacción X. Para este enfoque, las técnicas como se describen en los Esquemas de

Reacción II, III y IV pueden aplicarse para la preparación de un intermediario de la fórmula VIb. El intermediario de la fórmula VIb puede hacerse reaccionar con una amina substituida de la fórmula V, como se describe en el Esquema de Reacción II, para producir un compuesto de la fórmula IVe, el cual es un compuesto de la fórmula I donde Y es NH, y A_1 y A_2 son CR^7. El último intermediario puede tratarse en la manera descrita en el Esquema de Reacción V para obtener un compuesto de la fórmula IVf, el cual es un compuesto de la fórmula I donde Y es NR^7, y A_1 y A_2 son CR^7.

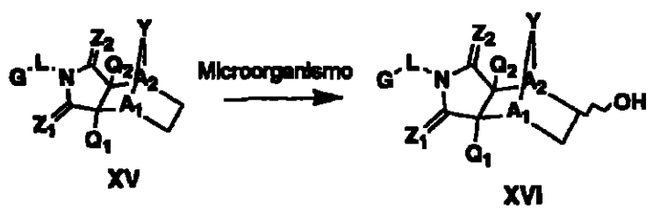
Esquema de Reacción XI



El Esquema de Reacción XI describe otro enfoque para incorporar una substitución adicional en un compuesto de la fórmula I. Como se ilustra en el Esquema de Reacción XI, un dieno de la fórmula IIc puede hacerse reaccionar con un dienófilo de la fórmula III, como se describe en el Esquema de Reacción I, para producir un compuesto de la fórmula IVg,

el cual es un compuesto de la fórmula I donde Y es SO y A_1 y A_2 son CR^7. Un compuesto de la fórmula IVg puede tratarse con un agente oxidante tal como mCPBA, como se describe en el Esquema de Reacción VI, para producir un compuesto de la fórmula IVh, el cual es un compuesto de la fórmula I donde Y es SO_2 y A_1 y A_2 son CR^7.

Esquema de Reacción XII



El Esquema de Reacción XII describe otro enfoque para incorporar una substitución adicional en un compuesto de la fórmula I. Como se ilustra en el Esquema de Reacción XII, un compuesto de la fórmula XV, el cual puede prepararse de conformidad con los Esquemas de Reacción anteriores, puede incubarse en presencia de una enzima o microorganismo apropiado lo que resulta en la formación de un análogo hidroxilado de la fórmula XVI. Tal proceso puede emplearse para producir la incorporación regioespecífica así como enantioespecífica de un grupo hidroxilo en una molécula de la fórmula XV por un microorganismo específico o por una serie de diferentes microorganismos. Tales microorganismos pueden,

por ejemplo, ser bacterianos, de levadura o fungales por naturaleza y pueden obtenerse de distribuidores tal como ATCC o identificados para su uso en este método tal como por los métodos conocidos por alguien experto en la técnica. El Compuesto XVI es un compuesto de la fórmula I donde Y es como se describe arriba y A_1 y A_2 son preferiblemente CR^7.

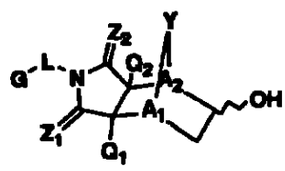
Esquema de Reacción XIII

El Esquema de Reacción XIII describe otro enfoque para incorporar una substitución adicional en un compuesto de la fórmula I. Como se ilustra en el Esquema de Reacción XIII, un compuesto de la fórmula XVII, el cual puede prepararse de conformidad con los Esquemas anteriores, puede incubarse en presencia de una enzima o microorganismo apropiado lo que resulta en la formación de un análogo diol de la fórmula XVIII. Tal proceso puede emplearse para producir la transformación regioespecífica así como enantioespecífica de un compuesto de la fórmula XVII a un diol 1-2 de la fórmula XVIII por un microorganismo específico o por una serie de microorganismos diferentes. Tales microorganismos pueden, por

ejemplo, ser bacterianos, de levadura o fungales por naturaleza y pueden obtenerse de distribuidores tales como ATCC o identificarse para su uso en este método tales como por métodos conocidos por alguien experto en la técnica. El Compuesto XVIII es un compuesto de la fórmula I donde Y es como se describe arriba y A_1 y A_2 son preferiblemente CR^7.

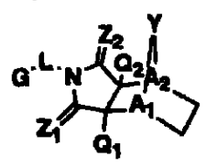
La presente invención también proporciona los métodos de los Esquemas de Reacción XII y XIII.

De esta manera, en una modalidad, la presente invención proporciona un método para la preparación de un compuesto de la siguiente fórmula XVI, o una sal del mismo:



XVI

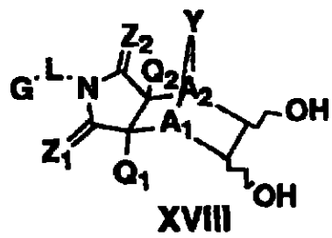
donde los símbolos son como se define en la presente, que comprende las etapas de poner en contacto un compuesto de la siguiente fórmula XV, o una sal del mismo:



XV

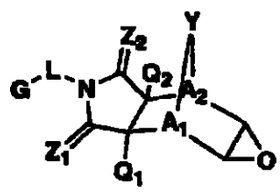
donde los símbolos son como se define arriba; con un enzima o microorganismo capaz de catalizar la hidroxilación de tal compuesto XV para formar el compuesto XVI, y efectuar la hidroxilación.

En otra modalidad preferida, la presente invención proporciona un método para la preparación de un compuesto de la siguiente fórmula XVIII, o una sal del mismo:



XVIII

donde los símbolos son como se define en la presente, que comprende las etapas de poner en contacto un compuesto de la siguiente fórmula XVII, o una sal del mismo:



XVII

donde los símbolos son como se define arriba; con un enzima o microorganismo capaz de catalizar la abertura del anillo epóxido del compuesto XVII para formar el diol de tal compuesto XVIII, y efectuar la abertura del anillo y la formación de diol.

Todas las estereoconfiguraciones de los centros quirales no específicos de los compuestos de la fórmula XV, XVI, XVII y XVIII se contemplan en los métodos de la presente invención, ya sea solos (esto es, substancialmente libres de otros isómeros) o en mezcla con otras formas

estereoisoméricas. La conversión de un isómero selectivamente (por ejemplo, la hidroxilación del isómero exo preferencialmente para la hidroxilación del isómero endo) cuando se pone en contacto una mezcla isomérica es una modalidad preferida de la invención. La conversión a un isómero selectivamente (por ejemplo, hidroxilación en la cara exo del "isómero exo" preferencialmente a la cara endo del "isómero endo" o la abertura regioselectiva de un epóxido para formar solo uno de dos posibles regioisómeros de un diol trans) es una modalidad preferida de la invención. La hidroxilación de un intermediario aquiral para formar un isómero óptico sencillo del producto hidroxilado, también es una modalidad preferida de la invención. La resolución de una mezcla racémica de un intermediario por la hidroxilación selectiva, o la abertura del anillo epóxido y la formación de diol, para generar uno de dos isómeros ópticos posibles, también es una modalidad preferida de la invención. El término "resolución" como se usa en la presente, significa resolución parcial, así como, preferiblemente, completa.

Los términos "proceso enzimático" o "método enzimático", como se usan en la presente, significan un proceso o método de la presente invención que emplea una enzima o microorganismo. El término "hidroxilación", como se usa en la presente, significa la adición de un grupo hidroxilo a un grupo metileno como se describe arriba. La hidroxilación

puede realizarse, por ejemplo, por el contacto con un oxígeno molecular de conformidad con los métodos de la presente invención. La formación de diol puede realizarse, por ejemplo, por el contacto con agua de conformidad con los métodos de la presente invención. El uso de "una enzima o microorganismo" en los presentes métodos, incluye el uso de dos o más, así como una enzima o microorganismo sencillo.

La enzima o microorganismo empleado en la presente invención puede ser cualquier enzima o microorganismo capaz de catalizar las conversiones enzimáticas descritas en la presente. Los materiales enzimáticos o microbianos, independientemente del origen o pureza, pueden emplearse en el estado libre o inmovilizarse en un soporte tal como por adsorción física o la operación de entrampar. Los microorganismos o enzimas apropiados para usarse en la presente invención pueden seleccionarse por separación por exclusión para la actividad deseada, por ejemplo, al poner en contacto un microorganismo o enzima candidato con un compuesto de partida XV o XVII o una sal del mismo, y notar la conversión al correspondiente compuesto XVI o XVIII o una sal del mismo. La enzima puede, por ejemplo, estar en forma de enzimas de animal o planta o mezclas de los mismos, células de microorganismos, células molidas, extractos de células, o de origen sintético.

Los microorganismos ejemplares incluyen aquellos dentro del género: *Streptomyces* o *Amycolatopsis*. Los microorganismos particularmente preferidos son aquellos dentro de la especie *Streptomyces griseus*, especialmente *Streptomyces griseus* ATCC 10137, y *Amycolatopsis orientalis* tales como ATCC 14930, ATCC 21425, ATCC 35165, ATCC 39444, ATCC 43333, ATCC 43490, ATCC 53550, ATCC 53630, y especialmente ATCC 43491. El término "ATCC" como se usa en la presente, se refiere al número de acceso del American Type Culture Collection, 10801 University Blvd., Manassas Virginia 20110-2209, del depositario para el organismo referido. Se entenderá que los mutantes de estos organismos también se contemplan por la presente invención, para usarse en los métodos descritos en la presente, tales como aquellos modificados por el uso de medios químicos, físicos (por ejemplo, rayos X) o biológicos (por ejemplo, por técnicas de biología molecular).

Las enzimas preferidas incluyen aquellas derivadas de microorganismos, particularmente aquellos microorganismos descritos arriba. Las enzimas pueden aislarse, por ejemplo, por métodos de extracción y purificación tales como por métodos conocidos por aquellos de experiencia ordinaria en la técnica. Una enzima puede, por ejemplo, usarse en su estado libre o en forma inmovilizada. Una modalidad de la invención es que donde una enzima se adsorbe en un portador apropiado, por ejemplo, tierra diatomácea (Celite Hyflo Supercel

porosa), polipropileno microporoso (polvo de polipropileno Enka Accurel®), o un adsorbente polimérico no iónico tal como Amberlite® XAD-2 (poliestireno) o XAD-7 (poliacrilato) de Rohm and Haas Co. Cuando se emplea para inmovilizar una enzima, el portador puede controlar el tamaño de partícula de la enzima y prevenir la agregación de las partículas de la enzima cuando se usan en un solvente orgánico. La inmovilización puede realizarse, por ejemplo, al precipitar una solución acuosa de la enzima con acetona fría en presencia de Celite Hyflo Supercel seguido por secado al vacío, o en el caso de un adsorbente polimérico no iónico, incubar las soluciones de enzima con un adsorbente en un agitador, remover el exceso de solución y secar las resinas adsorbentes de enzima bajo vacío. Aunque es deseable usar la menor cantidad posible de enzima, la cantidad de enzima requerida variará dependiendo de la actividad específica de la enzima usada.

La hidroxilación como se describe arriba, puede ocurrir in vivo. Por ejemplo, la enzima del hígado puede hidroxilar, con relación al isómero endo, selectivamente el isómero exo del compuesto de la presente invención. Al conducir los métodos de la presente invención fuera del cuerpo, la hidroxilasa microsomal del hígado puede emplearse como la enzima para la catálisis.

Estos procesos también pueden llevarse a cabo con el uso de células microbianas que contienen una enzima que tiene la capacidad de catalizar las conversiones. Cuando se usa un microorganismo para realizar la conversión, estos procedimientos se llevan a cabo convenientemente al agregar las células y el material de partida al medio de reacción deseado.

Donde se emplean microorganismos, las células pueden usarse en la forma de células húmedas intactas o células secas tales como liofilizadas, secadas por rocío o células secadas por calor, o en forma de material celular tratado tal como células rotas o extractos de células. Los extractos de células inmovilizados en polipropileno Celite® o Accurel® como se describe anteriormente, también pueden emplearse. El uso de organismos genéticamente modificados también se contempla. La células hospedadora puede ser cualquier célula, por ejemplo, *Escherichia coli*, modificada para contener un gen o genes para expresar una o más enzimas capaces de catalizar como se describe en la presente.

Donde se emplean uno o más microorganismos, los métodos enzimáticos de la presente invención pueden llevarse a cabo posterior a la fermentación del microorganismo (dos etapas de fermentación y conversión), o concurrentemente con esto, esto es, en el último caso, por fermentación y conversión in situ (fermentación y conversión de etapa sencilla).

El crecimiento de los microorganismos puede realizarse por alguien de experiencia ordinaria en la técnica por el uso de un medio apropiado. El medio apropiado para el crecimiento de microorganismos incluye aquellos que proporcionan los nutrientes necesarios para el crecimiento de las células microbianas. Un medio típico para el crecimiento incluye necesariamente fuentes de carbono, fuentes de nitrógeno, y elementos (por ejemplo en cantidades en trazas). También se pueden agregar inductores. El término "inductor", como se usa en la presente, incluye cualquier compuesto que aumenta la formación de la actividad enzimática deseada dentro de la célula microbiana.

Las fuentes de carbono pueden incluir azúcares tales como maltosa, lactosa, glucosa, fructosa, glicerol, sobitol, sacarosa, almidón, manitol, propilen glicol, y similares; ácidos orgánicos tales como acetato de sodio, citrato de sodio, y similares; y alcoholes tales como etanol, propanol y similares.

Las fuentes de nitrógeno pueden incluir N-Z amina A, licor primario de maíz, harina de fríjol de soya, extractos de carne, extractos de levadura, melazas, levadura de panadería, triptona, nutrisoya, peptona, levastamina, aminoácidos tales como glutamato de sodio y similares, nitrato de sodio, sulfato de amonio y similares.

Los elementos en trazas incluyen sales de magnesio, manganeso, calcio, cobalto, níquel, hierro, sodio y potasio. Los fosfatos también pueden agregarse en trazas o, preferiblemente, mayor que las cantidades trazas.

El medio empleado puede incluir más de una fuente de carbono o nitrógeno u otro nutriente.

El medio preferido para el crecimiento incluye el medio acuoso.

La agitación y aireación de la mezcla de reacción afecta la cantidad de oxígeno disponible durante el proceso de conversión cuando se conduce, por ejemplo, en cultivos de matraz agitado o tanques fermentadores durante el crecimiento de microorganismos.

La incubación del medio de reacción es preferiblemente a una temperatura entre alrededor de 4 y alrededor de 60°C. El tiempo de reacción puede variar apropiadamente dependiendo de la cantidad de enzima usada y su actividad específica. Los tiempos de reacción pueden reducirse al incrementar la temperatura de reacción y/o incrementar la cantidad de enzima agregada a la solución de reacción.

También se prefiere emplear un líquido acuoso como el medio de reacción, no obstante que también puede emplearse un líquido orgánico, o una mezcla de líquido orgánico/acuoso miscible o inmiscible (bifásico). La cantidad de enzima o microorganismo empleado con relación al material de partida

se selecciona para permitir una catálisis de las conversiones enzimáticas de la presente invención.

Los solventes para la fase orgánica de un sistema solvente bifásico pueden ser cualquier solvente orgánico inmiscible en agua, tales como tolueno, ciclohexano, xileno, triclorotrifluoroetano y similares. La fase acuosa es convenientemente de agua, preferiblemente agua desionizada, o una solución amortiguadora acuosa apropiada, especialmente una solución amortiguadora de fosfato. El sistema solvente bifásico comprende preferiblemente entre alrededor de 10 hasta 90 por ciento por volumen de fase orgánica, y entre alrededor de 90 hasta 10 por ciento por volumen de fase acuosa, y más preferiblemente contiene o alrededor de 20 por ciento por volumen de fase orgánica y a, o alrededor de 80 por ciento por volumen de la fase acuosa.

Una modalidad ejemplar de tal proceso inicia con la preparación de una solución acuosa de las enzimas o microbios a usarse. Por ejemplo, las enzimas preferidas o microbios pueden agregarse a una cantidad apropiada de un solvente acuoso, tal como solución amortiguadora de fosfato o similares. Esta mezcla se ajusta preferiblemente hasta, y se mantiene al pH deseado.

Los compuestos XVI y XVIII producidos por los procesos de la presente invención, pueden aislarse y purificarse, por

ejemplo, por métodos tales como extracción, destilación, cristalización, y cromatografía de columna.

Compuestos Preferidos.

Un subgénero preferido de los compuestos de la presente invención incluye compuestos de la fórmula I o sales de los mismos en donde uno o más, preferiblemente todos, de los siguientes substituyentes son como se definen a continuación:

G es un grupo arilo o heterociclo (por ejemplo, heteroarilo), donde el grupo es mono- o policíclico, y el cual está opcionalmente substituido en una o más posiciones, preferiblemente con hidrógeno, alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, halo, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, arilo o arilo substituido, heterociclo o heterociclo substituido, arilalquilo o arilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, CN, $R^1OC{=}O$, $R^1C{=}O$, $R^1HNC{=}O$, $R^1R^2NC{=}O$, $HOCR^3R^{3'}$, nitro, R^1OCH_2, R^1O, NH_2, NR^4R^5, $S{=}RO^1$, SO_2R^1, $SO_2NR^1R^{1'}$, $(R^1)(R^{1'})P{=}O$, o $(R^{1'})(NHR^1)P{=}O$;

Z_1 es O, S, NH, o NR^6;

Z_2 es O, S, NH, o NR^6;

A_1 es CR^7 o N;

A_2 es CR^7 o N;

Y es J-J'-J" donde J es $(CR^7R^{7'})n$ y n = 0-3, J' es un enlace u O, S, S=O, SO_2, NH, OC=O, C=O, NR^7, $CR^7R^{7'}$, $R^2P=O$, $R^2P=S$, $R^2OP=O$, $R^2NHP=O$, $OP=OOR^2$, $OP=ONHR^2$, $OP=OR^2$, OSO_2, NHNH, $NHNR^6$, NR^6NH, N=N, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, o heterociclo o heterociclo substituido, y J" es $(CR^7R^{7'})n$ y n = 0-3, donde Y no es un enlace;

W es $CR^7CR^{7'}$—$CR^7R^{7'}$, $CR^7R^{7'}$—C=O, NR^9—$CR^7R^{7'}$, $N=CR^8$, N=N, NR^9—$NR^{9'}$, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, o arilo o arilo substituido, en donde, cuando W no es NR^9—$CR^7R^{7'}$, $N=CR^8$, N=N, NR^9—$NR^{9'}$, o heterociclo o heterociclo substituido, entonces J' deberá ser O, S, S=O, SO_2, NH, NR^7, $OP=OOR^2$, $OP=ONHR^2$, OSO_2, NHNH, $NHNR^6$, NR^6NH, o N=N;

Q_1 es H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilalquilo o arilalquilo substituido, alquinilo o alquinilo substituido, arilo o arilo substituido, heterociclo (por ejemplo, heteroarilo) o heterociclo substituido (por ejemplo, heteroarilo substituido),

halo, CN, $R^1OC{=}O$, $R^4C{=}O$, $R^5R^6NC{=}O$, $HOCR^7R^{7'}$, nitro, R^1OCH_2, R^1O, NH_2, o NR^4R^5;

Q_2 es H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilalquilo o arilalquilo substituido, alquinilo o alquinilo substituido, arilo o arilo substituido, heterociclo (por ejemplo, heteroarilo) o heterociclo substituido (por ejemplo, heteroarilo substituido), halo, CN, $R^1OC{=}O$, $R^4C{=}O$, $R^5R^6NC{=}O$, $HOCR^7R^{7'}$, nitro, R^1OCH_2, R^1O, NH_2, o NR^4R^5;

L es un enlace, $(CR^7R^{7'})n$, NH, NR^5 o $NR^5(CR^7R^{7'})n$, donde n = 0-3;

R^1 y $R^{1'}$ son cada uno independientemente H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido;

R^2 es alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido;

R^3 y $R^{3'}$ son cada uno independientemente H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido, halo, CN, hidroxilamina, hidroxamida, alcoxi o alcoxi substituido, amino, NR^1R^2, tiol, alquiltio o alquiltio substituido;

R^4 es H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo

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substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido, $R^1C=O$, $R^1NHC=O$, o $SO_2NR^1R^{1'}$;

R^5 es alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido, $R^1C=O$, $R^1NHC=O$, SO_2R^1, o $SO_2NR^1R^{1'}$;

R^6 es alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido, CN, OH, OR^1, $R^1C=O$, $R^1NHC=O$, SO_2R^1, o $SO_2NR^1R^{1'}$;

R^7 y $R^{7'}$ son cada uno independientemente H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido, halo, CN, OR^4, nitro, hidroxilamina, hidroxilamida, amino, NHR^4, NR^2R^5, NOR^1, tiol, alquiltio o alquiltio substituido, $R^1C{=}O$, $R^1(C{=}O)O$, $R^1OC{=}O$, $R^1NHC{=}O$, SOR^1, $PO_3R^1R^{1'}$, $R^1R^{1'}NC{=}O$, $C{=}OSR^1$, SO_2R^1, o $SO_2NR^1R^{1'}$;

R^8 y $R^{8'}$ son cada uno independientemente H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido, nitro, halo, CN, OR^1, amino, NHR^4, NR^2R^5, NOR^1, alquiltio o alquiltio substituido,

$C{=}OSR^1$, $R^1OC{=}O$, $R^1C{=}O$, $R^1NHC{=}O$, $R^1R^{1'}NC{=}O$, $S{=}OR^1$, SO_2R^1, $PO_3R^1R^{1'}$, o $SO_2NR^1R^{1'}$;

R^9 y $R^{9'}$ son cada uno independientemente H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido; cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido, CN, OH, OR^1, $R^1C{=}O$, $R^1OC{=}O$, $R^1NHC{=}O$, o $SO_2NR^1R^{1'}$;

especialmente donde los grupos W e Y de este subgénero preferido están también dentro de las definiciones de W' e Y' de la fórmula Ia, con las condiciones (1) hasta (14) de tal fórmula Ia donde sea apropiado a este subgénero, y más preferiblemente donde (i) cuando Y' es -O- y W' es $CR^7R^{7'}$—$CR^7R^{7'}$, A_1 y A_2 no son simultáneamente CH; y (ii) cuando L es un enlace, G no es un grupo fenilo insubstituido.

Otro subgénero más preferido de los compuestos de la invención incluye compuestos de la fórmula I o sales de los mismos en donde uno o más, preferiblemente todos, de los siguientes substituyentes son como se definen a continuación:

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G es un grupo arilo o heterociclo (por ejemplo, heteroarilo), donde el grupo es mono- o policíclico, y el cual está opcionalmente substituido en una o más posiciones, preferiblemente con hidrógeno, alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, halo, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, arilo o arilo substituido, heterociclo o heterociclo substituido, arilalquilo o arilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, CN, $R^1C{=}O$, $R^1HNC{=}O$, $R^1R^2NC{=}O$, $HOCR^3R^{3'}$, nitro, R^1OCH_2, R^1O, NH_2, NR^4R^5, SO_2R^1, o $SO_2NR^1R^{1'}$;

Z_1 es O;

Z_2 es O;

A_1 es CR^7;

A_2 es CR^7;

Y es J-J'-J" donde J es $(CR^7R^{7'})n$ y n = 0-3, J' es un enlace u O, S, S=O, SO_2, NH, NR^7, $CR^7R^{7'}$, $R^2P{=}O$, $R^2P{=}S$, $R^2OP{=}O$, $R^2NHP{=}O$, $OP{=}OOR^2$, $OP{=}ONHR^2$, $OP{=}OR^2$, OSO_2, NHNH, $NHNR^6$, NR^6NH, N=N, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, o heterociclo o heterociclo substituido, y J" es $(CR^7R^{7'})n$ y n = 0-3, donde Y no es un enlace;

W es $CR^7R^{7'}$—$CR^7R^{7'}$, $CR^7R^{7'}$—C=O, NR^9—$CR^7R^{7'}$, N=CR^8, N=N, NR^9—$NR^{9'}$, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, o arilo o arilo substituido, en donde, cuando W no es NR^9—$CR^7R^{7'}$, N=CR^8, N=N, NR^9—$NR^{9'}$, o heterociclo o heterociclo substituido, entonces J' deberá ser O, S, S=O, SO_2, NH, NR^7, OP=OOR^2, OP=$ONHR^2$, OSO_2, NHNH, $NHNR^6$, NR^6NH, o N=N;

Q_1 es H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilalquilo o arilalquilo substituido, alquinilo o alquinilo substituido, arilo o arilo substituido, heterociclo (por ejemplo, heteroarilo) o heterociclo substituido (por ejemplo, heteroarilo substituido), halo, CN, R^4C=O, R^5R^6NC=O, $HOCR^7R^{7'}$, nitro, R^1OCH_2, R^1O, NH_2, o NR^4R^5;

Q_2 es H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilalquilo o arilalquilo substituido, alquinilo o alquinilo substituido, arilo o arilo substituido,

heterociclo (por ejemplo, heteroarilo) o heterociclo substituido (por ejemplo, heteroarilo substituido), halo, CN, $R^4C{=}O$, $R^5R^6NC{=}O$, $HOCR^7R^{7'}$, nitro, R^1OCH_2, R^1O, NH_2, o NR^4R^5;

L es un enlace;

R^1 y $R^{1'}$ son cada uno independientemente H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido;

R^2 es alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido;

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R^3 y $R^{3'}$ son cada uno independientemente H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido, halo, CN, alcoxi o alcoxi substituido, amino, NR^1R^2, alquiltio o alquiltio substituido;

R^4 es H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido, $R^1C{=}O$, $R^1NHC{=}O$, o $SO_2NR^1R^{1'}$;

R^5 es alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo

substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido, $R^1C{=}O$, $R^1NHC{=}O$, SO_2R^1, o $SO_2NR^1R^{1'}$;

R^6 es alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido, CN, OH, OR^1, $R^1C{=}O$, $R^1NHC{=}O$, SO_2R^1, o $SO_2NR^1R^{1'}$;

R^7 y $R^{7'}$ son cada uno independientemente H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o

arilalquilo substituido, halo, CN, OR^4, nitro, amino, NHR^4, NR^2R^5, alquiltio o alquiltio substituido, $R^1C{=}O$, $R^1(C{=}O)O$, $R1NHC{=}O$, SO_2R^1, $R^1R^{1'}NC{=}O$, o $SO_2NR^1R^{1'}$;

R^8 y $R^{8'}$ son cada uno independientemente H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido, nitro, halo, CN, OR^1, amino, NHR^4, NR^2R^5, alquiltio o alquiltio substituido, $R^1C{=}O$, $R^1NHC{=}O$, $R^1R^{1'}NC{=}O$, SO_2R^1, o $SO_2NR^1R^{1'}$; y

R^9 y $R^{9'}$ son cada uno independientemente H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o

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arilalquilo substituido, CN, OH, OR^1, $R^1C=O$, $R^1NHC=O$, o $SO_2NR^1R^{1'}$;

especialmente donde los grupos W e Y de este subgénero preferido están también dentro de las definiciones de W' e Y' de la fórmula Ia, con las condiciones (1) hasta (14) de tal fórmula Ia donde es apropiado a este subgénero, y más preferiblemente donde (i) cuando Y' es -O- y W' es $CR^7R^{7'}$—$CR^7R^{7'}$, A_1 y A_2 no son simultáneamente CH; y (ii) cuando L es un enlace, G no es un grupo fenilo insubstituido.

Un subgénero particularmente preferido de los compuestos de la invención, incluye compuestos de la fórmula I o sales de los mismos en donde uno o más, preferiblemente todos, de los substituyentes son como se define a continuación:

G es un grupo arilo (especialmente, fenilo o naftilo) o heterociclo (especialmente aquellos grupos heterociclo G de los compuestos de los Ejemplos en la presente), donde el grupo es mono- o policíclico, y el cual está opcionalmente substituido en una o más posiciones, preferiblemente con substituyentes como se ejemplifica en cualesquiera de los compuestos de los Ejemplos en la presente;

L es un enlace, $(CR^7R^{7'})n$ (donde n es 1 y R^7 y $R^{7'}$ son cada uno independientemente H, alquilo o alquilo substituido), o -CH2-NH-;

A_1 y A_2 son cada uno independientemente CR^7 donde R^7 (i) es hidrógeno, alquilo o alquilo substituido, arilalquilo o arilalquilo substituido, alquenilo o alquenilo substituido (por ejemplo, alquenilo substituido con arilo (especialmente, fenilo o naftilo) o arilo substituido, o alquenilo substituido con heterociclo o heterociclo substituido), arilo o arilo substituido, heterociclo o heterociclo substituido, heterocicloalquilo o heterocicloalquilo substituido, donde, para cada uno, los substituyentes preferidos son uno o más grupos seleccionados de V^1 (especialmente grupos A_1 y A_2 de la fórmula CR^7 donde R^7 para cada uno de A_1 y/o A_2 es seleccionado independientemente de alquilo C_{1-4} insubstituido, o alquilo C_{1-4} cuyo alquilo está substituido por uno o más grupos V^1), o (ii) forma, junto con R^7 de un grupo W (especialmente donde W es $CR^7R^{7'}$—$CR^7R^{7'}$), un anillo heterocíclico;

V^1 es OH, CN, halo, -O-arilo, -O-arilo substituido, -O-heterociclo (por ejemplo, -O- (piridinilo opcionalmente substituido) u -O-(pirimidinilo opcionalmente substituido)), -O-heterociclo substituido, -O-CO-alquilo, -O-CO-alquilo substituido, -O-(alquilsililo), -O-arilalquilo, -O-arilalquilo substituido, -O-CO-alquilo, -O-CO-alquilo substituido, -O-CO-arilalquilo, -O-CO-arilalquilo substituido, -O-CO-arilo, -O-CO-arilo

substituido, -O-CO-heterociclo, -O-CO-heterociclo substituido, -S-(arilo opcionalmente substituido)-NH-CO-(alquilo opcionalmente substituido), -SO-(arilo opcionalmente substituido)-NH-CO-(alquilo opcionalmente substituido), -SO2-(arilo opcionalmente substituido)-NH-CO-(alquilo opcionalmente substituido), -NH-SO2-arilo, -NH-SO2-arilo substituido, -NH-CO-O-(arilalquilo opcionalmente substituido), -NH-CO-O-alquilo, -NH-CO-O-alquilo substituido, -NH-CO-alquilo, -NH-CO-alquilo substituido, -NH-CO-arilo, -NH-CO-arilo substituido, -NH-CO-(arilalquilo opcionalmente substituido), -NH-CO-(alquilo opcionalmente substituido)-O-(arilo opcionalmente substituido), -N(alquilo opcionalmente substituido)(arilo opcionalmente substituido), -N(alquilo opcionalmente substituido)(arilalquilo opcionalmente substituido), -COH, -COOH, -CO-O-alquilo, -CO-O-alquilo substituido, -CO-O-arilalquilo opcionalmente substituido, -CO-arilo, -CO-arilo substituido, -O-CO-NH-arilo, -O-CO-NH-arilo substituido, -CO-NH-arilo, -CO-NH-arilo substituido, -CO-NH-arilalquilo, -CO-NH-arilalquilo substituido, -O-(arilo opcionalmente substituido)-NH-CO-(alquilo opcionalmente substituido);

Y es -O-, -SO-, $-N(V^2)-$, $-CH_2-N(V^2)-$, -CO-N(alquilo)-, $-CH_2-S-$, $-CH_2-SO_2-$;

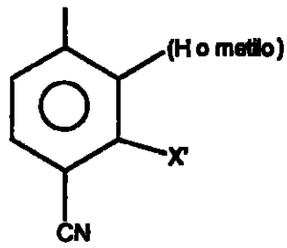
V^2 es hidrógeno, alquilo, arilalquilo, -CO-alquilo, -CO-O-arilo, -CO-O-arilalquilo;

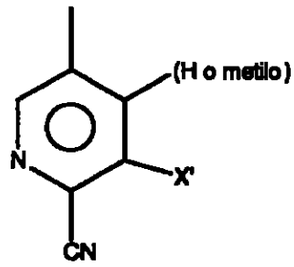
W es $CR^7R^{7'}$—$CR^7R^{7'}$ (donde R^7 y $R^{7'}$ son cada uno independientemente seleccionados de H, OH, alquilo o alquilo substituido (tal como hidroxialquilo), o donde R^7 forma un anillo heterocíclico junto con R^7 de A_1 o A_2), CR^8=$CR^{8'}$ (donde R^8 y $R^{8'}$ son cada uno independientemente seleccionados de H, alquilo o alquilo substituido (tal como hidroxialquilo)), $CR^7R^{7'}$—C=O (donde R^7 y $R^{7'}$ son cada uno hidrógeno, o donde R^7 forma un anillo heterocíclico junto con R^7 de A_1 o A_2), N=CR^8 (donde R^8 es alquilo), cicloalquilo o cicloalquilo substituido, o heterociclo o heterociclo substituido;

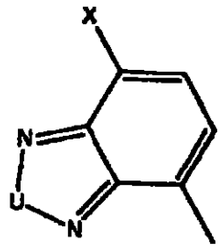
Z_1 y Z_2 son O; y

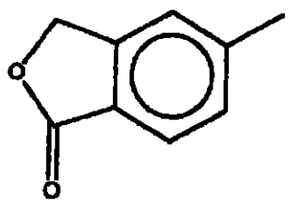
Q_1 y Q_2 son H.

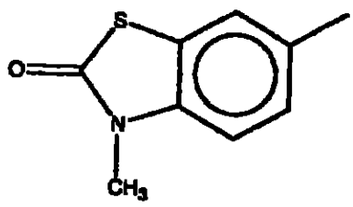
Los grupos preferidos G-L son grupos fenilo opcionalmente substituido, naftilo opcionalmente substituido y heterocíclico bicíclico fusionado opcionalmente substituido tales como grupos heterocíclicos fusionados a benzo opcionalmente substituidos (por ejemplo, enlazados al resto de la molécula a través de la porción benceno), especialmente tales grupos en donde el anillo heterocíclico enlazado al benceno tiene 5 miembros ejemplificados por benzoxazol, benzotiazol, benzotiadiazol, benzoxadiazol o benzotiofeno, por ejemplo:

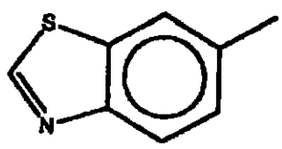

(H o metilo)
X'
CN


(H o metilo)
N
X'
CN

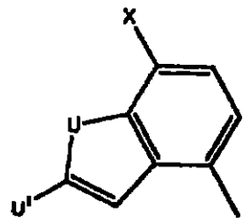

X
N
U
N

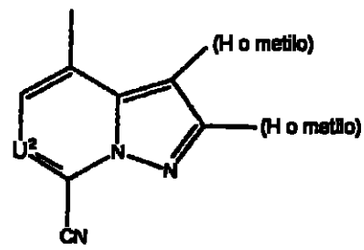

O
O

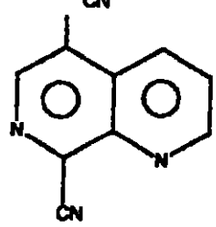

S
O
N
CH3

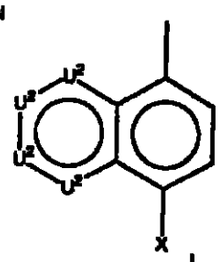

S
N

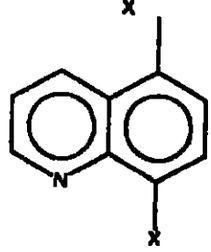
979



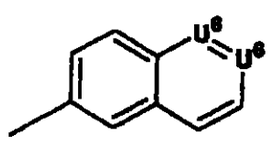


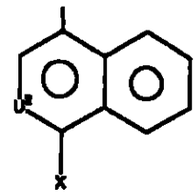


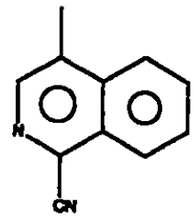


(por ejemplo,  donde X es OH o CN)

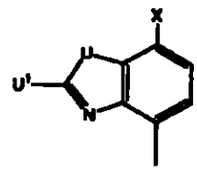
o



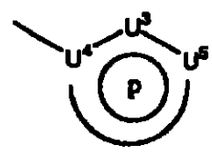


(por ejemplo, )

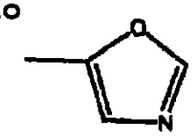
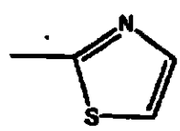
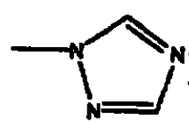
o



donde



X = halo (especialmente F), OH, CN, NO_2 o

(por ejemplo   o );

X' = halo (especialmente Cl, F, o I), CH_3, CF_3, CN o OCH_3;

U es O u S (donde S puede opcionalmente oxigenarse, por ejemplo, para SO);

U^1 es CH_3 o CF_3;

cada U^2 es independientemente N, CH o CF;

U^3 es N, O u S;

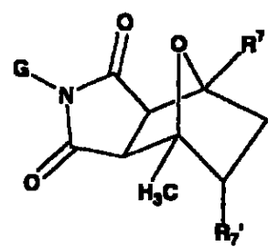
U^4 y U^5, junto con los átomos a los cuales se enlazan, forman un anillo heterocíclico de 5 miembros opcionalmente

substituido que puede ser parcialmente insaturado o aromático y que contiene de 1 hasta 3 heteroátomos en el anillo;

cada U^6 es independientemente CH o N; y

(p) significa enlaces dobles opcionales dentro del anillo formados por U^3, U^4 y U^5.

Un subgénero especialmente preferido incluye compuestos de la fórmula I que tienen la siguiente estructura, o sales de los mismos:



donde G es fenilo opcionalmente substituido, un grupo heterocíclico bicíclico fusionado a benzo o naftilo, R^7 es CH_3 o alquilo C_{1-4} substituido por V^1, y un $R^{7'}$ es H o hidroxilo y el otro es H.

Los compuestos preferidos de la invención incluyen:

[3aS-(3aα,4β,6β,7β,7aα)]-4-(Octahidro-6-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

[3aR(3aα,4β,6β,7β,7aα)]-4-(Octahidro-6-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-

(trifluorometil)benzonitrilo;

[3aS-(3aα,4β,5β,6α,7β,7aα)]-4-(Octahidro-5,6-dihidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

[3aS-(3aα,4β,5β,7β,7aα)]-5-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-3metil-2-piridincarbonitrilo;

[3aS-(3aα,4β,5β,7β,7aα)]-2-(2,1,3-Benzoxadiazol-5-il)hexahidro-5-hidroxi-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3(2H)-diona;

[3aS-(3aα,4β,5β,7β,7aα)]-5-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-3,4-dimetil-2-piridincarbonitrilo;

[3aR-(3aα,4β,5β,7β,7aα)]-5-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-3,4-dimetil-2-piridincarbonitrilo;

[3aS-(3aα,4β,5β,7β,7aα)]-2-(6-Benzotiazolil)hexahidro-5-hidroxi-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3(2H)-diona;

[3aR-(3aα,4β,5β,7β,7aα)]-2-(7-Cloro-2,1,3-benzoxadiazol-4-il)hexahidro-5-hidroxi-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3(2H)-diona;

[3aR-(3aα,4β,5α,7β,7aα)]-5-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-3-(trifluorometil)-2-piridincarbonitrilo;

[3aR-(3aα,4β,5α,7β,7aα)]-4-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-yodobenzonitrilo;

éster de metilo del ácido (3aα,4β,5α,6β,7β,7aα)-2-(4-Ciano-3-(trifluorometil)fenil)hexahidro-6-ciano-4,7-dimetil-1,3-dioxo-4,7-epoxi-1H-isoindol-5-carboxílico;

(3aα,4β,7β,7aα)-4-(Octahidro-4,7,8-trimetil-1,3-dioxo-4,7-imino-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

[3aR-(3aα,4β,5β,6α,7β,7aα)]-4-(Octahidro-5,6-dicloro-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

[3aS-(3aα,4β,5β,6α,7β,7aα)]-4-(Octahidro-5,6-dicloro-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

(3aα,4β,7β,7aα)-4-(Octahidro-4,7-dimetil-1,3,5-trioxo-4,7-epoxi-2H-isoindol-2-il)-2-yodobenzonitrilo;

(3aα,4β,5α,7β,7aα)-4-(Octahidro-5-[[[difluorometil]oxi]metil]-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

(3aα,4β,5α,7β,7aα)-4-(Octahidro-5-[[fenilmetoxicarbonil]amino]-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

(3aα,4β,5α,7β,7aα)-4-(Octahidro-5-[[propiloxicarbonil]amino]-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

(3aα,4β,5α,7β,7aα)-4-(Octahidro-5-[[[ciclopropilmetiloxi]carbonil]amino]-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

(3aα,4β,5α,7β,7aα)-4-(Octahidro-5-[[metoxicarbonil]amino]-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

[3aR-(3aα,4β,5β,7β,7aα)]-4-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2,3-diclorobenzonitrilo;

[3aR-(3aα,4β,4aα,5aα,6β,7aα)]-4-(Octahidro-4a-hidroxi-4,6-dimetil-1,3-dioxo-4,6-epoxiciclopropf[f]isoindol-2(1H)-il)-2-(trifluorometil)benzonitrilo;

(3aα,4β,5α,7β,7aα)-2-(4-Ciano-3-(trifluorometil)fenil)hexahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-N,N-dimetil-1H-isoindol-5-carboxamida;

[3aR-(3aα,4β,5β,6β,7β,7aα)]-4-(Octahidro-5-cloro-6-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

[3aS-(3aα,4β,5β,6β,7β,7aα)]-4-(Octahidro-5-cloro-6-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

(3aα,4β,5α,7β,7aα)-4-(Octahidro-5-[[[6-(trifluorometil)-4-pirimidinil]oxi]metil]-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

(3aα,4β,5α,7β,7aα)-4-(Octahidro-5-[[[5-cloro-2-piridinil]oxi]metil]-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

[3aR-(3aα,4β,5α,7β,7aα)]-4-(Octahidro-5-[[[fenilamino]carbonil]amino]-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

[3aR-(3aα,4β,5α,7β,7aα)]-4-(Octahidro-5-[[(1-metiletiloxi)carbonil]amino]-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

(3aα,4β,5α,7β,7aα)-4-(Octahidro-5-[[[5-fluoro-4-pirimidinil]oxi]metil]-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

[3aR-(3aα,4β,5α,7β,7aα)]-4-(Octahidro-5-[[etiloxicarbonil]amino]-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

éster de 4-piridinilmetilo del ácido [3aR-(3aα,4β,5α,7β,7aα)]-2-(4-Ciano-3-(trifluorometil)fenil)-hexahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-1H-isoindol-5-carboxílico;

[3aR-(3aα,4β,5α,7β,7aα)]-4-(Octahidro-5-[[4-piridinilmetoxicarbonil]amino]-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

3aα,4β,5β,7β,7aα)-4-(Octahidro-5-[[[2-metil-5-(trifluorometil)-2H-pirazol-3-il]oxi]metil]-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

éster de metilo del ácido (3aα,4β,5α,7β,7aα)-2-(4-Ciano-3-(trifluorometil)fenil)hexahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-1H-isoindol-5-carboxílico;

[3aR-(3aα,4β,5β,7β,7aα)]-4-(Octahidro-5-ciclopropilmetoxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

(3aα,4β,5α,7β,7aα)-4-(Octahidro-5-[[((fenilmetil)amino)carbonil]oxi]-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo; y

[3aR-(3aα,4β,5β,7β,7aα)]-4-(Octahidro-5-ciclopropiloxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

o sales, solvatos, profármacos o estereoisómeros farmacéuticamente aceptables de los mismos.

Los compuestos más preferidos de la invención incluyen:

[3aR-(3aα,4β,5β,7β,7aα)]-5-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-3-(trifluorometil)-2-piridincarbonitrilo;

[3aS-(3aα,4β,5β,7β,7aα)]-5-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-3-(trifluorometil)-2-piridincarbonitrilo;

[3aR-(3aα,4β,5β,7β,7aα)]-2-(4-Cloro-3-yodofenil)hexahidro-5-hidroxi-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3(2H)-diona;

[3aS-(3aα,4β,5β,6α,7β,7aα)]-4-(Octahidro-5,6-dihidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

[3aR-(3aα,4β,7β,7aα)]-4-(Octahidro-4,7-dimetil-1,3,5-trioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

[3aR-(3aα,4β,5α,7β,7aα)]-4-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

[3aS-(3aα,4β,5α,7β,7aα)]-4-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

[3aS-(3aα,4β,6β,7β,7aα)]-4-(Octahidro-6-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

[3aR-(3aα,4β,5β,7β,7aα)]-2-(4-Cloro-3-(trifluorometil)fenil)hexahidro-5-hidroxi-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3(2H)-diona;

[3aS-(3aα,4β,5β,7β,7aα)]-4-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-yodobenzonitrilo;

[3aR-(3aα,4β,5β,7β,7aα)]-4-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-yodobenzonitrilo;

[3aS-(3aα,4β,5β,7β,7aα)]-2-(4-Cloro-3-(trifluorometil)piridinil)hexahidro-5-hidroxi-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3(2H)-diona;

[3aR-(3aα,4β,5β,7β,7aα)]-4-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-3-metil-2-(trifluorometil)benzonitrilo;

[3aR-(3aα,4β,5β,7β,7aα)]-4-(Octahidro-5-metoxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

[3aR-(3aα,4β,5α,7β,7aα)]-5-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-3-(trifluorometil)-2-piridincarbonitrilo;

[3aS-(3aα,4β,5β,7β,7aα)]-4-(Octahidro-5-metoxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

[3aS-(3aα,4β,6β,7β,7aα)]-4-(Octahidro-6-fluoro-5,5-dihidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

[3aR-(3aα,4β,7β,7aα)]-5-(Octahidro-4,7-dimetil-1,3,5-trioxo-4,7-epoxi-2H-isoindol-2-il)-3-(trifluorometil)-2-piridincarbonitrilo;

[3aS-(3aα,4β,5β,7β,7aα)]-2-(4-Cloro-2-metil-3-(trifluorometil)fenil)hexahidro-5-hidroxi-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3(2H)-diona;

[3aR-(3aα,4β,5β,7β,7aα)]-2-(4-Cloro-2-metil-3-(trifluorometil)fenil)hexahidro-5-hidroxi-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3(2H)-diona;

(3aα,4β,6β,7β,7aα)-4-(Octahidro-6-fluoro-5,5-dihidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-yodobenzonitrilo;

éster de metilo del ácido (3aα,4β,5α,7β,7aα)-2-(4-Ciano-3-(trifluorometil)fenil)-hexahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-1H-isoindol-5-carboxílico;

[3aS-(3aα,4β,6β,7β,7aα)]-4-(Octahidro-6-fluoro-5,5-dihidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-yodobenzonitrilo;

(3aα,4β,5α,7β,7aα)-4-(Octahidro-5-etilsulfonamido-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

[3aR-(3aα,4β,5α,7β,7aα)]-4-(Octahidro-5-[[(4-fluorofenilamino)carbonil]oxi]-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

[3aR-(3aα,4β,5α,7β,7aα)]-4-(Octahidro-5-[[(1-metiletilamino)carbonil]oxi]-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

[3aS-(3aα,4β,5α,7β,7aα)]-4-(Octahidro-5-[[(1-metiletoxi)carbonil]amino]-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

[3aR-(3aα,4β,6β,7β,7aα)]-4-(Octahidro-6-fluoro-5,5-dihidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-yodobenzonitrilo;

[3aR-(3aα,4β,5α,7β,7aα)]-2-(4-Ciano-3-(trifluorometil)fenil)hexahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-N-metil-N-fenil-1H-isoindol-5-carboxamida;

[3R-(3aα,4β,5β,7β,7aα)]-4-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-cloro-3-metilbenzonitrilo;

[3aR-(3aα,4β,5α,7β,7aα)]-4-(Octahidro-5-[[etoxicarbonil]amino]-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

(3aα,4β,5α,7β,7aα)-4-(Octahidro-5-[[[2-metil-5-(trifluorometil)-2H-pirazol-3-il]oxi]metil]-4,7-dimetil-1,3-

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dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

éster de metilo del ácido [3aS-(3aα,4β,5α,6β,7β,7aα)]-2-(4-Ciano-3-(trifluorometil)fenil)-hexahidro-6-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-1H-isoindol-5-carboxilico;

(3aα,4β,5α,7β,7aα)-4-(Octahidro-5-[[[6-(trifluorometil)-4-pirimidinil]oxi]metil]-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

[3aR-(3aα,4β,5α,7β,7aα)]-4-(Octahidro-5-metoxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

(3aα,4β,5α,7β,7aα)-2-(4-Ciano-3-(trifluorometil)fenil)-hexahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-1H-isoindol-5-carbonitrilo;

[3aR-(3aα,4β,5β,6α,7β,7aα)]-4-(Octahidro-5,6-dihidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-3-metil-2-(trifluorometil)benzonitrilo;

[3aR-(3aα,4β,5α,7β,7aα)]-4-(Octahidro-5-[[[(ciclopropilmetil)amino]carbonil]amino]-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

[3aR-(3aα,4β,5α,7β,7aα)]-4-(Octahidro-5-[[(dimetilamino)sulfonil]amino]-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

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(3aα,4β,5α,7β,7aα)-4-(Octahidro-5-benzenesulfonamido-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

[3aR-(3aα,4β,6β,7β,7aα)]-4-(Octahidro-6-fluoro-5,5-dihidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

éster de metilo del ácido [3aR-(3aα,4β,5α,6β,7β,7aα)]-2-(4-Ciano-3-(trifluorometil)fenil)-hexahidro-6-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-1H-isoindol-5-carboxilico; y

[3aR-(3aα,4β,5α,7β,7aα)]-4-(Octahidro-5-[[(dimetilamino)sulfonil]amino]-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

o sales, solvatos, profármacos o estereoisómeros farmacéuticamente aceptables de los mismos.

Los compuestos donde R^7 es hidroxilo pueden proporcionar una solubilidad al agua incrementada y estabilidad metabólica, con relación a los compuestos correspondientes donde $R^{7'}$ es H, además de que tienen buena permeabilidad y altos niveles sanguíneos sistémicos. Estos compuestos que portan hidroxilo pueden obtenerse in vivo por el metabolismo del correspondiente compuesto donde $R^{7'}$ es H, así como por métodos preparativos sintéticos tales como aquellos descritos en la presente.

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Uso y utilidad

Los compuestos de la presente invención modulan la función de los receptores de hormona nuclear (NHR), e incluyen compuestos que son por ejemplo, agonistas, agonistas parciales, antagonistas o antagonistas parciales del receptor andrógeno (AR), el receptor de estrógeno (ER), el receptor de progesterona (PR), el receptor glucocorticoide (GR), el receptor mineralocorticoide (MR), el receptor esteroide xenobiótico (SXR), otros NHR de enlace esteroides, los receptores huérfanos u otros NHR. La modulación selectiva de uno de tales NHR con relación a los otros dentro de la familia NHR se prefiere. La "modulación" incluye por ejemplo, activación (por ejemplo actividad agonista tal como la actividad agonista del receptor andrógeno selectivo) o la inhibición (por ejemplo, actividad antagonista).

Los compuestos actuales son entonces útiles en el tratamiento de condiciones asociadas con NHR. Una "condición asociada con NHR", como se usa en la presente, denota una condición o trastorno que se puede tratar al modular la función de un NHR en un sujeto, en donde el tratamiento comprende la prevención (por ejemplo, tratamiento profiláctico), alivio parcial o cura de la condición o trastorno. La modulación puede suceder localmente, por ejemplo, dentro de ciertos tejidos del sujeto o más

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ampliamente a través de un sujeto que se trata por tal trastorno de la condición.

Los compuestos de la presente invención son útiles para el tratamiento de una diversidad de condiciones y trastornos que incluyen, pero no se limitan a, aquellos descritos a continuación:

Los compuestos de fórmula I se pueden aplicar como agonistas, agonistas parciales, antagonistas o antagonistas parciales del receptor estrógeno, preferiblemente selectivamente con ese receptor, en una configuración de condiciones médicas que involucran la modulación de la trayectoria del receptor estrógeno. Las aplicaciones de los compuestos incluyen, pero no se limitan a: osteoporosis, bochornos, sequedad vaginal, cáncer de próstata, cáncer de mama, cáncer de endometrio, cánceres que expresan el receptor estrógeno tal como los cánceres antes mencionados y otros, anticonceptivo, terminación del embarazo, menopausia, amenorrea, y dismenorrea.

Los compuestos de fórmula I se pueden aplicar como agonistas, agonistas parciales, antagonistas, o antagonistas parciales del receptor de progesterona, preferiblemente de forma selectiva con ese receptor, en una configuración de condiciones médicas que involucran la modulación de la trayectoria del receptor de la progesterona. Las aplicaciones de tales compuestos incluyen, pero no se limitan a, cáncer de

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mama, otros cánceres que contienen el receptor de progesterona, endometriosis, caquexia, anticoncepción, menopausia, ciclosincronía, meniginoma, dismenorrea, fibroides, terminación del embarazo, inducción del parto, y osteoporosis.

Los compuestos de fórmula I, se pueden aplicar como agonistas, agonistas parciales, antagonistas, o antagonistas parciales del receptor glucocorticoide, preferiblemente de forma selectiva a ese receptor, en una configuración de condiciones médicas que involucran la modulación de la trayectoria del receptor glucocorticoide. Las aplicaciones de los compuestos incluyen, pero no se limitan a: enfermedades inflamatorias, enfermedades autoinmunes, cáncer de próstata, cáncer de mama, enfermedad de Alzheimer, trastornos psicóticos, dependencia de drogas, diabetes mellitus no dependiente de la insulina, y como agentes de bloqueo del receptor de la dopamina, o de otra manera como agentes para el tratamiento de trastornos mediados por el receptor de la dopamina.

Los compuestos de la fórmula I se pueden aplicar como agonistas, agonistas parciales, antagonistas o antagonistas parciales del receptor mineralocorticoide, preferiblemente de forma selectiva con ese receptor en una configuración de condiciones médicas que involucran la modulación de la trayectoria del receptor mineralocorticoide. Las aplicaciones

de los compuestos incluyen, pero no se limitan a: síndrome de retiro de fármacos y enfermedades inflamatorias.

Los compuestos de fórmula I se pueden aplicar como agonistas, agonistas parciales, antagonistas o antagonistas parciales del receptor de la aldosterona, preferiblemente de forma selectiva con ese receptor, en una configuración de condiciones médicas que involucran la modulación de la trayectoria del receptor de la aldosterona. Una aplicación de los compuestos incluye, pero no se limita a: insuficiencia cardiaca congestiva.

Los compuestos de fórmula I se pueden aplicar como agonistas, agonistas parciales, antagonistas o antagonistas parciales del receptor andrógeno, preferiblemente de forma selectiva con ese receptor, en una configuración de condiciones médicas que involucran la modulación de la trayectoria del receptor andrógeno. Las aplicaciones de los compuestos incluyen, pero no se limitan a: hirsutismo, acné, seborrea, enfermedad de Alzheimer, alopecia androgénica, hipogonadismo, hiperpilosidad, hipertrofia benigna de la próstata, adenomas y neoplasias de la próstata (tal como cáncer avanzado metastático de la próstata), tratamiento de células de tumores benignos o malignos, que contienen el receptor andrógeno, tal como el caso de cáncer de mama, cerebro, piel, ovarios, vejiga, linfático, hígado y de riñón, cánceres pancreáticos, modulación de la expresión de VCAM y

aplicaciones en ellas para el tratamiento de enfermedad del corazón, modulaciones inmunes y de inflamación, modulación de la expresión VEGF y las aplicaciones en ella para su uso como agentes anti-angiogénicos, osteoporosis, espermatogénesis supresora, líbido, caquexia, endometriosis, síndrome poliquístico de ovarios, anorexia, complemento de andrógenos para niveles de testosterona disminuidos relacionados con la edad en los hombres, menopausia masculina, reemplazo de hormonas masculinas, disfunción sexual masculina y femenina, e inhibición de la atrofia muscular en pacientes ambulatorios. Por ejemplo, la modulación de depósito AR se contempla, siendo particularmente preferida la modulación AR selectiva de la próstata ("SARM"), tal como para el tratamiento de cánceres de etapa temprana de la próstata.

Los compuestos de la fórmula I se pueden aplicar como antagonistas del receptor andrógeno mutado (preferiblemente, selectivos), por ejemplo, que se encuentra en muchas líneas de tumor. Los ejemplos de tales mutantes son aquellos que se encuentran en líneas celulares de tumor de próstata representativas, tales como LNCap, (mutación T877A, Biophys. Acta, 187, 1052 (1990)), PCa2b. (mutaciones L701H y T877A, J. Urol., 162, 2192 (1999)) y CWR22, (mutaciones H874Y, Mol. Endo., 11.450 (1997)). Las aplicaciones de dichos compuestos incluyen, pero no se limitan a: adenomas y neoplasias de cáncer de mama, próstata y cáncer del endometrio.

Los compuestos de fórmula I se pueden aplicar como agonistas, agonistas parciales, antagonistas o antagonistas parciales del receptor esteroide xenobiótico, preferiblemente de forma selectiva con ese receptor, en una configuración de condiciones médicas que involucran la modulación de la trayectoria del receptor esteroide y xenobiótico. Las aplicaciones de los compuestos incluyen, pero no se limitan a: tratamiento de la desregulación de la homeostasis por colesterol, atenuación del metabolismo de agentes farmacéuticos por co-administración de un agente (compuesto de la presente invención) que modula los efectos del regulador P450 de SXR.

Junto con el NHR antes mencionado, existen también diversos NHR para los cuales no se pueden caracterizar los ligandos activadores o desactivadores. Estas proteínas se clasifican como NHR, debido a una homología fuerte de secuencia, a otros NHR, y se conocen como los receptores huérfanos. Debido a que los receptores huérfanos demuestran una homología de secuencia fuerte con otros NHR, los compuestos de fórmula I incluyen aquellos que sirven como moduladores de la función del NHR huérfano. Los receptores huérfanos que se modulan por los moduladores NHR, tales como los compuestos dentro del alcance de la fórmula I, se ejemplifican, pero no se limitan a, aquellos enlistados en la Tabla 1. Las aplicaciones terapéuticas ejemplares de los

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moduladores de los receptores huérfanos también se enlistan en la Tabla 1, pero no se limitan a los ejemplos en la presente.

Tabla 1. Receptores de hormonas nucleares huérfanos ejemplares, forma (M= monomérica, D= heterodimérica, H= homodimérica), expresión de tejidos y aplicaciones terapéuticas objetivo (SNC= sistema nervioso central).

Receptor	Forma	Expresión del tejido	Aplicación terapéutica objetivo
NURR1	M/D	Neuronas dopaminérgicas	Enfermedad de Parkinson
RZRβ	M	cerebro(pituitaria), músculo	Trastornos del dormir
RORα	M	Cerebelo, células Purkinje	artritis, ataxia Cerebelar
NOR-1	M	cerebro, músculo, corazón, adrenal, timo	trastornos de CNS, cáncer
NGFI-Bβ	M/D	cerebro	trastornos de SNC
COUP-Tfα	H	cerebro	trastornos de SNC
COUP-TFβ	H	cerebro	trastornos de SNC
COUP-TFγχ	H	cerebro	trastornos de SNC
Nur77	H	cerebro, timo, adrenales	trastornos de SNC

Rev-ErbAα	H	músculo, cerebro(ubicuo)	Obesidad
HNF4α	H	hígado, riñón, intestino	Diabetes
SF-1	M	gónadas, pituitaria	trastornos metabólicos
LXRα,β	D	Riñón (ubicuo)	trastornos metabólicos
GCNF	M/H	ovario, testículos	Infertilidad
ERRα,β	M	hueso, placenta	infertilidad, Osteoporosis
FXR	D	hígado, riñón	trastornos metabólicos
CARα	H	hígado, riñón	trastornos metabólicos
PXR	H	intestino, hígado	trastornos metabólicos
COUP-TF2 (ARP1)	D	testículos	oncología/angiogénesis
RORbeta	M	SNC, retina, glándula pineal	Trastornos metabólicos

La presente invención proporciona así métodos para el tratamiento de condiciones asociadas con NHR, que comprende la etapa de administrar a un sujeto que necesita del mismo, al menos un compuesto de fórmula I en una cantidad efectiva para ello. Se pueden emplear otros agentes terapéuticos tales como aquellos abajo descritos, con los compuestos de la invención en los métodos actuales (por ejemplo, separadamente o formulados juntos con una dosis fija). En los métodos de la

presente invención, tales u otros agentes terapéuticos se pueden administrar previo a, simultáneamente con o después de la administración de los compuestos de la presente invención.

La presente invención también proporciona composiciones farmacéuticas, que comprenden al menos uno de los compuestos de fórmula I capaces de tratar una condición asociada con NHR en una cantidad efectiva para ello, y un portador farmacéuticamente aceptable (vehículo o diluyente). Las composiciones de la presente invención pueden contener otros agentes terapéuticos como se describen abajo, y se pueden formular por ejemplo, al emplear vehículos o diluyentes sólidos o líquidos convencionales, así como aditivos farmacéuticos de un tipo adecuado para el modo de administración deseado (por ejemplo, excipientes, aglutinantes, conservadores, estabilizadores, sabores, etc.) según las técnicas tales como aquellas en el arte de la formulación farmacéutica.

Se debe observar que los compuestos de la presente invención son, sin limitaciones en cuanto a su mecanismo de acción, útiles en el tratamiento de cualquiera de las condiciones o trastornos enlistados o descritos en la presente, tales como enfermedades inflamatorias o cánceres, u otras enfermedades proliferativas, y en composiciones para el tratamiento de tales condiciones o trastornos. Tales condiciones o trastornos incluyen, sin limitación, cualquiera

de aquellas previamente descritas, así como aquellas que se describen a continuación tales como: mantenimiento de la resistencia y función del músculo (por ejemplo, en la edad avanzada); inversión o prevención de la debilidad o declinación funcional relacionada con la edad ("ARFD") en la edad avanzada (por ejemplo, sarcopenia); tratamiento de efectos laterales catabólicos de los glucocorticoides; prevención y/o tratamiento de masa ósea reducida, densidad o crecimiento (por ejemplo, osteoporosis y osteopenia); tratamiento del síndrome de fatiga crónica (CFS); malagia crónica; tratamiento de síndrome de fatiga aguda y pérdida muscular que sigue a una cirugía electiva (por ejemplo, rehabilitación post-quirúrgica); aceleración de la cicatrización de heridas; aceleración de la reparación de fracturas de hueso (tal como la aceleración de la recuperación de pacientes con fractura de cadera); aceleración de la cicatrización de fracturas complicadas, por ejemplo, osteogénesis de distracción en el reemplazo de articulaciones, prevención de la formación de adhesión post-quirúrgica; aceleración de la reparación o crecimiento de los dientes; mantenimiento de la función sensora (por ejemplo, oído, vista, olfato, y gusto); tratamiento de enfermedad periodontal; tratamiento de desgaste secundario a fracturas y desgaste en conexión con enfermedad pulmonar obstructiva crónica (COPD), enfermedad crónica del hígado, SIDA, pérdida

de peso, caquexia de cáncer, recuperación de trauma y de quemaduras, estado catabólico crónico (por ejemplo, coma), trastornos del comer (por ejemplo, anorexia) y quimioterapia; tratamiento de la cardiomiopatía, tratamiento de la trombocitopenia; tratamiento del retardo del crecimiento en conexión con la enfermedad de Crohn, tratamiento de síndrome de intestino corto, tratamiento del síndrome del intestino irritable, tratamiento de la enfermedad inflamatoria del intestino, tratamiento de la enfermedad de Crohn y colitis ulcerante; tratamiento de complicaciones asociadas con el transplante; tratamiento de estatura corta fisiológica incluyendo niños deficientes en la hormona del crecimiento y estatura corta asociada con enfermedad crónica; tratamiento de la obesidad; y retardo en el crecimiento asociado con la obesidad; tratamiento de la anorexia (por ejemplo, asociado con caquexia o envejecimiento); tratamiento de hipercortisolismo y síndrome de Cushing; enfermedad de Paget; tratamiento de osteoartritis; inducción de la liberación de la hormona de crecimiento pulsátil; tratamiento de osteocondrodisplasias; tratamiento de la depresión; nerviosidad, irritabilidad y estrés; tratamiento de energía mental reducida y baja auto-estima (por ejemplo, motivación/afirmatividad); mejora de función cognitiva (por ejemplo, el tratamiento de la demencia, incluyendo enfermedad de Alzheimer y pérdida de la memoria de corto plazo);

tratamiento del catabolismo en conexión con la disfunción pulmonar y dependencia de ventilador; tratamiento de la disfunción cardiaca (por ejemplo, asociada con la enfermedad valvular, infarto al miocardio, hipertrofia cardiaca o insuficiencia cardiaca congestiva); disminución de la presión sanguínea; protección contra la disfunción ventricular o prevención de eventos de reperfusión; tratamiento de adultos con diálisis crónica; inversión o disminución de estado catabólico del envejecimiento; atenuación o inversión de respuestas catabólicas de proteínas que siguen al trauma (por ejemplo, inversión del estado catabólico asociado con la cirugía, insuficiencia cardiaca congestiva, miopatía cardiaca, quemaduras, cáncer, COPD, etc.); reducción de caquexia y pérdida de proteína debida a enfermedad crónica tal como el cáncer o el SIDA; tratamiento de hiperinsulinemia incluyendo nesidioblastosis; tratamiento de pacientes inmunodeprimidos; tratamiento del desgaste en conexión con esclerosis múltiple u otros trastornos neurodegenerativos; promoción de la reparación de mielina; mantenimiento del grosor de la piel; tratamiento de homeostasis metabólica y homeostasis renal (por ejemplo, en la debilidad de edad avanzada); estimulación de osteoblastos, remodelación de huesos, crecimiento de cartílagos; regulación de la ingesta de alimento; tratamiento de la resistencia a la insulina, incluyendo NIDDM, en mamíferos, (por ejemplo, humanos);

tratamiento de la resistencia a la insulina en el corazón; mejora de la calidad del sueño y corrección del hiposomatotropismo relativo de la senectud, debido a un alto incremento en el sueño REM y una disminución en la latencia REM; tratamiento de hipotermia; tratamiento de insuficiencia cardiaca congestiva; tratamiento de lipodistrofia (por ejemplo, en pacientes que toman terapias de VIH o SIDA tales como inhibidores de la proteasa); tratamiento de la atrofia muscular (por ejemplo, debido a la inactividad física, reposo en cama o condiciones reducidas de soporte de peso); tratamiento de la incapacidad musculoesqueletal (por ejemplo, en la edad avanzada); mejora de la función pulmonar global; tratamiento del trastornos del dormir; y en el tratamiento del estado catabólico de enfermedades críticas prolongadas; tratamiento de hirsutismo, acné, seborrea, alopecia, androgénica, anemia, hiperpilosidad, hipertrofia benigna de próstata, adenomas y neoplasias de la próstata (por ejemplo, cáncer avanzado metastático de próstata) y células de tumores malignos que contienen el receptor andrógeno, tal como en el caso de cánceres de mama cerebro, piel, ovarios, vejiga, linfático, hígado y de riñón; cánceres de la piel, páncreas, endometrio, pulmón y colon; osteosarcoma; hipercalcemia de malignidades; enfermedad metastática de los huesos; tratamiento de la espermatogénesis, endometriosis, y síndrome policístico de ovarios; contraatacar la preclampsia,

eclampsia del embarazo y parto prematuro; tratamiento del síndrome premenstrual; tratamiento de sequedad vaginal; niveles de testosterona disminuidos en los hombres con relación a la edad, menopausia masculina, hipogonadismo, reemplazo de hormonas masculinas, disfunción sexual masculina y femenina (por ejemplo, disfunción eréctil, apetito sexual disminuido, bienestar sexual, libido disminuido), anticonceptivos masculinos y femeninos, pérdida del cabello, síndrome de Reaven, y aumento del desempeño/ fortaleza de músculos y huesos; y condiciones, enfermedades y malestares referenciados colectivamente como "Síndrome X" o síndrome metabólico como se detalla en Johannsson J. Clin. Endocrinol. Metab., 82, 727-34 (1997).

Los compuestos actuales tienen utilidad terapéutica en la modulación de la activación/proliferación de células inmunes, por ejemplo, como inhibidores competitivos de las reacciones de enlace intercelular ligando/receptor que involucran CAMs (moléculas de adhesión celular) y leucointegrinas. Por ejemplo, los compuestos actuales modulan LFA-ICAM 1, y son particularmente útiles como antagonistas LFA-ICAM 1, y en el tratamiento de todas las condiciones asociadas con LFA-ICAM 1 tal como trastornos inmunológicos. Las utilidades preferidas para los compuestos actuales incluyen pero no se limitan a: condiciones inflamatorias tales como aquellas que resultan de una respuesta de un

sistema inmune no específico de un material mamífero (por ejemplo, síndrome de distensión respiratoria en adultos, choque, toxicidad al oxígeno, síndrome de lesión múltiple en órganos secundaria a la septicemia, síndrome de lesión múltiple en órganos secundaria al trauma, lesión por reperfusión de tejido debido a una derivación cardiopulmonar, infarto al miocardio o uso con agentes de trombólisis, glomerulonefritis aguda, vasculitis, artritis reactiva, dermatosis con componentes inflamatorios agudos, apoplejía, lesión térmica, hemodiálisis, leucaferesis, colitis ulcerante, enterocolitis necrotizante y síndrome asociado con la transfusión de granulocitos) y condiciones que resultan de una respuesta del sistema inmune específico en un mamífero (por ejemplo, psoriasis, rechazo de transplantes de órgano/tejido, reacciones de injerto contra huésped y enfermedades autoinmunes incluyendo el síndrome de Raynaund, tiroiditis autoinmune, dermatitis, esclerosis múltiple, artritis reumatoide, diabetes mellitus dependiente de la insulina, uveitis, enfermedad inflamatoria del intestino incluyendo enfermedad de Crohn y colitis ulcerante, y lupus eritematoso sistémico). Los compuestos actuales se pueden usar en el tratamiento del asma, o como un adyuvante para minimizar la toxicidad con terapia de citocinas en el tratamiento de cánceres. Los compuestos actuales se pueden emplear en el tratamiento de todas las enfermedades que se

tratan actualmente a través de terapias de esteroides. Los compuestos actuales se pueden emplear para el tratamiento de estos y otros trastornos solos o con otros agentes inmunodepresores o anti-inflamatorios. De conformidad con la invención, se puede administrar un compuesto de la fórmula I previo al comienzo de la inflamación (de manera de suprimir una inflamación anticipada) o después del inicio de la inflamación. Cuando se suministran profilácticamente, los compuestos inmunodepresores, se suministran preferiblemente por adelantado de cualquier respuesta o síntoma inflamatorio (por ejemplo, previo al, en el, o poco después del momento de un transplante de órganos o tejidos, pero por adelantado de cualesquiera de los síntomas o rechazo de órganos). La administración profiláctica de un compuesto de la fórmula I, evita o atenúa cualquier respuesta inflamatoria posterior (tal como por ejemplo, rechazo de un órgano o tejido transplantado, etc). La administración de un compuesto de la fórmula I atenúa cualquier inflamación actual (tal como por ejemplo, el rechazo de un órgano o tejido transplantado).

Los compuestos de la fórmula I, se pueden administrar para cualquiera de los usos descritos en la presente por cualesquiera de los métodos adecuados, por ejemplo, oralmente tal como en forma de tabletas, cápsulas, gránulos o polvos; sublingualmente; bucalmente; parenteralmente; tal como por técnicas de inyección o infusión subcutánea e intravenosa,

intramuscular, o intraesternal (por ejemplo, como soluciones o suspensiones estériles inyectables acuosas o no acuosas); nasalmente, incluyendo la administración a las membranas nasales, tal como por un rocío de inhalación; tópicamente tal como en forma de una crema o ungüento; o rectalmente tal como en forma de supositorios; en formulaciones de dosis unitaria que contienen vehículos o diluyentes no tóxicos, farmacéuticamente aceptables. Los compuestos actuales pueden, por ejemplo, administrarse en una forma adecuada para liberación inmediata o liberación prolongada. La liberación inmediata o liberación prolongada, se puede alcanzar por el uso de composiciones farmacéuticas adecuadas que comprenden los compuestos actuales, o particularmente en el caso de la liberación prolongada, por el uso de dispositivos tales como implantes subcutáneos o bombas osmóticas. Los compuestos actuales también se pueden administrar por liposomas.

Las composiciones ejemplares para la administración oral, incluyen suspensiones que pueden contener por ejemplo, celulosa microcristalina para impartir volumen, ácido algínico o alginato de sodio, como un agente se suspensión, metilcelulosa como un aumentador de la viscosidad, y edulcorantes o agentes saborizantes tales como aquellos conocidos en el arte: y las tabletas de liberación inmediata que pueden contener, por ejemplo, celulosa microcristalina, fosfato de bicalcio, almidón, estearato de magnesio y/o

lactosa y/u otros excipientes, aglutinantes, agentes de dilución, desintegrantes, diluyentes y lubricantes tales como aquellos conocidos en la técnica. Los compuestos de fórmula I también se pueden suministrar a través de la cavidad oral por administración sublingual y/o bucal. Se pueden usar tabletas moldeadas, tabletas comprimidas, o tabletas secadas por congelación como formas ejemplares. Las composiciones ejemplares incluyen aquellas que formulan los compuestos actuales, con diluyentes de disolución rápida tales como manitol, lactosa, sacarosa, y/o ciclodextrinas. También se incluyen en tales formulaciones excipientes de alto peso molecular tales como celulosas (avicel) o polietilen glicoles (PEG). Tales formulaciones pueden también incluir un excipiente para ayudar a la adhesión mucosal tal como hidroxi propil celulosa (HPC), hidroxi propil metil celulosa (HPMC), carboxi metil celulosa de sodio (SCMC), copolímero de anhídrido maléico (por ejemplo, Gantrez), y agentes para controlar la liberación tales como copolímero poliacrílico (por ejemplo, Carbopol 934). Se pueden también agregar lubricantes, agentes mejoradores del flujo, sabores, agentes colorantes y estabilizadores para facilitar la fabricación y uso.

Las composiciones ejemplares para la administración nasal por aerosol o inhalación, incluyen soluciones salinas que pueden contener por ejemplo, alcohol bencílico u otros

conservadores adecuados, promotores de la absorción para aumentar la biodisponibilidad, y/u otros agentes dispersantes o de solubilización tales como aquellos que se conocen en el arte.

Las composiciones ejemplares para la administración parenteral incluyen soluciones o suspensiones inyectables que pueden contener, por ejemplo, diluyentes o solventes no tóxicos parenteralmente aceptables, tal como manitol, 1,3-butanodiol, agua, solución de Ringer, una solución isotónica de cloruro de sodio, u otros agentes adecuados de dispersión o humectantes o de suspensión, incluyendo mono o digliceridos sintéticos, y ácidos grasos incluyendo ácido oleico o Cremafor.

Las composiciones ejemplares para la administración rectal, incluyen supositorios que pueden contener por ejemplo, un excipiente adecuado no irritante tal como manteca de cacao, ésteres sintéticos de glicéridos o polietilenglicoles, que son sólidos a temperatura ordinaria, pero que se licuan o se disuelven en la cavidad rectal para liberar el fármaco.

Las composiciones ejemplares para administración tópica incluyen un portador tópico tal como Plastibase (aceite mineral gelificado con polietileno).

La cantidad efectiva de un compuesto de la presente invención, se puede determinar por alguien experto en la

técnica, e incluye cantidades de dosis ejemplares para un adulto humano desde alrededor de 1 hasta 100 (por ejemplo, 15 o menos, especialmente 1 a 3 o menos) mg/kg de peso corporal de compuesto activo por día, que se puede administrar en una dosis simple o en forma de dosis divididas individuales tales como desde 1 a 4 veces por día. Se entenderá que el nivel específico de dosis y la frecuencia de dosificación para algún sujeto en particular, se puede variar y dependerá de una diversidad de factores incluyendo la actividad del compuesto específico empleado, la estabilidad metabólica y longitud de acción de ese compuesto, la especie, edad, peso corporal, salud general, sexo y dieta del sujeto, el modo y tiempo de administración, tasa de excreción, combinación de fármacos y severidad de la condición particular. Los sujetos preferidos para el tratamiento incluyen animales, más preferiblemente especies mamíferas tales como humanos, y animales domésticos tales como perros, gatos y similares, sujetos a condiciones asociadas con NHR.

Como se mencionó anteriormente, los compuestos de la presente invención se pueden emplear solos o en combinación uno con el otro, y/u otros agentes terapéuticos adecuados, útiles en el tratamiento de condiciones asociadas con NHR, por ejemplo, un antibiótico u otro material farmacéuticamente activo.

Por ejemplo, los compuestos de la presente invención se pueden combinar con agentes promotores del crecimiento, tales como, pero no limitados a TRH, dietilestilbesterol, teofilina, encefalinas, prostaglandinas de la serie E, compuestos descritos en la patente de E.U.A. No. 3,239,345, por ejemplo, zeranol, y compuestos descritos en la patente E.U.A. No. 4,036,979, por ejemplo, sulbenox o péptidos descritos en la patente E.U.A. No. 4,411,890.

Los compuestos de la invención también se pueden usar en combinación con secretagogos de la hormona del crecimiento tales como GHRP-6, GHRP-1 (como se describe en la patente de E.U.A. No. 4,411,890 y las publicaciones WO 89/07110 y WO 89/07111), GHRP-2 (como se describe en WO 93/04081), NN703 (Novo Nordisk), LY444711 (Lilly), MK-677 (Merck), CP424391 (Pfizer) y B-HT920, o con el factor liberador de la hormona del crecimiento y sus análogos o la hormona del crecimiento y sus análogos o somatomedinas incluyendo IGF-1 y IGF-2, o con agonistas alfa-adrenérgicos tal como la clonidina o agonistas de la serotonina 5-HT_D tal como el sumatriptan, o agentes que inhiben la somatostatina o su liberación, tal como la fisostigmina y la piridostigmina. Un uso todavía adicional de los compuestos descritos de la invención, es en combinación con la hormona paratiroides, PTH (1-34) o bisfosfonatos, tales como MK-217 (alendronato).

Un uso todavía adicional de los compuestos de la invención, es en combinación con estrógenos, testosterona, un modulador receptor selectivo de estrógenos, tal como el tamoxifen o raloxifen, u otros moduladores receptores andrógenos, tales como aquellos descritos en Edwards, J. P. et al., Bio. Med. Chem. Let., 9, 1003-1008 (1999) y Hamann, L. G. et al., J. Med. Chem., 42, 210-212 (1999).

Un uso adicional de los compuestos de esta invención, es en combinación con los agonistas receptores de la progesterona ("PRA"), tal como el levonorgestrel, acetato de medroxiprogesterona (MPA).

Los compuestos de la presente invención se pueden emplear solos o en combinación uno con el otro y/u otros moduladores de los receptores de hormona nuclear, u otros agentes terapéuticamente adecuados útiles en el tratamiento de los padecimientos antes mencionados incluyendo: agentes antidiabéticos; agentes anti-osteoporosis; agentes anti-obesidad, agentes anti-inflamatorios, agentes anti-ansiedad, anti-depresores, agentes anti-hipertensivos, agentes anti-plaquetas, agentes anti-trombóticos y trombolíticos, glicósidos cardiacos; agentes que disminuyen los lípidos/colesterol; antagonistas del receptor mineralocorticoide; inhibidores de la fosfodiesterasa; inhibidores de la proteína de tirosina cinasa; miméticos tiroides (incluyendo agonistas del receptor tiroide); agentes

anabólicos; terapias de VIH o SIDA; terapias útiles en el tratamiento de enfermedad de Alzheimer y otros padecimientos cognitivos; terapias útiles en el tratamiento de trastorno del dormir; agentes anti-proliferativos y agentes anti-tumor.

Los ejemplos de los agentes antidiabéticos adecuados para su uso en combinación con los compuestos de la presente invención incluyen biguanidas (por ejemplo, metformina), inhibidores de la glucosidasa (por ejemplo, acarbosa), insulinas (incluyendo secretagogos de la insulina o sensibilizadores de la insulina), meglitinidas (por ejemplo, repaglinida), sulfonilureas (por ejemplo, glimepirida, gliburida y glipizida), combinaciones de biguanida/gliburida (por ejemplo, Glucovance®), tiazolidindionas (por ejemplo, troglitazona, rosiglitazona, y pioglitazona), agonistas PPAR-alfa, agonista PPAR-gamma, agonistas duales alfa/gamma PPAR, inhibidores SGLT2, inhibidores de la glicogen fosforilasa, inhibidores de proteínas de enlace de ácidos grasos (aP2) tales como aquellos descritos en el E.U.A. No. de serie 09/519,079 presentado el 6 de marzo de 2000, inhibidores del péptido-1 del tipo glucagón (GLP-1), y de la dipeptidil peptidasa IV (DP4).

Los ejemplos de agentes adecuados anti-osteoporosis para su uso en combinación con los compuestos de la presente invención, incluyen alendronato, risedronato, PTH, fragmento PTH, raloxifen, calcitonin, agonistas receptores de la

progesterona esteroidales o no esteroidales, antagonistas del ligando RANK, antagonistas receptores sensibilizados al calcio, inhibidores TRAP, moduladores receptores de estrógeno selectivos (SERM), estrógeno e inhibidores AP-1.

Los ejemplos de agentes anti-obesidad adecuados para su uso en combinación con los compuestos de la presente invención, incluyen inhibidores aP2, tales como aquellos descritos en el E.U.A. No. de serie 09/519,079 presentada el 6 de marzo de 2000, antagonistas gamma PPAR, agonistas delta PPAR, agonistas beta 3 adrenérgicos, tales como AJ9677 (Takeda/Dainippon), L750355 (Merck), o CP331648 (Pfizer) u otros agonistas beta 3 conocidos, como se describen en las patentes E.U.A. Nos. 5,541,204, 5,770,615, 5,491,134, 5,776,983 y 5,488,064, un inhibidor de la lipasa tal como el orlistat o como ATL-962 (Alizyme), un inhibidor de la reabsorción de serotonina (y dopamina), tal como sibutramina, topiramato (Johnson & Johnson) o axoquina (Regeneron), un fármaco beta receptor de la tiroides, tal como un ligando receptor de la tiroides como se describe en WO 97/21993 (U. Cal SF), WO 99/00353 (KaroBio) y GB98/284425 (KaroBio), y/o un agente anoréctico, tal como la dexamfetamina, fentermina, fenilpropanolamina o mazindol.

Los ejemplos de los agentes anti-inflamatorios adecuados para su uso en combinación con los compuestos de la presente invención, incluyen prednisona, dexametasona, Enbrel®,

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inhibidores de la ciclooxigenasa (esto es, inhibidores COX-1 y/o COX-2 tal como NSAIDs, aspirina, indometacina, ibuprofen, piroxicam, Naproxen®, Celebrex®, Vioxx®), agonistas/antagonistas CTLA4-Ig, agonistas del ligando CD40, inhibidores de la IMPDH, tal como antagonistas de integrina de micofenolato (CellCept®), antagonistas de la alfa-4 beta-7 integrina, inhibidores de adhesión de célula, antagonistas del gamma interferón, ICAM-1, antagonistas del factor de necrosis de tumor (TNF) (por ejemplo, infliximab, OR1384), inhibidores de la síntesis de prostaglandina, budesonida, clofazimina, CNI-1493, antagonistas CD4 (por ejemplo, priliximab), inhibidores de la proteína cinasa activados por el mitógeno p38, inhibidores de la proteína tirosina cinasa (PTK), inhibidores IKK, y terapias para el tratamiento de síndrome de intestino irritable (por ejemplo, agentes de abertura Zelmac® y Maxi-K® tales como aquellos descritos en la patente de E.U.A. No. 6,184,231 B1).

Los ejemplos de los agentes adecuados anti-ansiedad para su uso en combinación con los compuestos de la presente invención, incluyen diazepam, lorazepam, buspirona, oxazepam, y pamoato de hidroxizina.

Los ejemplos de los antidepresivos adecuados para su uso en combinación con los compuestos de la presente invención, incluyen citalopram, fluoxetina, nefazodona, sertralina, y paroxetina.

Ejemplos de los agentes anti-hipertensión adecuados para su uso en combinación con los compuestos de la presente invención, incluyen bloqueadores beta adrenérgicos, bloqueadores del canal del calcio (tipo-L y tipo-T; por ejemplo, diltiazem, verapamil, nifedipina, amlodipino y mibefradil), diuréticos (por ejemplo, clorotiazida, clorohidrotiazida, flumetiazida, hidroflumetiazida, bendroflumetiazida, metilclorotiazida, triclorometiazida, politiazida, benztiazida, tricrinafen de ácido etacrínico, clortalidona, furosemida, musolimina, bumetanida, triamtreneno, amilorida, espironolactona), inhibidores de la renina, inhibidores ACE (por ejemplo, captopril, zofenopril, fosinopril, enalapril, ceranopril, cilazopril, delapril, pentopril, quinapril, ramipril, lisinopril), antagonistas del receptor AT-1 (por ejemplo, losartan, irbesartan, valsartan), antagonistas del receptor ET (por ejemplo, sitaxsentan, atrsentan y los compuestos descritos en la patentes E.U.A. Nos. 5,612,359 y 6,043,265), antagonista Dual ET/AII (por ejemplo, los compuestos descritos de WO 00/01389), inhibidores neutrales de la endopeptidasa (NEP), inhibidores de la vasopepsidasa (inhibidores duales NEP-ACE) (por ejemplo, omapatrilat y gemopatrilat), y nitratos.

Los ejemplos de los agentes anti-plaquetas adecuados para su uso en combinación con los compuestos de la presente invención, incluyen bloqueadores GPIIb/IIIa (por ejemplo,

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abciximab, eptifibatide, tirofiban), antagonistas P2Y12 (por ejemplo, clopidogrel, ticlopidine, CS-747), antagonistas del receptor de tromboxano (por ejemplo, ifetroban), aspirina, e inhibidores PDE-III (por ejemplo, dipiridamol) con o sin aspirina.

Los ejemplos de los glicósidos cardiacos adecuados para su uso en combinación con los compuestos de la presente invención incluyen digitalis y ouabain.

Los ejemplos de los agentes que disminuyen los lípidos/colesterol adecuados para su uso en combinación con los compuestos de la presente invención, incluyen inhibidores de la HMG-CoA reductasa (por ejemplo, pravastatina, lovastatina, atorvastatina, simvastatina, NK-104 (a.k.a. itavastatina, o nisvastatina o nisbastatina) y ZD-4522 (a.k.a. rosuvastatina, o atavastatina o visastatina)), inhibidores de la escualeno sintetasa, fibratos, secuestrantes del ácido biliar, inhibidores ACAT, inhibidores MTP, inhibidores de la lipooxigenasa, inhibidores de la absorción del colesterol, e inhibidores de la proteína de transferencia del éster del colesterol (por ejemplo, CP-529414).

Los ejemplos de los antagonistas del receptor mineralocorticoide adecuado para su uso en combinación con los compuestos de la presente invención, incluyen espironolactona y eplerinona.

Los ejemplos de los inhibidores adecuados de la fosfodiesterasa, para su uso en combinación con los compuestos de la presente invención, incluyen inhibidores PDEIII tales como cilostazol, e inhibidores PDE V tales como el sildenafil.

Ejemplos de los miméticos de tiroides adecuados para su uso en combinación con los compuestos de la presente invención, incluyen tirotropina, politiroide, KB-130015, y dronedarona.

Los ejemplos de los agentes anabólicos adecuados para su uso en combinación con los compuestos de la presente invención incluyen testosterona, TRH dietilestilbesterol, estrógenos, β-agonistas, teofilina, esteroides anabólicos, deshidroepiandrosterona, encefalinas, prostaglandinas de la serie E, ácido retinóico y compuestos como se describen en la patente de E.U.A. No. 3,239,345, por ejemplo, Zeranol®; patente de E.U.A. No. 4,036,979, por ejemplo, Sulbenox® o péptidos como se describen en la patente de E.U.A. No. 4,411,890.

Los ejemplos de terapia para el VIH o SIDA adecuadas para su uso en combinación con los compuestos de la presente invención, incluyen sulfato de indinavir, saquinavir, mesilato de saquinavir, ritonavir, lamivudina, zidovudina, combinaciones de la lamivudina/zidovudina, zalcitabina, didanosina, stavudina, y acetato de megestrol.

Ejemplos de la terapias adecuadas para el tratamiento de la enfermedad de Alzheimer y trastornos cognitivos para su uso en combinación con los compuestos de la presente invención, incluyen donepezil, tacrina, revastigmina, 5HT6, inhibidores de secretasa gama, inhibidores de la secretasa beta, bloqueadores del canal SK, bloqueadores Maxi-K, y bloqueadores KCNQs.

Los ejemplos de la terapias adecuadas para el tratamiento de trastornos del dormir para su uso en combinación con los compuestos de la presente invención, incluyen análogos de menatonina, antagonistas del receptor de melatonina, agonistas, agonistas ML1B, y antagonistas del receptor GABA/NMDA.

Ejemplos de agentes anti-proliferativos adecuados para su uso en combinación con los compuestos de la presente invención, incluyen ciclosporina A, paclitaxel, FK 506, y adriamicina.

Ejemplos de los agentes anti-tumor adecuados para su uso en combinación de los compuestos de la presente invención, incluyen paclitaxel, adriamicina, epotilonas, cisplatina y carboplatina.

Los compuestos de la presente invención se pueden usar además en combinación con complementos nutricionales tales como aquellos descritos en la patente de E.U.A. 5,179,080, especialmente en combinación con proteína de suero de la

leche o caseína, aminoácidos (tal como leucina, aminoácidos ramificados e hidroximetilbutirato), triglicéridos, vitaminas (por ejemplo, A, B6, B12, folatos, C, D y E), minerales (por ejemplo, selenio, magnesio, zinc, cromo, calcio y potasio), carnitina, ácido lipóico, creatina, y coenzima Q-10.

Además, se pueden usar los compuestos de la presente invención en combinación con agentes terapéuticos usados en el tratamiento de la disfunción sexual, incluyendo pero no limitado a inhibidores PDE5, tal como inhibidores sildenafil o IC-351; con un agente anti-resorción, terapias de reemplazo de hormonas, análogos de vitamina D, calcitoninas, complementos de calcio y calcio elemental, inhibidores de la catepsina K, inhibidores MMP, antagonistas receptores de la vitronectina, antagonistas Src SH_2, inhibidores vaculares de la $-H^+-$ ATPasa, agonistas receptores de progesterona, ipriflavona, fluoruro, antagonistas RANK, PTH y sus análogos y fragmentos, Tibolona, inhibidores de la HMG-CoA reductasa, SERM's, inhibidores p38, prostanoides, inhibidores de la 17-beta hidroxiesteroide deshidrogenasa e inhibidores de la Src cinasa.

Los compuestos de la presente invención se pueden usar en combinación con anticonceptivos masculinos tales como el nonoxinol 9, o agentes terapéuticos para el tratamiento de la pérdida del cabello tal como el minoxidil y finasteride o agentes quimioterapéuticos tales como los agonistas LHRH.

Por su uso preferido anti-cáncer o anti-angiogénico, los compuestos de la presente invención se pueden administrar solos o en combinación con otros agentes anti-cáncer y citotóxicos y tratamientos útiles en el tratamiento del cáncer o de otras enfermedades proliferativas, por ejemplo, en donde el segundo fármaco tiene un mecanismo de acción igual o diferente que los compuestos actuales de fórmula I. Los ejemplos de las clases de agentes anti-cáncer y citotóxicos útiles en combinación con los compuestos actuales, incluyen pero no se limitan a: agentes alquilantes tales como mostaza de nitrógeno, sulfonatos de alquilo, nitrosoureas, etileniminas y triazenos; inhibidores EGFR tales como inhibidores EGFR de molécula pequeña, anticuerpos EGFR tales como C225 (Erbitux); antimetabolitos tales como antagonistas de folato, análogos de purina y análogos de pirimidina; antibióticos tales como antraciclinas, bleomicinas, mitomicina, dactinomicina, y plicamicina; enzimas tales como L-asparaginasa; inhibidores de la transferasa de la proteína de farnesilo; inhibidores de la 5α reductasa; inhibidores de la deshidrogenasa 17β-hidroxi esteroide tipo 3 o tipo 1; agentes hormonales tales como glucocorticoides, estrógenos o anti-estrógenos, andrógenos/anti-andrógenos, progestinas, y antagonistas de la hormona liberadora de la hormona luteinizante, acetato de

octreótido; agentes disruptores de microtúbulos, tales como ecteinascidinas o análogos y derivados; agentes estabilizantes de microtúbulos tales como taxanos, por ejemplo, paclitaxel (Taxol®), docetaxel (Taxotere®), y sus análogos, y epotilonas, tales como las epotilonas A-F y sus análogos; productos derivados de plantas tales como alcaloides vinca, epipodofilotoxinas, taxanos; e inhibidores de la topoisomerasa; inhibidores de la prenil-proteína transferasa; y agentes diversos tales como hidroxiurea, procarbazina, mitotano, hexametilmelamina, complejos de coordinación de platino tales como cisplatina y carboplatina; y otros agentes usados como agentes citotóxicos y anti-cáncer tales como los modificadores de la respuesta biológica, factores de crecimiento; moduladores inmunes y anticuerpos monoclonales. Los compuestos de la invención también se pueden usar en conjunto con terapia de radiación.

Los ejemplos representativos de esta clases de agentes anti-cáncer y citotóxicos, incluyen pero no se limitan a clorohidrato de mecloretamina, ciclofosfamida, clorambucil, melfalan, ifosfamida, busulfan, carmustin, lomustina, semustina, estreptozocina, tiotepa, dacarbazina, metotrexato, tioguanina, mercaptopurina, fludarabina, pentastatin, cladribin, citarabina, fluorouracil, clorohidrato de doxorubicina, daunorubicina, idarubicina, sulfato de bleomicina, mitomicina C, actinomicina D, safracinas,

saframicinas, quinocarcinas, discodermolidos, vincristina, vinblastina, tartrato de vinorelbina, etopósido, fosfato de etopósido, tenipósido, paclitaxel, tamoxifen, estramustina, fosfato sodio estramustina, flutamida, buserelin, leuprolide, pteridinas, diyneses, levamisol, aflacon, interferón, interleucinas, aldesleucina, filgrastim, sargramostim, rituximab, BCG, tretinoin, clorohidrato de irinotecan, betametosona, clorohidrato de gemcitabina, altretamina, y topoteca y cualesquiera de los análogos o derivados de los mismos.

Los miembros preferidos de estas clases incluyen, pero no se limitan a paclitaxel, cisplatin, carboplatin, doxorubicina, carminomicina, daunorubicina, aminopterin, metotrexato, metopterina, mitomicina C, ecteinascidin 743, o pofiromicina, 5-fluorouracil, 6-mercaptopurina, gemcitabina, arabinósido de citosina, podofilotoxina o derivados de la podofilotoxina tales como el etopósido, fosfato de etopósido o tenipósido, melfalan, vinblastina, vincristina, leurosidina, vindesina y leurosina.

Los ejemplos de los agentes anti-cáncer y otros citotóxicos, incluyen los siguientes: derivados de la epotilona como se encuentran en la patente alemana No. 4138042.8; WO 97/19086, WO 98/22461, WO 98/25929, WO 98/38192, WO 99/01124, WO 99/02224, WO 99/02514, WO 99/03848, WO 99/07692, WO 99/27890, WO 99/28324, WO 99/43653, WO

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99/54330, WO 99/54318, WO 99/54319, WO 99/65913, WO 99/67252, WO 99/67253 y WO 00/00485; inhibidores de la cinasa dependientes de la ciclina como se encuentran en WO 99/24416 (ver también la patente de E.U.A. No. 6,040,321); e inhibidores de la prenil-proteína transferasa como se encuentran en WO 97/30992 y WO 98/54966; y agentes tales como aquellos descritos genéricamente y específicamente en la patente de E.U.A No. 6,011,029 (los compuestos de cuya patente de E.U.A. se pueden emplear junto con cualesquiera moduladores NHR (incluyendo pero no limitado a aquellos de la presente invención) tales como moduladores AR, moduladores ER, con moduladores LHRH o con castración quirúrgica especialmente en el tratamiento del cáncer).

Las combinaciones de la presente invención, también se pueden formular o co-administrar con otros agentes terapéuticos que se seleccionan por su utilidad particular en la administración de terapias asociadas con las condiciones antes mencionadas. Por ejemplo, los compuestos de la invención se pueden formular con agentes para evitar náusea, hipersensibilidad e irritación gástrica, tales como los antieméticos, y antihistamínicos H_1 y H_2.

En cuanto a lo que se refiere al tratamiento del cáncer, los compuestos de esta invención se usan preferiblemente solos o en combinación con tratamientos anti-cáncer tales como terapia de radiación y/o con agentes citostáticos y/o

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citotóxicos, tales como, pero no limitados a agentes interactivos del ADN, tal como cisplatina o doxorubicina; inhibidores de la farnesil proteína transferasa, tales como aquellos descritos en la patente de E.U.A. No. 6,011,029; inhibidores de la topoisomerasa II, tales como el etopósido, inhibidores de topoisomerasa I, tal como CPT-11 o topotecan; agentes estabilizantes tales como paclitaxel, docetaxel, otros taxanos, o epotilonas; agentes hormonales, tales como el tamoxifen; inhibidores de la timidilato sintasa, tal como el 5-fluorouracil; antimetabolitos, tal como el metatotrexato; agentes antiangiogénicos, tal como la angiostatina, ZD6474, ZD6126 y comberstatina A2; inhibidores de la cinasa, tales como anticuerpos específicos her2, inhibidores Iressa y CDK; inhibidores de la histona desacetilasa, tal como CI-994 y MS-27-275. Tales compuestos se pueden combinar con agentes que suprimen la producción de testosterona en circulación tales como los agonistas o antagonistas de LHRH o con castración quirúrgica. Las terapias de combinación ejemplares (por ejemplo, para el tratamiento del cáncer de próstata) para su uso con un compuesto de la presente invención incluyen un modulador LHRH o prednisona.

La presente invención también contempla kit(s), por ejemplo, para el tratamiento del cáncer de próstata que comprenden un primer recipiente (tal como un vial) que

contiene una formulación farmacéutica que comprende un compuesto de la presente invención, el compuesto opcionalmente en un portador farmacéuticamente aceptable, y un segundo recipiente (tal como un vial) que contiene una formulación farmacéutica que comprende uno o más agentes (tal como un modulador LHRH) para usarse en combinación con el compuesto de la presente invención, los agentes opcionalmente en un portador farmacéuticamente aceptable.

Por ejemplo, las terapias conocidas para el cáncer avanzado metastático de la próstata, incluyen una "terapia de ablación de andrógeno completa" en donde se inhibe el crecimiento del tumor al controlar el suministro de andrógeno a los tejidos de próstata por medio de castración química (la castración sirve para inhibir la producción de la testosterona en circulación (T) y la dihidrotestosterona (DHT)) seguido por la administración de antagonistas del receptor andrógeno (AR) (que inhibe la función T/DHT derivada de la conversión de los precursores de andrógeno en circulación a T/DHT por el tejido de la próstata). Los compuestos de la presente invención, se pueden emplear como antagonistas AR en una terapia completa de ablación, solos o en combinación con otros antagonistas AR tales como Flutamida, Casodex, Nilutamide, o acetato de Ciproterona.

La presente invención proporciona compuestos que se pueden usar para tratar pacientes que padecen de cáncer de

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próstata, resistente a los antagonistas receptores de andrógenos que no están dentro de la fórmula I de la invención (o sales de los mismos), tal como la bicalutimida. La invención contempla así además, un método para el tratamiento de cáncer de próstata resistente a un antagonista receptor de andrógeno, diferente de aquellos de la fórmula I o sales de los mismos, que comprende la etapa de administrar a un paciente que necesita del mismo un compuesto capaz de reducir la tasa de crecimiento de la masa de tumor del cáncer en una cantidad efectiva del mismo. El término "reducir la tasa de crecimiento de la masa de tumor" denota la reducción en la tasa de crecimiento (incluyendo, por supuesto, la estabilización o reducción en el tamaño) de la masa de tumor con tratamiento con relación a la tasa de crecimiento con tratamiento con el antagonista receptor del andrógeno, diferente a aquellos de fórmula I o sales de los mismos. Los compuestos de la fórmula I y las sales farmacéuticamente aceptables de los mismos de la presente invención, se prefieren tales compuestos.

La presente invención también contempla el uso de un inhibidor anti-estrógeno y/o de aromatasa, en combinación con un compuesto de la presente invención, por ejemplo, para ayudar a mitigar los efectos laterales asociados con la terapia antiandrógeno tal como la ginecomastia. Los inhibidores ejemplares anti-estrógenos y/o aromatasa incluyen

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el anastrozol (Arimidex), citrato de tamoxifen (Nolvadex), exemestano (Aromasin), citrato de toremifen (Fareston), letrozol (Femara), clorohidrato de raloxifen (Evista), Faslodex, o 923 (Wyeth Ayerst).

Los compuestos de la presente invención se pueden emplear adyuvantes con la cirugía.

Otra aplicación de los compuestos actuales es en combinación con la terapia de anticuerpos tal como pero no limitada a terapia de anticuerpos contra PSCA. Una aplicación adicional es en conjunto con agentes moduladores inmunes/vacunas para el tratamiento del cáncer.

Los compuestos de la presente invención se pueden emplear de conformidad con los métodos descritos en la solicitud de patente provisional de E.U.A. No. de serie 60/284,438, titulada "Moduladores receptores de andrógenos selectivos y métodos para su identificación, diseño y uso" presentada el 18 de abril del 2001 por Mark E. Salvati et al., (Archivo del agente No. LD0250(PSP)), la solicitud de patente provisional se incorpora en la presente como referencia en su totalidad (incluyendo pero no limitándose a la referencia a todos los compuestos específicos dentro de la fórmula I de la presente invención) y la solicitud de patente E.U.A. No. de serie 09/885,827, titulada "Moduladores receptores de andrógeno selectivos y métodos para su identificación, diseño y uso" presentada el 20 Junio de 2001

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por Mark E. Salvati et al., (Archivo del agente No. LD0250(NP)), la solicitud de patente se incorpora en la presente como referencia en su totalidad (incluyendo pero no limitado a, la referencia a todos los compuestos específicos dentro de la fórmula I de la presente invención).

Para los racematos de los compuestos de la presente invención, un enantiómero puede por ejemplo, ser un antagonista completo AR mientras que el otro pueden ser un antagonista AR en tejido de tumor, mientras que no tenga actividad o actividad agonista en tejidos que no son de tumor que contienen el receptor andrógeno.

Los otros agentes terapéuticos anteriores, cuando se emplean en combinación con los compuestos de la presente invención, se pueden usar por ejemplo, en aquellas cantidades indicadas en Physicians' Desk Reference (PDR) o como se determine de otra manera por alguien experto en la técnica.

Se pueden emplear los siguientes ensayos para determinar la actividad de un compuesto como un modulador NHR. Se prefieren aquellos compuestos con una actividad superior a 20μm para el enlace o transactivación en cualquiera de estos ensayos. Se determinaron diversos compuestos de la presente invención por tener una actividad del modulador AR, utilizando el ensayo de transactivación y los ensayos de enlace estándar AR como se describen a continuación.

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Ensayos de transactivación:

Ensayos específico de AR:

Se probaron los compuestos de la presente invención, en ensayos de transactivación de un constructo reportero transfectado y usando el receptor andrógeno endógeno de las células hospedadoras. El ensayo de transactivación, proporciona un método para la identificación de agonistas funcionales y agonistas parciales que imitan, o antagonistas que inhiben, el efecto de las hormonas de origen, en este caso, la dihidrotestoterona (DHT). Este ensayo se puede usar para predecir la actividad in vivo, ya que hay una buena correlación en ambas series de datos. Ver por ejemplo, T. Berger et al., J. Steroid Biochem. Molec. Biol. 773 (1992), la descripción de la cual se incorpora en la presente como referencia.

Para el ensayo de transactivación, se introduce un plásmido reportero por transfección (un procedimiento para inducir a las células a tomar genes externos) dentro de las células respectivas. Este plásmido reportero, comprende el ADNc para una proteína reportera, tal como la fosfatasa alcalina secretada (SEAP), controlada por las secuencias en la dirección ascendente del oxígeno específico de la próstata (PSA) que contiene elementos de respuesta de andrógenos (AREs). Este plásmido reportero funciona como un reportero para la actividad moduladora de la transcripción del AR. Así,

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el reportero actúa como un substituto para los productos (mARN después proteína) que se expresan normalmente por un gen bajo el control del AR y su hormona de origen. Con objeto de detectar los antagonistas, se lleva a cabo el ensayo de transactivación en presencia de una concentración constante de la hormona natural AR (DHT) que se conoce que induce una señal reportera definida. Las concentraciones crecientes del antagonista sospechoso, disminuirán la señal del reportero (por ejemplo, la producción SEAP). Por otro lado, al exponer las células transfectadas a concentraciones crecientes de un agonista sospechoso se incrementará la producción de la señal del reportero.

Para este ensayo, se obtuvieron células LNCaP y MDA 453 de American Type Culture Collection (Rockville, MD), y se mantuvieron en RPMI 1640 o en un medio DMEM complementado con suero de bovino fetal al 10% (FBS; Gibco) respectivamente. Las células respectivas se transfectaron transitoriamente por electroporación según el procedimiento optimizado descrito por Heiser, 130 Methods Mol. Biol., 117 (2000), con el plásmido reportero potenciador/pSEAP2/PSA540. El plásmido reportero se construyó como sigue: se utilizó ADN genómico de placenta humana comercial, para generar la reacción del ciclo de polimerasa (PCR) un fragmento que contenía el sitio BgIII (posición 5284) y el sitio Hind III en la posición 5831 del promotor del antígeno específico de la próstata humana

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(número de acceso U37672), Schuur, et al., J. Biol. Chem., 271 (12): 7043-51 (1996). Este fragmento se sub-clonó en un pSEAP2/básico (Clontech) digerido previamente con BgIII y HindIII para generar el constructo pSEAP2/PSA540. Después, se amplificó un fragmento que soportaba al fragmento de la secuencia en la dirección ascendente de PSA humana entre las posiciones -5322 y -3873 por PCR, a partir del ADN genómico de placenta humana. Se introdujeron los sitios XhoI y a BgIII con los cebadores. El fragmento resultante se sub-clonó en pSEAP2/PSA540 digerido con XhoI y BgIII respectivamente, para generar el constructo pSEAP2/PSA540/potenciador. Se recolectaron células LNCaP y MDA 453 en medios que contenían 10% de carbón mineral agotado en FBS. Cada suspensión de célula se distribuyó en dos cubas Gene Pulser (Bio-Rad) que recibieron después 8 µg del constructo reportero y se trataron por electroforesis usando un pulsador de genes Bio-Rad a 210 voltios y 960 µ Faraday. Después de la transfección se lavaron e incubaron las células con medios que contenían suero de bovino fetal agotado con carbón mineral, en ausencia (blanco) o presencia (control) de dihidrotetosterona 1 nM (DHT; Sigma Chemical) y en presencia o ausencia de la bicalutamida anti-andrógeno estándar, o compuestos de la presente invención en concentraciones que van desde 10-10 a 10-5 M (muestra). Se usaron los duplicados para cada muestra.

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Las diluciones del compuesto se llevaron a cabo en una estación de trabajo de laboratorio Biomek 2000. Después de 48 horas, se ensayó una fracción del sobrenadante para la actividad SEAP usando el sistema de ensayo de gen reportero quimioluminiscente Phospha-Light (Tropix, Inc). Se determinó la viabilidad de las células restantes usando el ensayo de proliferación de célula no radioactivo acuoso CellTiter 96 (MTS Assay, Promega). Brevemente, se agregó a las células una mezcla de un compuesto de tetrazolio (3-(4,5-dimetiltiazol-2-il)-5-(3-carboximetoxifenil)-2-(4-sulfofenil)-2H-tetrazolio, sal interior; MTS) y un reactivo de acoplamiento de electrones (metosulfato de fenazina; PMS). El MTS (reactivo de Owen) se bioredujo por las células en formazan que es soluble en un medio de cultivo de tejido, y por lo tanto se puede medir la absorbancia a 490nm directamente de placas de ensayo de 96 pozos sin procesamiento adicional. La cantidad de producto de formazan como se mide por la cantidad de la absorbancia de 490nm es directamente proporcional al número de células vivas en cultivo. Para cada replicado, se normalizó la lectura SEAP por el valor Abs490 derivado del ensayo MTS. Para el modo antagonista, se calculó el porcentaje de inhibición como:

% Inhibición = 100 x (1 - [control promedio - blanco promedio / muestra promedio - blanco promedio])

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Se graficaron los datos y la concentración del compuesto que inhibía al 50% del SEAP normalizado se cuantificó (IC_{50}).

Para el modo agonista, el porcentaje de control se refirió como el efecto del compuesto de prueba en comparación con el efecto máximo observado con la hormona natural, en este caso DHT, y se calculó como:

% Control = 100 x muestra promedio - blanco promedio / control promedio - blanco promedio.

Se graficaron los datos y la concentración del compuesto que activa hasta niveles del 50% del SEAP normalizado para el control se cuantificó (EC_{50}).

Ensayo de Especificidad GR:

El plásmido reportero utilizado comprendía el ADNc para la proteína reportera SEAP, como se describe para el ensayo de transactivación específico de AR. Se controló la expresión de la proteína reportera SEAP por las secuencias de repetición de la terminal larga del virus del tumor mamario de ratón (MMTV LTR) que contienen 3 elementos de respuesta a hormonas (HREs) que se pueden regular por GR y PR ver, por ejemplo, G. Chalepakis et al., Cell, 53(3), 371 (1988). Este plásmido se transfectó en células A549, que expresan el GR endógeno, para obtener un ensayo de transactivación específico de GR. Se obtuvieron las células A549 de American Type Culture Collection (Rockville, MD), y se mantuvieron en

RPMI 1640 complementado con suero de bovino fetal al 10% (FBS; Gibco). La determinación de la actividad antagonista específica de GR de los compuestos de la presente invención, fue idéntica con aquella descrita para el ensayo de transactivación específico de AR, excepto de que el DHT se reemplazó con dexametasona 5 nM (Sigma Chemicals), un agonista específico para GR. La determinación de la actividad agonista específica de GR de los compuestos de la presente invención, se llevó a cabo como se describe en el ensayo de transactivación de AR, en donde se mide la activación del sistema reportero específico GR por la adición de un compuesto de prueba, en ausencia de un ligando agonista específico de GR conocido.

Ensayo específico PR:

El plásmido reportero utilizado comprendía del ADNc para la proteína reportera SEAP, como se describe para el ensayo de transactivación específico de AR. La expresión de la proteína reportera SEAP se controló por la secuencia de la repetición de la terminal larga del virus del tumor mamario de ratón (MMTV LTR) que contiene 3 elementos de respuestas de hormonas (HREs) que se pueden regular por GR y PR. Este plásmido se transfectó en T47D, que expresa el PR endógeno para obtener un ensayo de transactivación específico PR. Las células T47D se obtuvieron de American Type Culture

Collection (Rockville, MD), y se mantuvieron en medio de DMEM complementado con suero de bovino fetal al 10% (FBS; Gibco). La determinación de la actividad antagonista específica de PR de los compuestos de la presente invención, fue idéntica con aquella descrita para el ensayo de transactivación específico de AR, excepto que el DHT se reemplazó con Promegastona 1 nM (NEN), un agonista específico para PR. La determinación de la actividad agonista específica de PR de los compuestos de la presente invención, se llevó a cabo como se describe el ensayo de transactivación AR, en donde se mide la activación del sistema reportero específico PR por la adición de un compuesto de prueba, en ausencia de un ligando de agonista conocido específico PR.

Ensayo de Enlace AR:

Para el ensayo de enlace de célula completa, las células humanas LNCaP (T877A mutante AR) o MDA 453 (AR de tipo silvestre) en placas de microtitulación de 96-pozos que contienen RPMI 1640 o DMEM complementado con CA-FBS agotado con carbón mineral al 10% (Cocaleco Biologicals) respectivamente, se incubaron a 37°C para eliminar cualquier ligando endógeno que pudiera formar complejos con los receptores en las células. Después de 48 horas se efectuaron, un análisis de saturación para determinar la K_d para la dihidrotestosterona titulada, [^{3}H]-DHT, o un ensayo de enlace

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competitivo para evaluar la capacidad de los compuestos de prueba para competir con [^{3}H]-DHT. Para el análisis de saturación, se agregaron a la células medios (RPMI 1640 o DMEM - 0.2% CA-FBS) que contenían [^{3}H]-DHT (en concentraciones que van de 0.1 nM a 16 nM) en ausencia (enlace total) o presencia (enlace no específico) de un exceso molar de 500-veces de DHT sin etiquetar. Después de 4 horas a 37°C, se separó una alícuota de los medios de enlace totales en cada concentración de [^{3}H]-DHT para estimar la cantidad de [^{3}H]-DHT libre. Los medios restantes se separaron, se lavaron las células 3 veces con PBS y se cosecharon sobre placas UniFilter GF/B (Packard), Microscint (Packard) se agregó y la placas se contaron en un Top-Counter (Packard) para evaluar la cantidad de [^{3}H]-DHT enlazado.

Para el análisis de saturación, se definió como un enlace específico la diferencia entre el enlace total y el enlace no específico. El enlace específico se evaluó por análisis Scatchard para determinar la K_d para [^{3}H]-DHT. Ver por ejemplo, D. Rodbard, Mathematics y statistics of ligand assays: an illustrated guide: In: J. Langon y J. J. Clapp, eds., Ligand Assay, Masson Publishing U.S.A., Inc. New York, pp. 45-99, (1981), la descripción de la cual se incorpora en la presente como referencia.

Para los estudios de competencia se agregaron a las células medios que contenían [^{3}H]-DHT 1 nM y los compuestos

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de la invención ("compuestos de prueba") en concentraciones que iban desde 10^{-10} hasta 10^{-5} M. Se utilizaron dos réplicas para cada muestra. Después de 4 horas a 37°C, se lavaron las células, se cosecharon y cortaron como se describe arriba. Se graficaron los datos como la cantidad de [^{3}H]-DHT (% de control en ausencia del compuesto de prueba) que restaba sobre el rango de respuesta de la prueba de dosis para un compuesto dado. La concentración de un compuesto de prueba que inhibió 50% de la cantidad de [^{3}H]-DHT enlazada en ausencia de un ligando en competencia, se cuantificó (IC_{50}) después de una transformación log-logit. Los valores K_I se determinaron por aplicaciones de la ecuación de Cheng-Prusoff a los valores IC_{50}, en donde:

$$K_I = \frac{IC_{50}}{(1 + (^3\text{H-DHT}) \ / \ K_d \text{ por } ^3\text{H-DHT})}$$

Después de corregir por el enlace no específico, se determinaron los valores IC_{50}. El IC_{50} se define como la concentración del ligando en competencia necesaria para reducir el enlace específico por 50%. Las K_d para [^{3}H]-DHT para MDA 453 y LNCaP fueron 0.7 y 0.2 nM respectivamente.

Ensayo de proliferación de células de próstata humana

Los compuestos de la presente invención se probaron ("compuestos de prueba") en la proliferación de las líneas celulares de cáncer de próstata humana. Para ello, las

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células MDA PCa2b, una línea celular derivada de la metástasis de un paciente que falló en la castración, Navone et al., Clin. Cancer Res., 3, 2493-500 (1997), se incubaron con o sin los compuestos de prueba por 72 horas y se cuantificó la cantidad de [^{3}H]-timidina incorporada en el ADN como una manera de evaluar el número de células y por lo tanto la proliferación. La línea celular MDA PCa2b se mantuvo en medios BRFF-HPC1 (Biological Research Faculty & Facility Inc., MD) complementados con FBS al 10%. Para el ensayo se colocaron células en microplacas de 96-pozos biorecubiertas y se incubaron a 37°C en FBS al 10% (agotado con carbón mineral)/BRFF-BMZERO (sin andrógenos). Después de 24 horas, las células se trataron en ausencia (blanco) o presencia de DHT 1 nM (control) o con compuesto de prueba (muestra) de la presente invención en concentraciones que van desde 10^{-10} a 10^{-5} M. Se usaron los duplicados para cada muestra. Las diluciones del compuesto se llevaron a cabo en una estación de trabajo del laboratorio Biomek 2000. 72 horas después se agregaron 0.44 uCi de [^{3}H]-Timidina (Amersham) por pozo, y se incubaron por otras 24 horas seguidas por la tripsinización, cosechando las células en filtros GF/B. Se agregó PS de micro-escintilación a los filtros, antes de contarlos en un contador TopCount Beckman.

El % de inhibición se calculó como:

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% de Inhibición = 100 x (1 - [$promedio_{control}$ - $promedio_{blanco}$ / $promedio_{muestra}$ - $promedio_{blanco}$])

Se graficaron los datos y la concentración del compuesto que inhibía 50% de la incorporación de [^{3}H]-Timidina se cuantificó (IC_{50}).

Ensayo de transactivación de los Mioblastos de ratón C2C12:

Se desarrollaron 2 ensayos de transactivación funcional para evaluar la eficacia de los agonistas de andrógenos en un respaldo de células de músculo usando un reportero de luciferasa. El primer ensayo (ARTA estable 1) utiliza una línea de célula, estable 1 (clon #72), que expresa establemente el receptor andrógeno de rata de longitud completa, pero requiere de la transfección transitoria de un potenciador/reportero. Esta línea celular se derivó de células de mioblasto de ratón C2C12. El segundo ensayo (ARTA estable 2) utiliza una línea celular, estable 2 (clon #133), derivada de estable 1 que expresa establemente el rAR y el reportero de luciferasa/potencionador.

El constructo de reportero/potenciador usado en este sistema es pGL3/2XDR-1/luciferasa. Se reportó el 2XDR-1 por ser un elemento de respuesta específico de AR en células CV-1. Brown et. al., The Journal of Biological Chemistry 272, 8227-8235, (1997). Se desarrolló por mutagénesis aleatoria de una secuencia potenciadora de consenso AR/GR.

ARTA estable 1:

1. Se colocaron en placas células estables 1 en un formato de 96 pozos a 6,000 células/pozo en DMEM de alta glucosa sin rojo de fenol (Gibco BRL, Cat. No.: 21063-029) que contenía 10% de carbón mineral y dextrano tratado con FBS (HyClone Cat. No.: SH30068.02), solución amortiguadora HEPES 50 mM (Gibco BRL, Cat. No.: 15630-080), 1X MEM de Piruvato de sodio (Gibco BRL, Cat. No.: 11360-070), 0.5X Antibiótico-Antimicótico, y 800 µg/ml Geneticina (Gibco BRL, Cat. No.: 10131-035).
2. 48 horas después se transfectaron las células con pGL3/2XDR-1/luciferasa usando un reactivo LipofectAMINE Plus™ (Gibco BRL, Cat. No.: 10964-013). Específicamente, 5 ng/pozo pGL3/2XDR-1/luciferasa ADN y 50 ng/pozo de ADN de esperma de salmón (como portador) se diluyeron con 5 µl/pozo de medios Opti-MEMem (Gibco BRL, Cat. No.: 31985-070). A esto se le agregó 0.5 µl/pozo de reactivo plus. Esta mezcla se incubó por 15 minutos a temperatura ambiente. En un recipiente separado, se diluyeron 0.385 µl/pozo de reactivo de LipofectAMINE con 5 µl/pozo de Opti-MEM. La mezcla de ADN se combinó después con la mezcla del lipofectAMINE y se incubó por 15 minutos adicionales a temperatura ambiente. Durante este tiempo, se separaron los medios de las células y se reemplazaron

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con 60 µl/pozo de Opti-MEM. A esto se le agregó 10 µl/pozo de una mezcla de transfección de ADN/LipofectAMINE. Las células se incubaron por 4 horas.

3. La mezcla de transfección se separó de las células y se reemplazó con 90 µl de medios como en el número 1 arriba.

4. Se colocaron en cada pozo 10 µl/pozo de una dilución apropiada de fármacos.

5. 24 horas después se usó el sistema de ensayo de luciferasa Steady-Glo™ para detectar la actividad según las instrucciones de los fabricantes (Promega, Cat. No.: E2520).

ARTA estable 2

1. Se colocaron en placas células estables 2 en un formato de 96 pozos a 6,000 células/pozo en DMEM de alta glucosa sin rojo de fenol (Gibco BRL, Cat. No.: 21063-029) que contenía 10% de carbón mineral y dextrano tratado con FBS (HyClone Cat. No.: SH30068.02), solución amortiguadora HEPES 50 mM (Gibco BRL, Cat. No.: 15630-080), 1X MEM de Piruvato de sodio (Gibco BRL, Cat. No.: 11360-070), 0.5X Antibiótico-Antimicótico, 800 µg/ml Geneticina (Gibco BRL, Cat. No.: 10131-035) y 800 µg/ml de Higromicina β (Gibco, BRL, Cat. No.: 10687-010).

2. 48 horas después, se separaron los medios en la célula y se reemplazaron con 90 µl de solución fresca. Se colocaron 10 µl/pozo de una dilución adecuada de fármaco en cada pozo.

3. 24 horas después, se usó el sistema de ensayo de luciferasa Steady-GloTM para detectar la actividad de conformidad con la instrucciones del fabricante (Promega, Cat. No.: E2520).

Ver la solicitud No. de serie de patente E.U.A. 09/885,831, titulada "Líneas celulares y ensayos basados en células para la identificación de moduladores receptores de andrógeno" presentada el 20 junio de 2001 por Jacek Ostrowski et al., (archivo del abogado No. D0177), cuya solicitud de patente se incorpora en la presente como referencia en su totalidad.

Ensayos de proliferación

Ensayo de proliferación de células de mama murino:

La capacidad de los compuestos de la presente invención ("compuestos de prueba") para modular la función del AR, se determinó al probar los compuestos en un ensayo de proliferación usando la línea de célula de mama de murino con respuestas a andrógenos derivada del tumor de Shionogi, Hiraoka et al., Cancer Res., 47, 6560-6564 (1987). Se

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establecieron clones estables dependientes de AR de la línea de Shionogi parental, al pasar fragmentos de tumor bajo los procedimientos generales descritos generalmente en Tetuo, et. al., Cancer Research 25, 1168-1175 (1965). Del procedimiento anterior se aisló en una línea estable, SC114, caracterizada y utilizada para la prueba de los compuestos del ejemplo. Se incubaron las células SC114 con o sin los compuestos de prueba por 72 horas, y se cuantificó la cantidad de [3H]-timidina incorporada en el ADN, como un punto final substituto para evaluar el número de células, y por lo tanto la tasa de proliferación como se describe en Suzuki et. al., J. Steroid Biochem. Mol. Biol. 37,559-567 (1990). La línea celular SC114 se mantuvo en MEM que contenía 10^{-8} M de testosterona y FCS tratado con DCC al 2%. Para el ensayo, las células se colocaron en microplacas de 96-pozos en los medios de mantenimiento y se incubaron a 37°C. Al día siguiente se cambió el medio a un medio libre de suero [Ham F-12:MEM (1;1, v/v) que contenía 0.1% BSA] con (modo antagonista) o sin (modo agonista) testosterona 10^{-8} M y los compuestos de prueba de la presente invención en concentraciones que iban desde 10^{-10} a 10^{-5} M. Se usaron duplicados para cada muestra. Las diluciones de compuestos se llevaron a cabo en una estación de trabajo de laboratorio Biomek 2000. 72 horas después, se agregaron 0.44 uCi de [3H]-Timidina (Amersham) por pozo y se incubaron por otras 2 horas después de la tripsinización, y

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se cosecharon las células sobre filtros GF/B. Se agregó el PS de micro-escintilación a los filtros antes de contarlos en un contador TopCount Beckman.

Para el modo antagonista, se calculó el % de inhibición como:

% Inhibición = 100 x (1 - [$promedio_{muestra}$ - $promedio_{blanco}$ / $promedio_{control}$ - $promedio_{blanco}$])

Se graficaron los datos y se cuantificó la concentración del compuesto que inhibió el 50% de la incorporación de [^{3}H]-timidina (IC_{50}).

Para el modo agonista, se refirió el % de control como el efecto del compuesto probado en comparación con el efecto máximo observado con la hormona natural, en este caso de DHT, y se calculó como:

% Control = 100 x ($promedio_{muestra}$ - $promedio_{blanco}$)/ ($promedio_{control}$ - $promedio_{blanco}$)

Se graficaron los datos y la concentración del compuesto que inhibió el 50% de la incorporación de [^{3}H]-Timidina se cuantificó (EC_{50}).

Ensayo in vitro para medir la transrepresión de AP-1 inducida por GR:

El ensayo AP-1 es un ensayo del reportero de luciferasa basado en células. Las células A549, que contienen al receptor glucocorticoide endógeno, se transfectaron

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establemente con un sitio de enlace de ADN AP-1 colocado al gen de luciferasa. Las células se hacen crecer después en RPMI + suero de becerro fetal al 10% (tratado con carbón mineral) + Penicilina/Estreptomicina con 0.5 mg/ml de geneticina. Se colocan en placas las células el día anterior al ensayo a aproximadamente 40000 células/pozo. El día del ensayo, se separan los medios por aspiración, y se agregan 20 µl de solución amortiguadora de ensayo (RPMI sin rojo de fenol + 10% PCS (carbón mineral tratado) + Pen/Strep) a cada pozo. En este punto, se agregan a cada pozo 20 µl de solución amortiguadora de ensayo (experimentos de control), los compuestos de la presente invención ("compuestos de prueba") (disueltos en DMSO y se agregaron a concentraciones variables) o dexametasona (100 nM en DMSO, control positivo). Las placas se pre incuban después por 15 minutos a 37°C, seguido por la estimulación de las células con PMA 10 ng/ml. Las placas se incuban después por 7 horas a 37°C después de lo cual, se agrega a cada pozo un reactivo de sustrato de luciferasa en 40 µl. Se mide la actividad por análisis en un medidor de luminosidad en comparación con los experimentos de control tratados con solución amortiguadora o dexametasona. La actividad se designa como el porcentaje de inhibición del sistema reportero en comparación con el control de solución amortiguadora con PMA solo con 10 ng/ml. El control,

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dexametasona, a una concentración de ≤10 μM, suprime típicamente la actividad por 65%. Los compuestos de prueba que demuestran una inhibición de la inducción del PMA del 50% o superior a una concentración del compuesto de prueba de ≤10 μM se consideran activos.

Ensayo antagonista AR del ensayo de peso de próstata en húmedo:

La actividad de los compuestos de la presente invención como antagonistas AR, se investigó en un modelo inmaduro de rata macho, una prueba estándar reconocida de la actividad anti-andrógeno de un compuesto dado como se describe en L. G. Hershberger et al., Proc. Soc. Expt. Biol. Med., 83, 175 (1953); P. C. Walsh y R. P. Gittes, "Inhibition of extratesticular stimuli to prostate growth in the castrated rat by antiandrogens", Endocrinology, 86, 624 (1970); y B. J. Furr et al., "ICI 176,334: A novel non-steroid, peripherally selective antiandrogen", J. Endocrinol., 113, R7-9 (1987), las descripciones de las cuales se incorporan en la presente como referencia.

La base de este ensayo es el hecho de que los órganos accesorios sexuales masculinos, tales como la próstata y las vesículas seminales, juegan un papel importante en la función reproductora. Estas glándulas se estimulan para crecer y se

mantienen en tamaño y la función secretora por la presencia continua de testosterona de suero (T) que es el andrógeno principal de suero (>95%) producido por la células Leydig en los testículos bajo el control de la hormona pituitaria luteinizante (LH) y la hormona estimuladora del folículo (FSH). La testosterona se convierte a la forma más activa, dihidrotestosterona, (DHT), dentro de la próstata por la 5α-reductasa. Los andrógenos adrenales también contribuyen a alrededor de 20% del DHT en la próstata de la rata, en comparación con el 40% de aquella en hombres de 65 años de edad. F. Labrie et al., Clin. Invest. Mod., 16, 475-492 (1993). Sin embargo, esta no es una trayectoria principal, ya que tanto en los animales como en los humanos, la castración produce una involución casi completa de la próstata y de las vesículas seminales sin una adrenalectomía concomitante. Por lo tanto bajo condiciones normales, las adrenales no soportan un crecimiento importante de los tejidos de la próstata. M. C. Luke and D. S. Coffey, "The Physiology of Reproduction" ed. por E. Knobil y J. D. Neill, 1, 1435-1487 (1994). Ya que los órganos masculinos sexuales son los tejidos más responsables de la modulación de la actividad de los andrógenos, se usa este modelo para determinar el crecimiento dependiente de los andrógenos de los órganos sexuales accesorios en ratas inmaduras castradas.

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Ratas macho inmaduras (19-20 días de edad Sprague-Dawley, Harlan Sprague-Dawely) se castraron bajo anestesia de metofanos. Cinco días después de la cirugía, se dosificaron estas ratas castradas (60-70g, 23-25 días de edad) por 3 días. Se dosificaron los animales subcutáneamente (s.c.) con 1 mg/kg con proprionato de testosterona (TP) en aceite de cacahuete como vehículo, y los compuestos de prueba anti-andrógenos (los compuestos de la presente invención) se dosificaron oralmente por gavage (p.o.) en suspensiones disueltas de PEG 400 al 80% y Tween 80(PEGTW) al 20%. Se dosificaron los animales (v/p) con un 0.5 ml de vehículo /100g de peso corporal. Los grupos experimentales fueron como sigue:

1. Vehículo de control
2. Propionato de testosterona (TP) (3 mg/rata/día, subcutáneo)
3. TP plus Casodex (administrado p.o. en PEGTW, QD), un antiandrógeno reconocido como compuesto de referencia.
4. Para demostrar la actividad al antagonista, se administró un compuesto de la presente invención ("compuesto de prueba") (p.o. en PEGTW, QD) con TP (s.c. como se administra en el grupo 2) en un rango de dosis.
5. Para demostrar la actividad agonista, se administró solamente un compuesto de la presente invención

("compuesto de prueba") (p.o., en PEGTW, QD) en un rango de dosis.

Al final del tratamiento de 3 días, se sacrificaron los animales, y se pesó la próstata central. Para comparar los datos de experimentos diferentes, los pesos de los órganos sexuales se estandarizaron primero como mg por 100 g de peso corporal, y el incremento en el peso de los órganos inducido por TP, se consideró como el incremento máximo (100%). El ANOVA, seguido por una prueba exacta de Fischer o de Student de una hilera, se usó para el análisis estadístico.

La ganancia y pérdida de los pesos de los órganos sexuales, refleja los cambios de números de células (contenido de ADN) y masa celular (contenido de proteínas), dependiendo de la concentración de andrógeno en el suero. Ver Y. Okuda et al., J. Urol., 145, 188-191 (1991), la descripción de la cual se incorpora en la presente como referencia. Por lo tanto, la medición del peso húmedo del órgano es suficiente para indicar la bioactividad de los andrógenos y de los antagonistas de andrógenos. En ratas castradas inmaduras, el reemplazo de los andrógenos exógenos, incrementa las vesículas seminales (SV) y la próstata ventral (VP) en una forma dependiente de la dosis.

El incremento máximo en el peso de los órganos fue de 4 a 5 veces cuando se dosifican 3 mg/rata/día de testosterona (T) o 1 mg/rata/día de propionato de testosterona (TP) por 3

días. La EC_{50} de T y TP, fueron alrededor de 1 mg y 0.03 mg, respectivamente. El incremento del peso en VP y SV, también se correlaciona con el incremento en la concentración de suero T y DHT. Aunque la administración de T muestra concentraciones de suero 5 veces superior desde T y DHT a las 2 horas después de la inyección subcutánea que aquellas de TP, por lo tanto, estos altos niveles declinaron rápidamente. En contraste, las concentraciones de suero de T y DHT en animales tratados con TP, fueron justamente consistentes durante las 24 horas, y por lo tanto, la TP mostró alrededor de 10-30 veces de potencia superior que la T libre.

En este modelo inmaduro de rata castrada, se administró también simultáneamente un antagonista conocido AR (Casodex) con 0.1 mg de TP (ED_{80}), inhibiendo el incremento mediado por testosterona en los pesos de VP y SV en una forma dependiente de la dosis. Los efectos del antagonista fueron similares cuando se dosifican oralmente o subcutáneamente. Los compuestos de la invención también muestran una actividad antagonista AR, al suprimir el incremento mediado por testosterona en los pesos de VP y SV.

Ensayo agonista AR; ensayo de peso de próstata en húmedo y Elevador del Ano:

La actividad de los compuestos de la presente invención como agonistas AR se investigó en un modelo de ratas macho

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inmaduras, una prueba reconocida de efecto anabólico en el músculo y de los efectos sostenibles en órganos sexuales para un compuesto dado como se describe en L. G. Hershberger et al., Proc. Soc. Expt. Biol. Med., 83, 175 (1953); B. L. Beyler et al, "Methods for evaluating anabolic and catabolic agents in laboratory animals", J. Amer. Med. Women's Ass., 23,708 (1968); H. Fukuda et al., "Investigations of the levator ani muscle as an anabolic steroid assay", Nago Dai. Yak. Ken. Nem. 14, 84 (1966), las descripciones de las cuales se incorporan en la presente como referencia.

La base de este ensayo se encuentra en la acción bien definida de los agentes androgénicos en el mantenimiento y crecimiento de tejidos de músculo y los órganos sexuales accesorios en los animales y en el hombre. Los esteroides androgénicos tales como la testosterona (T) se han caracterizado bien por su capacidad para mantener la masa muscular. El tratamiento de animales o humanos después de las castraciones con una fuente exógena de T, resulta en una inversión de la atrofia muscular. Los efectos de T en la atrofia muscular en el músculo elevador del ano de la rata se han caracterizado bien. M. Masuoka et al., "Constant cell population in normal, testosterone deprived and testosterone stimulated levator ani muscles" Am. J. Anat. 119,263 (1966); Z. Gori et al., "Testosterone hypertrophy of levator ani muscle of castrated rats. I. Quantitative data" Boll. -Soc.

Ital. Biol. Sper. 42, 1596 (1966); Z. Gori et al., "Testosterone hypertrophy of levator ani muscle of castrated rats. II. Electron-microscopic observations" Boll. -Soc. Ital. Biol. Sper. 42, 1600 (1966); A. Boris et al., Steroids 15, 61 (1970). Como se describe arriba, los efectos de los andrógenos en el mantenimiento de los órganos sexuales masculinos accesorios, tales como la próstata y las vesículas seminales, está bien descrita. La castración resulta en una involución rápida y en la atrofia de la próstata y las vesículas seminales. Este efecto se puede invertir por la adición exógena de los andrógenos. Ya que el músculo elevador del ano y los órganos sexuales masculinos son los tejidos más responsables de los defectos de los agentes androgénicos, se usa este modelo para determinar la inversión dependiente del andrógeno de la atrofia en el músculo elevador del ano y en los órganos accesorios sexuales en ratas castradas inmaduras. Se adquirieron ratas castradas sexualmente maduras (200-250 g, 6-8 semanas de edad, Sprague-Dawley, Harlan) del vendedor (Taconic). Se dividieron las ratas en grupos y se trataron diariamente por 7 a 14 días con uno de los siguientes:

1. Vehículo de control
2. Propionato de testosterona (TP) (3 mg/rata/día, subcutáneo)
3. Casodex TP plus (administrado p.o. en PEGTW, QD), un antiandrógeno reconocido como compuesto de referencia.

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4. Para demostrar la actividad antagonista, se administró un compuesto de la presente invención ("compuesto de prueba") (p.o. en PEGTW, QD) con TP (s.c. subcutáneo como se administra en el grupo 2) en un rango de dosis.

5. Para demostrar la actividad agonista, se administró solo un compuesto de la presente invención ("compuesto de prueba") (p.o. en PEGTW, QD) en un rango de dosis.

Al final del tratamiento de 7-14 días, se sacrificaron los animales por dióxido de carbono, y se pesaron el elevador del ano, vesícula seminal y próstata ventral. Para comparar los datos de los diferentes experimentos, se estandarizaron primero el músculo elevador del ano y los pesos de los órganos sexuales como mg por 100 g de peso corporal, y el incremento en el peso de los órganos inducido por TP se consideró como el incremento máximo (100%). Se usó la Super-anova (un factor) para el análisis estadístico.

La ganancia y pérdida de peso en los órganos sexuales, refleja los cambios del número de células (contenido de ADN) y masa celular (contenido de proteínas), dependiendo de la concentración de andrógenos del suero. Ver Y. Okuda et al., J. Urol., 145, 188-191 (1991), la descripción de la cual se incorpora en la presente como referencia. Por lo tanto, la medición del peso en húmedo de los órganos es suficiente para indicar la bioactividad de los andrógenos y el antagonista de

andrógenos. En ratas castradas inmaduras, el reemplazo de los andrógenos exógenos incrementa el elevador del ano, vesículas seminales (SV) y próstata en una forma dependiente de la dosis.

El incremento máximo en el peso de los órganos fue de 4 a 5 veces cuando se dosificaban 3 mg/rata/día de testosterona (T) o 1 mg/rata/día de propionato de testosterona (TP) por 3 días. El EC_{50} de T y TP, fue de alrededor de 1 mg y 0.03 mg, respectivamente. El incremento en el peso de VP y SV, también se correlacionó con el incremento en la concentración de suero en T y DHT. Aunque la administración de T mostró concentraciones de suero 5 veces superiores de T y DHT, a las 2 horas después de la inyección subcutánea, que con aquella de TP, por lo tanto, estos altos niveles declinaron muy rápidamente. En contraste, las concentraciones de suero de T y DHT de animales tratados con TP, fueron bastante consistentes durante las 24 horas, y por lo tanto, la TP mostró alrededor de una 10-30 veces de potencia superior que el T libre.

Ensayo de xenoinjerto de próstata humana MDA PCa2b;

Prueba antitumor in vivo: los tumores de próstata humana MDA-PCa-2b se mantuvieron en ratones desnudos Balb/c nu/nu. Se propagaron los tumores como transplantes subcutáneos en ratones macho desnudos adultos (4-6 semanas de edad) usando

fragmentos de tumor obtenidos de ratones donadores. El paso de tumor sucedió cada 5-6 semanas.

Para el ensayo de la eficacia antitumor, se acumuló en número requerido de animales necesario para detectar una respuesta significativa al comienzo del experimento, y se le dio a cada uno, un implante subcutáneo de un fragmento de tumor (~50 mg) con un trocar calibre 13. Se dejaron crecer los tumores hasta aproximadamente 100-200 mg (los tumores fuera del rango se excluyeron) y se distribuyeron uniformemente los animales para los diversos grupos de tratamiento y de control. El tratamiento de cada animal se basó en el peso corporal individual. Se verificaron diariamente los animales tratados para una toxicidad diagonal/mortalidad relacionada con el tratamiento. Cada grupo de animales se pesó antes del inicio del tratamiento (Wt1) y después nuevamente al seguir la última dosis de tratamiento (Wt2). La diferencia en el peso corporal (Wt2-Wt1) proporciona una medida de la toxicidad relacionada con el tratamiento.

Se determinó la respuesta de tumor al medir los tumores con un calibrador 2 veces por semana, hasta que los tumores alcanzaron un tamaño "objetivo" predeterminado de 0.5 m. Se estimaron los pesos de tumor (mg) de la fórmula: Peso de tumor = (longitud x ancho 2) ÷ 2.

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El punto final de respuesta de tumor se expresó en términos de la inhibición del crecimiento del tumor (%T/C), definido como la relación de los pesos medianos de tumor de los tumores tratados (T) con aquel del grupo de control (C).

Para estimar la exterminación de las células de tumor, se calculó primero el tiempo de doblaje del volumen de tumor con la fórmula:

TVDT = tiempo mediano (días) para controlar los tumores para alcanzar su tamaño objetivo - tiempo mediano (días) para controlar los tumores para alcanzar la mitad del tamaño objetivo s y, exterminio de células Log = (T-C)+(3.32 x TVDT)

Las evaluaciones estadísticas de los datos se llevaron a cabo usando una prueba Wilcoxon generalizada de Gehan.

Tumor de próstata de Dunning:

El tumor de próstata Dunning R3327H es un adenocarcinoma derivado espontáneamente con respuesta a los andrógenos bien diferenciada de la próstata (Smolev JK, Heston WD, Scott WW, y Coffey DS, Cancer Treat Rep. 61, 273-287 (1977)). El crecimiento de la sublínea R3327H se ha seleccionado por su crecimiento reproducible y altamente dependiente de andrógeno en ratas macho intactas. Por lo tanto, este modelo y otras sublíneas de este tumor, se han usado ampliamente para evaluar actividades antitumor in vivo de antiandrógenos tales

como la flutamida y bacilutamida/Casodex (Maucher A., and von Angerer, J. Cancer Res. Clin. Oncol., 119, 669-674(1993), Furr B.J.A. Euro. URL. 18 (suppl. 3), 2-9 (1990), Shain S.A. and Huot RI. J. Steriod Biochem. 31, 711-718 (1988)).

Al comienzo del estudio, se transplantaron subcutáneamente la piezas de tumor Dunning (alrededor de 4 x 4 mm) al costado de las ratas Copenhagen macho maduras (6-7 semanas de edad, Harlan-Sprague Dawley, Indianápolis, MD). Alrededor de 6 semanas posteriores al implante, los animales con tumores de tamaño que se mide (alrededor de 80 -120 mm^2) se formaron aleatoriamente en grupos de tratamiento (8-10 ratas/grupo) y se iniciaron los tratamientos. Se castró un grupo de las ratas para servir como control negativo del crecimiento del tumor. Los animales se trataron diariamente con los compuestos de la invención actual, antiandrógenos estándar tales como la bacilutamida o vehículo (control) para un promedio de 10 a 14 semanas. Se disolvieron los compuestos de prueba en un vehículo de (2.5 ml/kg de peso corporal) 10% de polietilen glicol y en 1% de carboxi metil celulosa 0.05% Tween-80, PEG/CMC, (Sigma, St Louis, MO). Los experimentos terapéuticos típicos, incluirían 3 grupos de las 3 dosis escaladas para cada estándar o compuesto de prueba (en un rango de 300-3 mg/kg).

Los tumores en el grupo del vehículo (control) alcanzaron un tamaño de 1500 a 2500 mm^3, mientras que el

grupo de animales castrados, muestra típicamente una estasis de tumor después de 14 semanas de observación. Los animales tratados oralmente con 20 mg/kg de bicalutamida o flutamida, se esperaría que mostraran una reducción del 40% en los volúmenes de tumor, en comparación con el control después de 14 semanas de tratamiento. El tamaño de los tumores se midió semanalmente por un calibrador vernier (Froboz, Suiza), tomando mediciones perpendiculares de longitud y ancho. Los volúmenes de tumor se miden en mm^3 usando la fórmula: Longitud x ancho x altura = Volumen. Las diferencias estadísticas entre los grupos de tratamiento y de control se evalúan usando un análisis múltiple ANOVA seguido por una prueba t de Student no paramétrica de una hilera.

Ensayo de peso de próstata de rata madura:

La actividad de los compuestos de la presente invención se investigó en un modelo de rata macho madura, que es una variación del ensayo de peso de próstata en húmedo y elevador del ano antes descrita. Los ensayos anteriores in vivo son ensayos reconocidos para determinar los efectos anabólicos en el músculo y los efectos de sostenimiento en los órganos sexuales para un compuesto dado como se describe en L. G. Hershberger et al., 83 Proc. Soc. Expt. Biol. Med., 175 (1953); B. L. Beyler et al, "Methods for evaluating anabolic and catabolic agents in laboratory animals", 23 J. Amer. Med.

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Women's Ass., 708 (1968); H. Fukuda et al., "Investigations of the levator ani muscle as an anabolic steroid assay", 14 Nago Dai. Yak. Ken. Nem. 84 (1966), las descripciones de la cual se incorporan en la presente como referencia. La base de este ensayo yace en la acción bien definida de los agentes androgénicos, en el mantenimiento y crecimiento de los tejidos de músculo y los órganos sexuales accesorios en los animales y el hombre.

Los órganos sexuales accesorios masculinos, tales como la próstata y las vesículas seminales, juegan un papel importante en la función reproductora. Estas glándulas se estimulan para crecer, y se mantienen en su tamaño y función secretora, por la presencia continua de testosterona de suero (T), que es un andrógeno principal del suero (>95%) producido por las células Leydig en los testículos, bajo el control de la hormona pituitaria luteinizante (LH) y la hormona estimuladora del folículo (FSH). La testosterona se convierte a una forma más activa, la dihidrotestosterona (DHT), dentro de la próstata por la 5α-reductasa. Los andrógenos adrenales también contribuyen con alrededor de 20% del DHT total en la próstata de la rata, en comparación con un 40% de aquel en hombres de 65 años de edad. F. Labrie et. al. 16 Clin. Invest. Med., 475-492 (1993). Sin embargo, esta no es una trayectoria principal, ya que tanto en animales como en humanos, la castración conduce a una involución casi completa

de la próstata y de las vesículas seminales sin una adrenalectomía concomitante. Por lo tanto bajo condiciones normales, las adrenales no soportan un crecimiento importante de los tejidos de próstata. M. C. Luke y D. S. Coffey, "The Physiology of Reproduction" ed. By E. Knobil and J. D. Neill, 1, 1435-1487 (1994). Ya que los órganos sexuales masculinos y el elevador del ano son los tejidos más responsables en la modulación de la actividad de los andrógenos, se usa este modelo para determinar la actividad de los compuestos que modulan la trayectoria del receptor andrógeno en las ratas maduras.

Junto con su actividad mitogénica en los tejidos tales como la próstata, vesícula seminal y músculo, la testosterona sirve también como un regulador negativo para su propia biosíntesis. La producción de testosterona en las células Leydig de los testículos, se controla por el nivel de LH en circulación liberado de la glándula pituitaria. Los niveles de LH se controlan por sí mismos por el nivel de LHRH producidos en la región hipotalámica. Los niveles de testosterona en la sangre sirven para inhibir la secreción de LHRH y reduce posteriormente los niveles de LH y finalmente los niveles de testosterona en circulación. Al medir los niveles de sangre de LH como se efectúan por los compuestos de la presente invención ("compuestos de prueba"), es posible

determinar el nivel de la actividad agonista o antagonista de los compuestos en el eje hipotalámico de su ciclo endocrino.

Los conjuntos correspondientes de ratas Harlan Sprague-Dawely (40-42 días edad, 180-220 g), se dosificaron oralmente por gavage (p.o.) con los compuestos de prueba en suspensiones/disueltas de 80% PEG 400 y 20% Tween 20 (PEGTW) por 14 días. Se dosificaron oralmente 2 grupos de control uno intacto y uno castrado, solamente con el vehículo PEGTW. Se dosificaron los animales (v/p) a 0.5 ml de vehículo/100g de peso corporal. Los grupos experimentales fueron como sigue:

1. Vehículo intacto (p.o., PEGTW, QD)
2. Vehículo de control (p.o., PEGTW, QD)
3. Bicalutamida (Casodex, un antiandrógeno reconocido como compuesto de referencia) o un compuesto de la presente invención, p.o. en PEGTW QD. (en un rango de dosis). Al final de tratamiento de 14 días, se sacrificaron los animales, se separaron quirúrgicamente la próstata ventral, las vesículas seminales y el elevador del ano y se pesaron. Para comparar los datos de diferentes experimentos, los pesos de los órganos se estandarizaron primero como mg por 100 g de peso corporal, y se expresaron como un porcentaje del valor del órgano respectivo en el grupo intacto.

La hormona luteinizante de rata (rLH) se determina cuantitativamente con el kit Biotrak [125 I] (Amersham

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Pharmacia Biotek), siguiendo las direcciones del fabricante. El ensayo se basa en la competencia por LH presente en el suero de enlace de [^{125} I]rLH con una suspensión de perlas Amerlex-M/anticuerpos. La radioactividad que permanece después de la incubación con el suero, y los lavados posteriores se extrapolan en una curva estándar para obtener una lectura en ng/ml.

La ganancia y pérdida de peso de órganos sexuales y del elevador del ano, refleja los cambios del número de células (contenido ADN) y masa celular (contenido de proteínas), dependiendo de la concentración de andrógeno de suero, ver Y. Okuda et al, J. Urol., 145, 188-191 (1991), la descripción de la cual se incorpora como referencia en la presente. Por lo tanto la medición del peso de los órganos en húmedo, es suficiente para indicar la bioactividad de los andrógenos y del antagonista de andrógenos. En el ensayo con ratas maduras, los agentes agonistas activos no tendrán efecto o incrementarán el peso de uno o más de los órganos responsables de los andrógenos (elevador del ano, próstata, vesícula seminal) y no tendrán efecto o un efecto supresor en la secreción del LH. Los compuestos con actividad antagonista, disminuirán el peso de uno o más de los órganos responsables de los andrógenos (elevador del ano, próstata, vesícula seminal) y no tendrán efecto o un efecto supresor reducido en la secreción LH.

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Ensayo de xenoinjerto de próstata humana CWR22:

Prueba antitumor in vivo: Se mantuvieron tumores de próstata humanos CWR22 en ratones desnudos Balb/c nu/nu. Se propagaron los tumores como transplantes subcutáneos en ratones macho adultos desnudos (4-6 semanas de edad) usando fragmentos de tumor obtenidos de ratones donadores. El paso de los tumores sucedió cada 5-6 semanas.

Para un ensayo de eficacia anti-tumor, se acumuló el número requerido de animales necesario para detectar una respuesta significativa al comienzo del experimento, y se le dio a cada uno un implante subcutáneo de un fragmento de tumor (~50 mg) con un trocar de calibre 13. Se dejaron crecer los tumores hasta aproximadamente 100-200 mg (tumores fuera del rango fueron excluidos) y se distribuyeron uniformemente los animales en diversos grupos de control y de tratamiento. El tratamiento de cada animal se basó en su peso corporal e individual. Los animales tratados se verificaron diariamente para la toxicidad/mortalidad relacionada con el tratamiento. Cada grupo de animales se pesó antes del inicio del tratamiento (Wt1) y después siguiendo la última dosis de tratamiento (Wt2). La diferencia en el peso corporal (Wt2-Wt1) proporciona una medida de la toxicidad relacionada con el tratamiento.

La respuesta de tumor se determinó por la medición de los tumores con un calibrador dos veces por semana, hasta que

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los tumores alcanzaron un tamaño predeterminado "objetivo" de 0.5 gm. Se estimaron los pesos de tumor (mg) a partir de la fórmula: peso de tumor =: (longitud x ancho 2)÷2.

El punto terminal de respuesta de tumor, se expresó en términos de la inhibición del crecimiento de tumor (%T/C), definido como la relación de los pesos medianos de tumor de los tumores tratados (T) con aquel del grupo de control (C).

Para estimar la eliminación de células de tumor, el tiempo de doblaje de volumen de tumor se calculó primero con la fórmula:

TVDT = tiempo mediano (días) para los tumores de control para que alcancen el tamaño objetivo - tiempo mediano (días) para los tumores de control para alcanzar la mitad del tamaño objetivo y exterminio de células Log = (T-C)÷(3.32 x TVDT)

Las evaluaciones estadísticas de los datos se efectuaron usando una prueba Wilcoxon generalizada de Gehan.

Los siguientes ejemplos ilustran modalidades de la presente invención, y no se pretende que limiten el alcance de las reivindicaciones. Dentro de ciertos ejemplos, se prepara un compuesto de fórmula I y se emplea después para preparar además uno o más compuestos adicionales de fórmula I o sales de los mismos. Los métodos empleados para preparar un compuesto de la fórmula I o una sal del mismo como se

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describen en la presente se pueden emplear como sea adecuado para preparar otros compuestos de la invención.

Abreviaturas:

Las siguientes abreviaturas se usan en la presente:

DBU	= 1,8-diazabiciclo[5.4.0]undec-7-ena
4-DMAP	= 4-dimetilaminopiridina
ee	= exceso enantiomérico
DMF	= dimetilformamida
EtOAc	= acetato de etilo
LDA	= diisopropilamida de litio
Base Hünig	= N,N-diisopropiletilamina
Me	= metilo
RT	= tiempo de retención
TFA	= ácido trifluoroacético
THF	= tetrahidrofurano
CCD	= cromatografía de capa delgada
TMS	= trimetilsililo
pTSA	= ácido para-toluensulfónico
Δ	= calor
t-Bu	= tert-butilo
$PhCH_3$	= tolueno
Pd/C	= paladio sobre carbón mineral activado
TsCl	= cloruro de tosilo
TBSOTf	= tert-butildimetilsilil trifluorometan sulfonato

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TBS	= tert-butildimetilsilano
MeI	= yoduro de metilo
$(BOC)_2O$	= di-tert-butil dicarbonato
TEA	= trietiloamina
n-BuLi	= n-butillitio
rt	= temperatura ambiente
CL	= cromatografía líquida
Ts	= tosilo
Ph	= fenilo
EtOH	= etanol
DCE	= dicloroetano
DMSO	= dimetilsulfóxido
Ra-Ni	= Níquel Raney
MS	= mallas moleculares
EM(ES)	= espectrometría de masa por electro-rociado
mCPBA	= ácido m-cloroperoxibenzóico
sat	= saturado
AcOH	= ácido acético
MeOH	= metanol
Et_2O	= éter de dietilo
Ac	= acetilo
DEAD	= azodicarboxilato de dietilo
h	= horas
Et	= etilo

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WSDCC	= diimida de dicarbonilo soluble en agua, clorohidrato de 1-(3-dimetilaminopropil)-3-etilocarbodiimida
TBAF	= fluoruro de tetrabutilamonio
DBAD	= di-terbutilazodicarboxilato
DCC	= Diciclohexilcarbodiimida
Catalizador de Wilkinson	= RhCl(PPh3)3
ADDP	= 1,1-[azodicarbonil]dipiperidina
DMA	= dimetilacetamida
DME	= 1,2-dimetoxietano
BOP	= hexafluorofosfato de benzotriazol-1-iloxitris(dimetilamino)-fosfonio
HRMS	= espectrometría de masa de alta resolución
TBME = MTBE	= metil tert-butil éter (esto es, 2-metoxi-2-metil-propano)
$TiCl_2Cp_2$	= dicloruro de bis(ciclopentadienil)titanio
DPPA	= azida de difenilfosforilo
HMPA	= amida de hexametilfosforilo
V%	= por ciento en volumen
BH_3•DMS	= dimetilsulfato de borano
vvm	= volumen de gas por volumen de líquido por minuto.

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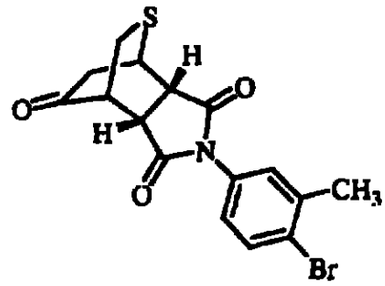
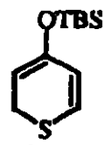
Ejemplo 1

(3aα,4α,7α,7aα)-2-(4-Bromo-3-metilfenilo)tetrahidro-4,7-etanotiopirano[3,4-c]pirrol-1,3,8(2H,4H)-triona(CL)



A. 4-(tert-Butildimetilsiloxi)-2H-tiopirano (1A)



La 2,3-Dihidro-4H-tiopiran-4-ona (1.50 g, 13.1 mmol, sintetizada como se describe en Richards et al., J. Org. Chem. 46,4836-4842 (1981)) se disolvió en CH_2Cl_2 (130 mL) y se agregó trietilamina (5.47 mL, 39.4 mmol). Se agregó después tert-butildimetilsilil trifluorometansulfonato (3.62 mL, 15.8 mmol). Después de 10 minutos, se separaron los volátiles in vacuo a 25°C. El aceite amarillo resultante se pasó a través de una columna corta de SiO_2 eluyendo con 3% TEA en hexanos para resultar 1.82 g (7.97 mmol, 61%) del compuesto 1A como un aceite color naranja.

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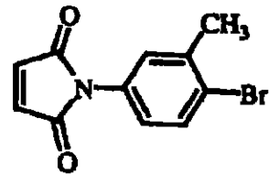
B. 1-[4-bromo-3-metilofenil]-1H-pirrol-2,5-diona (1B)



Se disolvieron 4-Bromo-3-metilanilina (1.55 g, 8.33 mmol) y anhídrido maleico (0.898 g, 9.16 mmol) en ácido acético (10 mL) y se calentaron a 115°C por 12 h. La reacción se enfrió después hasta 25°C y el ácido acético se separó in vacuo. El residuo resultante se suspendió en 5% K_2CO_3 (100 mL), se agitó por 25 minutos, se filtró y se lavó con agua. El material se secó después in vacuo para dar 1.65 g (6.20 mmol, 74%) del compuesto 1B como un sólido café claro. CLAR: 100% a 2.96 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm eluyendo con 10-90% de metanol acuoso durante 4 minutos conteniendo 0.1% TFA, 4 mL/min., observando a 220 nm).

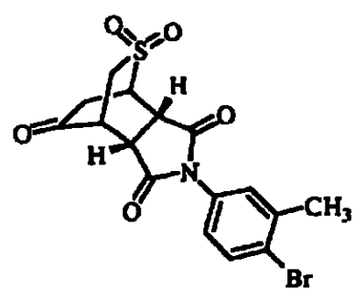
C. (3aα,4α,7α,7aα)-2-(4-Bromo-3-metilfenil)tetrahidro-4,7-etanotiopirano[3,4-c]pirrol-1,3,8(2H,4H)-triona(1C)

El compuesto 1A (0.313 g, 1.41 mmol) y el compuesto 1B (0.250 g, 0.940 mmol) se disolvieron en tolueno y se calentaron hasta reflujo por 5 h. El tolueno se separó después al pasar una corriente de argón a través del matraz de reacción. El residuo se purificó después por cromatografía instantánea en SiO_2 eluyendo con 20% de hexano en cloroformo.

Esto dio 0.168 g del intermediario del éter de enol como un sólido amarillo. El intermediario del éter de enol se disolvió en dicloroetano (2.0 mL) y se agregó TFA (0.25 mL). Después de 0.5 h, la reacción se apagó con $NaHCO_3$ acuoso saturado y se extrajo con CH_2Cl_2 (2 x 30 mL). Se secaron los compuestos orgánicos sobre sulfato de sodio anhidro y se evaporaron para dar 0.079 g (0.21 mmol, 22%) del compuesto 1C como un sólido blanco. CLAR: 99% a 3.010 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm eluyendo con 10-90% metanol acuoso durante 4 minutos conteniendo 0.1% TFA, 4 mL/min., observando a 220 nm). EM (ES): m/z 396.9 $[M+ NH_4]^+$.

Ejemplo 2

5,5-dióxido de (3aα,4α,7α,7aα)-2-(4-Bromo-3-metilfenil)tetrahidro-4,7-etanotiopirano[3,4-c]pirrol-1,3,8(2H,4H)-triona (2)

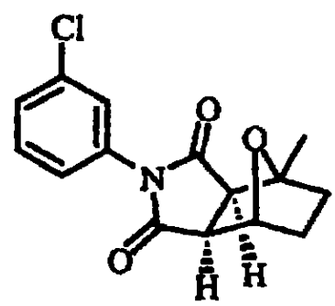


El compuesto 1C (0.040 g, 0.11 mmol) se disolvió en CH_2Cl_2 (4.0 mL) y se enfrió hasta 0°C. Se agregó m-CPBA (60% pureza, 0.061 g, 0.21 mmol) y la reacción se calentó después hasta 25°C. Después de 1 h, se agregó una mezcla 1:1 de

$NaHCO_3$ saturado y sulfito de sodio saturado (20 mL) con agitación vigorosa. Después de 15 minutos, la mezcla se extrajo con CH_2Cl_2 (2 x 30 mL) y los compuestos orgánicos se secaron sobre sulfato de sodio anhidro para dar 0.031 g (0.075 mmol, 71%) del compuesto 2 como un sólido blanco. No fue necesaria purificación. CLAR: 78% a 2.290 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm eluyendo con 10-90% de metanol acuoso durante 4 minutos conteniendo 0.1 % TFA, 4 mL/min., observando a 220 nm). EM (ES): m/z 429.8 $[M+NR_4]^+$.

Ejemplo 3

(3aα,4β,7β,7aα)-2-(3-Clorofenil)hexahidro-4-metil-4, 7-epoxi-1H-isoindol-1,3(2H)-diona(3)



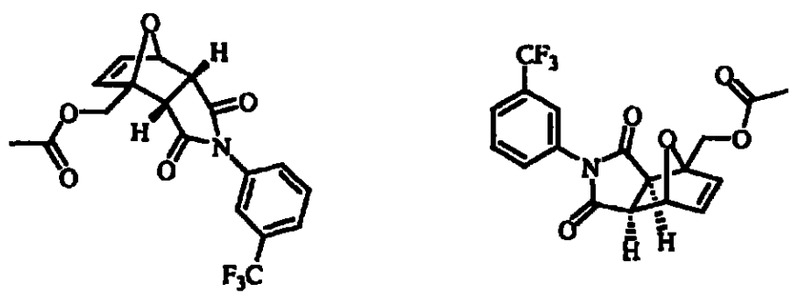
Se disolvieron 3-Cloroanilina (0.100 g, 0.787 mmol) y anhídrido 3,6-endoxo-3-metilhexahidroftálico (0.172 g, 0.945 mmol) en AcOH (2.0 mL) y se calentaron a 110°C por 11 h. La reacción se enfrió después hasta 25°C, se vació en K_2CO_3 acuoso saturado frío y se agitó vigorosamente por 10 min. La solución se filtró después y se lavó con agua. El filtrado

resultante se filtró in vacuo para dar 0.118 g (0.404 mmol, 51 %) del compuesto 3 como un sólido blanco. No fue necesaria purificación adicional. CLAR: 99% a 2.510 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm eluyendo con 10-90% de metanol acuoso durante 4 minutos conteniendo 0.1% TFA, 4 mL/min., observando a 220 nm). EM (ES): m/z 292.32 $[M+H]^+$.

Ejemplo 4

(3aα,4α,7α,7aα)- y (3aα,4β,7β,7aα)-4-[(Acetiloxi)metil]-3a,4,7,7a-tetrahidro-2[3-(trifluorometil)fenil]-4,7-epoxi-1H-isoindol-1,3(2H)-diona

(4i y 4ii, respectivamente)

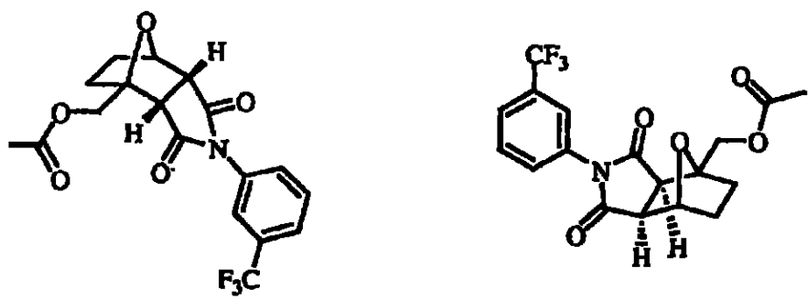


Se disolvieron 2-Acetoximetilfurano (0.599 mL, 4.78 mmol) y 1-[3-(trifluorometil)-fenil]-1H-pirrol-2,5-diona (0.500 g, 2.39 mmol, preparado como se describe en el Ejemplo 1B) se disolvió en cloruro de metileno (3.0 mL) a 25°C. Después de 22 h, se separaron los volátiles in vacuo y el residuo resultante se purificó por cromatografía instantánea sobre SiO_2 eluyendo con 0-15% acetona en cloruro de metileno

para dar 0.438 g (1.15 mmol, 48%) de un aceite amarillo como una mezcla 2:1 del compuesto 4i y del compuesto 4ii, que no se separó. CLAR: 100% a 3.093 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm eluyendo con 10-90% de metanol acuoso durante 4 minutos conteniendo 0.1 % TFA, 4 mL/min., observando a 220 nm). EM (ES): m/z 398.9 $[M+NH_4]^+$.

Ejemplo 5

(3aα,4α,7α,7aα)- y (3aα,4β,7β,7aα)-4-[(Acetiloxi)metil]-Hexahidro-2-[3-(trifluorometil)fenil]-4,7-epoxi-1H-isoindol-1,3(2H)-diona (5i y 5ii, respectivamente)

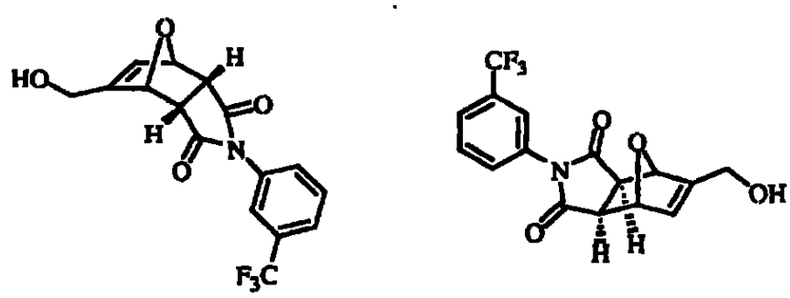


La mezcla 2:1 de los compuestos 4i y 4ii (0.361 g, 0.948 mmol) se disolvió en acetato de etilo (25 mL) y se agregó Pd/C (10% Pd, 0.2 g). Se introdujo hidrógeno por medio de un globo y la reacción se agitó a 25°C por 4 h, seguida por filtración a través de Celite y enjuagando con acetato de etilo. La concentración in vacuo dio 0.348 g (0.908 mmol, 96%) de un aceite amarillo que se determinó que era una mezcla 2:1 del compuesto 5i y compuesto 5ii (que no se separó). CLAR: 100% a 2.900 min. (tiempo de retención)

(Columna YMC S5 ODS de 4.6 x 50 mm eluyendo con 10-90% metanol acuoso durante 4 minutos conteniendo 0.1% TFA, 4 mL/min., observando a 220 nm). EM (ES): m/z 401.0 $[M+NH_4]^+$.

Ejemplo 6

(3aα,4α,7α,7aα)- y (3aα,4β,7β,7aα)-3a,4,7,7a-Tetrahidro-5-(hidroximetil)-2-[3-(trifluorometil)fenil]-4,7-epoxi-1H-isoindol-1,3(2H)-diona (6i y 6ii, respectivamente)



Se disolvieron 1-[3-(Trifluorometil)fenil]-1H-pirrol-2,5-diona (0.500 g, 2.39 mmol, preparada como se describe en el Ejemplo 1B) y 3-furanmetanol (0.412 mL, 4.78 mmol) en cloruro de metileno (3.0 mL) y se agitó a 25°C por 20 h. Los volátiles se separaron después in vacuo y el material resultante se purificó por cromatografía instantánea sobre SiO_2 eluyendo con cloroformo/acetona para dar 0.379 g (1.12 mmol, 47%) del compuesto 6i y 0.220 g del compuesto 6ii, ambos como sólidos blancos. Compuesto 6i: CLAR: 100% a 2.197 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm eluyendo con 10-90% metanol acuoso durante 4 minutos conteniendo 0.1% TFA, 4 mL/min., observando a 220 nm). EM

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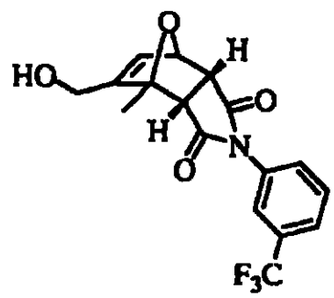
(ES): m/z 338.0 $[M-H]^-$. Compuesto 6ii: CLAR: 100% a 2.477 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm eluyendo con 10-90% de metanol acuoso durante 4 minutos conteniendo 0.1% TFA, 4 mL/min., observando a 220 nm). EM (ES): m/z 338.0 $[M-H]^-$.

Ejemplo 7

(3aα,4α,7α,7aα)-3a,4,7,7a-Tetrahidro-5-(hidroximetil)-4-metil-2-[3-(trifluorometil)fenil]-4,7-epoxi-1H-isoindol-1,3(2H)-diona(7)



Se disolvieron 2-Metil-3-furanmetanol (0.537 g, 4.78 mmol) y 1-[3-(trifluorometil)-fenil]-1H-pirrol-2.5-diona (0.500 g, 2.39 mmol, preparado como se describe en el Ejemplo 1B) se disolvió en dicloroetano (2.0 mL) y se agitó a 25°C por 20 h. La reacción se concentró después in vacuo y se purificó por cromatografía instantánea en SiO_2 eluyendo con acetato de etilo/cloruro de metileno para dar 0.317 g (0.897 mmol, 37.5%) del compuesto 7 como un sólido blanco. No se pudo aislar otro isómero posible después de la cromatografía. CLAR: 100% a 2.197 min. (tiempo de retención) (Columna YMC S5

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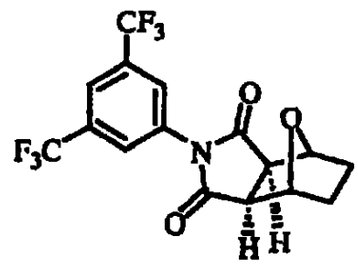
ODS de 4.6 x 50 mm eluyendo con 10-90% de metanol acuoso durante 4 minutos conteniendo 0.1% TFA, 4 mL/min., observando a 220 nm). EM (ES): m/z 351.9 $[M-H]^-$.

Ejemplo 8

(3aα,4β,7β,7aα)-2-[3,5-Bis(trifluorometil)fenil]hexahidro-4,7-epoxi-1H-isoindol-1,3(2H)-diona (8)



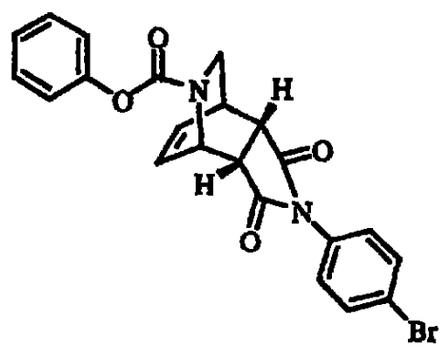
La 3,5-Bis(trifluorometil)anilina (0.017 g, 0.075 mmol) se disolvió en ácido acético (0.300 mL) y se transfirió a un vial cónico de 1.5 mL con una tapa de septo. Las soluciones de reserva de 95 aminas adicionales se prepararon como se describe arriba. A cada uno de los viales anteriores se le agregó 0.40 mL (0.12 mmol) de una solución de reserva de anhídrido exo-7-oxabiciclo[2.2.1]heptano-2,3-dicarboxílico en ácido acético. Los viales se sellaron después y se calentaron a 110°C por 11 h. Con el enfriamiento a 25°C, se separaron las tapas de los viales, se separó el ácido acético in vacuo. A cada vial se le agregó 1 mL de 2:1 acetona/cloruro de metileno y se calentaron los viales a 40°C por 1 h. Una vez que estuvieron todos los productos en solución, se

transfirieron por medio de un robot a tubos de filtrado con fritas gruesas prehumedecidas con 0.2 mL de agua. Se circuló nitrógeno a través de cada tubo hasta que se eliminaron los compuestos orgánicos volátiles. Se agregó después 1.5 mL de 10% de K_2CO_3 acuoso a cada tubo, seguido por una agitación vigorosa a 25°C por 15 min. Se drenaron después los tubos, se volvieron a sellar y se agregó 1.0 mL de agua a cada tubo, seguido de agitación. Los tubos se drenaron nuevamente y se lavaron por segunda vez con agua. Los residuos resultantes en cada tubo se secaron después in vacuo por 48 h. Después de secar, se agregó 1.0 mL de 20% TFA en cloruro de metileno a cada tubo y se agitaron las rejillas por 30 min. Se drenaron después los tubos en una placa de 96 pozos con micro-tubos presentes a la medida previamente tarados. Cada tubo se ensayó para la pureza del producto (CL analítica) e identidad (CL-EM). Se concentraron después los tubos in vacuo y se pesaron para los rendimientos. El tubo conteniendo la reacción de 3,5-bestrifluorometilanilina y anhídrido exo-7-oxabiciclo[2.2.1]heptano-2,3-dicarboxílico, produjo 0.022 g (0.058 mmol, 77%) del compuesto 8 como un sólido blanco. CLAR: 94% a 4.03 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm eluyendo con 10-90% metanol acuoso durante 4 minutos conteniendo 0.1% TFA, 4 mL/min., observando a 220 nm). EM (ES): m/z 434.2 $[M+Na+MeOH]^+$. Del resto de las 95 reacciones adicionales restantes corridas, se obtuvieron un

total de 80 compuestos finales en >70% pureza y >5 mg de rendimiento. Diversas muestras requirieron de purificación adicional, que se llevó a cabo en una columna corta de SiO_2 eluyendo con cloruro de metileno/acetona. Ver Tabla 2 a continuación.

Ejemplo 9

Éster de fenilo del ácido (3aα,4α,7α,7aα)-2-(4-Bromofenil)octahidro-1,3-dioxo-4,7-eteno-5H-pirrolo[3,4-c]piridina-5-carboxílico (9)

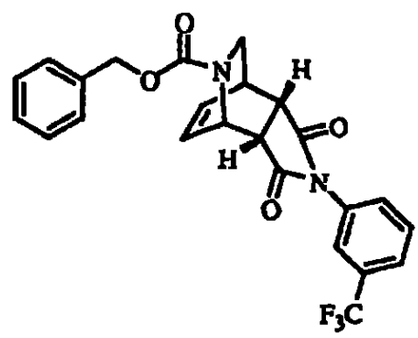


La 1-[4-Bromofenilo]-1H-pirrol-2,5-diona (0.250 g, 0.992 mmol, preparada como se describe en el Ejemplo 1B) y el éster de fenilmetilo del ácido 1(2H)-piridincarboxílico (0.299 g, 1.49 mmol, sintetizado como se describe en Richard et al. J. Org. Chem. 46, 4836-4842 (1981)) se disolvieron en tolueno y se calentaron a 85°C por 1 h. Al enfriar a 25°C, se separó el tolueno in vacuo. El residuo resultante se disolvió en una cantidad mínima de cloroformo y el producto se precipitó por la adición de hexanos. Después de 1 h a 25°C, el producto se

filtró y se lavó con 20% hexanos en frío en cloroformo para dar 0.243 g (0.536 mmol, 54%) del compuesto 9 como un sólido blanco (isómero sencillo). CLAR: 100% a 3.393 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm eluyendo con 10-90% metanol acuoso durante 4 minutos conteniendo 0.1% TFA, 4 mL/min., observando a 220 nm). EM (ES): m/z 454.98 $[M+H]^+$.

Ejemplo 10

Éster de fenilmetilo del ácido (3aα,4α,7α,7aα)-2-[4-Bromofenil)octahidro-1,3-dioxo-4,7-eteno-5H-pirrolo[3,4-c]piridina-5-carboxílico (10)

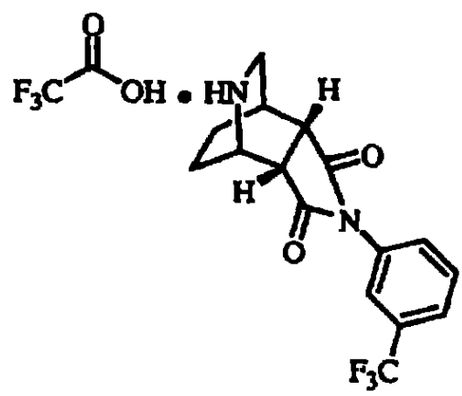


La 1-[3-(Trifluorometil)fenil]-1H-pirrol-2,5-diona (3.78 g, 15.7 mmol, preparada como se describe en el Ejemplo 1B) y el éster de fenilmetilo del ácido 1(2H)-piridincarboxílico (4.00 g, 18.8 mmol, sintetizado como se describe en Richard et al. J. Org. Chem. 46, 4836-4842 (1981)) se disolvieron en tolueno y se calentaron a 80°C por 3 h. Después de enfriar a 25°C, se separó el tolueno in vacuo y el residuo resultante se purificó por cromatografía instantánea sobre SiO_2 eluyendo

con metanol/cloruro de metileno para dar 3.20 g (7.01 mmol, 45%) del compuesto 10 como un aceite amarillo. CLAR: 95% a 3.510 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm eluyendo con 10-90% de metanol acuoso durante 4 minutos conteniendo 0.1% TFA, 4 mL/min., observando a 220 nm). EM (ES): m/z 457.2 $[M+H]^+$.

Ejemplo 11

Trifluoroacetato de (3aα,4α,7α,7aα)-Hexahidro-2-[3-(trifluorometil)fenil]-4,7-etano-1H-pirrol[3,4-c]piridina-1,3(2H)-diona (11)

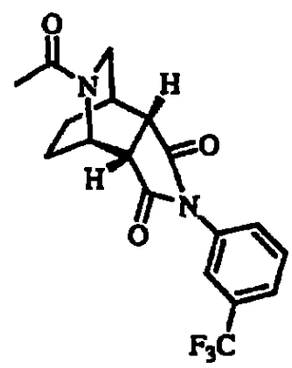


El compuesto 10 (3.20 g, 7.01 mmol) se disolvió en 100 mL de MeOH y se agregó 10% de catalizador Pd/C de Degussa (2.00 g, cat.). Se introdujo después hidrógeno por medio de un globo. Después de 1 h, se filtró la reacción a través de Celite y se enjuagó con MeOH. Se separaron los volátiles in vacuo y el material crudo resultante se purificó por CLAR preparativa de fase inversa para dar 2.50 g (5.70 mmol. 81%)

del compuesto 11 como la sal de TFA (sólido blanco). CLAR: 99% a 1.843 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm eluyendo con 10-90% metanol acuoso durante 4 minutos conteniendo 0.1% TFA, 4 mL/min., observando a 220 nm). EM (ES): m/z 325.12 $[M+H]^+$.

Ejemplo 12

(3aα,4α,7α,7aα)-5-Acetilhexahidro-2-[3-(trifluorometil)fenil]-4,7-etano-1H-pirrolo[3,4-c]piridina-1,3(2H)-diona (12)

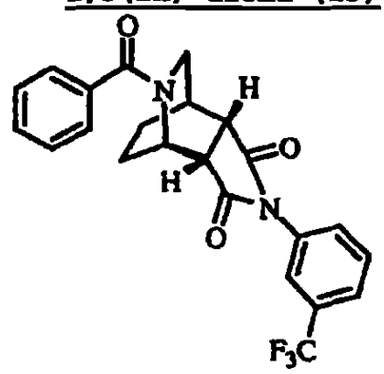


El compuesto 11 (0.10 g, 0.23 mmol) se suspendió en THF (5.0 mL) y se agregó TEA (0.097 mL, 0.46 mmol), resultando en una solución homogénea. Se agregó después cloruro de acetilo (0.033 mL, 0.46 mmol). Después de 2 h, la reacción se apagó con $NaHCO_3$ acuoso saturado y se extrajo con cloruro de metileno (3 x 15 mL). El material crudo se purificó por CCD preparativa eluyendo con cloroformo/acetona para dar 0.067 g (0.18 mmol, 79%) del compuesto 12 como un aceite incoloro. CLAR: 99% a 2.66 min. (tiempo de retención) (Columna YMC S5

ODS de 4.6 x 50 mm eluyendo con 10-90% de metanol acuoso durante 4 minutos conteniendo 0.1% TFA, 4 mL/min., observando a 220 nm). EM (ES): m/z 367.0 $[M+H]^+$.

Ejemplo 13

(3aα,4α,7α,7aα)-5-Benzoilhexahidro-2-[3-trifluorometil)fenil]-4,7-etano-1H-pirrolo[3,4-c]piridin-1,3(2H)-diona (13)



El compuesto 11 (0.10 g, 0.23 mmol) se suspendió en THF (5.0 mL) y se agregó TEA (0.097 mL, 0.46 mmol) resultando en una solución homogénea. Se agregó después cloruro de benzoilo (0.053 mL, 0.46 mmol). Después de 2 h, la reacción se apagó con $NaHCO_3$ saturado acuoso y se extrajo con cloruro de metileno (3 x 15 mL). El material crudo se purificó por CLAR preparativa de fase inversa para dar 0.020 g (0.047 mmol, 20%) del compuesto 13 como una espuma blanca. CLAR: 99% a 3.183 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm eluyendo con 10-90% de metanol acuoso durante 4 minutos

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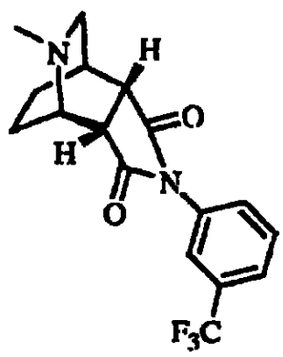
conteniendo 0.1 % TFA, 4 mL/min., observando a 220 nm). EM (ES): m/z 429.1 $[M+H]^+$.

Ejemplo 14

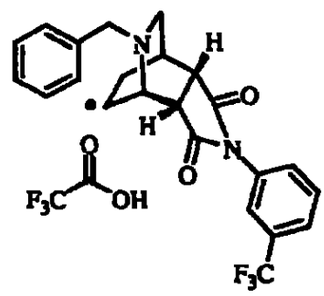
(3aα,4α,7α,7aα)-Hexahidro-5-metil-2-[3(trifluorometil)fenil]-4,7-etano-1H-pirrolo[3,4-c]piridina-1,3(2H)-diona(14)



El compuesto 11 (0.10 g, 0.23 mmol) se suspendió en THF (5.0 mL) y se agregó TEA (0.097 mL, 0.46 mmol) resultando en una solución homogénea. Se agregó sulfato de dimetilo (0.043 mL, 0.46 mmol) y la reacción se agitó a 25 °C. Después de 14 h, la reacción se concentró in vacuo y el material crudo se purificó por CCD preparativa eluyendo con 10% MeOH en cloruro de metileno para dar 0.030 g (0.088 mmol, 39%) del compuesto 14 como un sólido blanco. CLAR: 100% a 1.797 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm eluyendo con 10-90% de metanol acuoso durante 4 minutos conteniendo 0.1 % TFA, 4 mL/min., observando a 220 nm). EM (ES): m/z 339.21 $[M+H]^+$.

Ejemplo 15

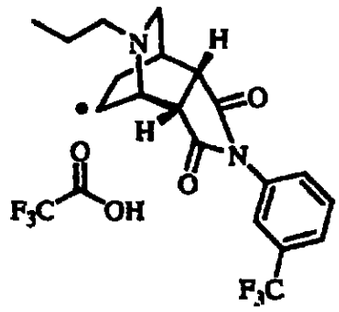
Trifluoroacetato de (3aα,4α,7α,7aα)-Hexahidro-5-(fenilmetil)-2-[3-(trifluorometil)fenil]-4,7-etano-1H-pirrolo[3,4-c]piridina-1,3(2H)-diona (15)



El compuesto 11 (0.10 g, 0.23 mmol) se disolvió en DMF (5.0 mL) y se agregó K_2CO_3 (0.063 g. 0.46 mmol). Se agregó después bromuro de bencilo (0.041 mL, 0.35 mmol). La reacción se agitó a 25°C por 1 h, se filtró y se concentró in vacuo. El material crudo se purificó por CLAR preparativa de fase inversa para dar 0.055 g (0.10 mmol, 43%) del compuesto 15 como un sólido blanco. CLAR: 100% a 2.31 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm eluyendo con 10-90% de metanol acuoso durante 4 minutos conteniendo 0.1% TFA, 4 mL/min., observando a 220 nm). EM (ES): m/z 415.36 $[M+H]^+$.

Ejemplo 16

Trifluoroacetato de (3aα,4α,7α,7aα)-Hexahidro-5-propil-2-[3-(trifluorometil)fenil]-4,7-etano-1H-pirrolo[3,4-c]piridina-1,3(2H)-diona (16)



El compuesto 11 (0.10 g, 0.23 mmol) se disolvió en DMF (5.0 mL) y se agregó K_2CO_3 (0.079 g, 0.57 mmol), seguido por 1-bromopropano (0.031 mL, 0.34 mmol). La reacción se agitó a 25°C por 6 h, después se filtró y se concentró in vacuo. El material crudo se purificó por CLAR preparativa de fase inversa para dar 0.070 g (0.15 mmol, 63%) del compuesto 16 como un sólido blanco. CLAR: 100% a 1.907 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm eluyendo con 10-90% de metanol acuoso durante 4 minutos conteniendo 0.1% TFA, 4 mL/min., observando a 220 nm). EM (ES): m/z 340.22 $[M+H]^+$.

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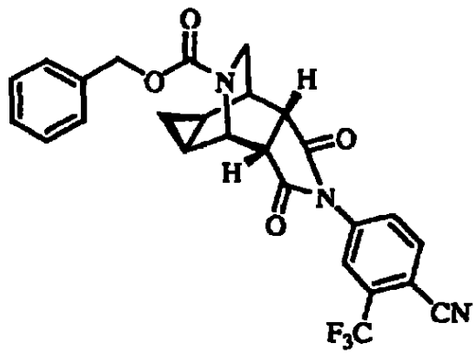
Ejemplo 17

Éster de fenilmetilo del ácido (3aα,4α,4aβ,5aβ,6α,6aα)-2[4-Ciano-3-(trifluorometil)fenil]decahidro-1,3-dioxo-4,6-(iminometano)cicloprop[f]isoindol-7-carboxílico (17)

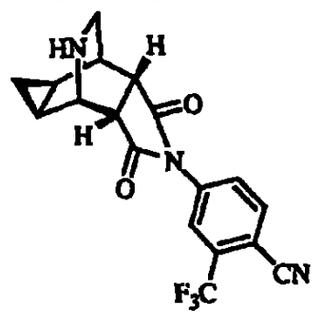


Se agregó la 1-Metil-3-nitro-1-nitrosoguanidina (2.5 g, 17 mmol) en porciones a una solución de 40% KOH/H_2O (15 mL) y Et_2O (25 mL) a 0°C. La capa de éter se hizo amarilla una vez que se terminó la adición. Después de 30 min. a 0°C, la capa de éter se vació en una solución del éster de fenilmetilo del ácido (3aα,4α,7α,7aα)-2-[4-ciano-3-(trifluorometil)fenil]-octahidro-1,3-dioxo-4,7-eteno-5H-pirrolo[3,4-c]piridina-5-carboxílico (0.500 g, 1.09 mmol, preparado como se describe en el Ejemplo 10) y $Pd(OAc)_2$(0.010 g) en THF (10 mL) a 0°C. La reacción se calentó después lentamente a 25°C, se agitó por 24 h y se filtró después a través de Celite enjuagando con THF. El material crudo se purificó después por cromatografía instantánea sobre SiO_2 eluyendo con $MeOH/CH_2Cl_2$ para dar 0.34 g (0.69 mmol, 63%) del compuesto 17 como un

sólido blanco y un isómero sencillo. CLAR: 100% a 3.61 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm eluyendo con 10-90% de metanol acuoso durante 4 minutos conteniendo 0.1% TFA, 4 mL/min., observando a 220 nm). EM (ES): m/z 496.25 $[M+H]^+$.

Ejemplo 18

(3aα,4α,4aβ,5aβ,6α,6aα)-4-[decahidro-1,3-dioxo-4,6-(iminometano)ciclopropf[f]isoindol-2-il]-2-(trifluorometil)benzonitrilo (18)



El compuesto 17 (0.200 g, 0.404 mmol) se disolvió en MeOH (20 mL) y se agregó 5% Pd/C (0.200 g). Se introdujo después hidrógeno por medio de un globo. Después de 3 h, la reacción se filtró a través de Celite, se enjuagó con MeOH y se separaron los volátiles in vacuo para dar 0.130 g (0.360 mmol, 89%) del compuesto 18 como un sólido blanco. CLAR: 100% a 1.80 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm eluyendo con 10-90% de metanol acuoso durante 4 minutos conteniendo 0.1 % TTA. 4 mL/min., observando a 220 nm). EM (ES): m/z 362.09 $[M+H]^+$.

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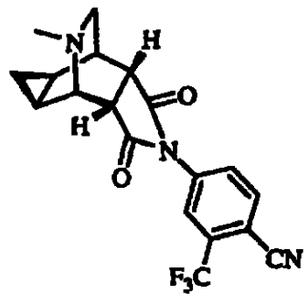
Ejemplo 19

(3aα,4α,4aβ,5aβ,6α,6aα)-4-[Decahidro-7-metil-1,3-dioxo-4,6-(iminometano)ciclopropp[f]isoindol-2-il]-2-(trifluorometil)benzonitrilo (19)



El compuesto 18 (0.100 g, 0.277 mmol) se disolvió en CH_3CN (2.0 mL). Se agregaron después TEA (0.19 mL, 1.4 mmol) y MeI (0.052 mL, 0.83 mmol) y la reacción se agitó a 25°C por 14 h. La reacción se concentró bajo presión reducida y el material crudo se dividió entre CH_2Cl_2/agua y la capa acuosa se extrajo con CH_2Cl_2 (3 x 15 mL). Los orgánicos combinados se secaron sobre Na_2SO_4 anhidro. El material crudo se purificó por cromatografía instantánea eluyendo con 3% MeOH/CH_2Cl_2 para dar 0.030 g (0.080 mmol, 29%) del compuesto 19 como un sólido amarillo claro. CLAR: 100% a 1.720 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm eluyendo con 10-90% metanol acuoso durante 4 minutos conteniendo 0.1% TFA, 4 mL/min., observando a 220nm). EM (ES): m/z 376.11 $[M+H]^+$.

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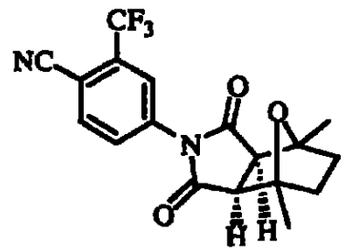
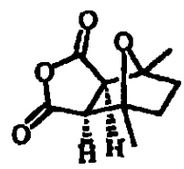
Ejemplo 20

(3aα,4β,7β,7aα)-4-(Octahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo (20B)



A. (3aα,4β,7β,7aα)-Hexahidro-4,7-epoxiisobenzofuran-1,3-diona (20A)



Se disolvió dimetil furano recientemente destilado (1.60 mL, 15.3 mmol) en CH_2Cl_2 (2.0 mL) y se agregó anhídrido maleico (1.00 g, 10.2 mmol). La reacción se agitó a 25°C por 16 h y se concentró después in vacuo para dar un sólido amarillo. Este sólido se disolvió en acetato de etilo (30 mL) y se agregó 10% Pd/C (0.200 g, cat.). Se introdujo después hidrógeno por medio de un globo y la reacción se agitó por 24 h. La mezcla de la reacción se filtró a través de Celite, enjuagando con EtOAc seguido por concentración in vacuo para dar 1.69 g (8.61 mmol, 84%) del compuesto 20A como un sólido blanco. Los experimentos de NOE bi-dimensional, confirmaron la asignación estructural que era la del compuesto 20A.

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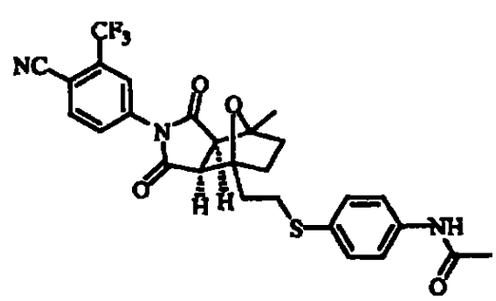
B. (3aα,4β,7β,7aα)-4-(Octahidro-4,7-dimetilo-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo(20B)

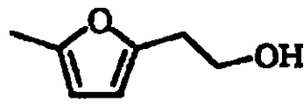
Una solución del compuesto 20A (603 mg, 3.21 mmol), 5-amino-2-cianobenzotrifluoruro (640 mg, 3.44 mmol) y TsOH (10 mg, cat.) en tolueno (5 mL), se calentó en un tubo sellado por 2 días. La mezcla de reacción se enfrió a temperatura ambiente y se concentró después bajo presión reducida. La purificación por cromatografía instantánea sobre gel de sílice eluyendo con 50% EtOAc/hexanos dio 400 mg (1.10 mmol, 34%) del compuesto 20B como un sólido blanco. CLAR: 99% a 3.04 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm, 10-90% metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ESI): m/z 382.2 $[M+NH_4]^+$.

Ejemplo 21

(3aα,4β,7β,7aα)-N-[4-[[2-[2-[4-Ciano-3-(trifluorometil)fenil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-4H-isoindol-4-il]etil]tio]fenil]acetamida (21E)

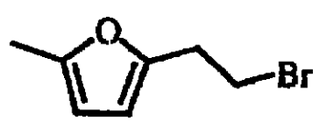


A. 5-Metil-2-furanoetanol (21A)



Una solución de n-BuLi (83.0 mL, 133 mmol, 1.6 M en hexanos) se agregó a una solución agitada de 2-metilfurano (10.0 mL, 111 mmol) en THF (85 mL) a 0°C bajo atmósfera inerte. La mezcla de reacción se agitó por 4 h a temperatura ambiente y después se enfrió hasta 0°C. Se agregó óxido de etileno (8.30 mL, 166 mmol) gota a gota y la mezcla de reacción se dejó calentar hasta temperatura ambiente durante la noche. Después de apagar con NH_4Cl acuoso saturado, se separaron las capas resultantes y la capa acuosa se extrajo con Et_2O (2 X 250 mL). Las capas orgánicas combinadas se secaron sobre Na_2SO_4 y se concentraron bajo presión reducida. La destilación a presión atmosférica (170-185 °C) dio 10.1 g (80.3 mmol, 72%) del compuesto 21A como un aceite amarillo ligero.

B. 2-(2-Bromoetil)-5-metilfurano (21B)



Se agregó Ph_3Br_2(3.68 g, 8.72 mmol) a una solución del compuesto 21A (1.00 g, 7.93 mmol) en DMF (8 mL) y la mezcla de reacción se agitó a temperatura ambiente por 1 h. La mezcla de reacción se le agregó a H_2O y se extrajo con EtOAc

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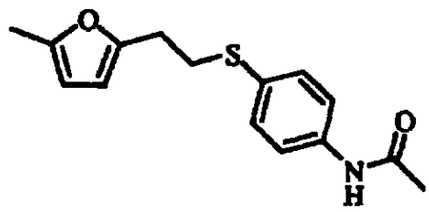
(3 X). Las capas orgánicas combinadas se lavaron con H_2O (2 X), se secaron sobre Na_2SO_4 y se concentraron bajo presión reducida. La purificación por cromatografía instantánea sobre gel de sílice eluyendo con 10% EtOAc/hexanos dio 0.507 g (2.68 mmol, 34%) del compuesto 21B.

C. N-[4[[2-(5-Metil-2-furanil)etil]tio]fenil]acetamida (21C)



A una solución de 4-acetamidotiofenol (442 mg, 2.64 mmol) en THF (1 mL) a 0°C bajo atmósfera inerte, se le agregó una solución de n-BuLi (2.00 mL, 3.17 mmol, 1.6 M en hexanos) en THF (1 mL). La solución de reacción se agitó a temperatura ambiente por 10 min., después se agregó una solución del compuesto 21B (500 mg, 2.64 mmol) en THF (3 mL). Después de que se consumió el material de partida (como se determina por CCD), la reacción se apagó con H_2O y la mezcla se extrajo con EtOAc (2X), se secó sobre Na_2SO_4 y se concentró bajo presión reducida. La purificación por cromatografía instantánea sobre gel de sílice eluyendo con 50% EtOAc/hexanos dio 0.644 g (2.34 mmol, 88%) del compuesto 21C. EM (ESI): m/z 276.09 $[M+H]^+$.

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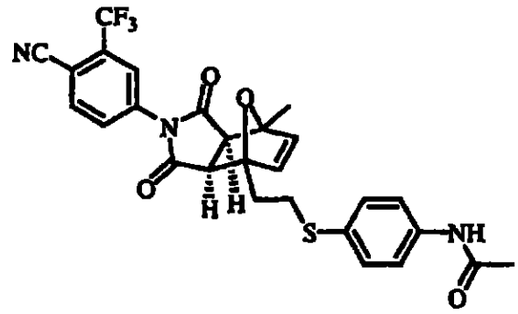
D. (3aα,4β,7β,7aα)-N-[4-[[2-[2-[4-Ciano-3-(trifluorometil)fenil]-1,2,3,3a,7,7a-hexahidro-7-metil-1,3-dioxo-4,7-epoxi-4H-isoindol-4-il]etilo]tio]fenilo]acetamida(21D)



Una solución del compuesto 21C (195 mg, 0.708 mmol) y 4-(2,5-dihidro-2,5-dioxo-1H-pirrol-1-il)-2-trifluorometilbenzonitrilo (377 mg, 1.416 mmol, preparada como se describe para el Ejemplo 1B) en CH_2Cl_2 (1.5 mL) se agitó a temperatura ambiente por dos días. La mezcla de reacción se concentró bajo presión reducida para dar el compuesto 21D como se determina por los análisis de RMN. El compuesto 21D se usó directamente en la siguiente etapa sin purificación.

E. (3aα,4β,7β,7aα)-N-[4-[[2-[2-[4-Ciano-3-(trifluorometil)fenil]-octahidro-7-metil-1,3-dioxo-4,7-epoxi-4H-isoindol-4-il]etil]tio]-fenil]acetamida (21E)

Una solución del compuesto crudo 21D (0.708 mmol) y 10% Pd/C (200 mg) en MeOH (20 mL) se agitó bajo una atmósfera de

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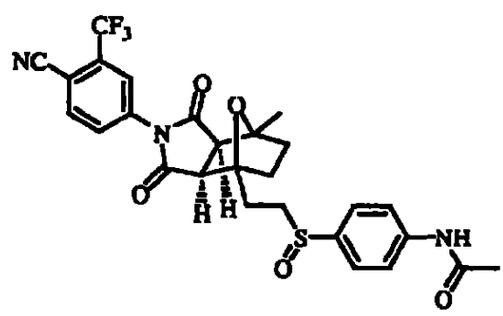
hidrógeno durante la noche. La purificación por CLAR de fase inversa [34.4 min. (tiempo de retención) (Columna YMC S5 ODS de 20 x 250 mm 0-100% de metanol acuoso durante 30 minutos conteniendo 0.1% TFA, 10 mL/min., observando a 220 nm)] seguida por cromatografía instantánea sobre gel de sílice eluyendo con 1% $MeOH/CH_2Cl_2$ dio 29 mg (0.053 mmol, 7.5%) del compuesto 21E como un polvo amarillo. CLAR: 99% a 3.44 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm. 10-90% de metanol acuoso durante 4 minutos conteniendo 0.2% de ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ESI): m/z 544.01 $[M+H]^+$.

Ejemplo 22

(3aα,4β,7β,7aα)-N-[4-[[2-[2-[4-ciano-3-(trifluorometil)fenil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-4H-isoindol-4-il]etil]sulfinil]fenil]acetamida (22)

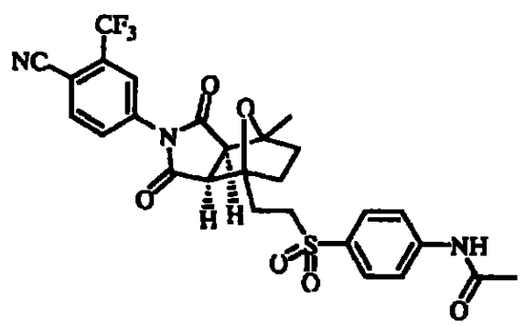


Se agregó en porciones mCPBA (12 mg, 0.050 mmol) a una solución del compuesto crudo 21E (65 mg, 0.12 mmol) en CH_2Cl_2 (6 mL) hasta que se consumió el material de partida. La purificación por CLAR de fase inversa [30.5 min. (tiempo de

retención) (Columna YMC S5 ODS de 30 x 250 mm. 0-100% de metanol acuoso durante 30 minutos conteniendo 0.1% 7FA, 25 mL/min., observando a 220 nm)] dio 27.5 mg (0.0491 mmol. 41%) del compuesto 22 como un sólido beige (~1:1 mezcla de diastereómeros). CLAR: 96% a 2.88 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm eluyendo con 10-90% de metanol acuoso durante 4 minutos conteniendo 0.1% TFA, 4 mL/min., observando a 220 nm). EM (ESI): m/z 559.97 $[M+H]^+$.

Ejemplo 23

(3aα,4β,7β,7aα)-N-[4-[[2-[2-[4-Ciano-3-(trifluorometil)fenil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-4H-isoindol-4-il]etil]sulfonil]fenil]acetamida (23)



Se agregó el mCPBA (26 mg, 0.11 mmol) a una solución del compuesto 21E (19 mg, 0.035 mmol) en CH_2Cl_2 (6 mL) y la reacción se agitó a temperatura ambiente hasta que el material de partida y el sulfóxido intermediario (compuesto 22) se consumieron como fue evidente por la CCD. La purificación por CLAR preparativa de fase inversa [53.3 min.

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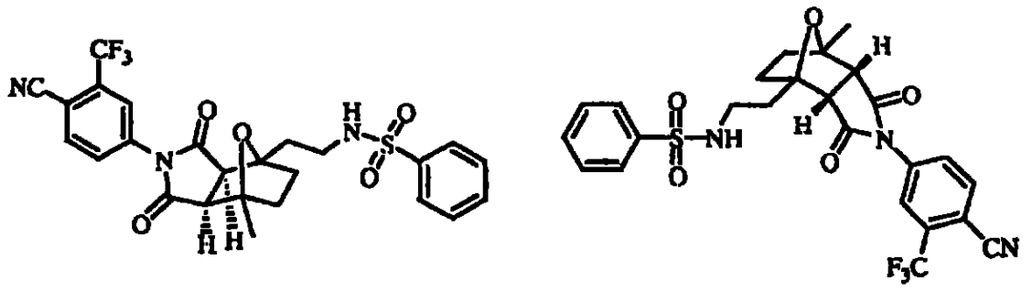
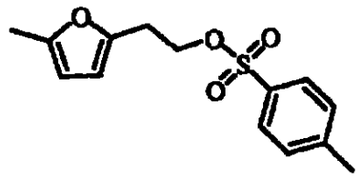
(tiempo de retención) (Columna YMC S5 ODS de 30 x 250 mm, 0-70% metanol acuoso durante 45 minutos conteniendo 0.1% TFA, 25 mL/min., observando a 220 nm)] dio 8.0 mg (0.014 mmol, 40%) del compuesto 23 como un sólido blanco. CLAR: 99% a 2.94 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm, 10-90% de metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ESI): m/z 575.95 $[M+H]^+$.

Ejemplo 24

(3aα,4β,7β,7aα)- y (3aα,4α,7α,7aα)-N-[2-[2-[4-Ciano-3-(trifluorometil)fenil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-4H-isoindol-4-il]etil]benzensulfonamida (24Ci y 24Cii, respectivamente)



A. 5-Metil-2-furanoetanol 4-metilbencensulfonato (24A)

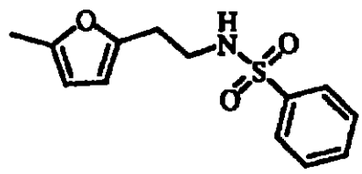


Se agregó cloruro de 4-Metilbencensulfonilo (907 mg, 4.76 mmol) a una solución del compuesto 21A (500 mg, 3.96

600

mmol) en 6 mL de piridina seca. La reacción se agitó a temperatura ambiente por 4 h y después se apagó con hielo. La mezcla de reacción se extrajo con CH_2Cl_2 y las capas orgánicas combinadas se lavaron con bicarbonato de sodio acuoso saturado y agua, se secaron y se concentraron bajo presión reducida para dar 900 mg (81%) del compuesto 24A como un aceite amarillo.

B. N-[2-(5-Metil-2-furanil)etil]bencensulfonamida (24B)



Se agregó bencensulfonamida (157 mg, 1.00 mmol) a una solución acuosa al 10% de hidróxido de sodio (0.40 mL, 1.0 mmol). Una solución del compuesto 24A (280 mg, 1.00 mmol) en acetona (1 mL) se agregó después. La mezcla de reacción se calentó a 90°C por 8 h después se enfrió a temperatura ambiente. Se agregó hielo y la mezcla se extrajo con CH_2Cl_2. Las capas orgánicas combinadas se lavaron con agua, se secaron y se concentraron bajo presión reducida. La purificación por cromatografía instantánea sobre gel de sílice, eluyendo con CH_2Cl_2 dio 60 mg (0.23 mmol, 23%) del compuesto 24B como aceite amarillo.

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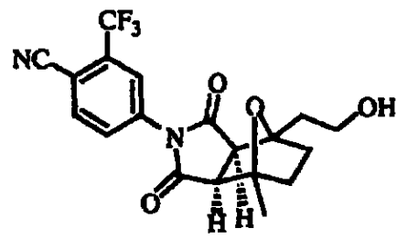
C. (3aα,4β,7β,7aα)- y (3aα,4α,7α,7aα)-N-[2-[2-[4-Ciano-3-(trifluorometil)fenil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-4H-isoindol-4-il]etil]bencensulfonamida (24Ci y 24Cii, respectivamente)

El 4-(2,5-Dihidro-2,5-dioxo-1H-pirrol-1-il)-2-trifluorometilbenzonitrilo (129 mg, 0.485 mmol, preparado como se describe en el Ejemplo 1B) se agregó a una solución del compuesto 24B (60 mg, 0.23 mmol) en CH_2Cl_2 (2 mL). La mezcla de reacción se agitó a temperatura ambiente por 2 días, se concentró bajo presión reducida y se purificó por cromatografía instantánea sobre gel de sílice, eluyendo con 70% EtOAc/hexanos, para dar 20 mg (0.038 mmol, 16%) del producto insaturado de Diels-Alder. El producto insaturado (20 mg) se disolvió inmediatamente en etanol (2 mL) y se agregó 10% Pd/C (10 mg, cat.). La solución se agitó a temperatura ambiente durante la noche bajo una atmósfera de hidrógeno. La mezcla se filtró y el filtrado se concentró bajo presión reducida. La purificación por CLAR preparativa de fase inversa dio 7.0 mg (0.013 mmol, 34%) del compuesto 24Ci y 2.0 mg (0.0037 mmol, 10%) del compuesto 24Cii. Compuesto 24Ci: CLAR: 96% a 3.17 min. (tiempo de retención) (YMC ODSA S5 C18 4.6 x 50 mm, 10%-90% metanol acuoso durante 4 min. gradiente con 0.1% TFA, observando a 220 nm). EM (ES): m/z: 533.99 $[M+H]^+$. Compuesto 24Cii: CLAR: 99% a 38.95 min. (tiempo de retención) (YMC ODS S5 20X250 mm, 10%-90% de

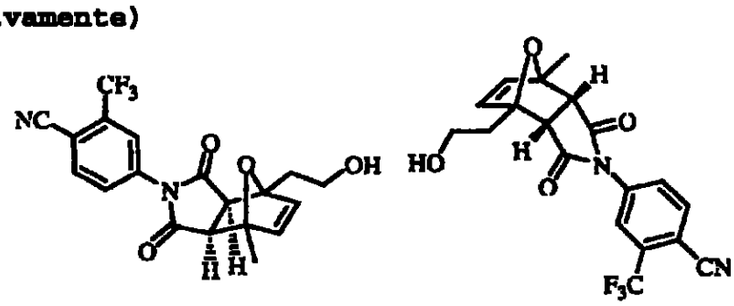
metanol acuoso durante 40 min. gradiente con 0.1% TFA, observando a 220 nm). EM (ES): m/z 533.99 $[M+H]^+$.

Ejemplo 25

(3aα,4β,7β,7aα)-4-[Octahidro-4-[2-hidroxietil)-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2-(trifluorometil)benzonitrilo(25B)



A. (3aα,4β,7β,7aα)- y (3aα,4α,7α,7aα)-4-[1,3,3a,4,7,7a-Hexahidro-4-(2-hidroxietil)-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2- (trifluorometil)benzonitrilo (25Ai y 25Aii, respectivamente)



Una solución del compuesto 21A (252 mg, 2.00 mmol) y 4-(2,5-dihidro-2,5-dioxo-1H-pirrol-1-il)-2-trifluorometilbenzonitrilo (798 mg, 3.00 mmol) en CH_2Cl_2 (10 mL) se agitó a temperatura ambiente por 2 días. La mezcla de reacción se concentró bajo presión reducida. La purificación

por cromatografía instantánea sobre gel de sílice eluyendo con 65% EtOAc/hexanos dio 217 mg del compuesto puro 25Ai, 73 mg del compuesto puro 25Aii y 310 mg de una mezcla de ambos compuestos 25Ai y 25ii. Todas las tres fracciones se aislaron como sólidos blancos con un rendimiento total aislado de 600 mg (1.53 mmol, 76.5%). Compuesto 25Ai: CLAR: 90% a 2.56 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm, 10-90% metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). Compuesto 25Aii: CLAR: 90% a 2.56 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm, 10-90% de metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm).

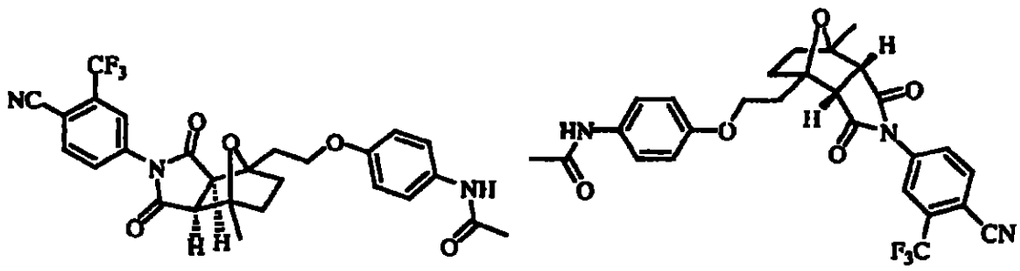
B. (3aα,4β,7β,7aα)-4-[Octahidro-4-(2-hidroxietil)-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2-(trifluorometil)benzonitrilo(25B)

Una solución del compuesto 25Ai (0.20 g, 0.51 mmol) y 10% Pd/C (43 mg, cat.) en EtOH (12 mL) se agitó bajo una atmósfera de hidrógeno a temperatura ambiente por 2 h. La mezcla de la reacción se filtró a través de Celite y se concentró bajo presión reducida para dar 0.20 g (0.51 mmol, 100%) del compuesto 25B como un sólido blanco. CLAR: 95% a 2.59 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm eluyendo con 10-90% de metanol acuoso durante 4 minutos

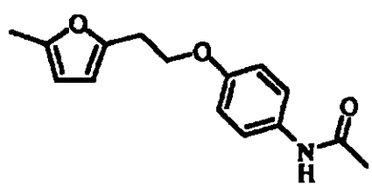
conteniendo 0.1% TFA, 4 mL/min., observando a 220 nm). EM (ESI): m/z 394.97 $[M+H]^+$.

Ejemplo 26

(3aα,4β,7β,7aα)- y (3aα,4α,7α,7aα)-N-[4-[2-[2-[4-Ciano-3-(trifluorometil)fenil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-4H-isoindol-4-il]etoxi]fenil]acetamida (26Ci y 26Cii, respectivamente)



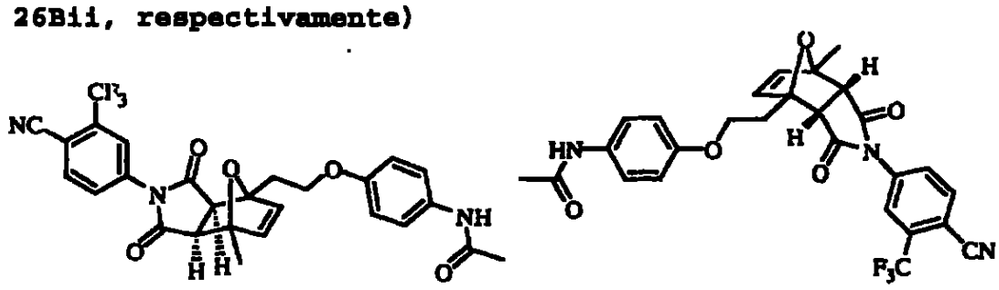
A. 2-[4-[2-(5-Metil-2-furanil)etoxi]fenil]acetamida (26A)



Se agregó trifenilfosfina (681 mg, 2.60 mmol) a una solución del compuesto 21A (252 mg, 2.00 mmol) y 4-acetamidofenol (302 mg, 2.00 mmol) en CH_2Cl_2 (4 mL). Se agregó THF (5 mL) para hacer la mezcla de reacción homogénea y la mezcla se enfrió después a 0°C. Se agregó gota a gota DEAD (0.41 mL, 2.6 mmol) y la mezcla de reacción se agitó a temperatura ambiente durante la noche, se concentró después bajo presión reducida. La purificación por cromatografía

instantánea sobre gel de sílice eluyendo con 60% EtOAc/hexanos seguida por CLAR preparativa de fase inversa dio 270 mg (1.04 mmol, 52%) del compuesto 26A como un sólido café claro. EM (ESI): m/z 260.09 $[M+H]^+$.

B. (3aα,4β,7β,7aα) y (3aα,4α,7α,7aα)-N-[4-[2-[2-[4-Ciano-3-(trifluorometil)fenil]-1,2,3,3a,7,7a-hexahidro-7-metil-1,3-dioxo-4,7-epoxi-4H-isoindol-4-il]etoxi]fenil]acetamida (26Bi y 26Bii, respectivamente)



Una solución del compuesto 26A (40 mg, 0.15 mmol) y 4-(2,5-dihidro-2,5-dioxo-1H-pirrol-1-il)-2-trifluorometilbenzonitrilo (88 mg, 0.31 mmol) en CH_2Cl_2 (2 mL) se agitó a temperatura ambiente por 2 días. La mezcla de reacción se concentró bajo presión reducida. La purificación por cromatografía instantánea sobre gel de sílice eluyendo con 75% EtOAc/hexanos dio 55 mg (0.105 mmol, 68%) de una mezcla 5:1 de los compuestos 26Bi y 26Bii como un sólido blanco, que se usó directamente en la siguiente etapa. CLAR: 90% a 3.28 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm, 10-90% de metanol acuoso durante 4 minutos

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conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm).

C. (3aα,4β,7β,7aα)- y (3aα,4α,7α,7aα)-N-[4-[2-[2-[4-Ciano-3-(trifluorometil)fenil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-4H-isoindol-4-il]etoxi]fenil]acetamida (26Ci y 26Cii, respectivamente)

Una solución de una mezcla de los compuestos 26Bi y 26Bii (55 mg, 0.105 mmol) y 10% Pd/C (12 mg, cat.) en EtOH (3 mL) se agitó bajo una atmósfera de hidrógeno a temperatura ambiente durante la noche. La mezcla de la reacción se filtró a través de Celite y se concentró bajo presión reducida para dar 50 mg del producto crudo. La purificación por cromatografía instantánea sobre gel de sílice eluyendo con 70% EtOAc/hexanos dio 18 mg (0.034 mmol, 32%) del compuesto 26Ci [CLAR: 96% a 3.33 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm, 10-90% de metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 528.01 $[M+H]^+$]; y 2.3 mg (0.0044 mmoles, 4%) de una mezcla 85:15 de 26Cii y 26Ci respectivamente como se determina por ^1H RMN. CLAR: 90% a 3.35 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm, 10-90% metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ESI): m/z 528.12 $[M+H]^+$.

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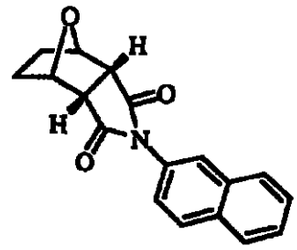
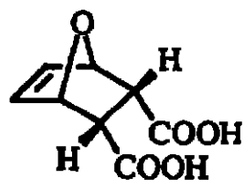
Ejemplo 27

(3aα,4α,7α,7aα)-Hexahidro-2-(2-naftalenil)-4,7-epoxi-1H-isoindol-1,3(2H)-diona (27D)

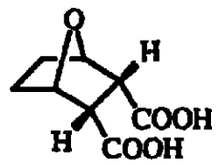


A. ácido (endo, endo)-7-Oxabiciclo[2.2.1]hept-5-eno-2,3-dicarboxílico (27A)



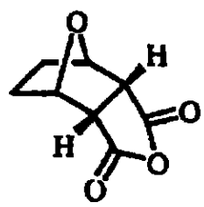
Los compuestos 27A, 27B y 27C fueron sintetizados de acuerdo con los métodos descritos en Sprague et al. J. Med. Chem. 28, 1580-1590 (1985). Una mezcla de furano (100 mL, 1.38 mol) y ácido maleico (160 g, 1.38 mol) en H_2O (340 mL) se agitó a temperatura ambiente por 5 días. La mezcla se colocó en un embudo separador y la capa acuosa se separó de la capa que contenía el furano sin reaccionar. La capa acuosa se trató con carbón mineral, se filtró a través de Celite y se colocó en el refrigerador. El producto deseado cristalizado de la solución al recolectarse, se filtró, se lavó con agua fría y se secó sobre P_2O_5 para dar 70 g (0.38 mol, 28%) del compuesto 27A como un sólido blanco.

B. Ácido (endo, endo)-7-Oxabiciclo[2.2.1]heptano-2,3-dicarboxílico (27B)



A una solución del compuesto 27A (69.0 g, 0.375 mol) en EtOH (700 mL) se agregó 10% Pd/C (4.5 g, cat.) y la mezcla se agitó bajo una atmósfera de hidrógeno a 55 psi (3.87 kg/cm^2) hasta que cesó la absorción de gas. La mezcla se filtró a través de Celite y se concentró in vacuo para dar 66.0 g (0.355 mol, 95%) del compuesto 27B como un sólido blanco.

C. (3aα,4α,7α,7aα)-Hexahidro-4,7-epoxiisobenzofuran-1,3-diona (27C)



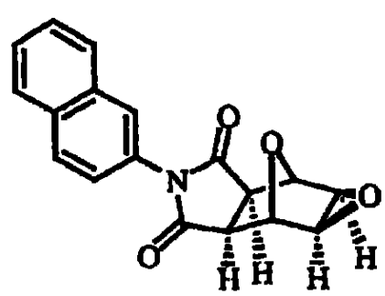
Una solución del compuesto 27B (66.0 g, 355 mol) en cloruro de acetilo (300 mL) se puso a reflujo por 1 h. La solución de reacción se concentró in vacuo y el residuo resultante se recristalizo de benceno para dar 49.2 g (0.292 mol, 82%) del compuesto 27C como un sólido blanco (>99% endo por ^{1}H RMN).

D. (3aα,4α,7α,7aα)-Hexahidro-2-(2-naftalenilo)-4,7-epoxi-1H-isoindol-1,3(2H)-diona (27D)

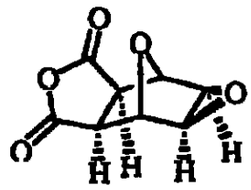
El compuesto 27C (45 mg, 0.30 mmol) se combinó con 2-aminonaftaleno (47 mg, 0.33 mmol) en ácido acético (1 mL) y se calentó a 115°C durante la noche. Después de que la reacción se enfrió a temperatura ambiente, se agregó una gota de agua, y se filtró el precipitado resultante. El material se lavó con metanol y se secó para proporcionar 65.7 mg (0.224 mmol, 74.7%) del compuesto 27D como un sólido cristalino blanco. CLAR: 99% a 2.68 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm, 10-90% de metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ESI): m/z 294.0 $[M+H]^+$.

Ejemplo 28

(1aα,2β,2aα,5aα,6β,6aα)-Hexahidro-4-(2-naftalenil)-2,6-epoxi-3H-oxireno[f]isoindol-3,5(4H)-diona (28B)



A. (1aα,2β,2aα,5aα,6β,6aα)-Tetrahidro-2,6-epoxioxireno[f]isobenzofuran-3,5(2aH,5aH)-diona(28A)



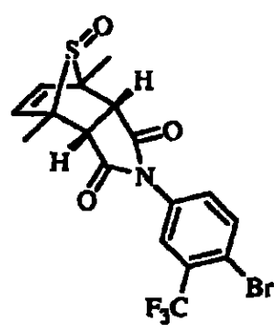
Como se describe en Yur'ev et al. J. Gen. Chem. U.S.S.R. (Trad. Al Inglés) 31, 772-775 (1961), una solución de anhídrido exo-7-oxabiciclo[2.2.1]heptano-2,3-dicarboxílico (5.00 g, 30.1 mmol), ácido fórmico (10 mL) y peróxido de hidrógeno (6 mL) se agitó a temperatura ambiente. Después de 30 min., la reacción se colocó en un baño de hielo (se volvió exotérmica con la evolución del gas) y se dejó calentar a temperatura ambiente lentamente. Después de agitar durante la noche, se colectó el precipitado resultante por filtración y se lavó con ácido acético glacial y se secó para dar 3.02 g de un polvo blanco. El sólido crudo se puso a ebullición en cloruro de acetilo (100 mL) por 10 horas y la mezcla se concentró a alrededor de 20 mL bajo presión reducida. El precipitado resultante se filtró, se lavó con dioxanos y se secó para dar 2.37 g (13.0 mmol, 43%) del compuesto 28A como un polvo blanco.

B. (1aα,2β,2aα,5aα,6β,6aα)-Hexahidro-4-(2-naftalenil)-2,6-epoxi-3H-oxireno[f]isoindol-3,5(4H)-diona(28B)

El compuesto 28A (100 mg, 0.520 mmol) se combinó con 2-aminonaftaleno (62.1 mg, 0.434 mmol) en ácido acético (2 mL) y se calentó a 115°C durante la noche. Después de que la reacción se dejó enfriar a temperatura ambiente, se agregó agua, y el precipitado resultante se filtró. El material se lavó secuencialmente con K_2CO_3 acuoso y agua y se secó después en un horno a vacío para proporcionar 113.7 mg (0.371 mmol, 85.5%) del compuesto 28B como un sólido cristalino blanco apagado. CLAR: 99% a 1.76 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm, 10-90% de metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ESI): m/z 308.0 $[M+H]^+$.

Ejemplo 29

8-óxido de (3aα,4α,7α,7aα)-2-[4-Bromo-3-(trifluorometil)fenil]-3a,4,7,7a-tetrahidro-4,7-dimetil-4,7-epitio-1H-isoindol-1,3-(2H)-diona (29)

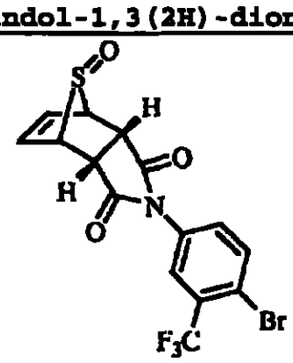


El 2,5-Dimetiltiofeno (0.048 mL, 0.42 mmol) y 4-(2.5-dihidro-2,5-dioxo-1H-pirrol-1-il)-2-trifluorometilbenzonitrilo (0.290 g, 0.625 mmol, preparado

como se describe por el Ejemplo 1B) se disolvieron en CH_2Cl_2 (8.0 mL) y se enfriaron a -20°C. Se agregaron lentamente $BF_3 \bullet Et_2O$ (0.412 mL, 3.36 mmol) seguido por la adición de mCPBA (~50%, 0.29 g, 0.84 mmol). Después de 2 horas a -20 °C, la mezcla de reacción se vació en $NaHCO_3$ acuoso saturado y se extrajo con CH_2Cl_2, (3 x 20 mL) y los compuestos orgánicos se secaron sobre Na_2SO_4 anhidro. El producto crudo se purificó por cromatografía instantánea sobre SiO_2 eluyendo con 5%-10%-20% EtOAc en CH_2Cl_2 para dar 0.119 g (0.265 mmol, 63%) del compuesto 29 como un sólido blanco. CLAR: 91% a 3.303 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm, 10-90% de metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ESI): m/z 480.2 $[M+H]^+$.

Ejemplo 30

8-óxido de (3aα,4α,7α,7aα)-2-[4-Bromo-3-(trifluorometil)fenil]-3a,4,7,7a-tetrahidro-4,7-epitio-1H-isoindol-1,3(2H)-diona (30)



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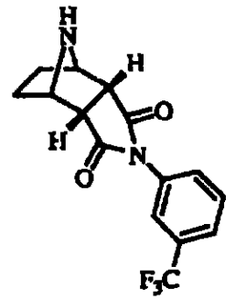
Tiofeno (0.375 mL, 4.69 mmol) y 4-(2,5-dihidro-2,5-dioxo-1H-pirrol-1-il)-2-trifluorometilbenzonitrilo (0.100 g, 0.313 mmol, preparado como se describe en el Ejemplo 1B) se disolvieron en CH_2Cl_2 (50 mL), se agregó mCPBA (~50%, 1.62 g, 4.69 mmol) y la mezcla resultante se agitó a 25°C por 3 h. Se agregó después trifenilfosfina (2.0 g). Después de 15 min., se separaron los volátiles in vacuo y el residuo resultante se disolvió en CH_2Cl_2 (200 mL) y se lavó con $NaHCO_3$ saturado acuoso (3 x 50 mL) y se secó sobre Na_2SO_4. El material crudo se purificó después por cromatografía instantánea sobre SiO_2 eluyendo con 1% - 3% - 5% metanol en CH_2Cl_2 para dar 0.059 g (0.14 mmol, 45%) del compuesto 30 como un polvo blanco. Los análisis de RMN y CL mostraron un diastereómero sencillo. CLAR: 100% a 3.437 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm, 10-90% metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ESI): m/z 443.2 $[M+H]^+$.

Ejemplo 31

(3aα,4α,7α,7aα)-Hexahidro-2-[3-(trifluorometil)fenil]-4,7-imino-1H-isoindol-1,3(2H)-diona (31D)



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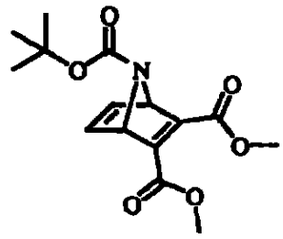
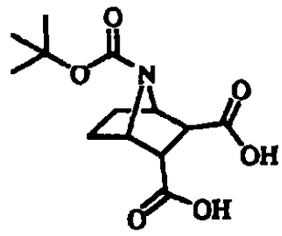
A. Éster de 7-(1,1-dimetiletil) 2,3-dimetilo del ácido 7-Azabiciclo[2.2.1]hepta-2,5-dieno-2,3,7-tricarboxílico (31A)



El éster de dimetilo del ácido acetilendicarboxílico recientemente destilado (6.7 mL, 54 mmol) y N-(tert-butiloxicarbonil)-1H-pirrol (9.0 mL, 54 mmol) se combinaron y se calentaron a 120°C por 3 h. La purificación por cromatografía instantánea sobre SiO_2 eluyendo con $EtOAc/CH_2Cl_2$ dio 8.3 g (27 mmol, 50%) del compuesto 31A como un sólido amarillo.

B. Ester de 7-(1,1-dimetiletilo) del ácido (exo,endo)-7-Azabiciclo[2.2.1]hept-2,5-dieno-2,3,7-tricarboxílico (31B)



El compuesto 31A (1.0 g, 3.5 mmol) se disolvió en MeOH (2.0 mL) y se agregó KOH acuoso (1 g en 5 mL de H_2O). La reacción se calentó a 50°C por 1 h. La reacción se enfrió después hasta 25°C y se agregó 10% Pd/C (0.5 g, cat.) y la mezcla se colocó en un aparato Parr por 14 h a 25°C. La

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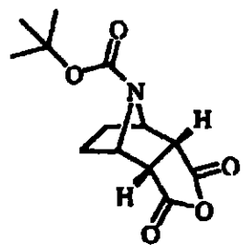
reacción se filtró después a través de Celite enjuagando con agua. La solución acuosa se acidificó hasta un pH de 2 por la adición de HCl 1 N y después se extrajo con EtOAc (2 x 100 mL). La concentración de los orgánicos dio el compuesto 31B como un sólido amarillo pálido.

C. Ester de 1,1-dimetiletilo del ácido (3aα,4α,7α,7aα)-Hexahidro-1,3-dioxo-4,7-iminoisobenzofuran-8-carboxílico (31C)



El compuesto crudo, 31B, se calentó hasta 120°C in vacuo en una cámara de sublimación, resultando en una sublimación de 0.051 g (0.19 mmol, 5.4%) del compuesto 31C como un sólido blanco, que se recolectó directamente y se usó en la siguiente etapa sin purificación adicional.

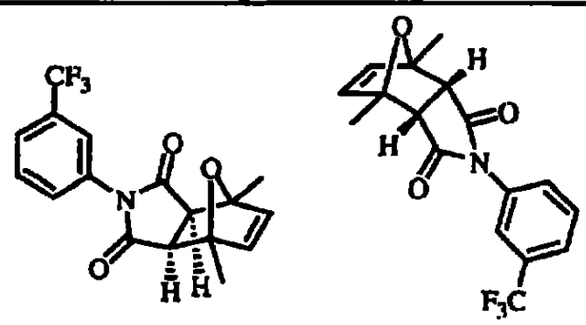
D. (3aα,4α,7α,7aα)-Hexahidro-2-[3-(trifluorometil)fenil]-4,7-imino-1H-isoindol-1,3(2H)-diona (31D)

El compuesto 31C (0.050 g, 0.19 mmol) y el 1-amino-3-(trifluorometil)benceno (0.030 g, 0.19 mmol) se disolvieron en AcOH (2.5 mL) y se calentaron a 115°C por 4.5 h. La

reacción se apagó por la adición de $NaHCO_3$ saturado acuoso y la mezcla se extrajo con cloruro de metileno (3 x 15 mL). El material crudo se purificó por CLAR preparativa de fase inversa para dar 0.030 g (0.097 mmol, 51%) del compuesto 31D como un sólido blanco. CLAR: 99% a 2.33 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm, 10-90% de metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ESI): m/z 311.15 $[M+H]^+$.

Ejemplo 32

(3aα,4β,7β,7aα)- y (3aα,4α,7α,7aα)-3a,4,7,7a,Tetrahidro-4,7-dimetil-2-[3-(trifluorometil)fenil]-4,7-epoxi-1H-isoindol-1,3(2H)-diona (32i y 32ii respectivamente)

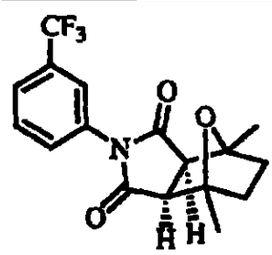


2,5-dimetilfurano recientemente destilado (0.32 mL, 2.6 mmol) se disolvió en CH_2Cl_2 (2.0 mL) y se agregó 1-[3-(trifluorometil)fenil]-1H-pirrol-2,5-diona (0.5 g, 2.5 mmol, preparada como se describe en el Ejemplo 1B). La reacción se agitó a 25°C por 16 h y se concentró después bajo presión reducida. La purificación por cromatografía instantánea sobre

gel de sílice eluyendo con 0.5% $MeOH/CH_2Cl_2$ dio 250 mg (0.741 mmol, 30%) del compuesto 32i, y 50 mg (0.15 mmol, 6%) del compuesto 32ii como sólidos blancos. Compuesto 32i: CLAR: 98% a 3.080 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm, 10-90% de metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 338.30 $[M+H]^+$. Compuesto 32ii: CLAR: 92% a 3.047 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm, 10-90% de metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm), EM (ES): m/z: 338.15 $[M+H]^+$.

Ejemplo 33

(3aα,4β,7β,7aα)-Hexahidro-4,7-dimetil-2-[3-trifluorometil)fenil]-4,7-epoxi-1H-isoindol-1,3(2H)-diona(33)



El compuesto 32i (0.080 g, 0.24 mmol) se disolvió en EtOAc (2 mL) y EtOH (1 mL) y se agregó 10% Pd/C (0.050 g, cat.). Se introdujo después hidrógeno por un globo y la reacción se agitó por 24 h. La mezcla se filtró a través de Celite, se enjuagó con EtOAc y se concentró in vacuo para dar 0.075 g (0.22 mmol, 93%) del compuesto 33 como un sólido

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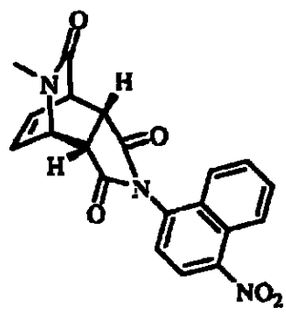
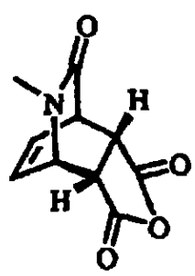
blanco. No fue necesaria purificación adicional. CLAR: 90% a 3.233 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm, 10-90% metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 340.40 $[M+H]^+$.

Ejemplo 34

(3aα,4β,7β,7aα)-Tetrahidro-5-metil-2-(4-nitro-1-naftalenil)-4,7-eteno-1H-pirrol[3,4-c]piridina-1,3,6(2H,5H)-triona (34B)



A. 4,5,7,7a-Tetrahidro-5-metil-4,7-etenofuro[3,4-c]piridina-1,3,6(3aH)-triona (34A)



El compuesto 34A fue sintetizado por una modificación de los métodos descritos por Tomisawa et al. Heterocycles 6, 1765-1766 (1977) & Tetrahedron Lett. 29, 2465-2468 (1969). Se suspendieron anhídrido maleico (2.00 g, 20.4 mmol) y 1-metil-2-piridona (2.22 g, 20.4 mmol) en 30 mL de tolueno anhidro.

619

El recipiente de reacción se acopló con una trampa Dean Stark y se puso a reflujo por 48 horas. La solución obscura coloreada se dejó enfriar a temperatura ambiente y después se separaron los volátiles in vacuo. La pasta café resultante (4 g) se disolvió en 10 mL de tolueno en ebullición y la solución caliente se filtró bajo un flujo de nitrógeno para eliminar los materiales en partículas. Al reposar a 25°C se precipitó el producto deseado de la solución. Se aisló el sólido por filtración y se lavó con tolueno frío para dar 1.0 g (4.8 mmol, 24%) del compuesto 34A, que se usó sin purificación adicional.

B. (3aα,4α,7α,7aα)-Tetrahidro-5-metil-2-(4-nitro-1-naftalenilo)-4,7-eteno-1H-pirrol[3,4-c]piridina-1,3,6(2H,5H)-triona (34B)

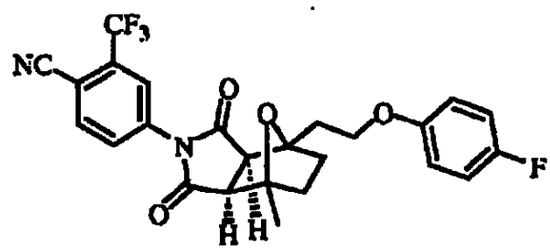
Se disolvieron el 1-Amino-4-nitronaftaleno (0.094 g, 0.50 mmol) y el compuesto 34A (0.130 g, 0.627 mmol) en AcOH (2.0 mL) y se calentaron a 110°C por 11 h. La reacción se enfrió después hasta 25°C y se vació en K_2CO_3 saturado acuoso frío y se agitó vigorosamente por 10 min. La solución se filtró y se lavó con agua. El filtrado resultante se concentró in vacuo y se purificó por cromatografía instantánea sobre gel de sílice eluyendo con 4:6 EtOAc/hexanos para dar 0.172 g (0.456 mmol, 91%) del compuesto 34B como un sólido blanco. CLAR: 92% a 2.472 min.

620

(tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm eluyendo con 10-90% de metanol acuoso durante 4 minutos conteniendo 0.1% TFA, 4 mL/min., observando a 220 nm). EM (ES): m/z 378.29 $[M+H]^+$.

Ejemplo 35

(3aα,4β,7β,7aα)-4-[4-[2-[4-Fluorofenoxi)etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2-(trifluorometil)benzonitrilo (35)

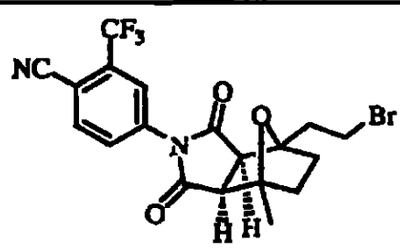


Se agregó DEAD (0.060 mL, 0.38 mmol) a una solución de trifenilfosfina (100 mg, 0.380 mmol) en THF (1.3 mL) a temperatura ambiente bajo una atmósfera inerte. Después de agitar por 10 min., se agregó 4-fluorofenol (43 mg, 0.380 mmol) en una porción. La mezcla de reacción se agitó por 5 min., se agregó el compuesto 25B (100 mg, 0.254 mmol) y se continuó la agitación por 3.5 h. La purificación por cromatografía instantánea sobre gel de sílice eluyendo con 50% EtOAc/hexanos seguida por CLAR preparativa de fase inversa [11.93 min. (tiempo de retención) (Columna YMC S5 ODS de 20 x 100 mm, 0-100% de metanol acuoso durante 10 minutos conteniendo 0.1% TFA, 20 mL/min., observando a 220 nm)] dio

72 mg (58%) del compuesto 35 como un sólido. CLAR: 99% a 3.74 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm, 10-90% de metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ESI): m/z 487.1 $[M-H]^+$.

Ejemplo 36

(3aα,4β,7β,7aα)-4-[4-(2-Bromoetil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2-(trifluorometil)benzonitrilo(36)

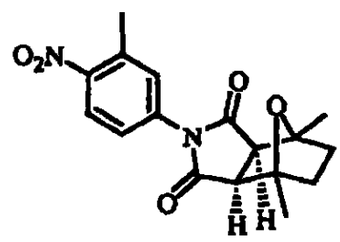


Una solución de 25B (495 mg, 1.26 mmol) y piridina (100 μL, 1.26 mmol) en CH_2Cl_2 (2 mL) se agregó a una solución de Ph_3PBr_2 (636 mg, 1.51 mmol) en CH_2Cl_2 (2 mL) a 0°C. La mezcla de reacción se agitó a temperatura ambiente por 3 horas, después se separó el solvente bajo presión reducida. El residuo resultante se lavó 2X con porciones de 10 mL de EtOAc-hexano (6:4) y los lavados combinados se purificaron por cromatografía instantánea sobre gel de sílice eluyendo con 60% EtOAc/hexano para dar 390 mg (0.853 mmol, 67.7%) del compuesto 36 como un sólido blanco. CLAR: 99% a 3.51 min.

(tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm, 10-90% de metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ESI): m/z 456.7 $[M-H]^-$.

Ejemplo 37

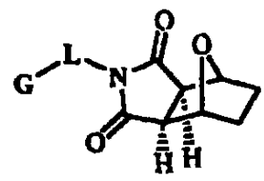
(3aα,4β,7β,7aα)-Hexahidro-4,7-dimetil-2-(3-metil-4-nitrofenil)-4,7-epoxi-1H-isoindol-1,3(2H)-diona (37)



Una combinación de 4-nitro-3-metilanilina (0.050 g, 0.33 mmol), compuesto 20A (0.083 g, 0.43 mmol), TEA (0.2 mL), $MgSO_4$ (0.075 g) y tolueno (0.8 mL) se combinaron en un tubo sellado y la mezcla se calentó a 120°C por 14 h. Después de enfriar hasta 25°C, la reacción se filtró, se enjuagó con CH_2Cl_2 y se concentraron bajo presión reducida. El producto crudo se purificó por CCD preparativa sobre SiO_2 eluyendo con CH_2Cl_2 para dar 0.075 g (0.23 mmol, 69%) del compuesto 37 como un sólido amarillo pálido. CLAR: 100% a 2.733 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 X 50 mm; 10-90% $MeOH/H_2O$ gradiente, + 0.1% TFA; 4 mL/min., detección a 220 nm). EM (ES): m/z 348.2 $[M+NH_4]^+$.

Ejemplos 38 al 121

Los compuestos adicionales de la presente invención se prepararon por procedimientos análogos a aquellos antes descritos. Los compuestos de los Ejemplos 38 al 121 tienen la siguiente estructura (L es un enlace):



en donde G, el nombre del compuesto, tiempo de retención, masa molecular, y el procedimiento empleado, son establecidos en la Tabla 2. Las técnicas de cromatografía usadas para determinar los tiempos de retención de los compuestos de la Tabla 2 son como sigue: CLEM = Columna YMC S5 ODS, 4.6 X 50 mm eluyendo con 10-90% MeOH/H_2O durante 4 minutos conteniendo 0.1% TFA; 4 mL/min., observando a 220 nm. La masa molecular de los compuestos enlistados en la Tabla 2, en donde se proporciona, se determinó por EM (ES) por la fórmula m/z.

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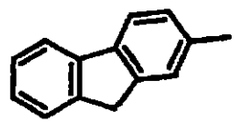
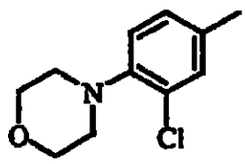
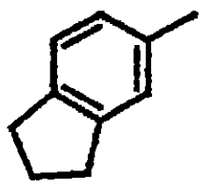
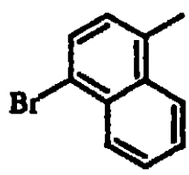
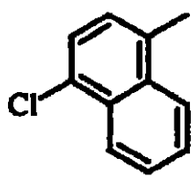
Tabla 2

Ej. No.	G	Nombre del Compuesto	Tiempo de Retención (Min.)/Masa Molecular	Pro. de Ej.
38		(3aα,4β,7β,7aα)-2-(2-fluorenil)hexahidro-4,7-epoxi-1H-isoindol-1,3(2H)-diona	3.72 CLEM/ 332.20 $[M+H]^+$	8
39		(3aα,4β,7β,7aα)-2-[3-cloro-4-(4-morfolinil)fenil]hexahidro-4,7-epoxi-1H-isoindol-1,3(2H)-diona	3.20 CLEM/ 363.20 $[M+H]^+$	8
40		(3aα,4β,7β,7aα)-2-(2,3-dihidro-1H-inden-5-il)hexahidro-4,7-epoxi-1H-isoindol-1,3(2H)-diona	3.26 CLEM/ 284.22 $[M+H]^+$	8
41		(3aα,4β,7β,7aα)-2-(4-bromo-1-naftalenil)hexahidro-4,7-epoxi-1H-isoindol-1,3(2H)-diona	3.73 CLEM/ 404.11 $[M+CH_3OH+H]^+$	8
42		(3aα,4β,7β,7aα)-2-(4-cloro-1-naftalenil)hexahidro-4,7-epoxi-1H-isoindol-1,3(2H)-diona	3.63 CLEM/ 328.14 $[M+H]^+$	8

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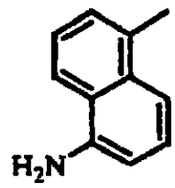
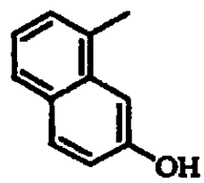
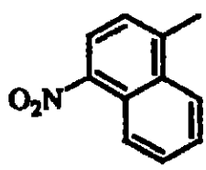
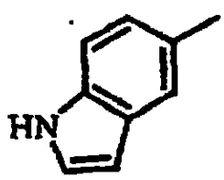
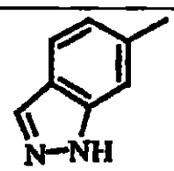
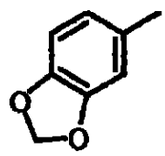
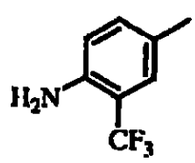
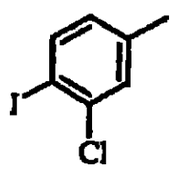
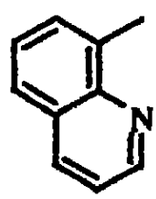
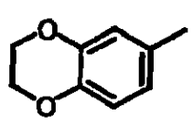
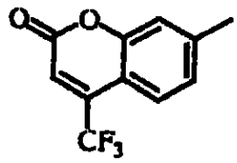
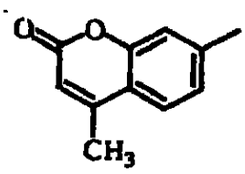
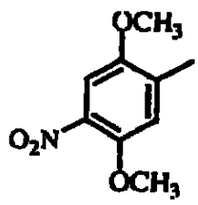
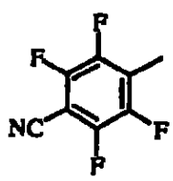
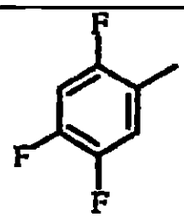
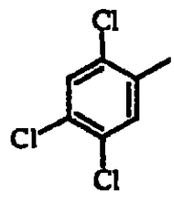
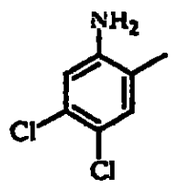
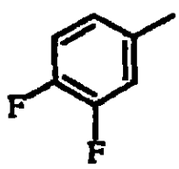
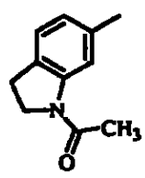
Ej. No.	G	Nombre del Compuesto	Tiempo de Retención (Min.)/Masa Molecular	Pro. de Ej.
43		(3aα,4β,7β,7aα)-2-(5-amino-1-naftalenil)hexahidro-4,7-epoxi-1H-isoindol-1,3(2H)-diona	1.64 CLEM/	8
44		(3aα,4β,7β,7aα)-2-hexahidro-2-(7-hidroxi-1-naftalenil)-4,7-epoxi-1H-isoindol-1,3(2H)-diona	2.54 CLEM/ 308.23 $[M-H]^-$	8
45		(3aα,4β,7β,7aα)-hexahidro-2-(4-nitro-1-naftalenil)- 4,7-epoxi-1H-isoindol-1,3(2H)-diona	3.117 CLEM/ 404.11 $[M+CH_3OH+H]^+$	8
46		(3aα,4β,7β,7aα)-hexahidro-2-(1H-indol-5-il)-4,7-epoxi-1H-isoindol-1,3(2H)-diona	2.39 CLEM/ 283.23 $[M+H]^+$	8
47		(3aα,4β,7β,7aα)-hexahidro-2-(1H-indazol-6-il)-4,7-epoxi-1H-isoindol-1,3(2H)-diona	2.35 CLEM/ 282.23 $[M+H]^+$	8

626

Ej. No.	G	Nombre del Compuesto	Tiempo de Retención (Min.)/Masa Molecular	Proc. de Ej.
48		(3aα,4β,7β,7aα)-2-(1,3-benzodioxol-5-il)hexahidro-4,7-epoxi-1H-isoindol-1,3(2H)-diona	2.47 CLEM/ 288.20 $[M+H]^+$	8
49		(3aα,4β,7β,7aα)-2-[4-amino-3-(trifluorometil)fenil]hexahidro-4,7-epoxi-1H-isoindol-1,3(2H)-diona	2.71 CLEM/ 327.20 $[M+H]^+$	8
50		(3aα,4β,7β,7aα)-2-(3-cloro-4-yodofenil)hexahidro-4,7-epoxi-1H-isoindol-1,3(2H)-diona	3.70 CLEM/ 435.2 $[M+CH_3OH]^+$	8
51		(3aα,4β,7β,7aα)-hexahidro-2-(8-quinolinil)-4,7-epoxi-1H-isoindol-1,3(2H)-diona	2.28 CLEM/ 295.22 $[M+H]^+$	8
52		(3aα,4β,7β,7aα)-2-(2,3-dihidro-1,4-benzodioxin-6-il)hexahidro-4,7-epoxi-1H-isoindol-1,3(2H)-diona	2.55 CLEM/ 302.23 $[M+H]^+$	8

627

Ej. No.	G	Nombre del Compuesto	Tiempo de Retención (Min.)/Masa Molecular	Pro. de Ej.
53		(3aα,4β,7β,7aα)-hexahidro-2-[2-oxo-4-(trifluorometil)-2H-1-benzopiran-7-il]-4,7-epoxi-1H-isoindol-1,3(2H)-diona	3.38 CLEM/ 412.17 $[M+CH_3OH+H]^+$	8
54		(3aα,4β,7β,7aα)-hexahidro-2-(4-metil-2-oxo-2H-1-benzopiran-7-il)-4,7-epoxi-1H-isoindol-1,3(2H)-diona	2.74 CLEM/ 326.20 $[M+H]^+$	8
55		(3aα,4β,7β,7aα)-2-(2,5-dimetoxi-4-nitrofenil)hexahidro-4,7-epoxi-1H-isoindol-1,3(2H)-diona	2.70 CLEM/ 349.23 $[M+H]^+$	8
56		(3aα,4β,7β,7aα)-2,3,5,6-tetrafluoro-4-(octahidro-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)benzonitrilo	2.97 CLEM	8

Ej. No.	G	Nombre del Compuesto	Tiempo de Retención (Min.)/Masa Molecular	Pro. de Ej.
57		(3aα,4β,7β,7aα)-hexahidro-2-(2,4,5-trifluorofenil)-4,7-epoxi-1H-isoindol-1,3(2H)-diona	2.90 CLEM	8
58		(3aα,4β,7β,7aα)-hexahidro-2-(2,4,5-triclorofenil)-4,7-epoxi-1H-isoindol-1,3(2H)-diona	3.64 CLEM/ 346.39 $[M]^+$	8
59		(3aα,4β,7β,7aα)-2-(2-amino-4,5-diclorofenil)hexahidro-4,7-epoxi-1H-isoindol-1,3(2H)-diona	3.23 CLEM	8
60		(3aα,4β,7β,7aα)-2-(3,4-difluorofenil)hexahidro-4,7-epoxi-1H-isoindol-1,3(2H)-diona	2.91 CLEM/ 280.23 $[M+H]^+$	8
61		(3aα,4β,7β,7aα)-1-acetil-2,3-dihidro-6-(octahidro-1,3-dioxo-4,7-epoxi-2H-isoindol-2il)	2.43 CLEM/ 359.26 $[M+CH_3CH+H]^+$	8

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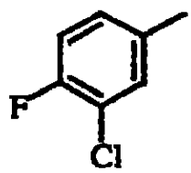
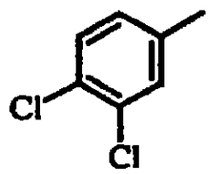
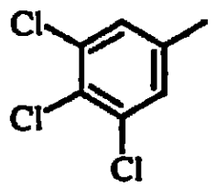
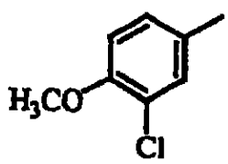
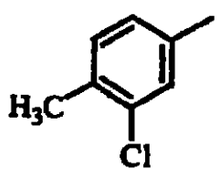
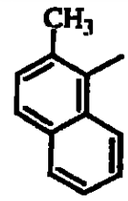
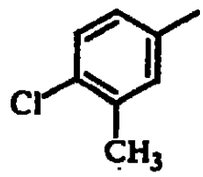
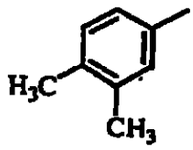
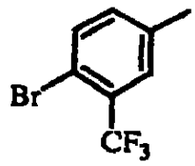
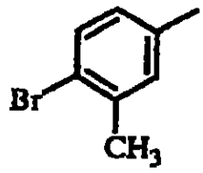
Ej. No.	G	Nombre del Compuesto	Tiempo de Retención (Min.)/Masa Molecular	Pro. de Ej.
62		(3aα,4β,7β,7aα)-2-(3-cloro-4-fluorofenil)hexahidro-4,7-epoxi-1H-isoindol-1,3(2H)-diona	3.21 CLEM/ 328.14 $[M+CH_3OH+H]^+$	8
63		(3aα,4β,7β,7aα)-2-(3,4-diclorofenil)hexahidro-4,7-epoxi-1H-isoindol-1,3(2H)-diona	3.54 CLEM/ 311.79 $[M-H]^-$	8
64		(3aα,4β,7β,7aα)-hexahidro-2-(3,4,5-triclorofenil)-4,7-epoxi-1H-isoindol-1,3(2H)-diona	4.05 CLEM/ 378.10 $[M+CH_3OH+H]^+$	8
65		(3aα,4β,7β,7aα)-2-(3-cloro-4-metoxifenil)hexahidro-4,7-epoxi-1H-isoindol-1,3(2H)-diona	2.99 CLEM/ 308.11 $[M+H]^+$	8
66		(3aα,4β,7β,7aα)-2-(3-cloro-4-metilfenil)hexahidro-4,7-epoxi-1H-isoindol-1,3(2H)-diona	3.39 CLEM/ 292.20 $[M+H]^+$	8

630

Ej. No.	G	Nombre del Compuesto	Tiempo de Retención (Min.)/Masa Molecular	Pró. de Ej.
67		(3aα,4β,7β,7aα)-hexahidro-2-(2-metil-1-naftalenil)-4,7-epoxi-1H-isoindol-1,3(2H)-diona	3.28 CLEM/ 308.23 $[M+H]^+$	8
68		(3aα,4β,7β,7aα)-2-(4-cloro-3-metilfenil)hexahidro-4,7-epoxi-1H-isoindol-1,3(2H)-diona	3.40 CLEM/ 292.20 $[M+H]^+$	8
69		(3aα,4β,7β,7aα)-2-(3,4-dimetilfenil)hexahidro-4,7-epoxi-1H-isoindol-1,3(2H)-diona	3.11 CLEM/ 272.23 $[M+H]^+$	8
70		(3aα,4β,7β,7aα)-2-[4-bromo-3-(trifluorometil)fenil]hexahidro-4,7-epoxi-1H-isoindol-1,3(2H)-diona	3.76 CLEM/ 421.98 $[M+CH_3CH+H]^+$	8
71		(3aα,4β,7β,7aα)-2-(4-bromo-3-metilfenil)hexahidro-4,7-epoxi-1H-isoindol-1,3(2H)-diona	3.50 CLEM/ 336.05 $[M+H]^+$	8

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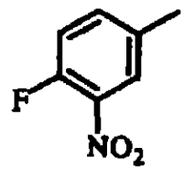
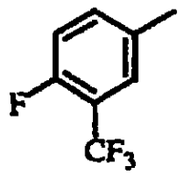
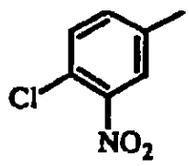
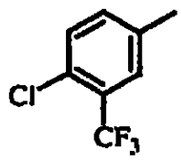
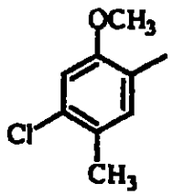
Ej. No.	G	Nombre del Compuesto	Tiempo de Retención (Min.)/Masa Molecular	Pro. de Ej.
72		(3aα,4β,7β,7aα)-2-(4-fluoro-3-nitrofenil)hexahidro-4,7-epoxi-1H-isoindol-1,3(2H)-diona	2.80 CLEM/ 305.25 $[M+H]^+$	8
73		(3aα,4β,7β,7aα)-2-[4-fluoro-3-(trifluorometil)fenil]hexahidro-4,7-epoxi-1H-isoindol-1,3(2H)-diona	3.45 CLEM/ 362.26 $[M+CH_3OH+H]^+$	8
74		(3aα,4β,7β,7aα)-2-(4-cloro-3-nitrofenil)hexahidro-4,7-epoxi-1H-isoindol-1,3(2H)-diona	3.19 CLEM/ 322.86 $[M]^+$	8
75		(3aα,4β,7β,7aα)-2-[4-cloro-3-(trifluorometil)fenil]hexahidro-4,7-epoxi-1H-isoindol-1,3(2H)-diona	3.68 CLEM/ 345.83 $[M]^+$	8
76		(3aα,4β,7β,7aα)-2-(4-cloro-2-metoxi-5-metilfenil)hexahidro-4,7-epoxi-1H-isoindol-1,3(2H)-diona	3.31 CLEM/ 322.20 $[M+H]^+$	8

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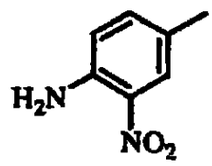
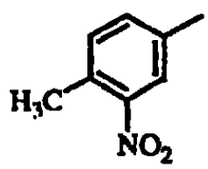
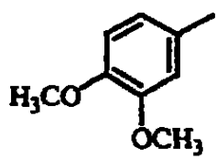
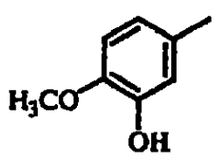
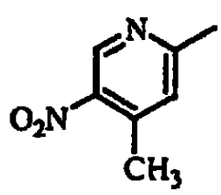
Ej. No.	G	Nombre del Compuesto	Tiempo de Retención (Min.)/Masa Molecular	Pro. de Ej.
77		(3aα,4β,7β,7aα)-2-(4-amino-3-nitrofenil)hexahidro-4,7-epoxi-1H-isoindol-1,3(2H)-diona	2.34 CLEM/ 302.27 $[M-H]^-$	8
78		(3aα,4β,7β,7aα)-hexahidro-2-(4-metil-3-nitrofenil)- 4,7-epoxi-1H-isoindol-1,3(2H)-diona	3.02 CLEM/ 335.20 $[M+CH_3OH+H]^+$	8
79		(3aα,4β,7β,7aα)-2-(3,4-dimetoxifenil)hexahidro-4,7-epoxi-1H-isoindol-1,3(2H)-diona	2.35 CLEM/ 304.25 $[M+H]^+$	8
80		(3aα,4β,7β,7aα)-hexahidro-2-(3-hidroxi-4-metoxifenil)-4,7-epoxi-1H-isoindol-1,3(2H)-diona	0.98 CLEM/ 321.19 $[M+CH_3OH]^+$	8
81		(3aα,4β,7β,7aα)-hexahidro-2-(4-metil-5-nitro-2-piridinil)-4,7-epoxi-1H-isoindol-1,3(2H)-diona	0.54 CLEM/ 304.20 $[M+H]^+$	8

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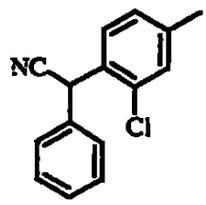
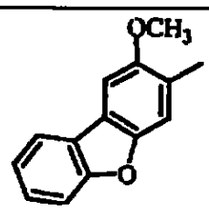
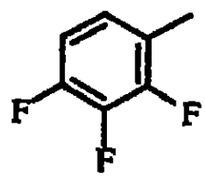
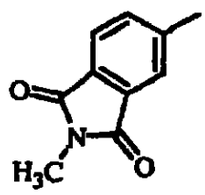
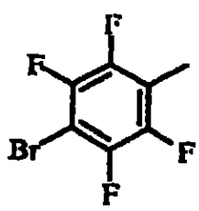
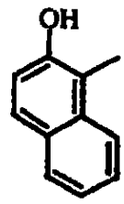
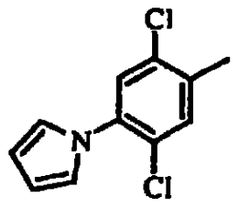
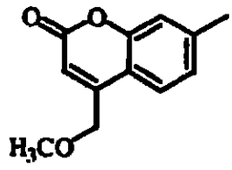
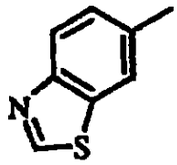
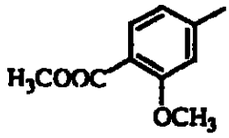
Ej. No.	G	Nombre del Compuesto	Tiempo de Retención (Min.)/Masa Molecular	Pro. de Ej.
82		(3aα,4β,7β,7aα)-2-cloro-4-(octahidro-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-α-fenilbencenacetonitrilo	3.67 CLEM/ 423.8 $[M+CH_3OH]^+$	8
83		(3aα,4β,7β,7aα)-hexahidro-2-(2-metoxi-3-dibenzofuranil)-4,7-epoxi-1H-isoindol-1,3(2H)-diona	3.66 CLEM/ 364.25 $[M+H]^+$	8
84		(3aα,4β,7β,7aα)-hexahidro-2-(2,3,4-trifluorofenil)-4,7-epoxi-1H-isoindol-1,3(2H)-diona	3.06 CLEM/ 298.14 $[M+H]^+$	8
85		(3aα,4β,7β,7aα)-2-(2,3-dihidro-2-metil-1,3-dioxo-1H-isoindol-5-il)hexahidro-4,7-epoxi-1H-isoindol-1,3(2H)-diona	2.70 CLEM/ 359.22 $[M+CH_3OH+H]^+$	8
86		(3aα,4β,7β,7aα)-2-(4-bromo-2,3,5,6-tetrafluorofenil)hexahidro-4,7-epoxi-1H-isoindol-1,3(2H)-diona	3.72 CLEM/ 426.07 $[M+CH_3OH+H]^+$	8

Ej. No.	G	Nombre del Compuesto	Tiempo de Retención (Min.)/Masa Molecular	Pro. de Ej.
87		(3aα,4β,7β,7aα)-hexahidro-2-(2-hidroxi-1-naftalenil)-4,7-epoxi-1H-isoindol-1,3(2H)-diona	2.52 CLEM/ 308.26 $[M-H]^-$	8
88		(3aα,4β,7β,7aα)-2-[2,5-dicloro-4-(1H-pirrol-1-il)fenil]hexahidro-4,7-epoxi-1H-isoindol-1,3(2H)-diona	3.70 CLEM/ 376.64 $[M-H]^-$	8
89		(3aα,4β,7β,7aα)-hexahidro-2-[4-(metoximetil)-2-oxo-2H-1-benzopiran-7-il]-4,7-epoxi-1H-isoindol-1,3(2H)-diona	2.79 CLEM/ 356.26 $[M+H]^+$	8
90		(3aα,4β,7β,7aα)-2-(6-benzotiazolil)hexahidro-4,7-epoxi-1H-isoindol-1,3(2H)-diona	2.46 CLEM/ 301.19 $[M+H]^+$	8
91		Éster de metilíco del ácido (3aα,4β,7β,7aα)-2-metoxi-4-(octahidro-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)benzóico	2.75 CLEM/ 332.25 $[M+H]^+$	8

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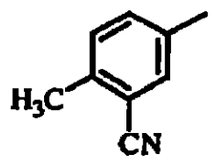
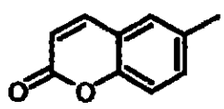
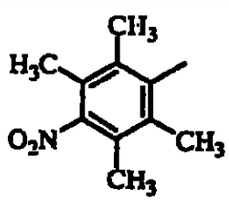
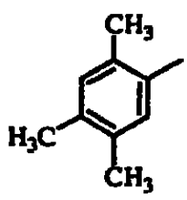
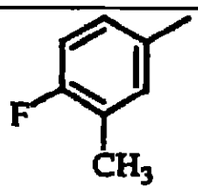
Ej. No.	G	Nombre del Compuesto	Tiempo de Retención (Min.)/Masa Molecular	Pro. de Ej.
92		(3aα,4β,7β,7aα)-2-metil-5-(octahidro-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)benzonitrilo	2.80 CLEM/ 315.26 $[M+CH_3OH+H]^+$	8
93		(3aα,4β,7β,7aα)-hexahidro-2-(2-oxo-2H-1-benzopiran-6-il)-4,7-epoxi-1H-isoindol-1,3(2H)-diona	2.45 CLEM/ 312.20 $[M+H]^+$	8
94		(3aα,4β,7β,7aα)-hexahidro-2-(2,3,5,6-tetrametil-4-nitrofenil)-4,7-epoxi-1H-isoindol-1,3(2H)-diona	3.59 CLEM/ 377.25 $[M+CH_3OH+H]^+$	8
95		(3aα,4β,7β,7aα)-hexahidro-2-(2,4,5-trimetilfenil)-4,7-epoxi-1H-isoindol-1,3(2H)-diona	3.33 CLEM/ 286.30 $[M+H]^+$	8
96		(3aα,4β,7β,7aα)-2-(4-fluoro-3-metilfenil)hexahidro-4,7-epoxi-1H-isoindol-1,3(2H)-diona	3.00 CLEM/ 276.23 $[M+H]^+$	8

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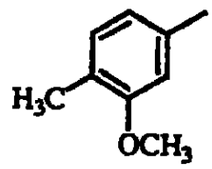
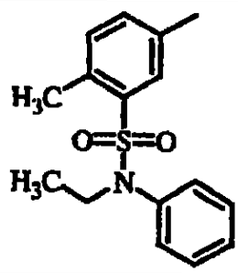
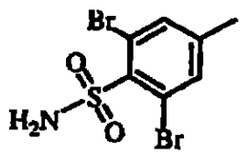
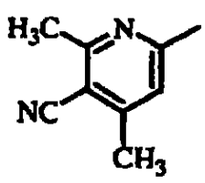
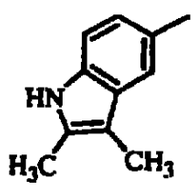
Ej. No.	G	Nombre del Compuesto	Tiempo de Retención (Min.)/Masa Molecular	Proc. de Ej.
97		(3aα,4β,7β,7aα)-hexahidro-2-(3-metoxi-4-metilfenil)-4,7-epoxi-1H-isoindol-1,3(2H)-diona	3.05 CLEM/ 288.23 $[M+H]^+$	8
98		(3aα,4β,7β,7aα)-N-etil-2-metil-5-(octahidro-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-N-fenilbencensulfonamida	3.56 CLEM/ 441.26 $[M+H]^+$	8
99		(3aα,4β,7β,7aα)-2,6-dibromo-4-(octahidro-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)bencensulfonamida	2.25 CLEM	8
100		(3aα,4β,7β,7aα)-2,4-dimetil-6-(octahidro-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-3-piridincarbonitrilo	2.75 CLEM/ 298.23 $[M+H]^+$	8
101		(3aα,4β,7β,7aα)-2-(2,3-dimetil-1H-indol-5-il)hexahidro-4,7-epoxi-1H-isoindol-1,3(2H)-diona	3.00 CLEM/ 311.26 $[M+H]^+$	8

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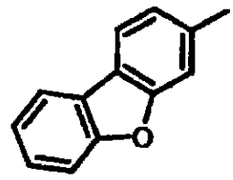
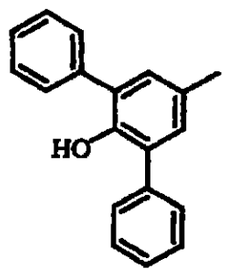
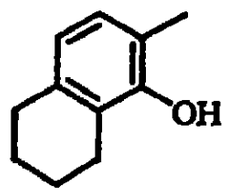
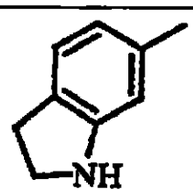
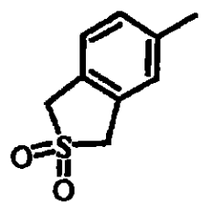
Ej. No.	G	Nombre del Compuesto	Tiempo de Retención (Min.)/Masa Molecular	Pro. de Ej.
102		(3aα,4β,7β,7aα)-2-(3-dibenzofuranil)hexahidro-4,7-epoxi-1H-isoindol-1,3(2H)-diona	3.72 CLEM/ 366.23 $[M+CH_3OH+H]^+$	8
103		(3aα,4β,7β,7aα)-hexahidro-2-(2'-hidroxi[1,1':3'1"-terfenil]-5'-il)- 4,7-epoxi-1H-isoindol-1,3(2H)-diona	3.70 CLEM/ 412.23 $[M+H]^+$	8
104		(3aα,4β,7β,7aα)-hexahidro-2-(5,6,7,8-tetrahidro-3-hidroxi-2-naftalenil)-4,7-epoxi-1H-isoindol-1,3(2H)-diona	3.24 CLEM/ 312.32 $[M+H]^+$	8
105		(3aα,4β,7β,7aα)-2-(2,3-dihidro-1H-indol-6-il)hexahidro-4,7-epoxi-1H-isoindol-1,3(2H)-diona	2.42 CLEM/ 285.29 $[M+H]^+$	8
106		(3aα,4β,7β,7aα)-2-(1,3-dihidro-2,2-dióxidobenzo[c]tiofen-5-il)hexahidro-4,7-epoxi-1H-isoindol-1,3(2H)-diona	1.99 CLEM/ 366.26 $[M+H]^+$	8

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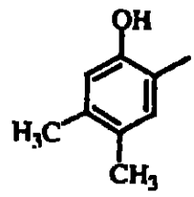
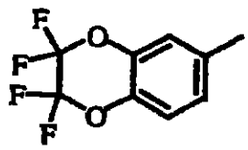
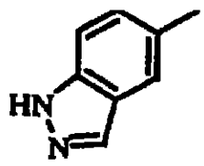
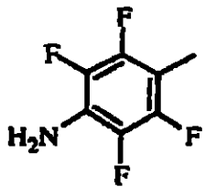
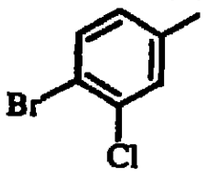
Ej. No.	G	Nombre del Compuesto	Tiempo de Retención (Min.)/Masa Molecular	Pro. de Ej.
107		(3aα,4β,7β,7aα)-hexahidro-2-(2-hidroxi-4,5-dimetilfenil)-4,7-epoxi-1H-isoindol-1,3(2H)-diona	2.78 CLEM/ 286.32 $[M-H]^-$	8
108		(3aα,4β,7β,7aα)-2-(2,3-dihidro-2,2,3,3-tetrafluoro-1,4-benzodioxin-6-il)hexahidro-4,7-epoxi-1H-isoindol-1,3(2H)-diona	3.82 CLEM/ 406.19 $[M+CH_3OH+H]^+$	8
109		(3aα,4β,7β,7aα)-hexahidro-2-(1H-indazol-5-il)-4,7-epoxi-1H-isoindol-1,3(2H)-diona	2.13 CLEM/ 284.23 $[M+H]^+$	8
110		(3aα,4β,7β,7aα)-2-(4-amino-2,3,5,6-tetrafluorofenil)-hexahidro-4,7-epoxi-1H-isoindol-1,3(2H)-diona	2.60 CLEM/ 363.22 $[M+CH_3OH+H]^+$	8
111		(3aα,4β,7β,7aα)-2-(4-bromo-3-clorofenil)hexahidro-4,7-epoxi-1H-isoindol-1,3(2H)-diona	3.64 CLEM/ 389.64 $[M+H]^+$	8

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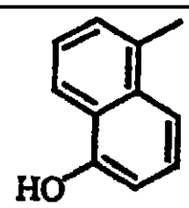
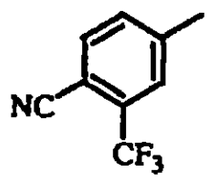
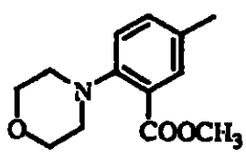
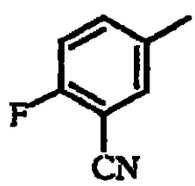
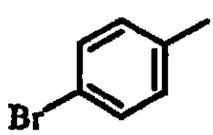
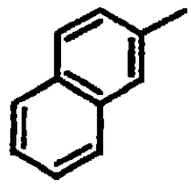
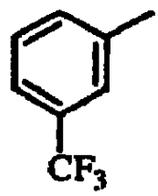
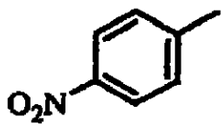
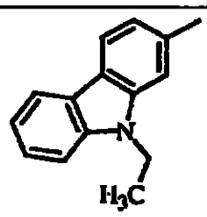
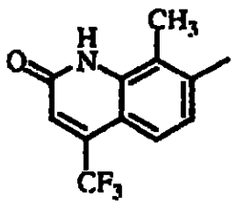
Ej. No.	G	Nombre del Compuesto	Tiempo de Retención (Min.)/Masa Molecular	Pro. de Ej.
112		(3aα,4β,7β,7aα)-hexahidro-2-(5-hidroxi-1-naftalenil)-4,7-epoxi-1H-isoindol-1,3(2H)-diona	2.48 CLEM/ 308.27 $[M-H]^-$	8
113		(3aα,4β,7β,7aα)-4-(octahidro-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo	3.28 CLEM/ 337.16 $[M+H]^+$	8
114		Éster de metilo del ácido (3aα,4β,7β,7aα)-2-(4-morfolinil)-5-(octahidro-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)benzóico	2.72 CLEM/ 387.17 $[M+H]^+$	8
115		(3aα,4β,7β,7aα)-2-fluoro-5-(octahidro-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)benzonitrilo	2.69 CLEM/ 319.26 $[M+CH_3OH+H]^+$	8
116		(3aα,4β,7β,7aα)-2-(4-bromofenil)hexahidro-4,7-epoxi-1H-isoindol-1,3(2H)-diona	5.80 CLEM/ 393.0 $[M+H]^+$	8

Ej. No.	G	Nombre del Compuesto	Tiempo de Retención (Min.)/Masa Molecular	Pro. de Ej.
117		(3aα,4β,7β,7aα)-hexahidro-2-(2-naftalenil)-4,7-epoxi-1H-isoindol-1,3(2H)-diona	6.92 CLEM/ 333.7 $[M+H]^+$	8
118		(3aα,4β,7β,7aα)-hexahidro-2-[3-(trifluorometil)fenil]-4,7-epoxi-1H-isoindol-1,3(2H)-diona	3.27 CLEM/ 312.2 $[M+H]^+$	8
119		(3aα,4β,7β,7aα)-hexahidro-2-(4-nitrofenil)-4,7-epoxi-1H-isoindol-1,3(2H)-diona	2.88 CLEM/ 343.2 $[M+H]^+$	8
120		(3aα,4β,7β,7aα)-2-(9-etil-9H-carbazol-3-il)hexahidro-4,7-epoxi-1H-isoindol-1,3(2H)-diona	3.73 CLEM/ 360.1 $[M+H]^+$	8
121		(3aα,4β,7β,7aα)-2-[1,2-dihidro-8-metil-2-oxo-4-(trifluorometil)-7-quinolinil]hexahidro-4,7-epoxi-1H-isoindol-1,3(2H)-diona	3.11 CLEM/ 393.0 $[M+H]^+$	8

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Ejemplos 122 al 164

Los compuestos adicionales de la presente invención se prepararon por los procedimientos análogos a aquellos antes descritos. La Tabla 3 proporciona el nombre del compuesto y estructura, tiempo de retención, así como el número de Ejemplo del procedimiento sobre el cual se basa la preparación de la Tabla 3, para los compuestos de los Ejemplos 122 al 164.

Las técnicas de cromatografía usadas para determinar los tiempos de retención de los compuestos de la Tabla 3 son como siguen:

CLEM = Columna YMC S5 ODS de 4.6 X 50 mm eluyendo con 10-90% MeOH/H_2O durante 4 minutos conteniendo 0.1 % TFA; 4 mL/min, observando a 220 nm.

CL = Columna YMC S5 ODS de 4.6 x 50 mm eluyendo con 10-90% MeOH/H_2O durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min, observando a 220 nm

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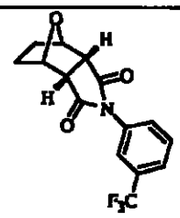
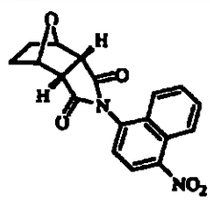
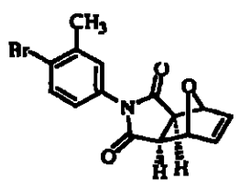
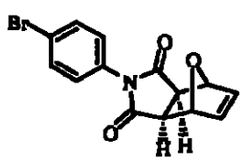
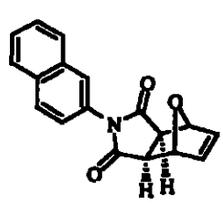
Tabla 3

Ej. No.	Estructura del compuesto	Nombre del Compuesto	Tiempo de Retención (Min.)/Masa Molecular	Pro. de Ej.
122		(3aα,4β,7β,7aα)-hexahidro-2-[3-(trifluorometil)fenil]-4,7-epoxi-1H-isoindol-1,3(2H)-diona	2.66 CLEM	27
123		(3aα,4β,7β,7aα)-hexahidro-2-(4-nitro-1-naftalenil)-4,7-epoxi-1H-isoindol-1,3(2H)-diona	2.76 CLEM	27
124		(3aα,4β,7β,7aα)-2-(4-bromo-3-metilfenil)-3a,4,7,7a-tetrahidro-4,7-epoxi-1H-isoindol-1,3(2H)-diona	6.36 CLEM	8
125		(3aα,4β,7β,7aα)-2-(4-bromofenil)-3a,4,7,7a-tetrahidro-4,7-epoxi-1H-isoindol-1,3(2H)-diona	5.72 CLEM	8
126		(3aα,4β,7β,7aα)-3a,4,7,a-tetrahidro-2-(2-naftalenil)-4,7-epoxi-1H-isoindol-1,3(2H)-diona	5.92 CLEM	8

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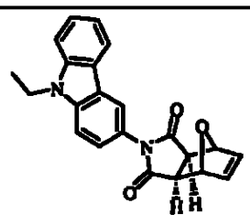
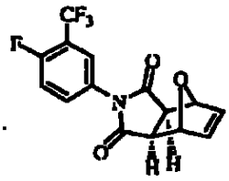
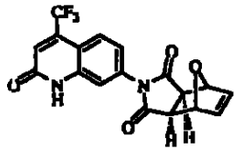
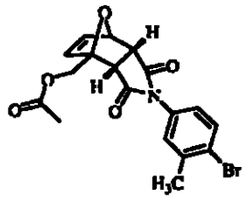
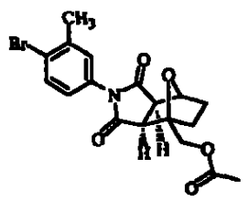
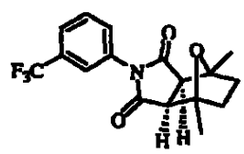
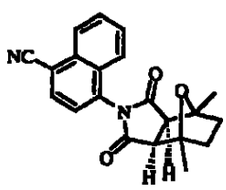
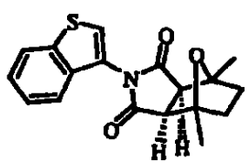
Ej. No.	Estructura del compuesto	Nombre del Compuesto	Tiempo de Retención (Min.)/Masa Molecular	Pro. de Ej.
127		(3aα,4β,7β,7aα)-2-(9-etil-9H-carbazol-3-il)-3a,4,7,7a-tetrahidro-4,7-epoxi-1H-isoindol-1,3(2H)-diona	3.73 CLEM	8
128		(3aα,4β,7β,7aα)-2-[4-fluoro-3-(trifluorometil)fenil]-3a,4,7,7a-tetrahidro-4,7-epoxi-1H-isoindol-1,3(2H)-diona	3.40 CLEM	8
129		(3aα,4β,7β,7aα)-2-[1,2-dihidro-8-metil-2-oxo-4-(trifluorometil)-7-quinolinil]-3a,4,7,7a-tetrahidro-4,7-epoxi-1H-isoindol-1,3(2H)-diona	3.14 CLEM	8
130		(3aα,4α,7α,7aα)-4-[(acetiloxi)metil]-2-(4-bromo-3-metilfenil)-3a,4,7,7a-tetrahidro- 4,7-epoxi-1H-isoindol-1,3(2H)-diona	2.95 CL	4

Ej. No.	Estructura del compuesto	Nombre del Compuesto	Tiempo de Retención (Min.)/Masa Molecular	Pro. de Ej.
131		(3aα,4β,7β,7aα)-4-[(acetiloxi)metil]-2-(4-bromo-3-metilfenil)-3a,4,7,7a-tetrahidro-4,7-epoxi-1H-isoindol-1,3(2H)-diona	2.97 CLEM	5
132		(3aα,4β,7β,7aα)-hexahidro-4,7-dimetil-2-[3-(trifluorometil)fenil]-4,7-epoxi-1H-isoindol-1,3(2H)-diona	3.08 CL	20
133		(3aα,4β,7β,7aα)-4-(octahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-1-naftalencarbonitrilo	3.00 CL	20
134		(3aα,4β,7β,7aα)-(benzo[b]tiofen-3-il)hexahidro-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3(2H)-diona	3.61 CL	20

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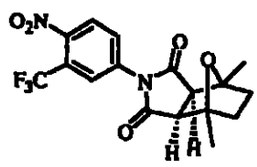
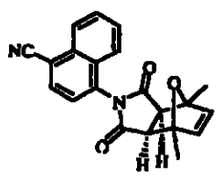
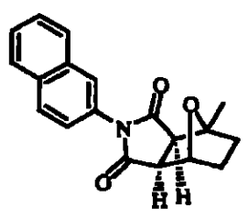
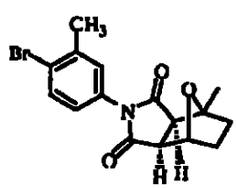
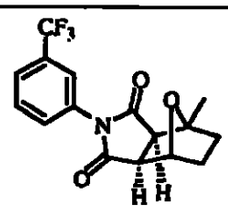
Ej. No.	Estructura del compuesto	Nombre del Compuesto	Tiempo de Retención (Min.)/Masa Molecular	Pro. de Ej.
135		(3aα,4β,7β,7aα)-hexahidro-4,7-dimetil-2-[4-nitro-3-(trifluorometil)fenil-4,7-epoxi-1H-isoindol-1,3(2H)-diona	3.21 CL	20
136		(3aα,4β,7β,7aα)-4-(1,3,3a,4,7,7a-hexahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-1-naftalencarbonitrilo	2.94 CL	32
137		(3aα,4β,7β,7aα)-hexahidro-4-metil-2-(2-naftalenil)-4,7-epoxi-1H-isoindol-1,3(2H)-diona	2.88 CL	3
138		(3aα,4β,7β,7aα)-2-(4-bromo-3-metilfenil)hexahidro-4-metil-4,7-epoxi-1H-isoindol-1,3(2H)-diona	3.11 CL	3
139		(3aα,4β,7β,7aα)-hexahidro-4-metil-2-[3-(trifluorometil)fenil]-4,7-epoxi-1H-isoindol-1,3(2H)-diona	2.90 CL	3

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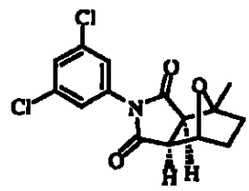
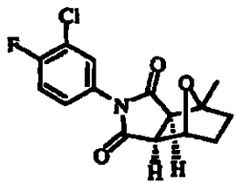
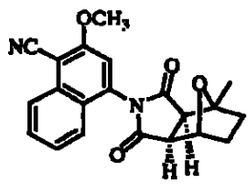
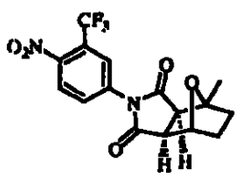
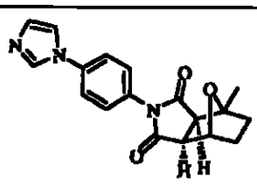
Ej. No.	Estructura del compuesto	Nombre del Compuesto	Tiempo de Retención (Min.)/Masa Molecular	Pro. de Ej.
140		(3aα,4β,7β,7aα)-2-(3,5-diclorofenil)hexahidro-4-metil-4,7-epoxi-1H-isoindol-1,3(2H)-diona	3.31 CL	3
141		(3aα,4β,7β,7aα)-2-(3-cloro-4-fluorofenil)-hexahidro-4-metil-4,7-epoxi-1H-isoindol-1,3(2H)-diona	2.72 CL	3
142		(3aα,4β,7β,7aα)-2-metoxi-4-(octahidro-1,3-dioxo-4-metil-4,7-epoxi-2H-isoindol-2,-il)-1-naftalencarbonitrilo	2.72 CL	3
143		(3aα,4β,7β,7aα)-hexahidro-4-metil-2-[4-nitro-3-(trifluorometil)fenil]-4,7-epoxi-1H-isoindol-1,3(2H)-diona	3.10 CL	3
144		(3aα,4β,7β,7aα)-hexahidro-2-[4-(1H-imidazol-1-il)fenil]-4-metil-4,7-epoxi-1H-isoindol-1,3(2H)-diona	1.16 CL	3

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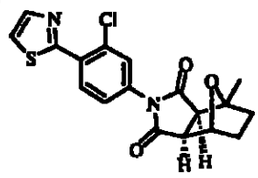
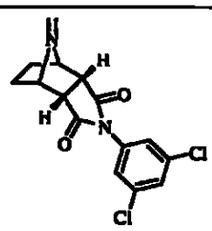
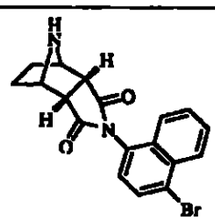
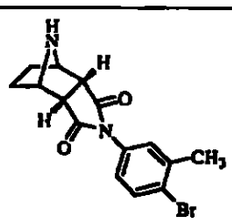
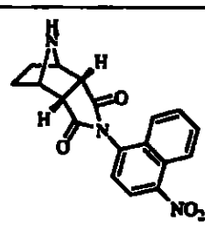
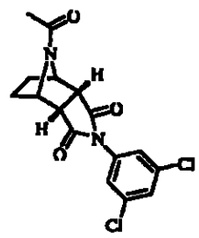
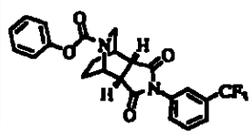
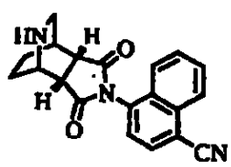
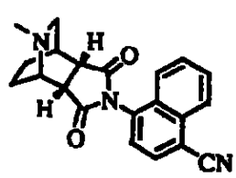
Ej. No.	Estructura del compuesto	Nombre del Compuesto	Tiempo de Retención (Min.)/Masa Molecular	Pro. de Ej.
145		(3aα,4β,7β,7aα)-2-[3-cloro-4-(2-tiazolil)fenil]hexahidro-4-metil-4,7-epoxi-1H-isoindol-1,3(2H)-diona	2.81 CL	3
146		(3aα,4α,7α,7aα)-2-(3,5-diclorofenil)hexahidro-4,7-imino-1H-isoindol-1,3(2H)-diona	2.72 CL	31
147		(3aα,4α,7α,7aα)-2-(4-bromo-1-naftalenil)hexahidro-4,7-imino-1H-isoindol-1,3(2H)-diona	2.95 CL	31
148		(3aα,4α,7α,7aα)-2-(4-bromo-3-metilfenil)hexahidro-4,7-imino-1H-isoindol-1,3(2H)-diona	2.65 CL	31
149		(3aα,4α,7α,7aα)-hexahidro-2-(4-nitro-1-naftalenil)-4,7-imino-1H-isoindol-1,3(2H)-diona	2.49 CL	31

Ej. No.	Estructura del compuesto	Nombre del Compuesto	Tiempo de Retención (Min.)/Masa Molecular	Pro. de Ej.
150		(3aα,4α,7α,7aα)-8-acetil-2-(3,5-diclorofenil)hexahidro-4,7-imino-1H-isoindol-1,3(2H)-diona	3.53 CL	31, 12
151		Éster de fenílico del ácido (3aα,4α,7α,7aα)-octahidro-1,3-dioxo-2-[3-(trifluorometil)fenil]-4,7-etano-5H-pirrolo[3,4-c]piridin-5-carboxílico	3.397 CL	9
152		(3aα,4α,7α,7aα)-4-(octahidro-1,3-dioxo-4,7-etano-2H-. pirrolo[3,4-c]piridin-2-il)-1-naftalencarbonitrilo	1.74 CL	11
153		(3aα,4α,7α,7aα)-4-(octahidro-5-metil-1,3-dioxo-4,7-etano-2H-pirrolo[3,4-c]piridin-2-il)-1-naftalencarbonitrilo	1.71 CL	14

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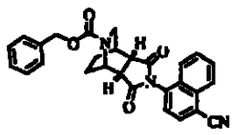
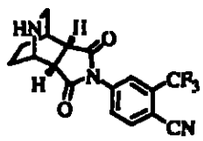
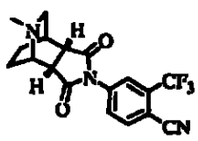
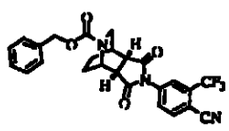
Ej. No.	Estructura del compuesto	Nombre del Compuesto	Tiempo de Retención (Min.)/Masa Molecular	Pro. de Ej.
154		Éster de fenilmetílico del ácido (3aα,4α,7α,7aα)-2-(4-ciano-1-naftalenil)octahidro-1,3-dioxo-4,7-eteno-5H-pirrolo[3,4-c]piridin-5-carboxílico	3.40 CL	10
155		(3aα,4α,7α,7aα)-4-(octahidro-1,3-dioxo-4,7-etano-2H-pirrolo[3,4-c[piridin-2-il)-2-(trifluorometil)benzonitrilo	1.74 CL	11
156		(3aα,4α,7α,7aα)-4-(octahidro-5-metil-1,3-dioxo-4,7-etano-2-h-pirrolo[3,4-c]piridin-2-il-2-(trifluorometil)benzonitrilo	1.65 CL	14
157		Éster de fenilmetílico del ácido (3aα,4α,7α,7aα)-2-[4-ciano-3-(trifluorometil)fenil]octahidro-1,3-dioxo-4,7-eteno-5H-pirrolo[3,4-c]piridin-5-carboxílico	3.53 CL	10

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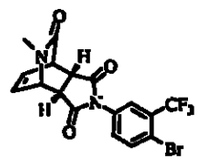
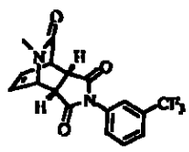
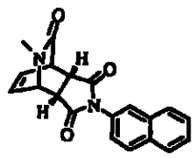
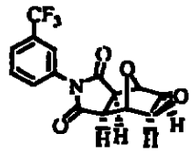
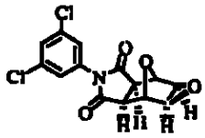
Ej. No.	Estructura del compuesto	Nombre del Compuesto	Tiempo de Retención (Min.)/Masa Molecular	Pro. de Ej.
158		(3aα,4α,7α,7aα)-2-[4-bromo-3-(trifluorometil)fenil]tetrahidro-5-metil-4,7-eteno-1H-pirrolo[3,4-c]piridin-1,3,6(2H,5H)-triona	2.95 CLEM	34
159		(3aα,4α,7α,7aα)-tetrahidro-5-metil-2-[3-(trifluorometil)fenil]-4,7-eteno-1H-pirrolo[3,4-c]piridin-1,3,6(2H,5H)-triona	2.53 CLEM	34
160		(3aα,4α,7α,7aα)-tetrahidro-5-metil-2-(2-naftalenil)-4,7-eteno-1H-pirrolo[3,4-c]piridin-1,3,6(2H,5H)-triona	2.58 CLEM	34
161		(1aα,2β,2aα,5aα,6β,6aα)-hexahidro-4-[3-(trifluorometil)fenil]-2,6-epoxi-3H-oxireno[f]isoindol-3,5-(4H)-diona	1.80 CLEM	28
162		(1aα,2β,2aα,5aα,6β,6aα)-4-(3,5-diclorofenil)-hexahidro-2,6-epoxi-3H-oxireno[f]isoindol-3,5(4H)-diona	1.45 CLEM	28

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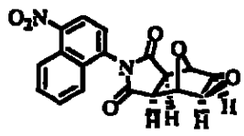
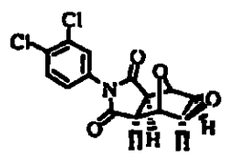
Ej. No.	Estructura del compuesto	Nombre del Compuesto	Tiempo de Retención (Min.)/Masa Molecular	Pro. de Ej.
163		(1aα,2β,2aα,5aα,6β,6aα)-hexahidro-4-(4-nitro-1-naftalenil)-2,6-epoxi-3H-oxireno[f]isoindol-3,5(4H)-diona	1.52 CLEM	28
164		(1aα,2β,2aα,5aα,6β,6aα)-4-(3,4-diclorofenil)-hexahidro-2,6-epoxi-3H-oxireno[f]isoindol-3,5-(4H)-diona	3.21 CLEM	28

Ejemplos 165 al 203

Los compuestos adicionales de la presente invención se prepararon y se describen además a continuación en la Tabla 4. La Tabla 4 proporciona el nombre del compuesto y estructura, así como el número de Ejemplo del procedimiento sobre el cual se basa la preparación de la Tabla 4, para los compuestos de los Ejemplos 165 al 203.

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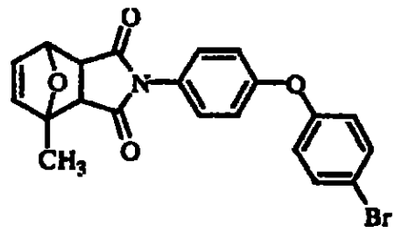
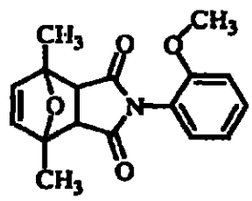
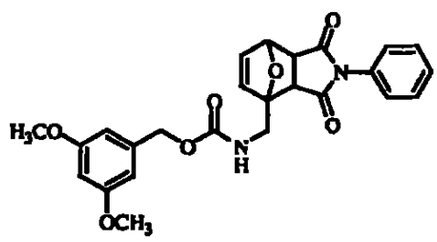
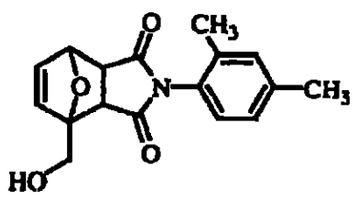
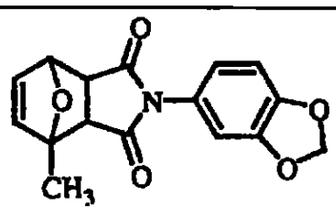
Tabla 4

Ej. No.	Estructura del compuesto	Nombre del Compuesto	Pro. de Ej.
165		2-[4-(4-bromo-fenoxi)fenil]-3a,4,7,7a-tetrahidro-4-metil-4,7-epoxi-1H-isoindol-1,3(2H)-diona	32
166		3a,4,7,7a-tetrahidro-2-(2-metoxifenil)-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3(2H)-diona	32
167		Éster de (3,5-dimetoxifenil)metílico del ácido [(1,2,3,3a,7,7a-hexahidro-2-fenil-4,7-epoxi-4H-isoindol-4-il)metil]carbámico	21-26
168		2-(2,4-dimetilfenil)-3a,4,7,7a-tetrahidro-4-(hidroximetil)-4,7-epoxi-1H-isoindol-1,3(2H)-diona	21-26
169		2-(1,3-benzodioxol-5-il)-3a,4,7,7a-tetrahidro-4-metil-4,7-epoxi-1H-isoindol-1,3(2H)-diona	32

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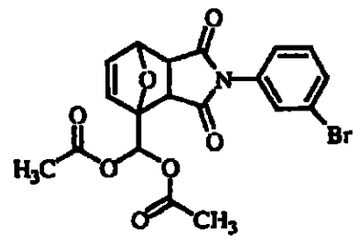
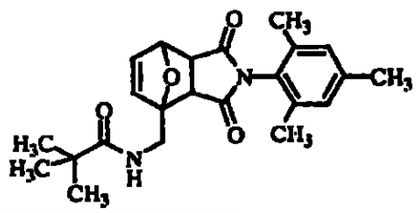
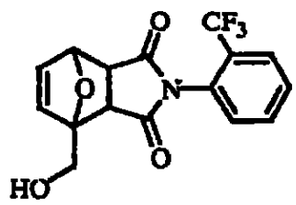
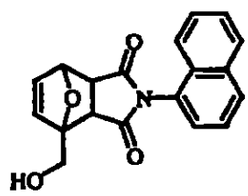
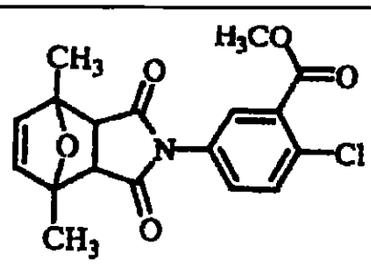
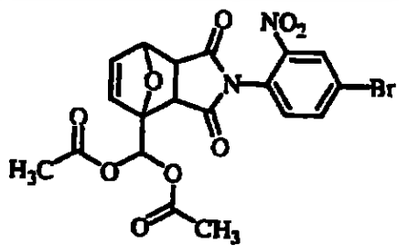
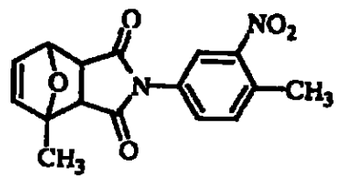
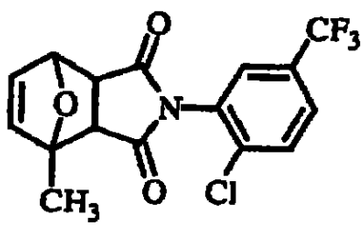
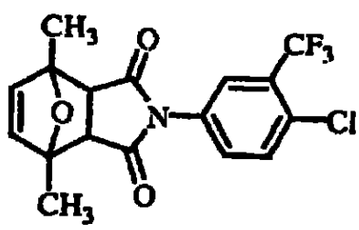
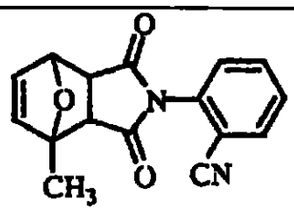
Ej. No.	Estructura del compuesto	Nombre del Compuesto	Pro. de Ej.
170		4-[bis(acetiloxi)metil]-2-(3-bromofenil)-3a,4,7,7a-tetrahidro-4,7-epoxi-1H-isoindol-1,3(2H)-diona	21-26
171		N-[[1,2,3,3a,7,7a-hexahidro-2(2,4,6-trimetilfenil)-4,7-epoxi-4H-isoindol-4-il]metil]-2,2-dimetilpropanamida	21-26
172		3a,4,7,7a-tetrahidro-4-(hidroximetil-2-[2-(trifluorometil)fenil]- 4,7-epoxi-1H-isoindol-1,3(2H)-diona	21-26
173		3a,4,7,7a-tetrahidro-4-(hidroximetil)-2-(1-naftalenil)-4,7-epoxi-1H-isoindol-1,3(2H)-diona	21-26
174		Éster de metilo del ácido 2-cloro-5-(1,3,3a,4,7,7a-hexahidro-4,7-dimetil-4,7-epoxi-2H-isoindol-2-il)-benzóico	32

Ej. No.	Estructura del compuesto	Nombre del Compuesto	Pro. de Ej.
175		4-[bis(acetiloxi)metil]-2-(4-bromo-2-nitrofenil)-3a,4,7,7a-tetrahidro-4,7-epoxi-1H-isoindol-1,3(2H)-diona	21-26
176		3a,4,7,7a-tetrahidro-4-metil-2-(4-metil-3-nitrofenil)-4,7-epoxi-1H-isoindol-1,3(2H)-diona	32
177		2-[2-cloro-5-(trifluorometil)fenil]-3a,4,7,7a-tetrahidro-4-metil-4,7-epoxi-1H-isoindol-1,3(2H)-diona	32
178		2-[4-cloro-3-(trifluorometil)fenil]-3a,4,7,7a-tetrahidro-4,7-epoxi-1H-isoindol-1,3(2H)-diona	32
179		2-(1,3,3a,4,7,7a-hexahidro-4-metil-4,7-epoxi-2H-isoindol-2-il)benzonitrilo	32

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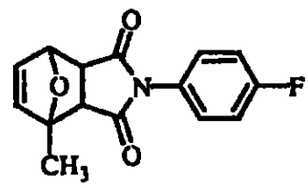
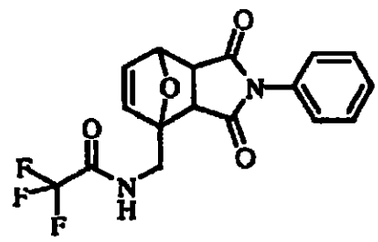
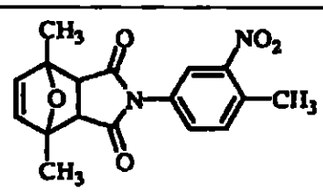
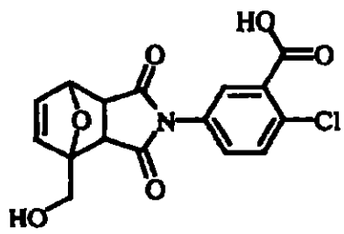
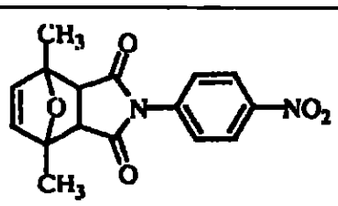
Ej. No.	Estructura del compuesto	Nombre del Compuesto	Pro. de Ej.
180		2-(4-fluorofenil)-3a,4,7,7a-tetrahidro-4-metil-4,7-epoxi-1H-isoindol-1,3(2H)-diona	32
181		2,2,2-trifluoro-N-[(1,2,3,3a,4,7,7a-hexahidro-2-fenil-4,7-epoxi-4H-isoindol-4-il)-metil]acetamida	21-26
182		3a,4,7,7a-tetrahidro-4,7-dimetil-2-(4-metil-3-nitrofenil)-4,7-epoxi-1H-isoindol-1,3(2H)-diona	32
183		Ácido 2-cloro-5-[1,3,3a,4,7,7a-hexahidro-4-(hidroximetil)-4,7-epoxi-2H-isoindol-2-il]benzóico	21-26
184		3a,4,7,7a-tetrahidro-4,7-dimetil-2-(4-nitrofenil)-4,7-epoxi-1H-isoindol-1,3(2H)-diona	32

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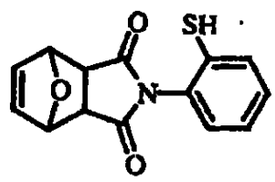
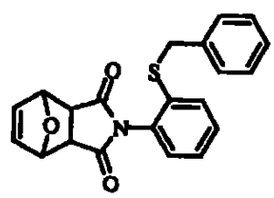
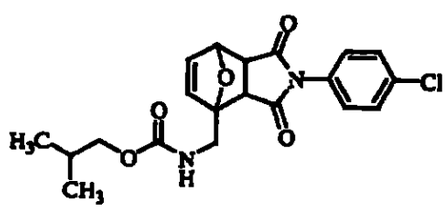
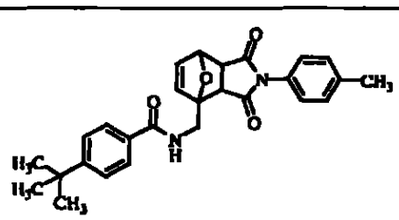
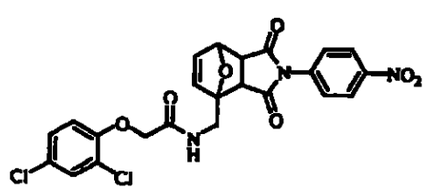
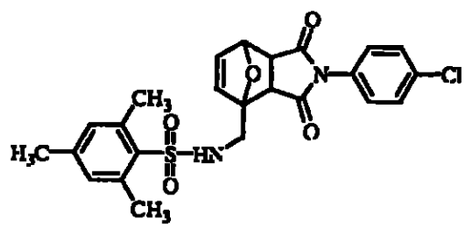
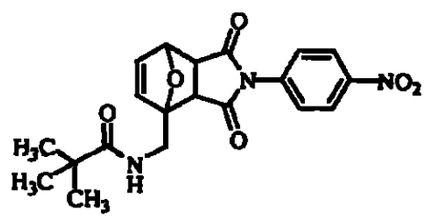
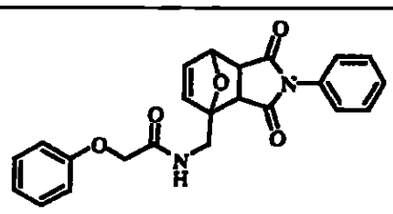
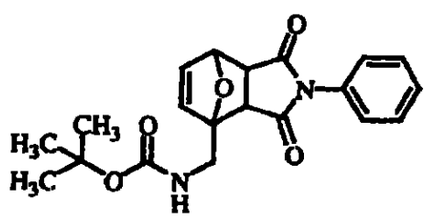
Ej. No.	Estructura del compuesto	Nombre del Compuesto	Pro. de Ej.
185		3a,4,7,7a-tetrahidro-2(2-mercaptofenil)-4,7-epoxi-1H-isoindol-1,3(2H)-diona	32
186		3a,4,7,7a-tetrahidro-2-[2-[(fenilmetil)tio]fenil]-4,7-epoxi-1H-isoindol-1,3(2H)-diona	32
187		Éster de 2-metilpropilo del ácido [[2-(4-clorofenil)-1,2,3,3a,4,7,7a-hexahidro-4,7-epoxi-4H-isoindol-4-il]metil]carbámico	21-26
188		4-(1,1-dimetiletil)-N-[[1,2,3,3a,4,7,7a-hexahidro-2-(4-metilfenil)-4,7-epoxi-4H-isoindol-il]metil]benzamida	21-26
189		2,4-dicloro-N-[[1,2,3,3a,4,7,7a-hexahidro-2-(4-nitrofenil)-4,7-epoxi-4H-isoindol-4-il]metil]benzamida	21-26

Ej. No.	Estructura del compuesto	Nombre del Compuesto	Pro. de Ej.
190		N-[[2-(4-clorofenil)-1,2,3,3a,4,7,7a-hexahidro-4,7-epoxi-4H-isoindol-4-il]metil]-2,4,6-trimetilbencensulfonamida	21-26
191		N-[[1,2,3,3a,4,7,7a-hexahidro-2-(4-nitrofenil)-4,7-epoxi-4H-isoindol-4-il]metil]-2,2-dimetilpropanamida	21-26
192		N-[(1,2,3,3a,4,7,7a-hexahidro-2-fenil-4,7-epoxi-4H-isoindol-4-il)-metil]-2-fenoxiacetamida	21-26
193		Éster de 1,1-dimetiletilo del ácido [(1,2,3,3a,4,7,7a-hexahidro-2-fenil-4,7-epoxi-4H-isoindol-4-il)-metil]carbámico	21-26

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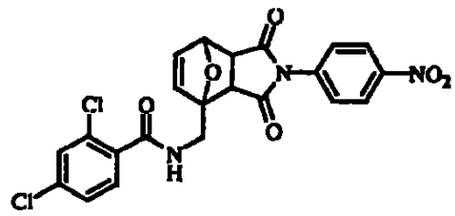
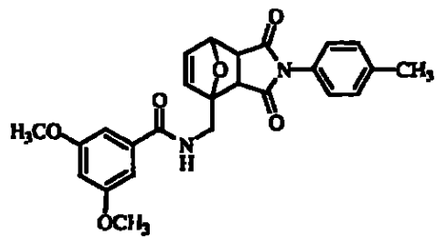
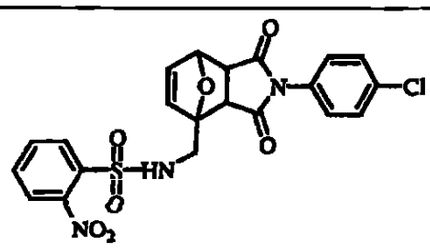
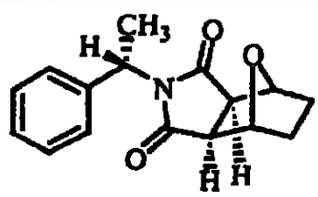
Ej. No.	Estructura del compuesto	Nombre del Compuesto	Pro. de Ej.
194		2-(2,4-diclorofenoxi)-N-[[1,2,3,3a,4,7,7a-hexahidro-2-(4-nitrofenil)-4,7-epoxi-4H-isoindol-4-il]-metil]acetamida	21-26
195		N-[[1,2,3,3a,4,7,7a-hexahidro-2-(4-metilfenil)-4,7-epoxi-4H-isoindol-4-il]metil]-3,5-dimetoxibenzamida	21-26
196		N-[[2-(4-clorofenil)-1,2,3,3a,4,7,7a-hexahidro-4,7-epoxi-4H-isoindol-4-il]metil]-2-nitrobencensulfonamida	21-26
197		(3aα,4β,7β,7aα)-hexahidro-2-[(1S)-1-feniletil]-4,7-epoxi-1H-isoindol-1,3(2H)-diona	8

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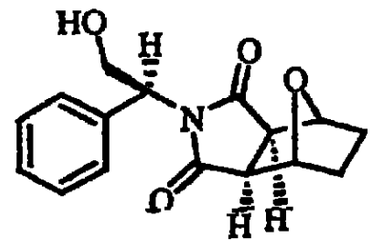
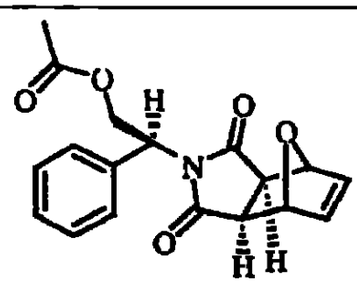
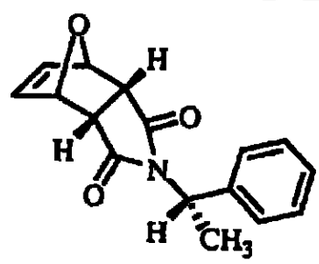
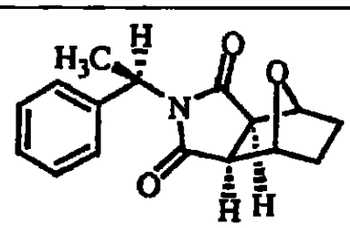
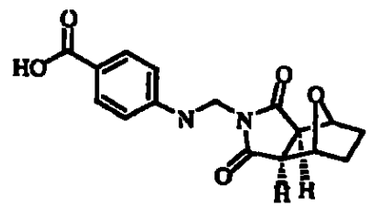
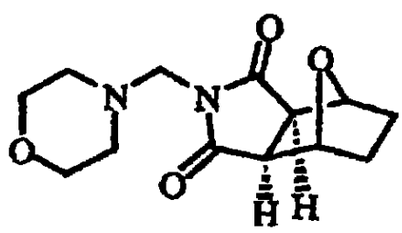
Ej. No.	Estructura del compuesto	Nombre del Compuesto	Pro. de Ej.
198		(3aα,4β,7β,7aα)-hexahidro-2-[(1S)-2-hidroxi-1-feniletil]-4,7-epoxi-1H-isoindol-1,3(2H)-diona	8
199		(3aα,4β,7β,7aα)-2-[(1S)-2-(acetiloxi)-1-feniletil]-3a,4,7,7a-tetrahidro-4,7-epoxi-1H-isoindol-1,3(2H)-diona	8
200		(3aα,4α,7α,7aα)-3a,4,7,7a-tetrahidro-2-[(1S)-1-feniletil]-4,7-epoxi-1H-isoindol-1,3(2H)-diona	8
201		(3aα,4β,7β,7aα)-hexahidro-2-[(1R)-1-feniletil]-4,7-epoxi-1H-isoindol-1,3(2H)-diona	8

Ej. No.	Estructura del compuesto	Nombre del Compuesto	Pro. de Ej.
202		Ácido (3aα,4β,7β,7aα)-4-[[[(octahidro-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)metil]amino]benzóico	8
203		(3aα,4β,7β,7aα)-hexahidro-2-(4-morfolinilmetil)-4,7-epoxi-1H-isoindol-1,3(2H)-diona	8

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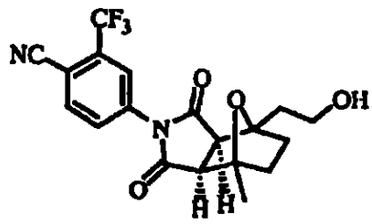
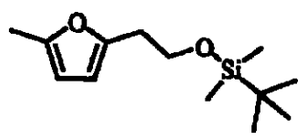
Ejemplo 204

(3aα,4β,7β,7aα)-4-[Octahidro-4-(2-hidroximetil)-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2-(trifluorometil)benzonitrilo (204D/25B)



A. 2-[2-[[1,1-Dimetiletil)dimetilsilil]oxi]etil]-5-metilfuran (204A)



A una solución del compuesto 21A (2.00 g, 15.9 mmol) en DMF (50 mL) se le agregó imidazol (1.62 g, 23.9 mmol), seguida por cloruro de tert-butildimetilsililo (2.63 g, 17.5 mmol). Después de 2 h a 25°C, la reacción se vació en éter de dietilo (300 mL) y se lavó con agua (1 x 100 mL), HCl 1N (1 x 100 mL), agua (1 x 100 mL), salmuera (1 x 50 mL) y se secó sobre $MgSO_4$ anhidro. El compuesto crudo 204A se analizó por CLEM y RMN y se determinó que era lo suficientemente puro para llevarse directamente a la siguiente etapa. CLAR: 100% a 4.347 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm eluyendo con 10-90% metanol acuoso durante 4 minutos conteniendo 0.1% TFA, 4 mL/min., observando a 220 nm).

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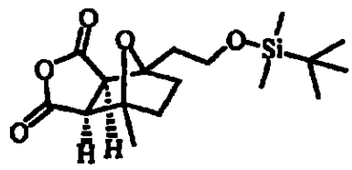
B. (3aα,4β,7β,7aα)-4-[2-[[(1,1-Dimetiletil)dimetilsilil]-oxi]etil]hexahidro-7-metil-4,7-epoxi-1H-isobenzofuran-1,3-(2H)-diona (204B)



El compuesto 204A (4.0 g, 18.9 mmol) y anhídrido maleico (1.42 g, 14.5 mmol) se disolvieron en dicloroetano (10 mL) y se agitaron a 25°C por 60 horas. Los volátiles se separaron después in vacuo y el aceite de color naranja resultante se disolvió en etanol absoluto (50 mL) y se agregó 10% Pd/C (1.00 g, cat.). Se introdujo después el hidrógeno por medio de un globo. Después de 3 h, la reacción se filtró a través de Celite enjuagando con EtOAc y se concentró in vacuo. El anhídrido crudo se purificó por cromatografía instantánea rápida sobre SiO_2 eluyendo con acetona/cloroformo (0 - 2 - 4% acetona) para dar 1.30 g (3.82 mmol, 20%) del compuesto 204B como un aceite transparente, además de 3.00 g (12.5 mmol, 66%) del compuesto de partida 204A. La caracterización por espectroscopia por RMN de protones mostró solamente al isómero exo. 1H RMN (400 MHz, CDCl3) δ = 3.83 (2H, t, J = 6.0 Hz), 3.22 (1H, d, J = 8.2 Hz), 3.06 (1H, d, J = 8.2 Hz), 1.70 - 2.25 (6H, m), 1.55 (3H, s), 0.82 (9H, s), 0.00 (6H, s).

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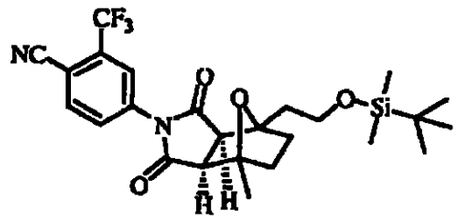
C. (3aα,4β,7β,7aα)-4-[4-[2-[[(1,1-Dimetiletil)dimetilsilil]-oxi]etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2-(trifluorometil)benzonitrilo(204C)



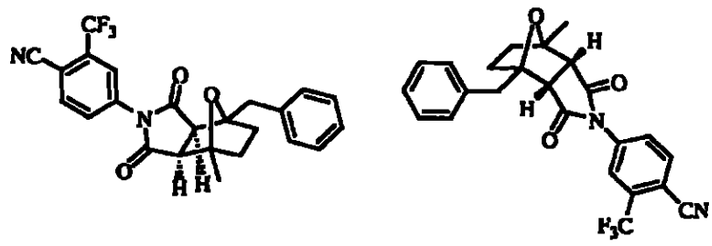
El compuesto 204B (0.250 g, 0.734 mmol) y el 4-amino-2-trifluorometil-benzonitrilo (0.124 g, 0.668 mmol) se suspendieron en tolueno seco (2.0 mL) en un tubo sellado. Se agregaron después $MgSO_4$ (0.200 g) y trietilamina (0.5 mL) y el tubo se selló y se colocó en un baño de aceite a 125°C. Después de 40 h, la reacción se enfrió a 25°C, se filtró y se concentró in vacuo. El material crudo se purificó por cromatografía instantánea sobre SiO_2 eluyendo con CH_2Cl_2 para dar 0.111 g (0.281 mmol, 30%) del compuesto 204C como un sólido amarillo. CLAR: 92% a 4.203 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm eluyendo con 10-90% de metanol acuoso durante 4 minutos conteniendo 0.1% TFA, 4 mL/min., observando a 220 nm). EM (ESI): m/z 531.1 $[M+Na]^+$.

D. (3aα,4β,7β,7aα)-4-[Octahidro-4-(2-hidroxietil)-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2-(trifluorometil)benzonitrilo(204D)

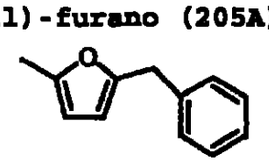
El compuesto 204C (0.031 g, 0.061 mmol) se disolvió en THF (0.5 mL) y se transfirió a un recipiente de polipropileno seguido por enfriamiento a 0°C. Se agregó después HF•piridina (~47% HF, 0.1 mL). Después de 15 min., la reacción estuvo completa como se determina por CL y se vació en $NaHCO_3$ acuoso frío saturado. La mezcla se extrajo con CH_2Cl_2 (3 x 10 mL). Las capas orgánicas combinadas se lavaron con HCl 1 N (1 x 20 mL) y se secaron sobre Na_2SO_4 anhidro. El compuesto 204D se aisló como un aceite amarillo y se comparó con el material preparado en el Ejemplo 25. No fue necesaria purificación.

Ejemplo 205

(3aα,4β,7β,7aα)-y (3aα,4α,7α,7aα)-4-[Octahidro-4-metil-1,3-dioxo-7-(fenilometil)-4,7-epoxi-2H-isoindol-2-il]-2-trifluorometil)benzonitrilo (205Ci y 205Cii. respectivamente)



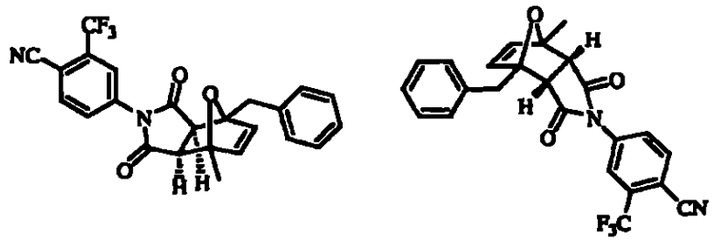
A. 2-Metil-5-(fenilmetil)-furano (205A)



Se agregó n-BuLi (1.8 mL, 4.51 mmol, 2.5 M en hexano) a una solución de 2-metilfurano (0.37 mL, 4.10 mmol) en THF

anhidro (3 mL) a -25 °C. La solución resultante se agitó a temperatura ambiente por 3 h y se enfrió después a -15°C. Se agregó bromuro de bencilo (0.59 mL, 4.92 mmol), que se pasó a través de un tapón de óxido de aluminio, y la solución se calentó a temperatura ambiente y se agitó durante la noche. Se agregó la solución saturada de NH_4Cl (5 mL)y la mezcla se agitó por 1 h. La mezcla de reacción se extrajo después con éter (2 x 5 mL) y los extractos orgánicos combinados se secaron y se concentraron bajo presión reducida. La purificación por cromatografía instantánea sobre gel de sílice eluyendo con hexanos dio 323 mg (1.88 mmol, 46%) del compuesto 205A como un aceite incoloro. CLAR: 95% a 3.72 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm, 10-90% de metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm) y alrededor de 400 mg de una mezcla de producto y bromuro de bencilo (~2:1 por CLAR).

B. (3aα,4β,7β,7aα)- y (3aα,4α,7α,7aα)-4-[Octahidro-4-metil-1,3-dioxo-7-(fenilmetil)-4,7-epoxi-2H-isoindol-2-il]-2-(trifluorometil)benzonitrilo (205Bi y 205Bii, respectivamente)



Una solución del compuesto 205A (124 mg, 0.72 mmol) y 4-(2,5-dihidro-2,5-dioxo-1H-pirrol-1-il)-2-trifluorometilbenzonitrilo (290 mg, 1.09 mmol) en CH_2Cl_2 (2 mL) se agitó a temperatura ambiente. Después de 4 días, la mezcla de reacción se concentró bajo presión reducida. La purificación por cromatografía instantánea sobre gel de sílice eluyendo con CH_2Cl_2 dio 62 mg (0.14 mmol, 20%) de una mezcla de los compuestos 205Bi y 205Bii como un sólido blanco, que se usó directamente en la siguiente etapa. CLAR: 93% a 3.69 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm, 10-90% de metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm).

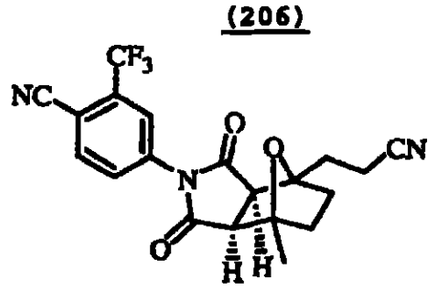
C. (3aα,4β,7β,7aα)- y (3aα,4α,7α,7aα)-4-[Octahidro-4-metil-1,3-dioxo-7-(fenilmetil)-4,7-epoxi-2H-isoindol-2-il]-2-(trifluorometil)-benzonitrilo (205ci y 205Cii, respectivamente)

Una solución de una mezcla de los compuestos 205Bi y 205Bii (62 mg, 0.14 mmol) y 10% Pd/C (12 mg, cat.) en EtOH (3.5 mL) se agitó bajo una atmósfera de hidrógeno a

temperatura ambiente por 2 h. La mezcla de la reacción se filtró a través de Celite y se concentró bajo presión reducida. La purificación por cromatografía instantánea sobre gel de sílice eluyendo con 35% EtOAc/hexanos dio 22 mg (0.05 mmol, 35%) del compuesto 205Ci y 12 mg (0.027 mmoles, 19%) del compuesto 205Cii. Compuesto 205Ci: CLAR: 98% a 3.75 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm, 10-90% de metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ESI): m/z 458.2 $[M+NH_4]^+$. Compuesto 205Cii: CLAR: 97% a 3.78 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm, 10-90% de metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ESI): m/z 473.45 $[M+CH_3OH]^+$.

Ejemplo 206

(3aα,4β,7β,7aα)-2-[4-Ciano-3-(trifluorometil)fenil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-4H-isoindol-4-propanonitrilo (206)

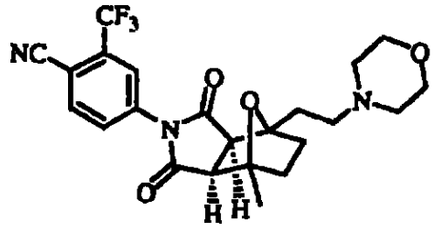


Una solución del compuesto 36 (34 mg, 0.074 mmol) y NaCN (24 mg, 0.49 mmol) en DEMO (1 mL) se calentó a 100°C por 0.5

h. Después del enfriamiento, la mezcla de reacción se vació en H_2O (5 mL) y la capa acuosa se extrajo con EtOAc (2 x 5 mL). Las capas orgánicas combinadas se lavaron con H_2O (2 x 5 mL), se secaron sobre Na_2SO_4 y se concentraron bajo presión reducida. La purificación por cromatografía instantánea sobre SiO_2 eluyendo con 50% EtOAc/hexanos seguida por CLAR preparativa de fase inversa [30.41 mm (tiempo de retención) (YMC S5 ODS 30 X 250 mm, 10-90% de metanol acuoso durante 30 minutos conteniendo 0.1% TFA, 25 mL/min., observando a 220 nm)] dio 6.6 mg (0.016 mmol, 22%) del compuesto 206 como un sólido blanco. CLAR: 99% a 2.89 min. (tiempo de retención) (Columna YMC S5 ODS de 4 6 x 50 mm eluyendo con 10-90% de metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm) EM (ES):m/z 402.1 $[M-H]^-$.

Ejemplo 207

Trifuoroacetato de (3aα,4β,7β,7aα)-4-(Octahidro-4-metil-7-[2-(4-morfolinil)etil]-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2-(trifluorometil)benzonitrilo, (1:1) (207)



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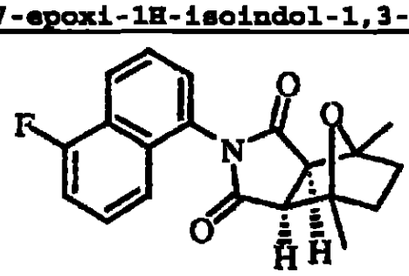
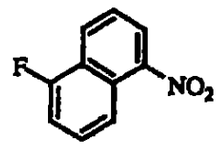
Una solución del compuesto 36 (15.6 mg, 0.0341 mmol) y morfolina (6.0 µL, 0.068 mmol) en tolueno (1 mL) se calentó a 100°C durante la noche. Después del enfriamiento, la mezcla de reacción se concentró bajo presión reducida. La purificación por cromatografía instantánea sobre SiO_2 eluyendo con 10% $MeOH/CH_2Cl_2$, seguida por CLAR preparativa de fase inversa [23.96 min. (tiempo de retención) (YMC S5 ODS 30 x 250 mm, 10-90% de metanol acuoso durante 30 minutos conteniendo 0.1% TFA, 25 mL/min., observando a 220 nm)] dio 8.7 mg (0.015 mmol, 44%) del compuesto 207 (sal de TFA) como un sólido blanco. CLAR: 99% a 2.02 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm eluyendo con 10-90% de metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm) EM (ES): m/z 464.3 $[M+H]^+$.

Ejemplo 208

(3aα,4β,7β,7aβ)-2-(5-fluoro-1-naftalenilo)hexahidro-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3-(2H)-diona (208C)



A. 1-Fluoro-5-nitronaftaleno (208A)



A una solución de HCl 6N (12 mL) se agregaron 1.47 g (7.83 mmol) de 5-nitro-1-naftilamina finamente pulverizada, como se describe en J. Chem. Soc. 1187 (1949). La mezcla se enfrió hasta 0°C y se agregó lentamente una solución fría de $NaNO_2$ (547 mg, 7.93 mmol) en 2 mL H_2O, de manera que la temperatura se mantuvo cercana a 0°C. Después de que se terminó la adición, la mezcla de reacción se agitó por 30 min. y se filtró. Se enfrió el filtrado a 0°C y se trató con una solución fría $NaBF_4$ 4.5 M (5 mL) para dar la precipitación completa del borofluoruro de diazonio. La mezcla se mantuvo a 0°C por 30 min. antes de que se filtrara y los precipitados se lavaron con una solución fría $NaBF_4$ 4.5 M (5 mL), etanol enfriado con hielo (10 mL) y Et_2O (20 mL). Los sólidos obtenidos se secaron con aire para resultar en 1.74 g (77%) de la sal de diazonio correspondiente.

A 1.70 g (5.92 mmol) del borofluoruro de diazonio se le agregaron 5 g de arena y se mezclaron completamente los componentes. La mezcla de reacción se calentó cuidadosamente bajo presión reducida hasta que se presentó la descomposición. Hacia el final de la reacción se calentó además por 30 min. a 130°C para asegurar la conversión completa. Después de enfriar la mezcla de reacción se

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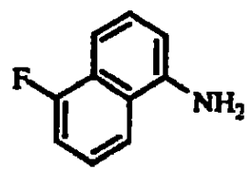
disolvió en acetona y se preabsorbieron los contenidos en gel de sílice. La purificación se aCLanzó por cromatografía instantánea sobre gel de sílice, eluyendo con 0 hasta 10% de EtOAc en hexanos para dar 449 mg (2.35 mmol, 40%) del compuesto 208A como un sólido blanco.

B. 1-Amino-5-fluoronaftaleno (208B)



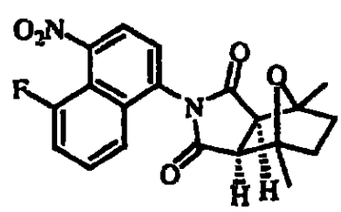
Una solución del compuesto 208A (62 mg, 0.32 mmol) en 1 mL de EtOH conteniendo 0.1 mL de HCl 12 N se calentó hasta reflujo. Se agregó polvo de hierro (62 mg, 1.11 mmol) en porciones pequeñas y se continuó el calentamiento por 2 h. La mezcla se enfrió, se neutralizó con una solución NaOH 1 N y la capa acuosa se extrajo con CH_2Cl_2. Las fases orgánicas combinadas se secaron sobre $MgSO_4$ y se concentraron in vacuo para dejar un residuo que se purificó por cromatografía instantánea sobre gel de sílice eluyendo con 40 a 80% de EtOAc en hexanos para dar 42 mg (0.26 mmol, 80%) del compuesto 208B como un sólido amarillo.

C. (3aα,4β,7β,7aα)-2-(5-Fluoro-1-naftalenilo)hexahidro-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3(2H)-diona (208C)

El compuesto 208B (42 mg, 0.26 mmol), compuesto 20A (54 mg, 0.27 mmol), $MgSO_4$ (69 mg, 0.58 mmol) y trietilamina (191 µL, 1.37 mmol) se tomaron en 2 mL de tolueno y se colocaron en un tubo sellado. El tubo sellado se calentó a 135°C por 14 h. La mezcla de reacción enfriada se filtró a través de una almohadilla corta de Celite eluyendo con CH_2Cl_2 y el solvente se separó bajo presión reducida. El residuo se purificó por CLAR preparativa de fase inversa (YMC S5 ODS 20 x 100 mm eluyendo con 30-100% metanol acuoso durante 10 min. conteniendo 0.1% TFA, 20 mL/min.) para dar 15 mg (0.044 mmol, 17%) del compuesto 208C como un sólido amarillo claro. CLAR: 16% a 2.96 min. y 77% a 3.06 min. (atropisómeros, tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm eluyendo con 10-90% de metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 340.2 $[M+H]^+$.

Ejemplo 209

(3aα,4β,7β,7aα)-2-(5-Fluoro-4-nitro-1-naftalenil)hexahidro-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3(2H)-diona(209C)



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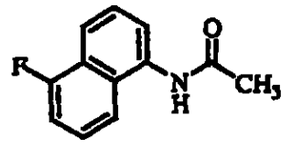
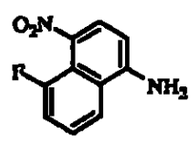
A. N-(5-Fluoro-1-naftalenil)acetamida (209A)



Una solución de 141 mg (0.74 mmol) del compuesto 208A en 2 mL de AcOH se calentó hasta reflujo y se trató con porciones pequeñas de polvo de hierro (118 mg, 2.11 mmol). La mezcla se conservó a reflujo por 15 min. antes de que se agregaran 73 µL (0.78 mmol) de Ac_2O. Después de 15 min. adicionales a reflujo, la mezcla se enfrió y se filtró eluyendo con CH_2Cl_2. El filtrado se concentró después bajo presión reducida y el residuo se purificó por cromatografía instantánea sobre gel de sílice eluyendo con 20 a 50% de EtOAc para dar 145 mg (0.71 mmol, 97%) del compuesto 209A como un sólido blanco.

B. 1-Amino-5-fluoro-4-nitronaftaleno (209B)



El compuesto 209A (133 mg, 0.645 mmol) se disolvió en 1 mL de AcOH y la solución resultante se enfrió hasta 10°C. A esta temperatura, se agregaron 80.0 µL (2.00 mmol) de HNO_3 rojo fumante y la agitación continuó por 15 min. antes de que se apagara la reacción por la adición de hielo triturado. La capa acuosa se extrajo con CH_2Cl_2 y las fases orgánicas

combinadas se secaron sobre $MgSO_4$ y se concentraron in vacuo. El residuo resultante se disolvió en 3 mL de EtOH, se calentó hasta reflujo y se trató con 0.5 mL de solución acuosa de NaOH al 40%. La agitación se continuó por 15 min. antes de que la reacción se enfrió y se diluyó con H_2O. La capa acuosa se extrajo con CH_2Cl_2 y las fases orgánicas combinadas se secaron sobre $MgSO_4$ y se concentraron in vacuo. El residuo resultante se purificó por cromatografía instantánea sobre gel de sílice, eluyendo con 40 a 70% de EtOAc en hexano para resultar 36 mg (0.17 mmol, 27%) del compuesto 209B como un sólido amarillo.

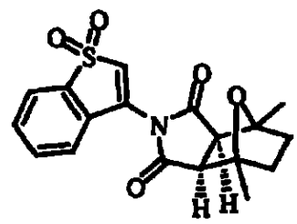
C. 3aα,4β,7β,7aα)-2-(5-Fluoro-4-nitro-1-naftalenilo)hexahidro-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3(2H)-diona (209C)

El compuesto 209B (36 mg, 0.18 mmol) reaccionó en un tubo sellado con el compuesto 20A (38 mg, 0.19 mmol), $MgSO_4$ (46 mg, 0.39 mmol) y Et_3N (128 µL, 0.920 mmol) en 250 µL de tolueno según el procedimiento anterior descrito en el Ejemplo 208C para dar, después de la purificación por CLAR preparativa de fase inversa (YMC S5 ODS 20 x 100 mm eluyendo con 30-100% metanol acuoso durante 10 min. conteniendo 0.1% TFA, 20 mL/min.), 27 mg (0.070 mmol, 39%) del compuesto 209C como un sólido amarillo. CLAR: 8% a 2.88 min. y 84% a 3.06

min. (atropisómeros, tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm eluyendo con 10-90% de metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 402.0 $[M+H]^+$.

Ejemplo 210

(3aα,4β,7β,7aα)-2-(1,1-Dioxidobenzo[b]tiofen-3-il)hexahidro-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3(2H)-diona(210)



Se agregó mCPBA (160 mg, 0.641 mmol, 70% pura) a una solución del compuesto 134 (70.0 mg, 0.214 mmol) en CH_2Cl_2 (2 mL) a temperatura ambiente. Después de que el material de partida se consumió, la reacción se apagó con $NaHCO_3$, saturado y se extrajo con CH_2Cl_2. La capa orgánica se lavó con NaOH 1 N, se secó sobre Na_2SO_4 y se concentró bajo presión reducida para dar 63.9 mg (0.178 mmol, 83%) del compuesto 210 como un sólido blanco. CLAR: 99% a 3.81 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm eluyendo con 10-90% de metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 360.0 $[M+H]^+$.

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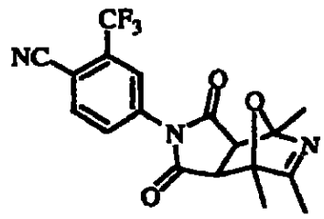
Ejemplo 211

4-(1,3,3a,4,7,7a-Hexahidro-4,6,7-trimetil-1,3-dioxo-4,7-epoxi-2H-pirrol[3,4-c]piridin-2-il)-2-(trifluorometil)benzonitrilo(211)



El 2,4,5-Trimetil oxazol (0.48 mL, 4.14 mmol) se disolvió en tolueno (2.0 mL) y se agregó 4-(2,5-dihidro-2,5-dioxo-1H-pirrol-1-il)-2-trifluorometilbenzonitrilo (1.00 g, 3.76 mmol). La mezcla de reacción se agitó a 75°C bajo nitrógeno por 2.5 hrs. La solución se enfrió a temperatura ambiente y el precipitado resultante se filtró y se lavó con tolueno para dar 0.51 g (35%) del compuesto 211 como un sólido gris claro. Los análisis RMN revelaron que el compuesto 211 fue un isómero (exo/endo) sin embargo, no se pudo determinar la identidad del isómero por análisis de RMN. CLAR: 100% a 2.85 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm eluyendo con 10-90% de metanol acuoso durante 4 minutos conteniendo 0.1% TFA, 4 mL/min., observando a 220 nm). EM (ES): m/z 378.42 $[M+H]^+$.

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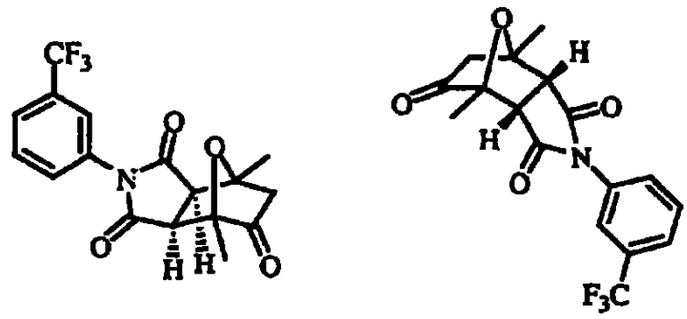
Ejemplo 212

(3aα,4β,7β,7aα)-Tetrahidro-4,7-dimetil-2-[3-(trifluorometil)fenil-4,7-epoxi-1H-isoindol-1,3,5(2H,4H)-triona y (3aα,4α,7α,7aα)-Tetrahidro-4,7-dimetil-2-[3-(trifluorometil)fenil]-4,7-epoxi-1H-isoindol-1,3,5(2H,4H)-triona (212i y 212ii, respectivamente)

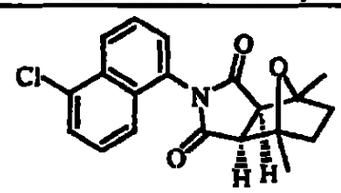


Se suspendieron 2,2-Dimetil-3(H)-furanona (0.500 g, 4.46 mmol) y 1-[3-(trifluorometil)fenil]-1H-pirrol-2,5-diona (1.07 g, 4.46 mmol, preparado como se describe en el Ejemplo 1B) en tolueno (20 mL) en un tubo sellado. La mezcla se calentó a 110°C por 4 h y se enfrió después hasta 25°C seguida por concentración in vacuo. El residuo resultante se purificó por cromatografía instantánea sobre SiO_2 eluyendo con cloruro de metileno para dar 0.411 g (26%) del compuesto 212i como un sólido blanco y 0.193 g (12%) del compuesto 212ii como un sólido blanco. Se confirmaron las asignaciones estructurales por experimentos de RMN de protones 1-D NOE. Compuesto 212i: CLAR: 100% a 2.817 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm eluyendo con 10-90% metanol acuoso durante

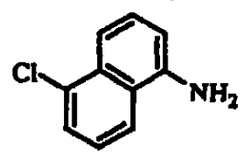
4 minutos conteniendo 0.1% TFA, 4 mL/min., observando a 220 nm). EM (ES): m/z 376.0 $[M + Na]^+$. Compuesto 212ii: CLAR: 100% a 3.013 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm eluyendo con 10-90% de metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 354.02 $[M+H]^+$.

Ejemplo 213

(3aα,4β,7β,7aα)-2-(5-Cloro-1-naftalenilo)hexahidro-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3(2H)-diona (213B)



A. 1-Amino-5-cloronaftaleno (213A)



A una solución de 1.74 g (6.06 mmol) del borofluoruro de diazonio (descrito en el Ejemplo 208A) en acetona (7 mL), se agregaron 693 mg (7.00 mmol) de CuCl en porciones pequeñas. Después de que había cesado la evolución del nitrógeno, se eliminó la acetona bajo presión reducida y se tomó el residuo en CH_2Cl_2 (30 mL). La fase orgánica se lavó con H_2O (30 mL), se secó sobre $MgSO_4$, se concentró in vacuo y se purificó finalmente por cromatografía instantánea (gel de sílice,

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EtOAc en hexano 0 hasta 15%) para dar 754 mg (70%) de 1-cloro-5-nitronaftaleno.

El 1-cloro-5-nitronaftaleno antes sintetizado (540 mg, 2.6 mmol) se disolvió en 10 mL de AcOH, seguido por tratamiento con 415 mg (7.43 mmol) de polvo de hierro y posteriormente acilado con Ac_2O (0.26 mL, 2.73 mmol) según el procedimiento descrito en el Ejemplo 209A para dar 543 mg (95%) de 1-acetamino-5-cloronaftaleno.

Una solución del 1-acetamino-5-cloronaftaleno antes sintetizado (52 mg, 0.24 mmol) en 3 mL de EtOH se calentó hasta reflujo y se trató con 0.5 mL de solución acuosa al 40% de NaOH. La mezcla se puso a reflujo hasta que no se pudo detectar más material de partida, se enfrió y se concentró bajo presión reducida. El residuo se absorbió en CH_2Cl_2 (50 mL) y se lavó con H_2O (25 mL). La capa orgánica se secó sobre $MgSO_4$ y se concentró in vacuo para dejar 41 mg (98%) del compuesto 213A como un sólido blanco.

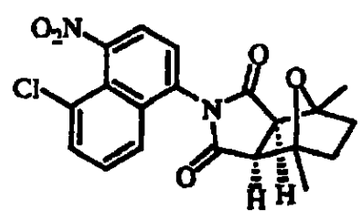
B. (3aα,4β,7β,7aα)-2-(5-Cloro-1-naftalenil)hexahidro-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3(2H)-diona(213B)

El compuesto 213A (24 mg, 0.14 mmol) reaccionó en un tubo sellado con el compuesto 20A (29 mg, 0.15 mmol), $MgSO_4$ (36 mg, 0.30 mmol) y Et_3N (100 µL, 0.710 mmol) en 250 µL de tolueno de acuerdo con el procedimiento descrito en el

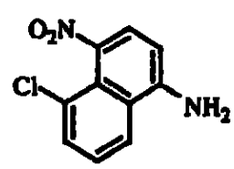
Ejemplo 208C para dar, después de la purificación por CLAR preparativa de fase inversa (YMC 85 ODS 20 x 100 mm eluyendo con 30-100% de metanol acuoso durante 10 min. conteniendo 0.1% TFA, 20 mL/min.), 27 mg (40%) del compuesto 213B como un sólido blanco. CLAR: 98% a 1.82 min. (tiempo de retención) (Columna YMC S5 TurboPack Pro 4.6 x 33 mm eluyendo con 10-90% de metanol acuoso durante 2 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 356.4 $[M+H]^+$.

Ejemplo 214

(3aα,4β,7β,7aα)-2-(5-cloro-4-nitro-1-naftalenilo)hexahidro-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3-(2H)-diona (214B)



A. 1-Amino-6-cloro-4-nitronaftaleno (214A)



El 1-Acetamino-5-cloronaftaleno (150 mg, 0.68 mmol, preparado como se describe en el Ejemplo 213A) se disolvió en

1 mL de AcOH y se trató con 82 µL de HNO_3 rojo fumante y se desaciló posteriormente con 1 mL 40% de una solución acuosa de NaOH en 3 mL de EtOH según el procedimiento descrito en el Ejemplo 209A para resultar 49 mg (32%) del compuesto 214A como un sólido amarillo.

B. (3aα,4β,7β,7aα)-2-(5-Cloro-4-nitro-1-naftalenil)Hexahidro-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3(2H)-diona (214B)

El compuesto 214A (27 mg, 0.12 mmol) reaccionó en un tubo sellado con el compuesto 20A (26 mg, 0.13 mmol), $MgSO_4$ (32 mg, 0.27 mmol) y Et_3N (88 µL, 0.63 mmol) en 250 µL de tolueno según el procedimiento descrito en el Ejemplo 208C para dar, después de la purificación por CLAR preparativa de fase inversa (YMC S5 ODS 20 x 100 mm eluyendo con 30-100% de metanol acuoso durante 10 min. conteniendo 0.1% TFA, 20 mL/min.) 22 mg (45%) del compuesto 214B como un sólido amarillo. CLAR: 24% a 3.06 min. y 76% a 3.25 min. (atropisómeros, tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm eluyendo con 10-90% metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 418.0 $[M+NH_4]^+$.

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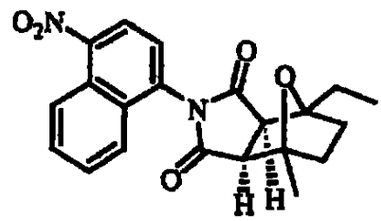
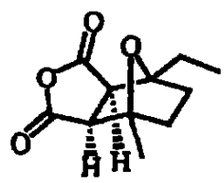
Ejemplo 215

(3aα,4β,7β,7aα)-4-Etilhexahidro-7-metil-2-[4-nitro-1-naftalenil)-4,7-epoxi-1H-isoindol-1,3(2H)-diona(215B)



A. (3aα,4β,7β,7aα)-4-Etilhexahidro-7-metil-4,7-epoxiisobenzofuran-1,3-diona (215A)



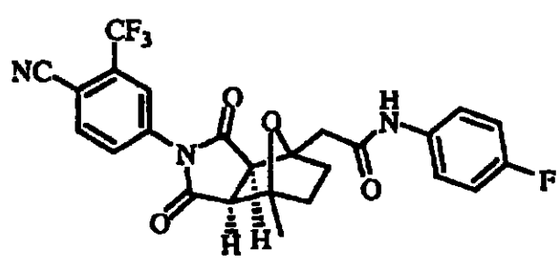
El 2-Etil-5-metilfurano (1.89 mL, 15.3 mmol) se disolvió en cloruro de metileno (10 mL) y se agregó anhídrido maleico (1.00 g, 10.2 mmol). La reacción se agitó a 25°C por 18 h y después se concentró in vacuo. El biciclo crudo resultante se disolvió en EtOAc (50 mL) y se agregó 10% Pd/C (0.40 g). Se introdujo después hidrógeno por medio de un globo. Después de 4 h, la reacción se filtró a través de Celite, enjuagando con EtOAc. La concentración in vacuo dio el compuesto crudo 215A (1.93 g) como un sólido blanco. Este material se llevó directamente a la siguiente reacción sin purificación.

B. (3aα,4β,7β,7aα)-4-Etilhexahidro-7-metil-2-(4-nitro-1-naftalenil)-4,7-epoxi-1H-isoindol-1,3(2H)-diona(215B)

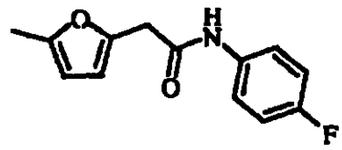
El compuesto 215A (0.168 g, 0.798 mmol) y 1-amino-4-nitronaftaleno (0.10 g, 0.53 mmol) se suspendieron en tolueno (0.8 mL) y TEA (0.2 mL) y se agregó sulfato de magnesio (0.1 g). La mezcla se calentó a 135°C en un tubo sellado por 18 h. La reacción se enfrió después hasta temperatura ambiente y se filtró, enjuagando con cloroformo. La concentración dio el producto crudo que se purificó por CCD preparativa sobre SiO_2 eluyendo con cloruro de metileno. Esto dio 0.077 g (0.20 mmol, 38%) del compuesto 215B como un sólido amarillo. CLAR: 100% a 3.260 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm eluyendo con 10-90% metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 381.05 $[M+H]^+$.

Ejemplo 216

(3aα,4β,7β,7aα)-2-(4-Ciano-1-naftalenil)-N-[4-fluorofenil)octahidro-7-metil-1,3-dioxo-4,7-epoxi-4H-isoindol-acetamida (216B)



A. N-(4-Fluorofenil)-5-metil-2-furanacetamida (216A)



El ácido 5-Metil-2-furanacético (1.00 g, 7.14 mmol, sintetizado como se describe en WO 9507893, Ejemplo 19) se disolvió en CH_3CN/DMF (4:1, 25 mL), se agregó después 1-[3-(dimetilamino)propil]-3-etiCLarbodiimida (1.37 g, 7.14 mmol) y 1-hidroxi-7-azabenzotriazol (0.972 g, 7.14 mmol) seguido por 4-fluoroanilina (0.676 mL, 7.14 mmol). Después de 3 h, la reacción se diluyó con EtOAc (150 mL) y se lavó con HCl 1 N (1 x 30 mL), $NaHCO_3$ acuoso saturado (1 x 30 mL), salmuera (1 x 40 mL) y se secaron sobre sulfato de sodio. El compuesto 216A (1.58 g, 95%)) se aisló como una espuma amarilla después de concentración in vacuo. No fue necesaria purificación adicional. CLAR: 78% a 2.647 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm eluyendo con 10-90% de metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm).

B. 3aα,4β,7β,7aα)-2-(4-Ciano-1-naftalenilo)-N-(4-fluorofenil)octahidro-7-metil-1,3-dioxo-4,7-epoxi-4H-isoindol-4-acetamida (216B)

El compuesto 216A (0.200 g, 0.858 mmol) y 4-(2,5-dihidro-2,5-dioxo-1H-pirrol-1-il)-2-trifluorometilbenzonitrilo (0.164 g, 0.616 mmol) se

disolvieron en benceno y se calentaron a 60°C por 14 h. La reacción se enfrió después y se concentró in vacuo. El aceite color naranja resultante se disolvió en EtOAc (15 mL) y se agregó 10% Pd/C (0.050 g). Se introdujo el hidrógeno por medio de un globo. Después de 3 h, la reacción se filtró a través de Celite enjuagando con EtOAc y se concentró in vacuo. El material crudo resultante se purificó por CCD preparativa sobre sílice eluyendo con 5% de acetona en cloruro de metileno para dar 0.166 g (54%) del compuesto 216B como un sólido blanco. La espectroscopia de RMN mostró solamente un isómero sencillo que se determinó que era exo por los experimentos NOE. CLAR: 95% a 3.200 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm eluyendo con 10-90% de metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES)- m/z 484.0 $[M+H]^+$.

Ejemplo 217

(3aα,4β,7β,7aα)-Hexahidro-4-metil-2-(2-naftalenil)-4,7-epoxi-1H-isondol-1,3(2H)-diona, enantiómero de elución más rápida y (3aα,4β,7β,7aα)-Hexahidro-4-metil-2-(2-naftalenil)-4,7-epoxi-1H-isoindol-1,3(2H)-diona, enantiómero de elución más lenta (217i y 217ii, respectivamente)

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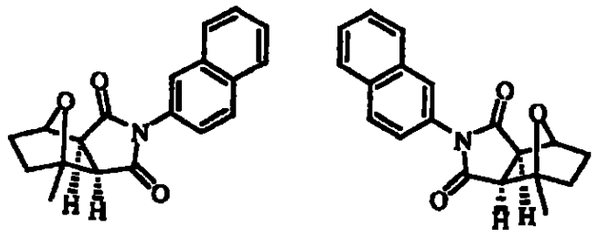
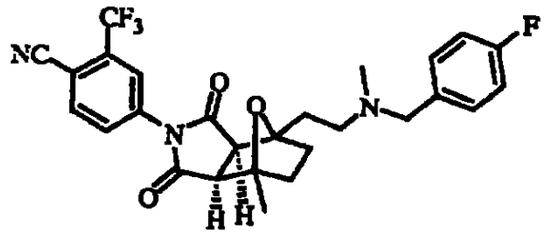


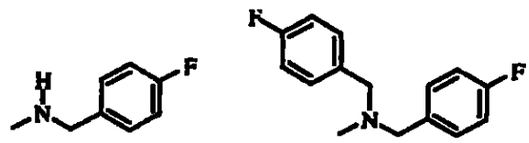
El compuesto racémico 137 se separó en antípodos individuales por cromatografía líquida de fase inversa quiral. Se usó una columna Chiralpak AD-R (4.6 x 250 mm) eluyendo con 70% acetonitrilo/30% agua a 1 mL/min. Se usó la detección UV a 220 nm. El isómero de elución más rápida, compuesto 217i (tiempo de retención = 15.66 min.), se encontró que fue 99.9% ee y el isómero de elución más lenta, compuesto 217ii (tiempo de retención = 15.66 min.) fue 99.6% ee por cromatografía de fase inversa quiral analítica.

Ejemplo 218

(3aα,4β,7β,7aα)-4-[4-[2-[[(4-Fluorofenil)metil]metilamino]etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2-(trifluorometil)benzonitrilo (218B)



A. (4-Fluorobencil)metilamina y Bis(4-fluorobencil)metilamina (218A y 218A')



218A 218A'

Los compuestos 218A y 218A' se elaboraron de conformidad con el procedimiento descrito por Singer et al. J. Med. Chem. 29, 40-44 (1986). Se puso a reflujo el bromuro de 4-Fluorobencilo (189 mg, 1.00 mmol) en una solución de etanol (1.5 mL) y metilamina (5 mL, solución 2M en MeOH) por 3 h. Se agregó una porción adicional de metilamina (2 mL) y la mezcla se puso a reflujo por una hora adicional. La solución se enfrió y se concentró in vacuo, y el residuo se disolvió en una mezcla de HCl 2 N (3 mL) y éter (1.5 mL). Las capas se separaron y la capa acuosa se extrajo con una porción adicional de éter. La solución acuosa se enfrió hasta 0°C, se tituló hasta un pH de 11 con NaOH y se extrajo con CH_2Cl_2. Los extractos se secaron sobre $MgSO_4$ y se concentraron in vacuo para dar 120 mg de una mezcla 2.5:1 del compuesto 218A y compuesto 218A' respectivamente. La mezcla cruda se recuperó sin purificación adicional.

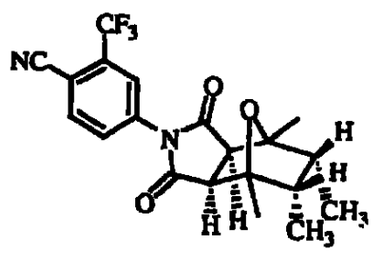
B. (3aα,4β,7β,7aα)-4-[4-[2-[[(4-Fluorofenil)metil]-metilamino]etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2-(trifluorometil)benzonitrilo(218B)

Una solución del compuesto 36 (34.3 mg, 0.075 mmol) y de los compuestos 218A y 218A' (21 mg, alrededor de 0.088 mmol

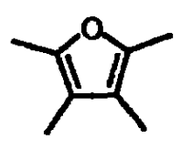
(de 218A)) en tolueno (0.4 mL) se calentó a 100°C durante la noche. La mezcla de reacción se enfrió a temperatura ambiente y después se concentró bajo presión reducida. La purificación por cromatografía instantánea sobre gel de sílice eluyendo con 25% acetona/75% CH_2Cl_2 dio 30 mg (0.058 mmol, 78%) del 218B como un sólido amarillo. CLAR: 99% a 2.46 min. (tiempo de retención) (YMC S5 ODS 4.6 x 50 mm, 10-90% de metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, observando a 220 nm). EM (ES): m/z 516.26 $[M+H]^+$.

Ejemplo 219

(3aα,4β,5β,6β,7β,7aα)-4-(Octahidro-4,5,6,7-tetrametil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo (219D)



A. 2,3,4,5-Tetrametilfurano (219A)



Se hizo el compuesto 219A de conformidad con los procedimientos descritos en Hancock et al. J. Org. Chem. 42, 1850-1856 (1977) y Amarnath et al. J. Org. Chem., 60, 301-307 (1995). Se puso a reflujo 2-Propanona (100 mL, 1.1 mol) sobre

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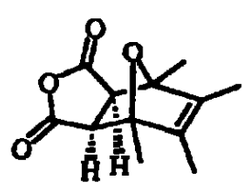
PbO_2 (26.7 g, 0.112 mol) por 28 h. Después de enfriar a temperatura ambiente, la mezcla de reacción se filtró y el residuo se lavó con acetona. El filtrado se concentró bajo presión reducida para eliminar la acetona y después se destiló a 20 Torr. La fracción que apareció entre 100-120°C se recolectó para dar 6.75 g (42.5%) de 3,4-dimetilhexano-2,5-diona como un aceite amarillo ligero.

Una solución de 3,4-dimetilhexano-2,5-diona (3.00 g, 21.1 mmol) y ácido p-toluensulfónico (401 mg, 2.11 mmol) en benceno (30 mL) se calentó hasta reflujo en una trampa Dean-Stark durante la noche. La mezcla de reacción se destiló a presión atmosférica para eliminar el exceso de benceno. La mezcla restante se transfirió a un matraz más pequeño y se destiló a presión atmosférica. La fracción que apareció entre 80-100°C se recolectó para dar 509 mg (19%) del compuesto 219A como un aceite amarillo ligero.

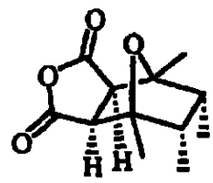
B. (3aα,4β,7β,7aα)-4-Etil-3a,4,7,7a-tetrahidro-4,5,6,7-tetrametilo-4,7-epoxiisobenzofuran-1,3-diona(219B)



Una solución del compuesto 219A (400 mg, 3.22 mmol) y anhídrido maleico (442 mg, 4.51 mmol) en Et_2O (1.5 mL) se agitó a temperatura ambiente durante la noche. La mezcla de

reacción se colocó después en un refrigerador por 5 días, tiempo después del cual, se recolectaron los cristales resultantes y se secaron para dar 0.26 g (37%) del compuesto 219B como cristales café claro. El compuesto crudo 219B se llevó a la siguiente etapa sin purificación adicional.

C. (3α,4β,5α,6α,7β,7aα)-4-Etilhexahidro-4,5,6,7-tetrametil-4,7-epoxiisobenzofuran-1,3-diona(219C)



Una solución del compuesto 219B (120 mg, 0.545 mmol) y 10% Pd/C (24 mg, cat.) en EtOAc (2 mL) se agitó bajo un globo de hidrógeno a temperatura ambiente durante la noche. La mezcla de reacción se filtró a través de Celite y se concentró bajo presión reducida para dar 100 mg (0.446 mmol, 82%) del compuesto 219C como un sólido blanco, que se llevó sin purificación adicional.

D. (3aα,4β,5β,6β,7β,7aα)-4-(Octahidro-4,5,6,7-tetrametilo-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo(219D)

Una solución del compuesto 219C (44.4 mg, 0.2 mmol), 5-amino-2-cianobenzotrifluoruro (45 mg, 0.24 mmol), TEA (0.04

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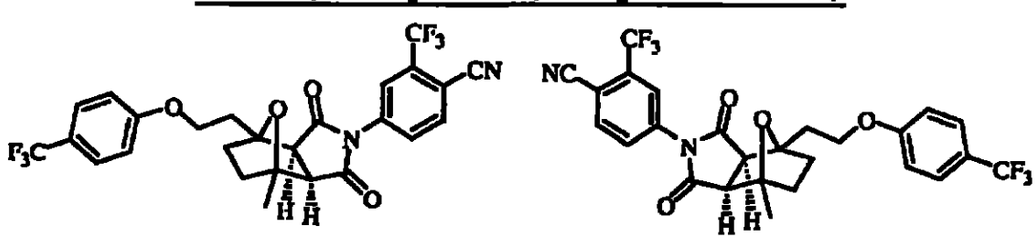
mL) y $MgSO_4$ (20 mg) en tolueno (0.2 mL) se calentó a 135°C durante la noche. La mezcla de reacción se enfrió a temperatura ambiente, se filtró y se concentró después bajo presión reducida. La purificación por cromatografía instantánea sobre gel de sílice eluyendo con 40% EtOAc/hexanos seguida por lavado del sólido resultante con MeOH dio 17 mg (0.043 mmol, 22%) del compuesto 219D como un sólido blanco. CLAR: 90% a 3.11 min. (tiempo de retención) (YMC 85 ODS 4.6 x 50 mm, 10-90% de metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, observando a 220 nm). EM (ES): m/z 391.2 $[M-H]^-$.

Ejemplo 220

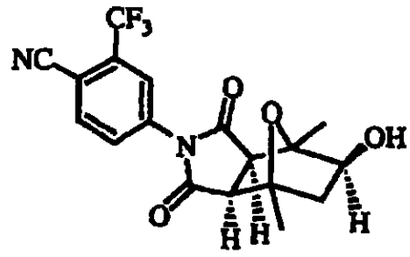
(3aα,4β,7β,7aα)-4-[Octahidro-4-metil-1,3-dioxo-7-[2-[4-(trifluorometil)fenoxi]etil]-4,7-epoxi-2H-isoindol-2-il]-2-(trifluorometil)benzonitrilo, antípodo de elución más rápida y (3aα,4β,7β,7aα)-4-[Octahidro-4-metil-1,3-dioxo-7-[2-[4-(trifluorometil)fenoxi]etil]-4,7-epoxi-2H-isoindol-2-il]-2-(trifluorometil)benzonitrilo, enantiómero de elución más lenta (220i y 220ii, respectivamente)



El compuesto racémico 35 se separó en antípodos individuales por cromatografía líquida de fase inversa quiral. Se usó una columna Chiralpak AD (50 x 500 mm) eluyendo con 85% hexanos/7.5% metanol/7.5% etanol, a 50mL/min. Se usó una detección UV a 220 nm. El compuesto isómero de elución más rápida 220i (tiempo de retención = 55.86 min.) se encontró que tenía 95.8% ee ($[\alpha]_D^{25}$ = -53.02°, C = 3.134 mg/cc en CH_2Cl_2) y el compuesto isómero de elución más lenta 220ii (tiempo de retención = 62.86 min.) tuvo 86% ee ($[\alpha]_D^{25}$ = +48.74°, C = 2.242 mg/cc en CH_2Cl_2) por cromatografía en fase normal quiral analítica.

Ejemplo 221

(3aα,4β,5β,7β,7aα)-4-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo(221B)



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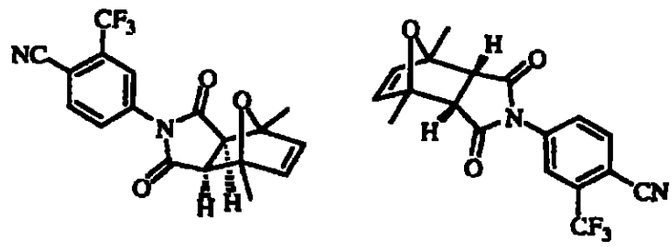
A. (3aα,4β,7β,7aα)-4-(hexahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo (221Ai) y (3aα,4α,7α,7aα)-4-(hexahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo (221Aii)



Una solución de 2,5-dimetilfurano (0.800 mL, 7.51 mmol) y 4-(2,5-dihidro-2,5-dioxo-1H-pirrol-1-il)-2-trifluorometil benzonitrilo (sintetizado como se describe en el Ejemplo 1B, usando 4-ciano-3-trifluorometilanilina en lugar de 4-bromo-3-metilanilina) (1.00 g, 3.75 mmol) en benceno (4 mL) se calentó a 60°C durante la noche. La mezcla de reacción se concentró bajo presión reducida y se colocó en una bomba de alto vacío hasta que se solidificó el aceite para dar una mezcla 3:1 (determinada por CL y RMN) de los compuestos 221Ai y 221Aii, respectivamente, como un sólido café, que se usó directamente en la siguiente etapa sin purificación adicional.

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B. (3aα,4β,5β,7β,7aα)-4-(ctahidro-5-hidroxi-4,7-dimetilo-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo(221B)

Se agregó BH_3•THF (3.75 mL, 3.75 mmol, 1M en THF) a una solución de compuestos crudos 221Ai y 221Aii (3.75 mmol) en THF (12.5 mL) a 0°C. Después de que el material de partida se consumió, la mezcla de reacción se concentró bajo presión reducida. El residuo resultante se disolvió después en tolueno (12.5 mL), Me_3NO (845 mg, 11.2 mmol) y la mezcla se calentó hasta reflujo durante la noche. La mezcla de reacción se enfrió después a temperatura ambiente, se agregó al H_2O y se extrajo con EtOAc (3X). Las capas orgánicas combinadas se secaron sobre $MgSO_4$ y se concentraron bajo presión reducida. La purificación por cromatografía instantánea sobre SiO_2 eluyendo con 75% EtOAc/hexanos dio 0.354 g (25%) del compuesto 221B como un polvo café claro. CLAR: 90% a 2.45 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm eluyendo con 10-90% de metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 381.11 $[M+H]^+$.

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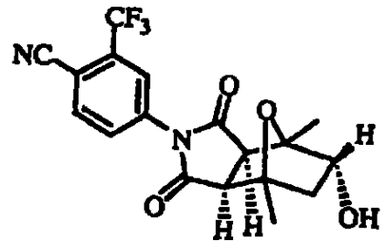
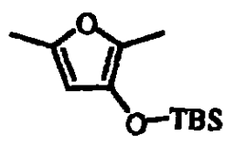
Ejemplo 222

(3aα,4β,5α,7β,7aα)-4-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo(222D)



A. 3-[[(1,1-Dimetiletil)dimetilsilil]oxi]-2,5-dimetilfurano (222A)



La 2,5-Dimetilo-3(3H)-furanona (2.00 g, 17.8 mmol) se disolvió en cloruro de metileno (180 mL). Se agregó TEA (7.43 mL, 53.5 mmol) seguido por TBSOTf (4.92 mL, 21.4 mmol) a 25°C. Después de 1 h, la reacción se concentró in vacuo y la suspensión espesa resultante se corrió a través de una columna de gel de sílice acondicionada con 3% de TEA en hexanos. El producto se eluyó con 3% TEA/hexanos para dar 3.6 g (89%) del compuesto 222A como un aceite color naranja que se usó directamente en reacciones posteriores.

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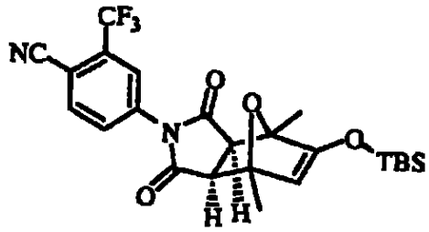
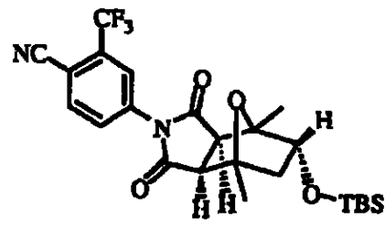
B. (3aα,4β,7β,7aα)-4-[5-[[(1,1-Dimetiletil)dimetilsilil]oxi]-1,3,3a,4,7,7a-hexahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2-(trifluorometil)benzonitrilo(222B)



El 4-(2,5-Dihidro-2,5-dioxo-1H-pirrol-1-il)-2-trifluorometilbenzonitrilo (1.00 g, 3.85 mmol) se disolvió en benceno (5.0 mL) y el compuesto 222A (1.30 g, 5.77 mmol) se agregó. La mezcla de reacción se calentó hasta 60°C por 2 h y después se enfrió hasta 25°C. La solución se concentró después in vacuo para dar el compuesto 222B como un aceite amarillo que se llevó a la siguiente reacción sin purificación. CLAR: 60% a 4.013 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm eluyendo con 10-90% metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm).

C. (3aα,4β,5α,7β,7aα)-4-[5-[[(1,1-Dimetiletil)dimetilsilil]oxi]octahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2-(trifluorometil)benzonitrilo(222C)



El compuesto 222B (3.85 mmol) se disolvió en acetato de etilo (75 mL) y se agregó 10% Pd/C (1.20 g). Se introdujo después hidrógeno por medio de un globo. Después de 24 h, la reacción se filtró a través de Celite enjuagando con acetato de etilo y se concentró in vacuo para dar un aceite amarillo. El producto crudo se purificó por cromatografía instantánea sobre gel de sílice eluyendo con cloruro de metileno/acetona (0% -1% - 2% acetona) para dar 0.710 g (35%) compuesto 222C como un sólido amarillo. CLAR: 100% a 4.160 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm eluyendo con 10-90% de metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 517.6 $[M+Na]^+$.

D. (3aα,4β,5α,7β,7aα)-4-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo(222D)

El compuesto 222C (0.040 g, 0.081 mmol) se disolvió en THF (1.0 mL) y se agregó HF•Piridina (0.5 mL). Después de 2 h, la reacción se vacío cuidadosamente en $NaHCO_3$ frío acuoso

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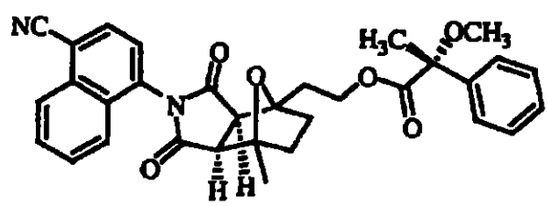
saturado. La mezcla se extrajo después con cloruro de metileno (3 x 10 mL). Los orgánicos combinados se lavaron con HCl 1 N (1 x 10 mL) y se secaron sobre sulfato de sodio anhidro. La concentración in vacuo dio 0.031 g (10%) del compuesto 222D como un sólido amarillo. Los experimentos NOE confirmaron el isómero asignado. CLAR: 98% a 2.777 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm eluyendo con 10-90% de metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 403.06 $[M+Na]^+$.

Ejemplo 223

Éster 2-[(3aα,4β,7β,7aα)-2-(4-ciano-1-naftalenil)octahidro-7-metil-1,3-dioxo-4,7-epoxi-4H-isoindol-4-il]etilo del ácido (αR)-α-Metoxibencenacético (223C)



A. **(3aα,4β,7β,7aα)-4-[4-[2-[[(1,1-Dimetiletil)dimetilsilil]oxi]etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo (223A)**

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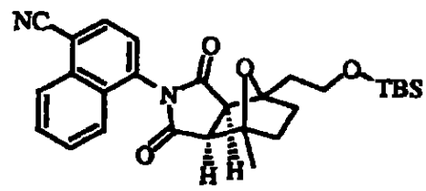
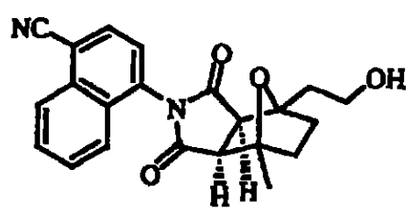


Una solución de 4-amino-1-naftalencarbonitrilo (19.2 g, 114 mmol) y anhídrido maleico (14.0 g, 113 mmol) en AcOH (230 mL) se calentó a 115°C por 12 h. Después de enfriar a temperatura ambiente, la mezcla de reacción se concentró bajo presión reducida y se diluyó después con CH_2Cl_2 (2.5 L). La capa orgánica se lavó 3X con H_2O (3 L), IX con Na_2CO_3 acuoso sat. (1 L) y 1X con salmuera (1 L), se secó sobre $MgSO_4$ y se concentró hasta ~200 mL bajo presión reducida. La purificación por cromatografía instantánea sobre resina de intercambio de cationes (60 g, CUBX13M6 de United Chemical Technologies) eluyendo con CH_2Cl_2, dio 25.0 g (88%) del 4-(2,5-dihidro-2,5-dioxo-1H-1-il)-1-naftalencarbonitrilo como un sólido amarillo. CLAR: 96% a 2.48 min. (tiempo de retención) (Columna Phenomenex-prime S5-C18 4.6 x 50 mm, 10-90% de metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 249.25 $[M+H]^+$.

El 4-(2,5-Dihidro-2,5-dioxo-1H-1-il)-1-naftalencarbonitrilo (1.00 g, 4.03 mmol) se suspendió en benceno (6.0 mL) en un tubo sellado y se agregó el compuesto 204A (1.11 g, 5.24 mmol). La reacción se calentó a 60°C por 16 h y se enfrió después hasta 25°C. El benceno se separó in

vacuo para dar un sólido amarillo. El sólido se disolvió en acetato de etilo (40 mL) y se agregó Pd/C (10% Pd, 0.300 g). Se introdujo después el hidrógeno por medio de un globo. Después de 4 h, la reacción se filtró a través de Celite enjuagando con acetato de etilo. La concentración in vacuo dio un sólido amarillo pálido que se purificó por cromatografía instantánea sobre gel de sílice eluyendo con acetona/cloroformo (0% - 1.5% - 3% acetona) para dar 1.53 g (77%) del compuesto 223A como una espuma amarilla. CLAR: 86% a 4.173 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm eluyendo con 10-90% de metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm).

B. (3aα,4β,7β,7aα)-4-[Octahidro-4-(2-hidroxietil)-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo (223B)



El compuesto 223A (1.37 g, 2.97 mmol) se disolvió en THF (8.0 mL) y se transfirió a una botella de polipropileno y se enfrió hasta 0°C. Se agregó después HF•Piridina (2.0 mL). Después de 20 min., la reacción se vació cuidadosamente en

bicarbonato de sodio acuoso saturado frío y se extrajo con cloruro de metileno (3 x 30 mL). Los compuestos orgánicos se lavaron después con HCl 1 N y se secaron sobre sulfato de sodio anhidro. La concentración in vacuo dio 0.99 g (89%) del compuesto 223B como una espuma amarilla que no se purificó adicionalmente. CLAR: 96% a. 2.443 y 2.597 min. (atropisómeros, tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm eluyendo con 10-90% de metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 399.02 $[M+Na]^+$.

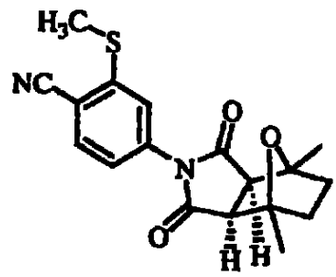
C. Éster de 2-[(3aα,4β,7β,7aα)-2-(4-ciano-1-naftalenil)octahidro-7-metil-1,3-dioxo-4,7-epoxi-4H-isoindol-4-il]etilo del ácido (αR)-α-Metoxibencenacético, (223C)

El compuesto 223B (0.200 g, 0.575 mmol) se agregó a una solución de WSDCC (0.138 g, 0.719 mmol) y ácido (R)-mandélico (0.096 g, 0.57 mmol) en diclorometano (6.0 mL). El 4-DMAP (0.005 g) se agregó después y la reacción se agitó a 25°C por 4 h. La mezcla se diluyó después con diclorometano, se lavó con HCl 1 N (2 x 10 mL) seguida por bicarbonato de sodio (1 x 10 mL) y se secaron sobre sulfato de sodio anhidro. La concentración in vacuo dio 0.220 g (71%) del compuesto 223C como un sólido amarillo que no se purificó adicionalmente. CLAR: 100% a 3.283 min. (tiempo de retención) (Columna YMC S5

ODS de 4.6 x 50 mm eluyendo con 10-90% de metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 547.26 $[M+Na]^+$.

Ejemplo 224

(3aα,4β,7β,7aα)-2-(Metiltio)-4-(octahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)benzonitrilo (224)

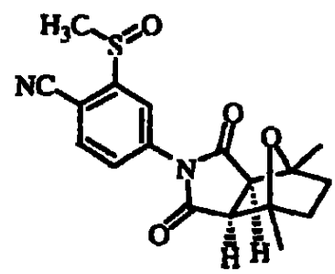


El 4-Amino-2-(metiltio)benzonitrilo (100 mg, 0.609 mmol, sintetizado como se describe en EP 40931 A1) reaccionó en un tubo sellado con el compuesto 20A (131 mg, 0.668 mmol), $MgSO_4$ (161 mg, 1.34 mmol) y Et_3N (0.440 mL, 3.17 mmol) en 0.50 mL de tolueno según el procedimiento descrito en el Ejemplo 208C para dar, después de la purificación por CLAR preparativa de fase inversa (YMC S5 ODS 20 x 100 mm eluyendo con 30-100% de metanol acuoso durante 10 min. conteniendo 0.1% TFA, 20 mL/min.), 137 mg (0.400 mmol, 66%) del compuesto 224 como un sólido blanco. CLAR: 100% a 2.73 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm eluyendo con 10-90% de metanol acuoso durante 4 minutos conteniendo 0.2% de ácido

fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 401.0 $[M-H+OAc]^-$.

Ejemplo 225

(3aα,4β,7β,7aα)-2-(Metilsulfinil)-4-(Octahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)benzonitrilo (225)



A una suspensión enfriada con hielo del compuesto 224 (30 mg, 0.088 mmol) en 2 mL de H_2O/MeOH (1:1) se agregó oxona (80 mg, 0.26 mmol) en una porción sólida. La mezcla resultante se agitó por 4 h a 0°C antes de que se diluyera con H_2O (10 mL) y se extrajo con CH_2Cl_2 (2 x 20 mL). Las capas orgánicas combinadas se secaron y se concentraron in vacuo para dejar un residuo que se purificó al filtrar el material a través de una almohadilla corta de gel de sílice eluyendo con CH_2Cl_2, para dar 32 mg (0.088 mmol, 100%) del compuesto 225 como un aceite incoloro. CLAR: 99% a 2.01 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm eluyendo con 10-90% de metanol acuoso durante 4 minutos conteniendo 0.2% de ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 376.0 $[M+NH_4]^+$.

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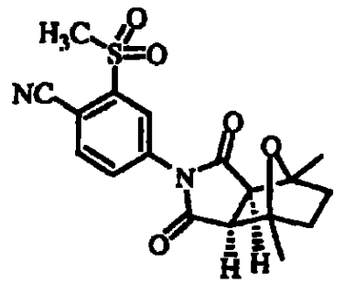
Ejemplo 226

(3aα,4β,7β,7aα)-2-(Metilsulfonil)-4-(Octahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)benzonitrilo (226)

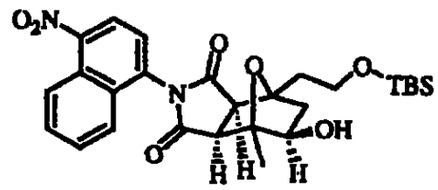


A una solución del compuesto 225 (48 mg. 0.14 mmol) en CH_2Cl_2 (2 mL) se le agregó mCPBA (145 mg, 50% mezcla, 0.420 mmol) en una porción sólida. La mezcla resultante se dejó calentar a temperatura ambiente y se agitó por 60 h, tiempo en el cual no se pudo detectar más material de partida por CLAR. La reacción se apagó por la adición de una solución saturada de $NaHCO_3$ (5 mL), las capas se separaron y la capa acuosa se extrajo con CH_2Cl_2 (20 mL). Las fases orgánicas combinadas se secaron sobre $MgSO_4$ y se concentraron in vacuo. El residuo restante se purificó por CLAR preparativa de fase inversa (YMC S5 ODS 20 x 100 mm eluyendo con 30-100% de metanol acuoso durante 10 min. conteniendo 0.1% TFA, 20 mL/min.) para resultar en 48 mg (0.13 mmol, 92%) del compuesto 226 como un sólido blanco. CLAR: 100% a 2.07 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm eluyendo con 10-90% de metanol acuoso durante 4 minutos

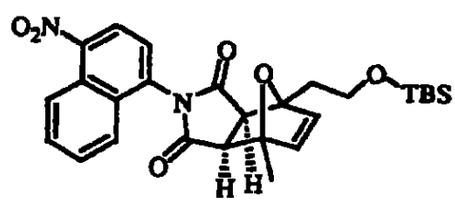
conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 392.0 $[M+NH_4]^+$.

Ejemplo 227

(3aα,4β,5β,7β,7aα)-7-[2-[[(1,1-Dimetiletil)dimetilsilil]oxi]etil]hexahidro-5-hidroxi-4-metil-2-(4-nitro-1-naftalenilo)-4,7-epoxi-1H-isoindol-1,3(2H)-diona (227B)



A. (3aα,4β,7β,7aα)-4-[2-[[(1,1-Dimetiletil)dimetilsilil]oxi]etil]-3a,4,7,7a-tetrahidro-7-metil-2-(4-nitro-1-naftalenil)-4,7-epoxi-1H-isoindol-1,3(2H)-diona (227A)



Una solución del compuesto 204A (455 mg, 1.89 mmol) y 1-[4-nitronaftalen]-1H-pirrol-2,5-diona (254 mg, 0.947 mmol, preparada como se describe para el 4-(2,5-dihidro-2,5-dioxo-1H-1-il)-1-naftalencarbonitrilo, Ejemplo 223A) en benceno (2 mL) se calentó a 60°C durante la noche. La mezcla de reacción se concentró bajo presión reducida para dar el compuesto

crudo 227A como un sólido café, que se usó directamente en la siguiente etapa sin purificación adicional.

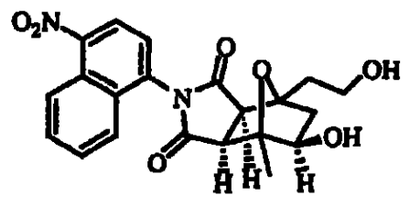
B. (3aα,4β,5β,7β,7aα)-7-[2-[[(1,1-Dimetiletil)dimetilsilil]oxi]etil]hexahidro-5-hidroxi-4-metil-2-(4-nitro-1-naftalenilo)-4,7-epoxi-1H-isoindol-1,3(2H)-diona (227B)

Se agregó BH_3•THF (0.95 mL, 0.95 mmol, 1M en THF) a una solución del compuesto crudo 227A (0.48 g, 0.95 mmol) en THF (2 mL) a 0°C. Después de que el compuesto 227A se consumió, como fue evidente por CLAR, la mezcla de reacción se concentró bajo presión reducida. El residuo resultante se disolvió después en tolueno (2 mL), se agregó Me_3NO (71.0 mg, 2.84 mmol) y la mezcla se calentó hasta reflujo durante la noche. La mezcla de reacción se enfrió después a temperatura ambiente, se agregó al H_2O y se extrajo con EtOAc (3X). Las capas orgánicas combinadas se secaron sobre $MgSO_4$ y se concentraron bajo presión reducida. La purificación por cromatografía instantánea sobre SiO_2 eluyendo con 75% EtOAc/hexanos, dio 130 mg (26%) del compuesto 227B como un sólido café. CLAR: 94% a 3.92 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm eluyendo con 10-90% de metanol acuoso durante 4 minutos conteniendo 0.2% de ácido

fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 527.5 $[M+H]^+$.

Ejemplo 228

(3aα,4β,5β,7β,7aα)-Hexahidro-5-hidroxi-7-(2-hidroxietil)-4-metil-2-(4-nitro-1-naftalenil)-4,7-epoxi-1H-isonidol-1,3(2H)-diona (228)

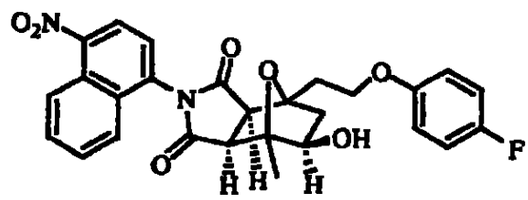


Una mezcla de TBAF (0.3 mL, 0.3 mmol, 1 M solución en THF) y HF (0.3 mL, 50% en H_2O) en CH_3CN (6 mL) se agregó a una solución de 227B (104 mg, 0.197 mmol) en THF (2 mL) a 0°C. La mezcla de reacción se agitó durante la noche a temperatura ambiente. Después de que el material de partida se consumió, como fue evidente por CCD, se agregaron H_2O y EtOAc y las capas se separaron. La capa acuosa se extrajo con EtOAc (IX) y las capas orgánicas combinadas se lavaron con H_2O (IX) y salmuera (IX), se secaron sobre Na_2SO_4, y se concentraron bajo presión reducida. La purificación por cromatografía instantánea sobre SiO_2 eluyendo con 5% $MeOH/CH_2Cl_2$, dio 61 mg (75%) del compuesto 228 como un sólido amarillo. CLAR: 99% a 2.47 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm eluyendo con 10-90% de metanol acuoso durante 4 minutos conteniendo 0.2% ácido

fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 411.2 $[M-H]^-$.

Ejemplo 229

(3aα,4β,5β,7β,7aα)-7-[2-(4-Fluorofenoxi)etil]hexahidro-5-hidroxi-4-metil-2-(4-nitro-1-naftalenil)-4,7-epoxi-1H-isoindol-1,3(2H)-diona (229)

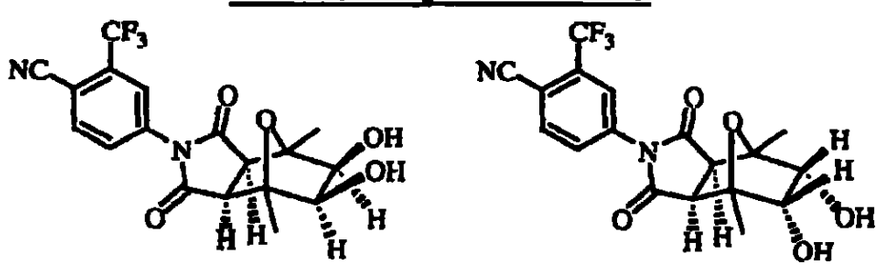


Se agregó DBAD (37.7 mg, 0.164 mmol) a una solución de PPh_3 (43.0 mg, 0.164 mmol) en THF (1 mL). Después de agitar por 10 min., se agregó 4-fluorofenol (18.3 mg, 0.164 mmol) y la mezcla de reacción se agitó por 5 min. adicionales. Una solución del compuesto 228 (45.0 mg, 0.109 mmol) en THF (1 mL) se agregó y la mezcla se agitó a temperatura ambiente durante la noche. La CLAR mostró que la mezcla de reacción cruda contiene principalmente el diol de partida (compuesto 228), entonces se agregó esta mezcla a una mezcla preformada como antes de PPh_3 (86 mg), DBAD (75.4 mg) y fenol (36.6 mg) en THF (4 mL) a temperatura ambiente. Se continuó la agitación hasta que todo el compuesto 228 se consumió. La reacción se concentró después bajo presión reducida. La purificación por CLAR preparativa de fase inversa [15.2 min. (tiempo de retención) (Columna YMC S5 ODS A de 20 x 100 mm,

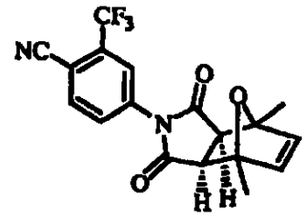
10-90% de metanol acuoso durante 15 minutos conteniendo 0.1% TFA, 20 mL/min., observando a 220 nm) dio 25.0 mg (45%) del compuesto 229 como un sólido amarillo ligero. CLAR: 99% a 3.53 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm eluyendo con 10-90% de metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 505.2 $[M-H]^-$.

Ejemplo 230

(3aα,4β,5β,6β,7β,7aα)-4-(Octahidro-5,6-dihidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo y (3aα,4β,5α,6α,7β,7aα)-4-(Octahidro-5,6-dihidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo (230Bi y 230Bii, Respectivamente)



A. (3aα,4β,7β,7aα)-4-(1,3,3a,4,7,7a-Hexahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo(230A)



2,5-Dimetil furano (1.23 mL, 11.5 mmol) y 4-(2,5-dihidro-2,5-dioxo-1H-pirrol-1-il)-2-trifluorometilbenzonitrilo (2.00 g, 7.69 mmol) se disolvieron en benceno (10 mL) y se calentaron a 60°C por 18 h. Los orgánicos volátiles se separaron in vacuo. El compuesto crudo resultante 230A se llevó sin purificación. CLAR: 71% a 3.007 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm eluyendo con 10-90% de metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm).

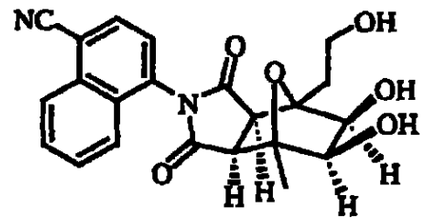
B. (3aα,4β,5β,6β,7β,7aα)-4-(Octahidro-5,6-dihidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo y (3aα,4β,5α,6α,7β,7aα)-4-(Octahidro-5,6-dihidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo (230Bi y 230Bii)

El compuesto 230A (0.100 g, 0.281 mmol) se disolvió en acetona y se agregó N-metilmorfolina-N-óxido (50% solución acuosa, 0.10 mL, 0.42 mmol). Se agregó después OsO_4 (4%

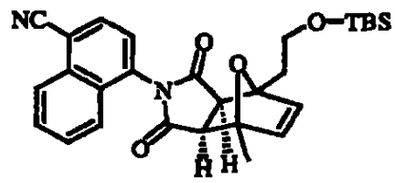
solución acuosa, 0.014 mmol). Después de 3 h a 25°C, la reacción estuvo completa y se agregó sulfito de sodio (0.250 g) con agitación vigorosa. Después de 15 min., se agregó salmuera (10 mL) y la solución se extrajo con EtOAc (3 x 15 mL). Los orgánicos se secaron sobre sulfato de sodio anhidro y se concentraron después in vacuo. La mezcla cruda de diol se purificó por CCD preparativa eluyendo con 18% de acetona en cloroformo para dar 0.038 g (34%) del compuesto 230Bi (cara beta) y 0.012 g (11%) del compuesto 230Bii (cara alfa) como sólidos amarillo pálido. Compuesto 230Bi: CLAR: 100% a 2.567 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm eluyendo con 10-90% de metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 397.08 $[M+H]^+$. Compuesto 230Bii: CLAR: 100% a 2.417 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm eluyendo con 10-90% de metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 397.08 $[M+H]^+$.

Ejemplo 231

(3aα,4β,5β,6β,7β,7aα)-4-[Octahidro-5,6-dihidroxi-4-(hidroxietil)-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo, (231C)



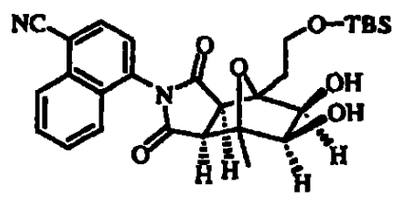
A. (3aα,4β,7β,7aα)-4-[4-[2-[[(1,1-Dimetiletil)dimetilsilil]oxi]etil]-1,3,3a,4,7,7a-hexahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo (231A)



El compuesto 204A (29.0 g, 120 mmol) y 4-(2,5-dihidro-2,5-dioxo-1H-1-il)-1-naftalencarbonitrilo (20.0 g, 80.6 mmol) se suspendieron en benceno (80 mL) y se calentó a 60°C por 14 h. La mezcla se concentró después in vacuo a 40°C por 40 min. La suspensión espesa resultante se enfrió hasta 25°C y después se suspendió en MeOH (200 mL) y se agitó a temperatura ambiente por 30 min. La solución se enfrió después a 0°C por 30 min. y después se filtró enjuagando con MeOH frío. El sólido resultante se secó in vacuo para dar 26.1 g (55%) del compuesto crudo 231A como un sólido blanco. La solución de metanol se concentró in vacuo y se volvió a suspender en MeOH (50 mL) y se enfrió a -20°C por 4 h. La solución se filtró después enjuagando con MeOH frío. El sólido resultante se secó in vacuo para dar 3.8 g (10%) del

compuesto 231A como un sólido blanco. CLAR: 95% a 4.227 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm eluyendo con 10-90% de metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm)

B. (3aα,4β,5β,6β,7β,7aα)-4-[4-[2-[[1(1,1-Dimetiletil)dimetilsilil]oxi]etil]octahidro-5,6-dihidroxi-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo (231B)



El compuesto 231A (0.400 g, 0.851 mmol) se disolvió en acetona (9.0 mL) y se agregó N-metilmorfolina-N-óxido (50% solución acuosa, 0.150 mL, 1.28 mmol). Se agregó después OsO_4 (4% solución acuosa, 0.043 mmol). Después de 3 h a 25°C, la reacción estuvo completa y se agregó sulfito de sodio (1.0 g) con agitación vigorosa. Después de 15 minutos, se agregó salmuera (30 mL) y la solución se extrajo con EtOAc (3 x 50 mL). Los orgánicos se secaron sobre sulfato de sodio anhidro y después se concentraron in vacuo. El diol crudo se purificó por cromatografía instantánea sobre sílice eluyendo con 5-25% acetona en cloroformo para dar 0.355 g (80%) del compuesto 231B como un sólido amarillo. CLAR: 93% a 3.903 min. (tiempo

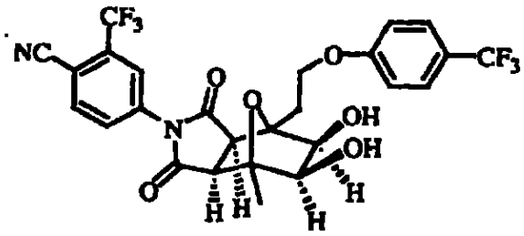
de retención) (Columna YMC S5 ODS de 4.6 x 50 mm eluyendo con 10-90% de metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 522.00 $[M+H]^+$.

C. (3aα,4β,5β,6β,7β,7aα)-4-[Octahidro-5,6-dihidroxi-4-(hidroxietil)-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo(231C)

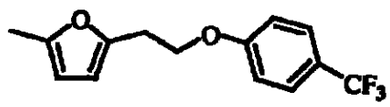
El compuesto 231B (0.400 g, 0.766 mmol) se disolvió en THF (5.0 mL) y se transfirió a una botella de polipropileno y se enfrió hasta 0°C. Se agregó después HF•Piridino (1.0 mL). Después de 20 min., la reacción se vació cuidadosamente en bicarbonato de sodio acuoso, saturado, frío y se extrajo con cloruro de metileno (3 x 30 mL). Los orgánicos se lavaron después una vez con HCl 1 N y se secaron sobre sulfato de sodio anhidro. La concentración in vacuo dio 0.290 g (93%) del compuesto 231C (0.290 g) como una espuma amarilla que no se purificó adicionalmente. CLAR: 92% a 2.273 y 2.423 min. (atropisómeros, tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm eluyendo con 10-90% de metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min, observando a 220 nm). EM (ES): m/z 409.10 $[M+H]^+$.

Ejemplo 232

(3aα,4β,5β,6β,7β,7aα)-4-[Octahidro-5,6-dihidroxi-4-metil-1,3-dioxo-7-[2-[4-(trifluorometil)fenoxi]etil]-4,7-epoxi-2H-isoindol-2-il]-2-(trifluorometil)benzonitrilo, (232C)

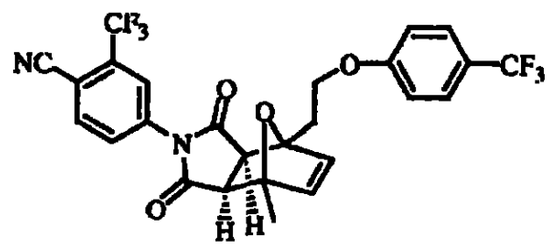


A. 2-Metil-5-[2-[4-(trifluorometil)fenoxi]etil]furano (232A)



A una solución de trifenilofosfina (1.56 g, 5.95 mmol) en THF (40 mL) se agregó DBAD (1.37 g, 5.95 mmol). Después de 10 min., se agregó 4-trifluorometilfenol (0.964 g, 5.95 mmol). Después de 10 minutos adicionales, se agregó el compuesto 21A (0.500 g, 3.97 mmol). Después de 14 h a 25°C, la reacción se concentró in vacuo y se purificó por cromatografía instantánea sobre sílice eluyendo con cloroformo para dar 0.713 g (44%) del compuesto 232A como un aceite transparente.

B. (3aα,4β,7β,7aα)-4-[1,3,3a,4,7,7a-hexahidro-4-metil-1,3-dioxo-7-[2-[4-(trifluorometil)fenoxi]etil]-4,7-epoxi-2H-isoindol-2-il]-2-(trifluorometil)benzonitrilo(232B)



El compuesto 232A (0.301 g, 1.15 mmol) y 4-(2,5-dihidro-2,5-dioxo-1H-pirrol-1-il)-2-trifluorometilbenzonitrilo (0.220 g, 0.846 mmol) se suspendieron en benceno (1.5 mL) y se calentaron a 60°C por 14 h. La mezcla se concentró después in vacuo a 40°C por 40 minutos. El producto crudo se purificó por cromatografía instantánea sobre sílice eluyendo con 10 - 0% hexanos en cloruro de metileno para dar 0.199 g (44%) del compuesto 232B como un sólido amarillo. El compuesto 232B se caracterizó como el diastereómero exo por los experimentos NOE. CLAR: 94% a 3.993 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm eluyendo con 10-90% de metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm).

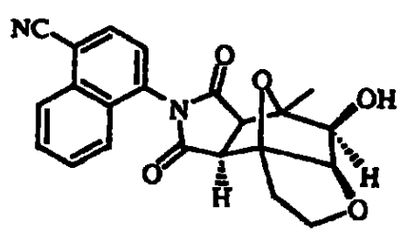
C. (3aα,4β,5β,6β,7β,7aα)-4-[Octahidro-5,6-dihidroxi-4-metil-1,3-dioxo-7-[2-[4-(trifluorometil)fenoxi]etil]-4,7-epoxi-2H-isoindol-2-il]-2-(trifluorometil)benzonitrilo, (232C)

El compuesto 232B (0.075 g, 0.14 mmol) se disolvió en acetona (2.0 mL) y se agregó N-metilmorfolina-N-óxido (50% solución acuosa, 0.025 mL, 0.21 mmol). Se agregó después el

OsO_4 (4% solución acuosa, 0.007 mmol). Después de 3 h a 25°C, la reacción se completó y se agregó sulfito de sodio (0.25 g) con agitación vigorosa. Después de 15 minutos, se agregó salmuera (5 mL) y la solución se extrajo con EtOAc (3 x 10 mL). Los orgánicos se secaron sobre sulfato de sodio anhidro y después se concentraron in vacuo. El diol crudo se purificó por CCD preparativa sobre gel de sílice, eluyendo con 10% de acetona en cloroformo para dar 0.038 g (48%) del compuesto 232C como un sólido amarillo. CLAR: 98% a 3.747 min. (tiempo de retención) (YMC 85 ODS columna 4.6 x 50 mm eluyendo con 10-90% de metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 593.08 $[M+Na]^+$.

Ejemplo 233

(3aα,4β,5β,5β,8aβ,8bα)-4-(Decahidro-5-hidroxi-4-metil-1,3-dioxo-4,8a-epoxi-2H-furo[3,2-e]isoindol-2-il)-1-naftalencarbonitrilo, (233)

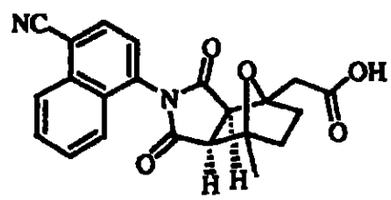


A una solución de trifenilfosfina (0.072 g, 0.28 mmol) en THF (3.0 mL) se agregó DBAD (0.063 g, 0.28 mmol). Después de 10 min., se agregó 4-cianofenol (0.033 g, 0.28 mmol).

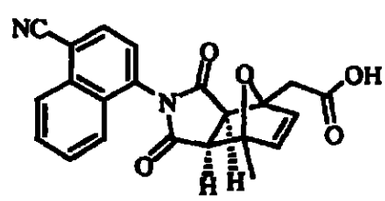
Después de 10 minutos adicionales, se agregó el compuesto 231C (0.075 g, 0.18 mmol). Después de 3 h a 25°C, la reacción se concentró in vacuo y se purificó por CCD preparativa sobre gel de sílice, eluyendo con 15% acetona en cloroformo para dar 0.068 g (95%) del compuesto 233 como un sólido blanco. CLAR: 95% a 2.430 y 2.560 min. (atropisómeros, tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm, 10-90% de metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 391.09 $[M+H]^+$.

Ejemplo 234

Ácido (3aα,4β,7β,7aα)-2-(4-Ciano-1-naftalenil)octahidro-7-metil-1,3-dioxo-4,7-epoxi-4H-isoindol-4-acético, (234B)



A. Ácido (3aα,4β,7β,7aα)-2-(4-Ciano-1-naftalenil)-1,2,3,3a,7,7a-hexahidro-7-metil-1,3-dioxo-4,7-epoxi-4H-isoindol-4-acético (234A)



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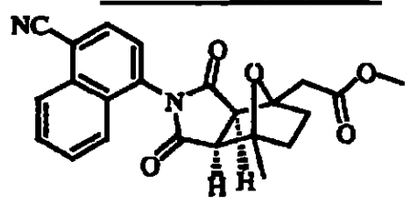
Se disolvieron el ácido 5-Metil-2-furanacético (0.500 g, 3.57 mmol) y 4-(2,5-dihidro-2,5-dioxo-1H-1-il)-1-naftalencarbonitrilo (0.899 g, 3.57 mmol) en benceno (3.0 mL) y se calentaron a 60°C por 2 h y después se enfriaron a 25°C. Después de 12 h, se precipitó un sólido blanco de la solución, el cual se recolectó y enjuagó con éter de dietilo para dar 1.20 g (87%) del compuesto 234A como un sólido amarillo ligero. El análisis RMN mostró solamente un diastereómero. CLAR: 86% a 2.767 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm, 10-90% de metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 389.45 $[M+H]^+$.

B. Ácido (3aα,4β,7β,7aα)-2-(4-Ciano-1-naftalenil)octahidro-7-metil-1,3-dioxo-4,7-epoxi-4H-isoindol-4-acético, (234B)

El compuesto 234A (1.10 g, 2.82 mmol) se disolvió en EtOH/EtOAc (1:1, 50 mL) y se agregó 10% Pd/C (0.4 g, cat.). Se introdujo H_2 por medio de un globo. Después de 5 h a 25°C, la reacción se filtró a través de Celite enjuagando con EtOAc y se concentró in vacuo para dar 1.00 g (91%) del compuesto 234B como un sólido amarillo. CLAR: 80% a 2.84 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm, 10-90% de metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 391.1 $[M+H]^+$.

Ejemplo 235

Ester de metilo del ácido (3aα,4β,7β,7aα)-2-(4-Ciano-1-naftalenil)octahidro-7-metil-1,3-dioxo-4,7-epoxi-4H-isoindol-4-acético, (235)



El compuesto 234B (0.050 g, 0.13 mmol) se disolvió en acetonitrilo (2.0 mL), después se agregó DCC (0.025 g, 0.13 mmol) seguido por HOAc (0.018 g, 0.13 mmol). El aCLohol de 4-fluorobencilo (0.014 mL, 0.13 mmol) se agregó después y la reacción se agitó por 3 h. La mezcla de reacción se concentró in vacuo y se purificó por CLAR preparativa de fase inversa (YMC S5 ODS 20 x 100 mm, 10-90% de metanol acuoso durante 15 min. conteniendo 0.1% TFA, 20 mL/min., observando a 220 nm). La purificación produjo 0.040 g (82%) del compuesto 235 como un sólido blanco, más que el éster de bencilo esperado. No se observó nada del éster de bencilo anticipado por RMN o CL-EM. CLAR: 100% a 3.033 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm, 10-90% metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 405.51 $[M+H]^+$.

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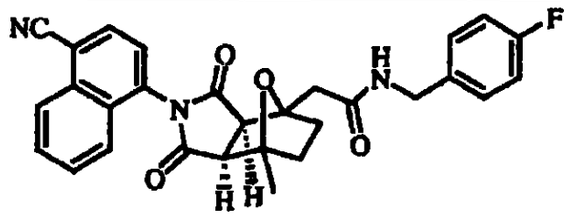
A13

Ejemplo 236

(3aα,4β,7β,7aα)-2-(4-Ciano-1-naftalenil)-N-[(4-fluorofenil)metil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-4H-isoindol-4-acetamida. (236)



El compuesto 234B (0.10 g, 0.27 mmol) se disolvió en acetonitrilo (4.0 mL). HOAc (0.035 g, 0.27 mmol) y DCC (0.049 g, 0.27 mmol) se agregaron después seguido por 4-fluorobencilamina (0.030 mL, 0.27 mmol). Después de 4 h a 25°C, la reacción se concentró in vacuo y se purificó por CLAR preparativa de fase inversa (YMC S5 ODS 20 x 100 mm, 10-90% de metanol acuoso durante 15 minutos conteniendo 0.1% TFA, 20 mL/min., observando a 220 nm) para dar 0.085 g (67%) del compuesto 236 como un sólido blanco. CLAR: 100% a 3.277 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm, 10-90% metanol acuoso durante 4 minutos conteniendo 0.2% de ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 498.43 $[M+H]^+$.

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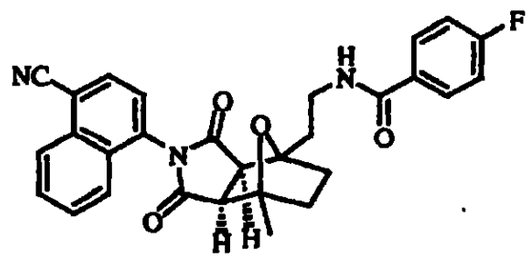
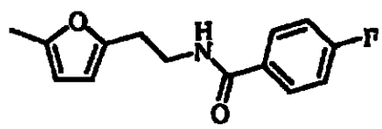
Ejemplo 237

(3aα,4β,7β,7aα)-N-[2-[2-(4-Ciano-1-naftalenil)octahidro-7-metil-1,3-dioxo-4,7-epoxi-4H-isoindol-4-il]etil]-4-fluorobenzamida. (237B)



A. 4-Fluoro-N-[2-(5-metil-2-furanil)etil]benzamida (237A)



Se agregó cloruro de 4-Fluorofenilacetilo (0.290 mL, 2.44 mmol) gota a gota a una solución de β-(5-metil-2-furanil)etanamina (300 mg, 2.44 mmol, elaborado según el procedimiento de Yur'ev et al. J. Gen. Chem. USSR (Trad. Inglés) 33, 3444-8 (1963)) en THF (2.5 mL) a temperatura ambiente, seguido por la adición gota a gota de Et_3N (0.340 mL, 2.44 mmol). Una vez que se consumió el material de partida, como fue evidente por CLAR, la reacción se apagó con H_2O y se extrajo con CH_2Cl_2. Las capas orgánicas combinadas se secaron sobre $MgSO_4$ y se concentraron bajo presión reducida. La purificación por cromatografía instantánea sobre gel de

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sílice eluyendo con un gradiente de 0-50% EtOAc/hexano dio 523 mg (95%) del compuesto 237A como un sólido blanco. CLAR: 99% a 2.84 min. (tiempo de retención) (Columna Phenomenex-prime S5-C18 4.6 x 50 mm eluyendo con 10-90% de metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 248.15 $[M+H]^+$.

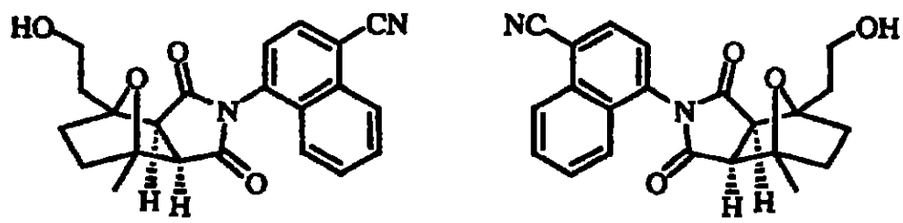
B. (3aα,4β,7β,7aα)-N-[2-[2-(4-Ciano-1-naftalenil)octahidro-7-metil-1,3-dioxo-4,7-epoxi-4H-isoindol-4-il]etilo]-4-fluorobenzamida, (237B)

Una solución del compuesto 237A (221 mg, 0.896 mmol) y 4-(2,5-dihidro-2,5-dioxo-1H-1-il)-1-naftalencarbonitrilo (222 mg, 0.896 mmol) en benceno (4 mL) se calentó a 60°C durante la noche. La mezcla de reacción se concentró bajo presión reducida y se disolvió en EtOAc (30 mL). Se agregó 10% Pd/C (50 mg) y la mezcla se agitó bajo un globo de hidrógeno durante la noche. La mezcla de la reacción se filtró a través de una almohadilla de Celite y se concentró bajo presión reducida. La purificación por cromatografía instantánea sobre gel de sílice eluyendo con 25%-75% EtOAc/hexano (gradiente) dio 160 mg (36%) del compuesto 237B como un sólido blanco apagado. CLAR: 97% a 3.13 y 3.23 min. (atropisómeros, tiempo de retención) (Columna Phenomenex-prime S5-C18 4.6 x 50 mm eluyendo con 10-90% de metanol acuoso durante 4 minutos

conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 498.11 $[M+H]^+$.

Ejemplo 238

[3aR-(3aα,4β,7β,7aα)-4-[Octahidro-4-(2-hidroxietil)-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo y [3aS-(3aα,4β,7β,7aβ]-4-[Octahidro-4-(2-hidroxietil)-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo, (238i y 238ii)

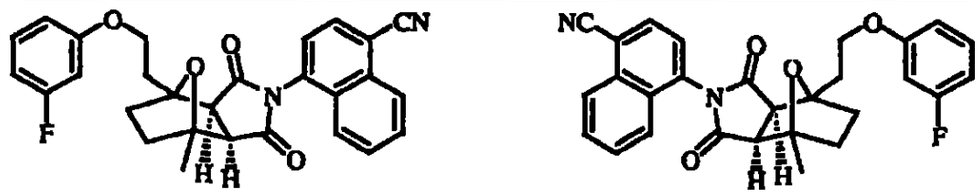


El compuesto racémico 223B se separó en sus enantiómeros por CLAR quiral preparativa de fase normal (Columna CHIRALPAK AD 5 x 50 cm; eluyendo con 20% MeOH/EtOH (1:1) en heptano (isocrática) a 50 mL/min., observando a 220 nm) para dar el compuesto de elución más rápida 238i (CLAR quiral: 13.54 min.; columna CHIRALPAK AD 4.6 x 250 mm ; eluyendo con 20% MeOH/EtOH (1:1) en heptano a 1 mL/min.) y el compuesto de elución más lenta 238ii (CLAR quiral: 14.99 min.; columna CHIRALPAK AD 4.6 x 250 mm; eluyendo con 20% MeOH/EtOH (1:1) en heptano a 1 mL/min.). La conformación absoluta de los compuestos 238i y 238ii no se estableció. Por simplicidad en

nomenclatura, el compuesto 238i se designó en la presente por tener una configuración "R" y el compuesto 238ii por tener una configuración "S". Los productos enantioméricamente puros derivados del compuesto 238i se designan en la presente por tener una configuración "R", y productos enantioméricamente puros derivados del compuesto 238ii se designan en la presente por tener una configuración "S".

Ejemplo 239

[3aR-(3aα,4β,7β,7aα)]-4-[4-[2-(3-Fluorofenoxi)etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo y [3aS-(-(3aα,4β,7β,7aα)]-4-[4-[2-(3-Fluorofenoxi)etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo. (239i y 239ii)



A una solución de trifenilfosfina (0.052 g, 0.20 mmol) en THF (2.0 mL) se agregó DBAD (0.046 g, 0.20 mmol). Después de 10 min., se agregó 3-fluorofenol (0.018 mL, 0.20 mmol). Después de 10 minutos adicionales, se agregó el compuesto 238i (0.050 g, 0.13 mmol). Después de 3 h a 25°C, la reacción se concentró in vacuo y se purificó por CLAR preparativa de fase inversa (YMC S5 ODS 20 x 100 mm, 10-90% de metanol acuoso durante 15 minutos

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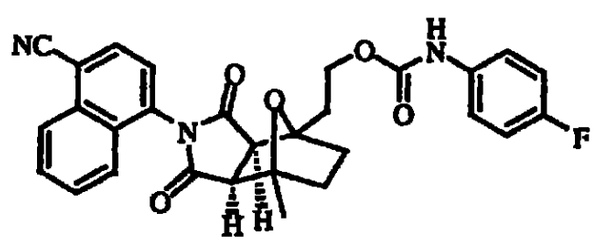
conteniendo 0.2% TFA, 20 mL/min., observando a 220 nm) para dar 0.031 g (33%) del compuesto 239i como un sólido blanco. Este proceso se repitió con el compuesto 238ii para resultar el compuesto 239ii. Compuesto 239i: CLAR: 100% a 3.80 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm, 10-90% de metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 471.65 $[M+H]^+$, $[\alpha]_D^{25}$= -47.371 (c = 4.412 mg/cc, CH_2Cl_2). Compuesto 239ii: CLAR: 100% a 3.80 min. (tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm, 10-90% de metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 471.65 $[M+H]^+$, $[\alpha]_D^{25}$= +24.3 (c = 4.165 mg/cc, CH_2Cl_2).

Ejemplo 240

Éster del 2-[(3aα,4β,7β,7aα)-2-(4-ciano-1-naftalenil)octahidro-7-metil-1,3-dioxo-4,7-epoxi-4H-isoindol-4-]etilo del Ácido (4-Fluorofenil)carbámico. (240)

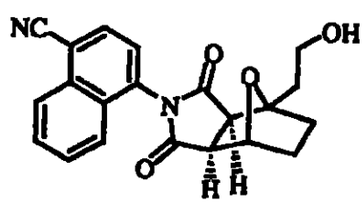


El compuesto 223B (0.100 g, 0.279 mmol) se disolvió en dicloroetano (3.0 mL) y se agregó 4-fluorofenilisocianato

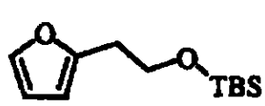
(0.048 mL, 0.42 mmol) seguido por calentamiento a 60°C. Después de 2 h, la reacción se enfrió hasta 25°C y se diluyó con cloruro de metileno. La mezcla se lavó una vez con bicarbonato de sodio acuoso saturado (20 mL) y después los orgánicos se secaron sobre sulfato de sodio anhidro. El material crudo se purificó por cromatografía instantánea sobre gel de sílice eluyendo con 15% acetona en cloroformo para dar 0.098 g (68%) del compuesto 240 como una espuma amarilla. CLAR: 98% a 3.320 y 3.457 min. (atropisómeros, tiempo de retención) (Columna YMC S5 ODS de 4.6 x 50 mm, 10-90% de metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 514.13 $[M+H]^+$.

Ejemplo 241

(3aα,4β,7β,7aα)-4-[Octahidro-4-(2-hidroxietil)-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo. (241D)

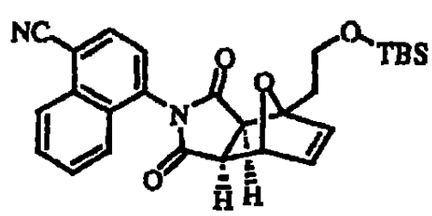


A. 2-[2-[[(1,1-Dimetiletil)dimetilsilil]oxi]etil]furano (241A)



El 2-(2-Hidroxietil)furano (1.00 g, 8.93 mmol. Ejemplo 255A) se disolvió en DMF a 25°C y se agregó imidazol (0.790 g, 11.6 mmol). Se agregó después TBSCl (1.35 g, 8.93 mmol) en porciones durante 5 minutos. Después de 2 h, la reacción se vació en dietil éter (300 mL) y se lavó secuencialmente con agua (1 x 100 mL), HCl 1N (1 x 100 mL), y salmuera (1 x 100 mL). Los orgánicos combinados se secaron después sobre sulfato de magnesio y se concentraron in vacuo. El compuesto 241A se aisló como un aceite transparente (1.77 g) y se llevó sin purificación. CLAR: 100% a 4.233 min. (tiempo de retención) (Columna YMC S5 ODS 4.6 x 50 mm, 10-90% metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm).

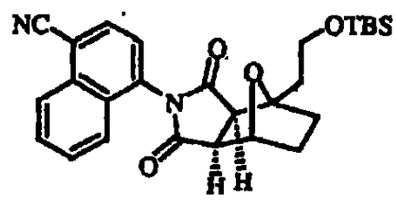
B. (3aα,4β,7β,7aα)-4-[4-[2-[[(1,1-Dimetiletil)dimetilsilil]oxi]etil]-1,3,3a,4,7,7a-hexahidro-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo (241B)



Se suspendió 4-(2,5-Dihidro-2,5-dioxo-1H-1-il)-1-naftalencarbonitrilo (0.721 g, 3.40 mmol) en benceno (5.0 mL) en un tubo sellado y se agregó el compuesto 241A (1.00 g, 4.42 mmol). La reacción se calentó a 60°C por 16 h y después

se enfrió hasta 25°C. El benceno se separó in vacuo para dar un sólido amarillo. El material crudo se purificó por cromatografía instantánea sobre gel de sílice eluyendo con 1-5% acetona en cloroformo para dar 1.37 g (85%) de compuesto 241B como un sólido amarillo. Los experimentos por RMN confirmaron la asignación del isómero exo. CLAR: 100% a 4.030 y 4.110 min. (atropisómeros, tiempo de retención) (Columna YMC S5 ODS 4.6 x 50 mm, 10-90% metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm).

C. (3aα,4β,7β,7aα)-4-[4-[2-[[(1,1-Dimetiletil)dimetilsilil]oxi]etil]octahidro-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo(241C)



El Compuesto 241B (0.500 g, 1.14 mmol) se disolvió en acetato de etilo (40 mL) y se agregó 10% Pd/C (0.200 g). Se introdujo hidrógeno por medio de un globo. Después de 4 h, la reacción se filtró a través de Celite, se enjuagó con acetato de etilo y se concentró in vacuo para dar un sólido amarillo pálido, que se purificó por cromatografía instantánea sobre gel de sílice eluyendo con acetona/cloroformo (0% - 1.5% - 3%

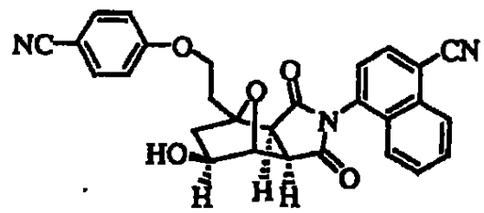
acetona) para dar 0.450 g (83%) de compuesto 241C como una espuma amarilla.

D. (3aα,4β,7β,7aα)-4-[Octahidro-4-(2-hidroxietil)-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo, (241D)

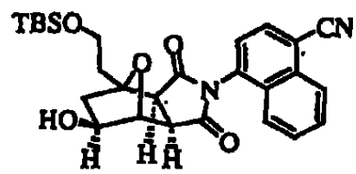
El compuesto 241C (0.283 g, 0.594 mmol) se disolvió en una solución de HCl al 2% conc. en etanol absoluto (10 mL). Después de 1 h, la reacción se apagó con bicarbonato de sodio acuoso saturado y se extrajo con cloruro de metileno (4 x 20 mL). Los orgánicos combinados se secaron sobre sulfato de sodio y se concentraron in vacuo para dar 0.211 g (98%) de compuesto 241D como un sólido blanco. CLAR: 100% a 2.14 min. (tiempo de retención) (Columna YMC S5 ODS 4.6 x 50 mm, 10-90% metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 363.45 $[M+H]^+$.

Ejemplo 242

(3aα,4β,6β,7β,7aα)-4-[4-[2-(4-Cianofenoxi)etil]octahidro-6-hidroxi-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo. (242C)



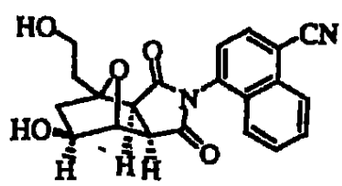
A. (3aα,4β,6β,7β,7aα)-4-[4-[2-[[(1,1-Dimetiletil)dimetilsilil]oxi]etil]octahidro-6-hidroxi-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo (242A)



El compuesto 241B (1.00 g, 2.28 mmol) y catalizador de Wilkinson (0.105 g, 0.114 mmol) se agitaron rápidamente bajo vacío a 25°C por 1 h y después se purgaron con N_2. Se agregó después THF (30 mL) seguido por catecolborano (0.487 mL, 4.57 mmol) después de que la olefina se había disuelto completamente. Después de 1 h, la reacción se enfrió hasta 0°C y se agregó una solución amortiguadora de fosfato de pH 7.2 (33 mL) seguido por EtOH (13 mL) y H_2O_2, (30% solución acuosa, 3.0 g). Después de 3 h a 0°C la reacción se completó por CL y la mezcla se extrajo con cloruro de metileno (3 x 50 mL). Los orgánicos combinados se lavaron con una mezcla 1:1 de sulfito de sodio al 10%/NaOH 1N (50 mL) y una vez con salmuera (50 mL). Se combinaron y extrajeron todas las fases acuosas con cloruro de metileno (50 mL) y la fase orgánica

combinada con las extracciones previas. Todos los orgánicos se secaron después sobre sulfato de sodio anhidro y se concentraron después in vacuo. El material crudo se purificó por cromatografía instantánea sobre gel de sílice eluyendo con 10-20% acetona en cloroformo para dar 0.634 g de compuesto 242A como una espuma blanca. CLAR: 96% a 3.797 min. (tiempo de retención) (Columna YMC S5 ODS 4.6 x 50 mm, 10-90% metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 493.13 $[M+H]^+$.

B. (3aα,4β,6β,7β,7aα)-4-[Octahidro-6-hidroxi-4-(2-hidroxietil)-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo (242B)



El compuesto 242A (0.400 g, 0.813 mmol) se disolvió en una solución de 2% de HCl 12 N en etanol absoluto (10 mL). Después de 1 h, la reacción se apagó con bicarbonato de sodio acuoso saturado y se extrajo con EtOAc (4 x 20 mL). Los orgánicos combinados se secaron sobre sulfato de sodio y se concentraron in vacuo para dar 0.305 g de compuesto 242B como un sólido blanco. CLAR: 90% a 2.043 min. (tiempo de retención) (Columna YMC S5 ODS 4.6 x 50 mm, 10-90% metanol

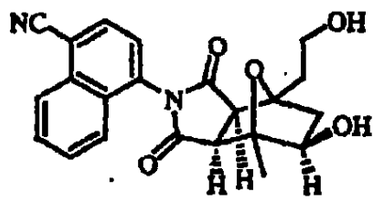
acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 379.09 $[M+H]^+$.

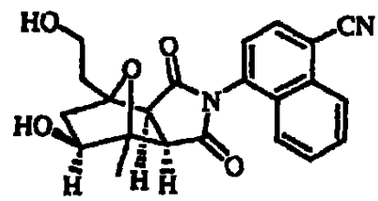
C. (3aα,4β,5β,7β,7aα)-4[4-[2-(4-Cianofenoxi)etil]octahidro-6-hidroxi-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo, (242C)

A una solución de trifenilfosfina (0.054 g, 0.207 mmol) en THF (2.0 mL) se agregó DBAD (0.048 g, 0.207 mmol). Después de 10 min., se agregó 4-cianofenol (0.025 g, 0.207 mmol). Después de 10 minutos adicionales, se agregó el compuesto 242B (0.050 g, 0.138 mmol). Después de 3 h a 25°C, la reacción se concentró in vacuo y se purificó por CCD preparativa sobre sílice eluyendo con 25% acetona/cloroformo para dar 0.056 g de compuesto 242C como un sólido blanco. CLAR: 90% a 2.987 min. (tiempo de retención) (Columna YMC S5 ODS 4.6 x 50 mm, 10-90% metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 480.10 $[M+H]^+$.

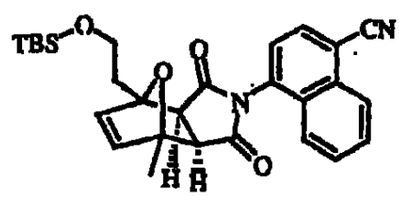
Ejemplo 243

[3aS-(3aα,4β,5β,7β,7aα)-4-[Octahidro-5-hidroxi-7-(2-hidroxietil)-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo y [3aR-(3aα,4β,5β,7β,7aα)]-4-[Octahidro-5-hidroxi-7-(2-hidroxietil)-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo. (243Di y 243Dii)





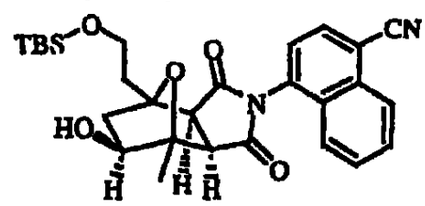
A. (3aα,4β,7β,7aα)-4-[4-[2-[[(1,1-Dimetiletil)dimetilsilil]oxi]etilo]-1,3,3a,4,7,7a-hexahidro-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo (243A)



Se agregó el 4-(2,5-Dihidro-2,5-dioxo-1H-1-il)-1-naftalencarbonitrilo (18.3 g, 68.7 mmol) a una solución del compuesto 204A (26.6 g, 110.6 mmol) en benceno (75 mL) y se calentó a 60°C durante la noche. Después de enfriar a temperatura ambiente, la mezcla de reacción se concentró bajo presión reducida. El residuo se trató con MeOH (250 mL) con agitación a 0°C por 10 min. El sólido resultante se filtró,

se lavó con MeOH frío (2 X 10 mL) y se secó para dar 26.7 g (79.5%) de compuesto 243A como un sólido amarillo. Los análisis CLAR del sólido anterior revelaron que era 95% puro (Condiciones CLAR: 95% a 2.48 min. (tiempo de retención) (Columna Phenomenex-prime S5-C18, 4.6 x 50 mm, 10%-90% metanol acuoso durante un gradiente de 4 minutos con 0.2% H_3PO_4, detectando a 220 nm)). El filtrado se concentró después bajo presión reducida y el sólido resultante se cromatografió, eluyendo con 3% acetona/$CHCl_3$, para dar 4.36 g adicionales de compuesto 243A (13%), para dar un rendimiento final total de 92.5%.

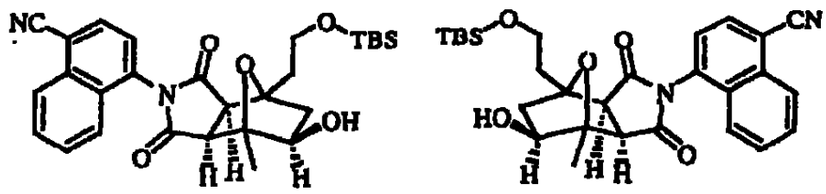
B. (3aα,4β,5β,7β,7aα)-4-[7-[2-[[(1,1-Dimetiletil)dimetilsilil]oxi]etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo (243B)



Una mezcla de 243A (10 g, 20.46 mmol) y $RhCl(PPh_3)_3$ (0.947 mg, 1.02 mmol) se evacuó y se llenó con argón (3X). Se agregó THF (200 mL) y una vez que se habían disuelto todos los materiales en partículas, se agregó catecolborano (4.4 mL, 40.93 mmol) lentamente gota a gota. Cuando se detuvo la formación de producto, como se determinó por CLAR, la mezcla

de reacción se enfrió hasta 0°C y se apagó con solución amortiguadora de fosfato (330 mL, pH 7.2) después se agregaron EtOH (130 mL) y H_2O_2, (300 mL, 30% sol. acuosa). Una vez que se consumió el boronato, la mezcla se extrajo con CH_2Cl_2 (3X) y las capas orgánicas combinadas se lavaron con 1 N NaOH, 10% $NaHSO_3$ acuoso (1:1, 1X) y salmuera (1X). Los lavados combinados se extrajeron con CH_2Cl_2 (1X) y las capas orgánicas combinadas se secaron sobre Na_2SO_4. La purificación por cromatografía instantánea sobre gel de sílice eluyendo con 10% hasta 30% gradiente acetona/$CHCl_3$ durante 25 min. dio 7.1 g (68%) de 243B como un sólido amarillo claro. Condiciones CLAR: 98% a 3.82 min. (tiempo de retención) (Columna Phenomenex-prime S5-C18 4.6 x 50 mm, 10%-90% metanol acuoso durante un gradiente de 4 minutos con 0.2% H_3PO_4, detectando a 220 nm).

C. [3aR-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[[(1,1-Dimetiletil)dimetilsilil]oxi]etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo y [3aS-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[[(1,1-Dimetiletil)dimetilsilil]oxi]etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo (243Ci y 243Cii)



El compuesto racémico 243B se separó en enantiómeros individuales por cromatografía líquida en fase normal quiral. Se usó una columna Chiralpak OD (50 x 500 mm), eluyendo con 13% EtOH/hexanos durante 99 min. a 50mL/min. detectando a 220 nm. El compuesto isómero de elución más rápida 243Ci tuvo un tiempo de retención = 45 min. y el compuesto isómero de elución más lenta 243Cii tuvo un tiempo de retención = 66 min.

D. [3aS-(3aα,4β,5β,7β,7aα)]-4-[Octahidro-5-hidroxi-7-(2-hidroxietil)-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo y [3aR-(3aα,4β,5β,7β,7aα)]-4-[Octahidro-5-hidroxi-7-(2-hidroxietil)-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo, (243Di y 243Dii)

El compuesto 243Ci (0.84 g, 2.14 mmol) se disolvió en 2% de HCl 12N/EtOH (20 mL), se agitó por 5 minutos y se concentró bajo presión reducida. La purificación por cromatografía instantánea sobre gel de sílice eluyendo con 5-10% MeOH/CH_2Cl_2; dio 0.57 g (88%) de 243Di. El compuesto 243Di que procedía del isómero de elución más rápida (243Ci) se encontró que era 99.7% ee por cromatografía analítica quiral

en fase normal. Condiciones CLAR: 99.7% a 2.17 min. (tiempo de retención) (ChiraCLel OJ 44.6 X 250 mm, 10 micras, 40°C, isocrática 80% Heptano / 20% EtOH/MeOH (1:1), 1.0 mL/min., detección a 288 nm).

El compuesto 243Cii (0.86 g, 2.19 mmol) se disolvió en 2% de HCl 12N/EtOH (20 mL), se agitó por 5 minutos y se concentró bajo presión reducida. La purificación por cromatografía instantánea sobre gel de sílice eluyendo con 5-10% MeOH/CH_2Cl_2 dio 0.60 g (90%) de 243Dii. El compuesto 243Dii que procede del isómero de elución más lenta (243Cii) se encontró que tiene 87.1% ee por cromatografía quiral de fase analítica. Condiciones CLAR: 87.1% a 18.4 min. (tiempo de retención) (ChiraCLel OJ 44.6 X 250 mm, 10 micras, 40°C, isocrática 80% heptano / 20% EtOH/MeOH (1:1), 1.0 mL/min., detección a 288 nm).

La conformación absoluta de los compuestos 243Di y 243Dii no se determinó. Por simplicidad en nomenclatura, el compuesto 243Di se designa en la presente como que tiene una configuración "S" y el compuesto 243Dii como que tiene una configuración "R". Los productos enantioméricamente puros derivados del compuesto 243Di se designan en la presente como que tienen una configuración "S" y los productos enantioméricamente puros derivados del compuesto 243Dii se designan en la presente como que tienen una configuración "R".

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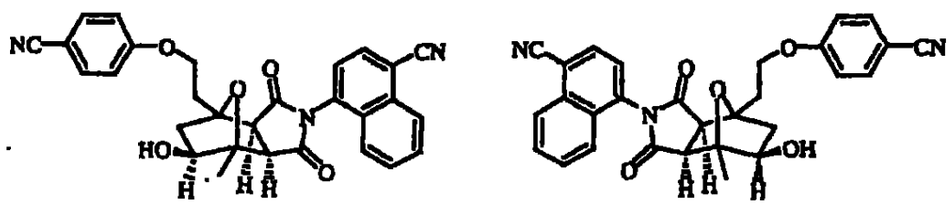
Ejemplo 244

[3aS-(3aα,4β,5β,7β,7aα)-4-[7-[2-(4-Cianofenoxi)etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo y [3aR-(3aα,4β,5β,7β,7aα)]-4-[7-[2-(4-Cianofenoxi)etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo. (244i y 244ii)



Se agregó DBAD (26 mg, 0.115 mmol) a una solución de PPh_3 (30 mg, 0.115 mmol) en THF (0.65 mL). Después de agitar por 10 min., se agregó 4-cianofenol (13.6 mg, 0.115 mmol) y la mezcla de reacción se agitó por 5 min. adicionales. El compuesto 243Di (30 mg, 0.076 mmol) se agregó y la mezcla se agitó a temperatura ambiente por 1 h. La reacción se concentró bajo presión reducida. La purificación por cromatografía instantánea sobre gel de sílice eluyendo con 30% acetona/70% $CHCl_3$, dio 23.1 mg (0.047 mmol, 61.7%) de compuesto 244i. Condiciones CLAR: 95% a 3.06 min. (tiempo de retención) (YMC S5 ODS 4.6 x 50 mm, 10%-90% metanol acuoso durante un gradiente de 4 minutos con 0.2% H_3PO_4, detectando a

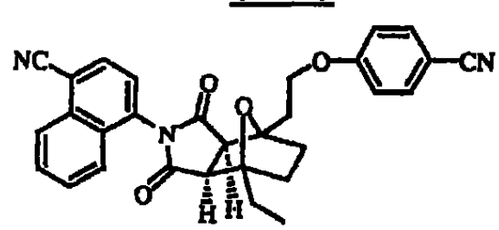
220 nm). EM (ES): m/z 494.09 $[M+H]^+$. $[\alpha]_D$ = 53.30°, C = 4.5 mg/cc en THF, @ 589 nm)

Se agregó DBAD (26 mg, 0.115 mmol) a una solución de PPh_3 (30 mg, 0.115 mmol) en THF (0.65 mL). Después de agitar por 10 min., se agregó 4-cianofenol (13.6 mg, 0.115 mmol) y la mezcla de reacción se agitó por 5 min. adicionales. El compuesto 243Dii (30 mg, 0.076 mmol) se agregó y la mezcla se agitó a temperatura ambiente por 1 h. La reacción se concentró bajo presión reducida. La purificación por cromatografía instantánea sobre gel de sílice eluyendo con 30% acetona/70% $CHCl_3$ dio 20.3 mg (0.041 mmol, 54.2%) de compuesto 244ii. Condiciones CLAR: 90% a 3.07 min. (tiempo de retención) (YMC S5 ODS 4.6 x 50 mm, 10%-90% metanol acuoso durante un gradiente de 4 minutos con 0.2% H_3PO_4, detectando a 220 nm). EM (ES): m/z 494.09 $[M+H]^+$. $[\alpha]_D$ = -42.87°, C = 6.6 mg/cc en THF, @ 589 nm)

Ejemplo 245

(3aα,4β,7β,7aα)-4-[4-[2-(4-Cianofenoxi)etil]-7-etiloctahidro-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitril .

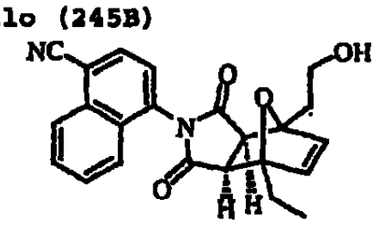
(245D)



A. 2-Etil-5-(2-hidroxietil)furano (245A)

Se agregó n-BuLi (2.5 M en hexano, 4.4 mL, 11 mmol) a una solución de 2-etilfurano (1.05 mL, 10 mmol) en THF (10 mL) a -25°C. La solución se calentó hasta temperatura ambiente y se agitó por 3 h. Se agregó óxido de etileno (0.75 mL) a -78°C. La reacción se agitó por 0.5 h a -15°C y durante la noche a temperatura ambiente. Se agregó NH_4Cl acuoso saturado y la mezcla se extrajo con éter (3X). Los extractos combinados se lavaron con agua (1X) y salmuera (1X) y se secaron sobre Na_2SO_4. La purificación por cromatografía instantánea sobre gel de sílice eluyendo con 30% EtOAc/70% hexano dio 1.12 g (8.02 mmol, 80.2%) de compuesto 245A como un aceite amarillo.

B. (3aα,4β,7β,7aα)-4-[4-Etil-1,3,3a,4,7,7a-hexahidro-7-(2-hidroxietil)-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo (245B)



Una solución del compuesto 245A (280 mg, 2.00 mmol) y el 4-(2,5-dihidro-2,5-dioxo-1H-1-il)-1-naftalencarbonitrilo (496 mg, 2.00 mmol) en benceno (2 mL) se agitó a 60°C por 2 h. La

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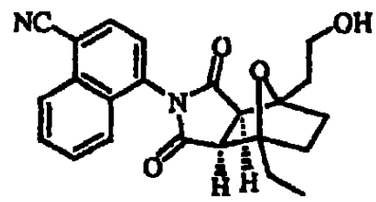
mezcla de reacción se concentró bajo presión reducida. El sólido amarillo, compuesto 245B, se usó directamente en la siguiente etapa.

C. (3aα,4β,7β,7aα)-4-[4-Etiloctahidro-7-(2-hidroxietil)-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo (245C)



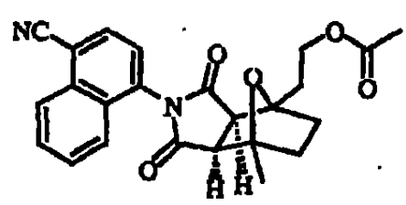
Una mezcla de compuesto 245B (764 mg, 1.97 mmol) y 10% Pd/C (115 mg, cat.) en EtOAc (36 mL) se agitó bajo una atmósfera de hidrógeno a temperatura ambiente por 2 h. La mezcla de reacción se filtró a través de Celite y se concentró bajo presión reducida para dar 779 mg de compuesto crudo 245C. La purificación de este producto crudo por cromatografía instantánea sobre gel de sílice eluyendo con 70% EtOAc/30% hexano dio 235 mg (0.6 mmol, 30.1%) de compuesto 245C. Condiciones CLAR: 99% a 2.84 min. (tiempo de retención) (YMC S5 ODS 4.6 x 50 mm, 10%-90% metanol acuoso durante un gradiente de 4 minutos con 0.2% H_3PO_4, detectando a 220 nm). EM (ES): m/z 391.12 $[M+H]^+$.

D. (3aα,4β,7β,7aα)-4-[4-[2-(4-Cianofenoxi)etil]-7-metiloctahidro-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo (245D)

Se agregó DBAD (44.2 mg, 0.192 mmol) a una solución de PPh_3 (50.4 mg, 0.192 mmol) en THF (1 mL). Después de agitar por 10 min., se agregó 4-cianofenol (23 mg, 0.192 mmol) y la mezcla de reacción se agitó por 5 min. adicionales. El compuesto 245C (50 mg, 0.128 mmol) se agregó y la mezcla se agitó a temperatura ambiente por 2 h. La reacción se concentró bajo presión reducida. La purificación por cromatografía instantánea sobre gel de sílice eluyendo con 40% EtOAc/60% hexano dio 43 mg (0.087 mmol, 68.4%) de compuesto 245D como un sólido blanco. Condiciones CLAR: 99% a 3.65 min. (tiempo de retención) (YMC S5 ODS 4.6 x 50 mm, 10%-90% metanol acuoso durante un gradiente de 4 minutos con 0.2% H_3PO_4, detectando a 220 nm). EM (ES): m/z 492.16 $[M+H]^+$.

Ejemplo 246

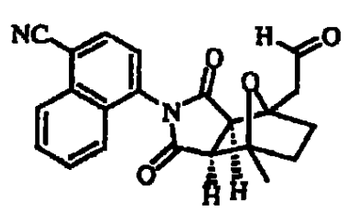
(3aα,4β,7β,7aα)-4-[2-(Acetiloxi)etil]-2-(4-ciano-1-naftalenil) hexahidro-7-metil-4,7-epoxi-1H-isoindol-1,3(2H)-diona, (246)



El compuesto 223B (0.100 g, 0.279 mmol) se disolvió en cloruro de metileno (3.0 mL) a 25°C y se agregaron piridina (0.071 mL, 0.837 mmol) y 4-DMAP (1.0 mg). Se agregó después anhídrido acético (0.053 mL, 0.559 mmol) y la reacción se agitó por 20 h a 25°C. Después de 20 h, se agregó bicarbonato de sodio saturado acuoso y la reacción se agitó por 30 min. La mezcla se extrajo después con cloruro de metileno (2 x 20 mL). Los orgánicos se lavaron después una vez con HCl 1N (10 mL) y después se secaron sobre sulfato de sodio anhidro. Después de la concentración in vacuo, el material crudo se purificó por CCD preparativa sobre sílice eluyendo con 12% acetona en cloroformo para dar 0.073 g de compuesto 246 como una espuma amarilla. CLAR: 95% a 2.837 y 3.027 min (atropisómeros, tiempo de retención) (Columna YMC S5 ODS 4.6 x 50 mm, 10-90% metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 441.10 $[M+Na]^+$.

Ejemplo 247

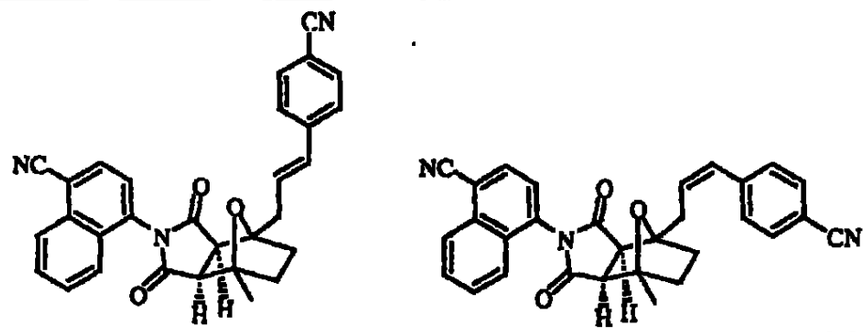
(3aα,4β,7β,7aα)-4-[Octahidro-4-metil-1,3-dioxo-7-(2-oxoetil)-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo, (247)



Se agregó cloruro de oxalilo (solución 2.0 M, 1.73 mL, 3.5 mmol) a cloruro de metileno seco (10 mL) y se enfrió hasta -78°C. Se agregó después DEMO (0.283 mL, 3.99 mmol) gota a gota con la evolución de gas. Después de 15 min., se agregó después el compuesto 223B (1.00 g, 2.66 mmol) en cloruro de metileno (10 mL). Después de 15 min., se agregó TEA (1.10 mL, 7.98 mmol) y la reacción se calentó lentamente hasta 25°C. Se agregó después agua (30 mL) y la mezcla se diluyó con cloruro de metileno (100 mL). Los orgánicos se lavaron después una vez con HCl 1 N (30 mL), una vez con agua (30 mL) y una vez con salmuera (30 mL) y después se secaron sobre sulfato de sodio anhidro. El producto crudo se aisló por concentración in vacuo para dar el compuesto 247 como una espuma color naranja. El compuesto crudo 247 se llevó directamente a la siguiente reacción. CLAR: 100% a 2.70 min (tiempo de retención) (Columna YMC S5 ODS 4.6 x 50 mm, 10-90%. metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 483.65 $[M+H]^+$.

Ejemplo 248

[3aα,4β,7β,7aα]-4[4-[3-(4-Cianofenilo)-2-propenil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo y [3aα,4β,7β,7aα]-4-[4-[3-(4-Cianofenil)-2-propenil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo (248i y 248ii)

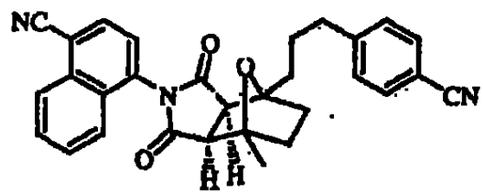


Se suspendió cloruro de (4-cianobencil)-trifenilfosfonio (0.072 g, 0.174 mmol) en THF (2.0 mL) y se enfrió hasta 0°C. Se agregó después n-BuLi (solución 1.6 M, 0.092 mL, 0.147 mmol) gota a gota resultando en una solución homogénea. La solución se calentó hasta 25°C por 15 min. y después se enfrió hasta 0°C. El compuesto 247 (0.050 g, 0.134 mmol) se agregó después en THF. Después de 1 h, la reacción se apagó con cloruro de amonio acuoso saturado y después se extrajo con cloruro de metileno (3 x 20 mL). Los orgánicos combinados se secaron sobre sulfato de sodio anhidro y después se concentraron in vacuo. El material crudo se purificó por CCD preparativa eluyendo con 5% acetona en cloroformo para dar 0.010 g de una mezcla de compuestos 248i y 248ii como un

sólido blanco. Una mezcla 1:1 de los isómeros de olefinas caracterizada por espectroscopia RMN. CLAR: 100% a 3.517 min. (tiempo de retención) (Columna YMC S5 ODS 4.6 x 50 mm, 10-90% metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM(ES): m/z 474.2 $[M+H]^+$.

Ejemplo 249

(3aα,4β,7β,7aα)-4-[4-[3-(4-Cianofenil)propil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo, (249)



La mezcla de compuestos 248i y 248ii (0.008 g, 0.017 mmol) se disolvió en EtOH (3.0 mL) y se agregó Pd/C (10% Pd, 0.008 g). Se introdujo después H_2 por medio de un globo. Después de 18 h, la reacción se filtró a través de Celite, eluyendo con EtOAc, seguido por la concentración in vacuo. Se aisló el compuesto 249 como un sólido blanco (0.007 g). CLAR: 90% a 3.520 min. (tiempo de retención) (Columna YMC S5 ODS 4.6 x 50 mm, 10-90% metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 476.13 $[M+H]^+$.

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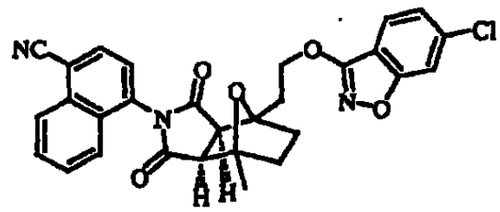
Ejemplo 250

(3aα,4β,7β,7aα)-4-[4-[2-[(6-Cloro-1,2-bencisoxazol-3-il)oxi]etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo, (250)

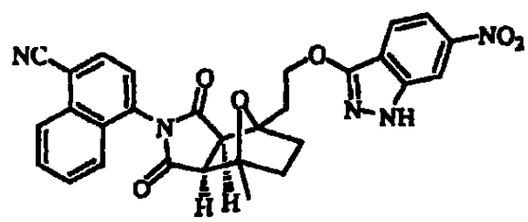


A una solución de PPh_3 (52 mg, 0.20 mmol) en 0.5 mL de THF, se agregó DBAD (46 mg, 0.20 mmol) como una porción sólida. La mezcla resultante se agitó por 10 min. antes de que se agregara 6-cloro-3-hidroxi-1,2-bencisoxazol (34 mg, 0.20 mmol). Se continuó la agitación por 10 min. antes de que se introdujera una solución del compuesto 223B (50 mg, 0.13 mmol) en 0.5 mL de THF por medio de una cánula. La mezcla resultante se agitó a temperatura ambiente por 24 h, se concentró in vacuo y se purificó por CLAR preparativa de fase inversa (Columna YMC S5 ODS 20 x 100 mm; eluyendo con 30-100% MeOH acuoso conteniendo 0.1% TFA durante 10 min. a 20 mL/min) para resultar un sólido blanco. Los sólidos obtenidos se disolvieron en CH_2Cl_2, se lavaron con solución saturada de $NaHCO_3$, se secaron sobre Na_2SO_4 y se concentraron in vacuo para dar 50 mg (71%) de compuesto 250 como un aceite incoloro. CLAR: 3.89 min. y 4.02 min. (atropisómeros, tiempo de retención) (Columna YMC S5 ODS 4.6 x 50 mm Ballistic, 10-

90% metanol acuoso durante 4 minutos conteniendo 0.2% H_3PO_4, 4 mL/min., observando a 220 nm). EM S): m/z 528.4 $[M+H]^+$.

Ejemplo 251

(3aα,4β,7β,7aα)-4-[Octahidro-4-metil-7-[2-[(6-nitro-1H-indazol-3-il)oxi]etil]-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo. (251)

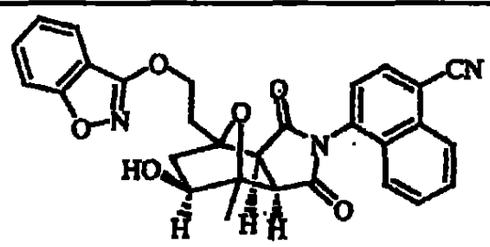


A una solución del compuesto 223B (50 mg, 0.13 mmol) en tolueno (1 mL) se agregó ADDP (50 mg, 0.20 mmol), 6-nitro-3-indazolinona (36 mg, 0.20 mmol) y n-BU_3P (50 µL, 0.2 mmol). La mezcla resultante se calentó a 80°C por 24 h, se concentró in vacuo y se purificó por una combinación de CLAR preparativa de fase inversa (Columna YMC S5 ODS 20 x 100 mm; eluyendo con 30-100% MeOH acuoso conteniendo 0.1% TFA durante 10 min. a 20 mL/min.) y cromatografía instantánea (gel de sílice, 25% acetona en $CHCl_3$) para dar 17 mg (25%) de compuesto 251 como un sólido amarillo. CLAR: 3.60 min. y 3.74 min. (atropisómeros, tiempo de retención) (Columna YMC S5 ODS 4.6 x 50 mm Ballistic, 10-90% metanol acuoso durante 4

minutos conteniendo 0.2% H_3PO_4, 4 mL/min., observando a 220 nm). EM (ES): m/z 537.6 $[M+H]^+$.

Ejemplo 252

[3aS-(3aα,4β,5β,7β,7aα)-4-[7-[2-(1,2-Bencisoxazol-3-iloxi)etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo. (252)

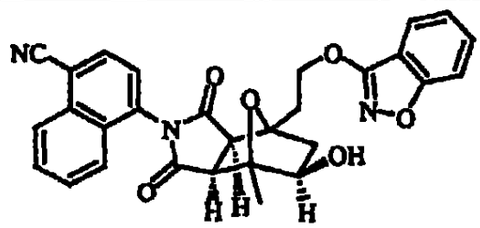


Se hicieron reaccionar PPh_3 (47 mg, 0.18 mmol), DBAD (41 mg, 0.18 mmol), 3-hidroxi-1,2-bencisoxazol (24 mg, 0.18 mmol) y el compuesto 243Di (35 mg, 0.09 mmol) de acuerdo con el procedimiento dado para el compuesto 250. La purificación se aCLanzó por CLAR de fase inversa (Columna YMC S5 ODS 20 x 100 mm; eluyendo con 30-100% MeOH acuoso conteniendo 0.1% TFA durante 10 min. a 20 mL/min.) para dar un sólido blanco. Los sólidos obtenidos se disolvieron en CH_2Cl_2, se lavó con una solución saturada de $NaHCO_3$, se secó sobre Na_2SO_4 y se concentró bajo presión reducida para lograr 29 mg (64%) de compuesto 252 como un aceite incoloro. CLAR: 96% a 3.29 min. (atropisómeros, tiempo de retención) (Columna YMC S5 ODS 4.6 x 50 mm Ballistic, 0-100% metanol acuoso durante 4 minutos

conteniendo 0.2% H_3PO_4, 4 mL/min., observando a 220 nm). EM (ES): m/z 510.2 $[M+H]^+$.

Ejemplo 253

[3aR-(3aα,4β,5β,7β,7aα)]-4-[7-[2-(1,2-Bencisoxazol-3-iloxi)etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo. (253)

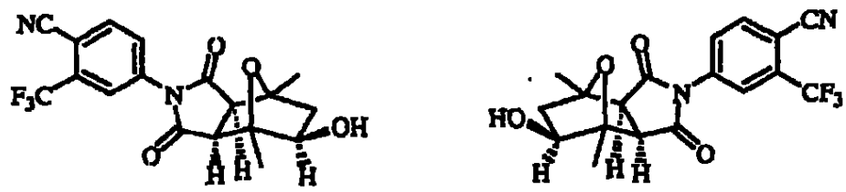


Se hicieron reaccionar el PPh_3 (47 mg, 0.18 mmol), DBAD (41 mg, 0.18 mmol), 3-hidroxi-1,2-bencisoxazol (24 mg, 0.18 mmol) y compuesto 243Dii (35 mg, 0.09 mmol) de acuerdo con el procedimiento dado por el compuesto 250. La purificación se aCLanzó por CLAR de fase inversa (Columna YMC S5 ODS 20 x 100 mm; eluyendo con 30-100% de MeOH acuoso conteniendo 0.1% TFA durante 10 min. a 20 mL/min.) para resultar un sólido blanco. Los sólidos obtenidos se disolvieron en CH_2Cl_2, se lavaron con una solución saturada de $NaHCO_3$, se secaron sobre Na_2SO_4 y se concentró bajo presión reducida para lograr 23 mg (51%) de compuesto 253 como un aceite incoloro. CLAR: 95% a 3.29 min. (atropisómeros. tiempo de retención) (Columna YMC S5 ODS 4.6 x 50 mm Ballistic, 0-100% metanol acuoso durante 4 minutos

conteniendo 0.2% H_3PO_4, 4 mL/min., observando a 220 nm). EM (ES): m/z 510.4 $[M+H]^+$.

Ejemplo 254

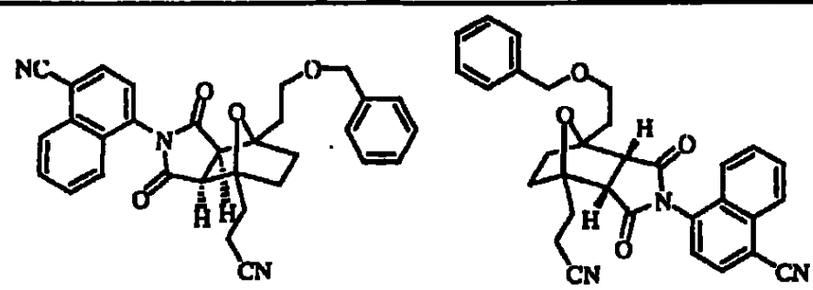
[3aR-(3aα,4β,5β,7β,7aα)]-4-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo y [3aS-(3aα,4β,5β,7β,7aα)]-4-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo, (254i y 254ii)



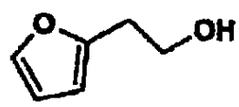
El compuesto racémico 221B se separó en sus enantiómeros por CLAR quiral preparativa de fase normal(columna CHIRALPAK AD 5 x 50 cm; eluyendo con 20% MeOH/EtOH (1:1) en heptano (isocrática) a 50 mL/min.) para dar el compuesto de elución más rápida 254i (Chiral CLAR: 10.02 min.; columna CHIRALPAK AD 4.6 x 250 mm; eluyendo con 20% MeOH/EtOH (1:1) en heptano a 1 mL/min.) y el de elución más lenta 254ii (CLAR quiral: 14.74 min.; columna CHIRALPAK AD 4.6 x 250 mm; eluyendo con 20% MeOH/EtOH (1:1) en heptano a 1 mL/min). (Los nombres de los compuestos del título se basan en la determinación de la estereoquímica absoluta).

Ejemplo 255

(3aα,4β,7β,7aα)-2-(4-Ciano-1-naftalenil)octahidro-1,3-dioxo-7-[2-(fenilmetoxi)etil]-4,7-epoxi-4H-isoindol-4-propanonitrilo y (3aα,4α,7α,7aα)-2-(4-Ciano-1-naftalenil)octahidro-1,3-dioxo-7-[2-(fenilmetoxi)etil]-4,7-epoxi-4H-isoindol-4-propanonitrilo. (255H1 y 255Hii)



A. 2-(2-Hidroxietil)furano (255A)



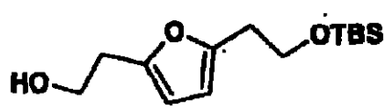
Se preparó el 2-(2-Hidroxietil)furano de acuerdo con la siguiente referencia: Harmata, M, et al. J. Org. Chem. 60, 5077-5092 (1995). Se agregó n-BuLi (2.5 M en hexano, 44 mL, 110 mmol) a una solución de furano (8 mL, 110 mmol) en 100 mL de THF a -78°C. La solución se agitó a 0°C por 4 h y después se agregó óxido de etileno (7.5 mL) a -78°C. La mezcla de reacción se agitó a -15°C por 1 h y después durante la noche a temperatura ambiente. La reacción se apagó con NH_4Cl saturado y se extrajo con éter (3X). Los extractos combinados se lavaron con agua (1X) y salmuera (1X). La solución de éter

se secó sobre Na_2SO_4 y se concentró bajo presión reducida. La purificación por cromatografía instantánea sobre gel de sílice eluyendo con 40% EtOAc/60% hexano dio 5.4 g (48.2 mmol, 43.8%) de compuesto 255A como un aceite café claro.

B. 2-[2-[[(1,1-Dimetiletil)dimetilsilil]oxi]etil]furano(255B)

Se agregaron imidazol (3.65 g, 53.6 mmol) y TBSCl (6.47 g, 42.9 mmol) a la solución del compuesto 255A (4.00 g, 35.7 mmol) en 50 mL de DMF. La mezcla se agitó a temperatura ambiente por 2 h y después la mezcla de reacción se vació en éter. La solución de éter se lavó con agua (1X), HCl 1N (1X), agua (1X) y salmuera (1X). La capa orgánica se secó sobre Na_2SO_4 y se concentró bajo presión reducida. La purificación por cromatografía instantánea sobre gel de sílice eluyendo con 30% CH_2Cl_2/70% hexano dio 7.4 g (32.7 mmol, 91.7%) de 255B como un aceite incoloro.

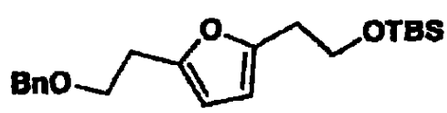
C. 2-[2-[[(1,1-Dimetiletil)dimetilsilil]oxi]etil]-5-(2-hidroxietil)furano (255C)



Se agregó t-BuLi (1.2 M en pentano, 10 mL, 16.99 mmol) a una solución agitada de 255B (3.49 g, 15.44 mmol) en 13 mL de

THF a -78°C gota a gota. La mezcla se agitó por 4 h adicionales a 0°C. Óxido de etileno (1.05 mL) se agregó a -78°C a la solución de reacción. La mezcla se calentó a temperatura ambiente y se agitó durante la noche. Se agregó NH_4Cl saturado acuoso y se separó la mayor parte del THF bajo presión reducida. La mezcla se extrajo con éter (3X) y las capas orgánicas combinadas se lavaron con agua (1X) y salmuera (1X) y se secaron sobre Na_2SO_4. La purificación por cromatografía instantánea sobre gel de sílice eluyendo con 5% EtOAc/95% CH_2Cl_2 dio 2.8 g (10.4 mmol, 67%) de compuesto 255C como un aceite amarillo.

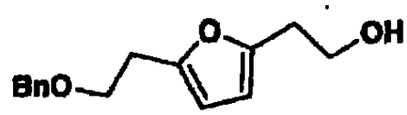
D. 2-[2-[[(1,1-Dimetiletil)dimetilsilil]oxi]etil]-5-[2-(fenilmetoxi)etil]furano(255D)



El alcohol 255C (1.00 g, 3.7 mmol) en 12 mL de THF se trató con 60% de NaH (177.8 mg, 4.44 mmol), bromuro de bencilo (0.53 mL, 4.44 mmol) y yoduro de tetrabutilamonio (50 mg, 5%) por 3 h a temperatura ambiente. Se agregó agua y la mezcla se extrajo con EtOAc (3X). Los extractos combinados se lavaron con agua (1X) y salmuera (1X) y se secaron sobre Na_2SO_4. La purificación por cromatografía instantánea sobre gel de sílice eluyendo con 20% hexano/80% CH_2Cl_2 dio 1.10 g (3.05 mmol, 82.6%) de compuesto 255D como un aceite amarillo.

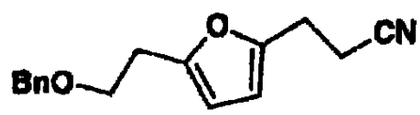
256

E. 2-(2-Hidroxietil)-5-[2-(fenilmetoxi)etil]furano (255E)



Se agregó fluoruro de tetrabutilamonio (1.0 M en THF, 3.06 mL, 3.06 mmol) a la solución del compuesto 255D (1.1 g, 3.06 mmol) en 10 mL de THF a 0°C. La mezcla de reacción se agitó a temperatura ambiente por 10 minutos, se apagó con NH_4Cl saturado y se extrajo con éter (3X). Los extractos combinados se secaron sobre Na_2SO_4. La purificación por cromatografía instantánea sobre gel de sílice eluyendo con 10% EtOAc/90% CH_2Cl_2 dio 750 mg (3.05 mmol, 99.6%) de compuesto 255E como un aceite amarillo claro.

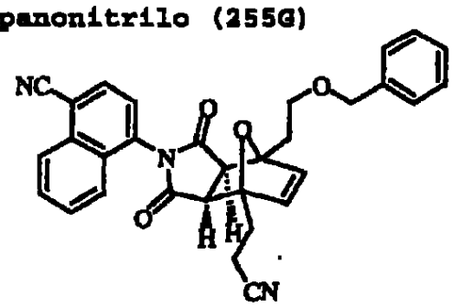
F. 5-[2-(Fenilmetoxi)etil]furan-2-propanonitrilo (255F)



Se agregó DEAD (1.285 mL, 8.17 mmol) a una solución agitada de Ph_3P (2.14 g, 8.17 mmol) en 12 mL de THF seco a 0°C. La solución se agitó por 30 min. a temperatura ambiente y se agregó el compuesto 255E (670 mg, 2.72 mmol). La reacción se agitó por 15 min. y se agregó acetona cianohidrina (0.745 mL, 8.17 mmol) a -15°C. La reacción se agitó por 30 min. a -15°C, después a temperatura ambiente durante la noche. La mezcla se concentró después bajo presión reducida. La purificación por cromatografía instantánea sobre

gel de sílice eluyendo con 100% CH_2Cl_2 dio 180 mg (0.705 mmol, 26%) de compuesto 255F como un aceite incoloro.

G. (3aα,4β,7β,7aα)-2-(4-Ciano-1-naftalenil)-1,2,3,3a,7,7a-hexahidro-1,3-dioxo-7-[2-(fenilmetoxi)etil]-4,7-epoxi-4H-isoindol-4-propanonitrilo (255G)



Una solución del compuesto 255F (180 mg, 0.706 mmol) y 4-(2,5-dihidro-2,5-dioxo-1H-1-il)-1-naftalencarbonitrilo (263 mg, 1.06 mmol) en CH_2Cl_2 (3 mL) se agitó a temperatura ambiente por 3 días. La mezcla de reacción se concentró bajo presión reducida. La purificación por cromatografía instantánea sobre gel de sílice eluyendo con 5% EtOAc/CH_2Cl_2, dio 318 mg (0.63 mmol, 89.6%) del compuesto 255G como un sólido gris claro que se usó directamente en la siguiente etapa.

H. (3aα,4β,7β,7aα)-2-(4-Ciano-1-naftalenil)octahidro-1,3-dioxo-7-[2-(fenilmetoxi)etil]-4,7-epoxi-4H-isoindol-4-propanonitrilo y (3aα,4α,7α,7aα)-2-(4-Ciano-1-

naftalenil)octahidro-1,3-dioxo-7-[2-(fenilmetoxi)etil]-4,7-epoxi-4H-isoindol-4-propanonitrilo (255Hi y 255Hii)

Una mezcla de compuesto 255G (318 mg, 0.63 mmol) y 10% Pd/C (64 mg) en EtOH (10 mL) y EtOAc (5 mL) se agitó bajo una atmósfera de hidrógeno a temperatura ambiente durante la noche. La mezcla de reacción se filtró a través de Celite y se concentró bajo presión reducida para dar 320 mg de los compuestos crudos 255Hi y 255Hii. La purificación de 25 mg de este producto crudo por cromatografía instantánea sobre gel de sílice eluyendo con 55% EtOAc/hexano dio 6.5 mg (0.013 mmol, 26% (basado en 25 mg)) de compuesto 255Hi y 8.1 mg (0.016 mmol, 32.4% (basado en 25 mg)) de compuesto 255Hii. Compuesto 255Hi: Condiciones CLAR: 98% a 3.57 min. (tiempo de retención) (YMC S5 ODS 4.6 x 50 mm, 10%-90% metanol acuoso durante un gradiente de 4 minutos con 0.2% H_3PO_4, detectando a 220 nm, EM(ES): m/z 506.15 $[M+H]^+$. Compuesto 255Hii: Condiciones CLAR: 98% a 3.51 min. (tiempo de retención) (YMC S5 ODS 4.6 x 50 mm, 10%-90% metanol acuoso durante un gradiente de 4 minutos con 0.2% H_3PO_4 detectando a 220 nm). EM (ES): m/z 506.15 $[M+H]^+$.

Ejemplo 256

(3aα,4β,7β,7aα)-2-(4-Ciano-1-naftalenil)octahidro-7-(2-hidroxietil)-1,3-dioxo-4,7-epoxi-4H-isoindol-4-propanonitrilo

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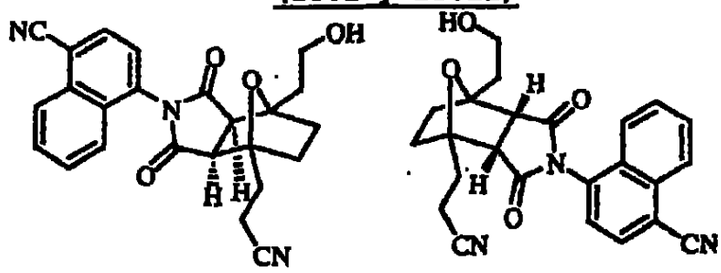
y (3aα,4α,7α,7aα)-2-(4-Ciano-1-naftalenil)octahidro-7-(2-hidroxietil-1,3-dioxo-4,7-epoxi-4H-isoindol-4-propanonitrilo, (256i y 256ii)

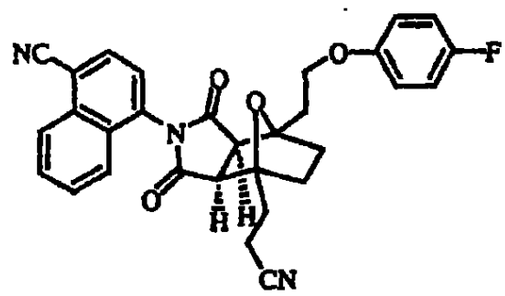


Una mezcla de compuestos 255Hi y 255Hii (200 mg, 0.396 mmol) y $PdCl_2$ (8.4 mg, cat.) en EtOH (1 mL) y EtOAc (3 mL) se agitó bajo una atmósfera de hidrógeno (30 psi-2.11 kg/cm^2) a temperatura ambiente durante la noche. La mezcla de reacción se filtró a través de Celite y se concentró bajo presión reducida. La purificación por cromatografía instantánea sobre gel de sílice eluyendo con 5% MeOH/CH_2Cl_2 seguida por una segunda columna eluyendo con 100% EtOAc dio 28.9 mg (0.0696 mmol, 17.6%) de compuesto 256ii y 26.5 mg (0.0639 mmol, 16.1%) de compuesto 256i. Compuesto 256ii: Condiciones CLAR: 90% a 2.44 min. (tiempo de retención) (YMC S5 ODS 4.6 x 50 mm, 10%-90% metanol acuoso durante un gradiente de 4 minutos con 0.2% H_3PO_4, detectando a 220 nm.). EM(ES): m/z 416.11 $[M+H]^+$. Compuesto 256i: Condiciones CLAR: 99% a 2.47 min. (tiempo de retención) (YMC S5 ODS 4.6 x 50 mm, 10%-90% metanol acuoso durante un gradiente de 4 minutos con 0.2% H_3PO_4, detectando a 220 nm). EM(ES): m/z 416.11 $[M+H]^+$.

760

Ejemplo 257

(3aα,4β,7β,7aα)-2-(4-Ciano-1-naftalenil)-7-[2-(4-fluorofenoxi)etil]octahidro-1,3-dioxo-4,7-epoxi-4H-isoindol-4-propanonitrilo. (257)

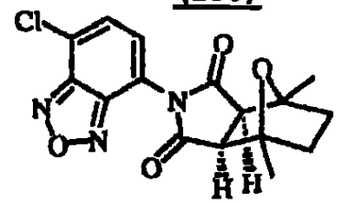


Se agregó DBAD (15 mg, 0.065 mmol) a una solución de PPh_3 (17 mg, 0.065 mmol) en THF (0.3 mL). Después de agitar por 10 min., se agregó 4-fluorofenol (7.33 mg, 0.065 mmol) y la mezcla de reacción se agitó por 5 min. adicionales. Se agregó el compuesto 256i (18.1 mg, 0.044 mmol) y la mezcla se agitó a temperatura ambiente por 3 h. La reacción se concentró bajo presión reducida. La purificación por cromatografía instantánea sobre gel de sílice eluyendo con 60% EtOAc/30% hexano dio 5.9 mg (0.0116 mmol, 26.34%) de compuesto 257. Condiciones CLAR: 98% a 3.59 min. (tiempo de retención) (YMC S5 ODS 4.6 x 50 mm, 10%-90% metanol acuoso durante un gradiente de 4 minutos con 0.2% H_3PO_4, detectando a 220 nm). EM (ES): m/z 510.14 $[M+H]^+$.

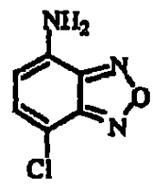
261

Ejemplo 258

(3aα,4β,7β,7aα)-2-(7-Cloro-2,1,3-benzoxadiazol-4-il)hexahidro-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3(2H)-diona, (258)



A. 4-Amino-7-cloro-2,1,3-benzoxadiazol (258A)



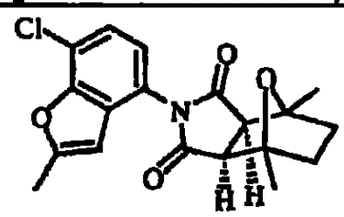
Una solución de 1.0 g (5.02 mmol) de 4-cloro-7-nitrobenzofurazano en 20 mL de AcOH, 10 mL de EtOAc y 2 mL de H_2O se calentó a 50°C y se trató con polvo de hierro (1.4 g, 251 mmol). La mezcla se calentó a 80°C por 30 min. y después se dejó enfriar a temperatura ambiente. La mezcla se filtró a través de Celite eluyendo con EtOAc. El filtrado se lavó con $NaHCO_3$ acuoso saturado, se secó sobre $MgSO_4$, y se concentró bajo presión reducida para dar el compuesto 258A (0.80 g, 94%) como un sólido rojo.

B. (3aα,4β,7β,7aα)-2-(7-Cloro-2,1,3-benzoxadiazol-4-il)hexahidro-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3(2H)-diona, (258B)

El compuesto 258A (42 mg, 0.25 mmol) reaccionó en un tubo sellado con el compuesto 20A (73.5 mg, 0.375 mmol), $MgSO_4$ (75 mg, 0.625 mmol) y Et_3N (170 µL, 1.25 mmol) en 250 µL de tolueno según el procedimiento anterior descrito en el ejemplo 208C para dar después de la purificación por CLAR preparativa de fase inversa (YMC S5 ODS 20 x 100 mm eluyendo con 30-100% metanol acuoso conteniendo 0.1% TFA durante 12 min., 20 mL/min.) 23 mg (26%) de compuesto 258B como un sólido amarillo. CLAR: 97.6% a 2.87 min. (tiempo de retención) (Columna YMC S5 ODS 4.6 x 50 mm eluyendo con 10-90% metanol acuoso conteniendo 0.2% ácido fosfórico durante 4 minutos, 4 mL/min., observando a 220 nm). EM (DCI): m/z 347.9 $[M]^+$.

Ejemplo 259

(3aα,4β,7β,7aα)-2-(7-Cloro-2-metil-4-benzofuranil)hexahidro-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3(2H)-diona.(259)

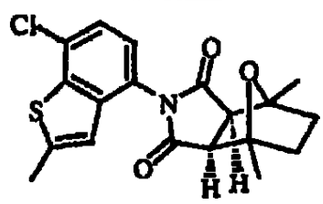


La 7-Cloro-2-metil-4-benzofuranamina (38 mg, 0.25 mmol, preparada según el procedimiento descrito por Enomoto y Takemura en EP 0476697 A1) reaccionó en un tubo sellado con compuesto 20A (73.5 mg, 0.375 mmol), $MgSO_4$ (75 mg, 0.625 mmol) y Et_3N (170 µL, 1.25 mmol) en 250 µL de tolueno de

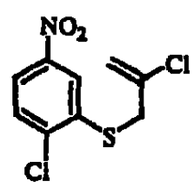
acuerdo con el procedimiento descrito en ejemplo 208C para dar, Después de purificación por CLAR preparativa de fase inversa (YMC S5 ODS 20 x 100 mm eluyendo con 30-100 metanol acuoso conteniendo 0.1% TFA durante 12 min., 20 mL/min.), 42 mg (47%) de compuesto 259 como un sólido blanco. CLAR: 98% a 3.45 min. (tiempo de retención) (Columna YMC S5 ODS 4.6 x 50 mm eluyendo con 10-90% metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (DCI):m/z 359.9 $[M]^+$.

Ejemplo 260

(3aα,4β,7β,7aα)-2-(7-Cloro-2-metilbenzo[b]tiofen-4-il)hexahidro-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3(2H)-diona, (260)



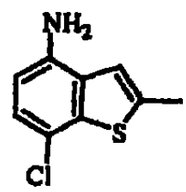
A. 1-Cloro-2-(2-cloro-alilsulfanil)-4-nitro-benceno (260A)



Una solución de 2-cloro-5-nitro-bencenotiol (1.0 g, 5.27 mmol, preparada según el procedimiento descrito por Still et al. Synth. Comm. 13, 1181 (1983)) en 15 mL de DMF, se trató

con 2,3-dicloropropeno (693 µL, 7.52 mmol) y K_2CO_3 (433 mg, 3.13 mmol). La mezcla se calentó a 80°C por 2 h y se dejó después enfriar a temperatura ambiente. Se agregaron EtOAc (200 mL) y H_2O (100 mL). La fase orgánica se lavó con H_2O (2 x 250 mL), NaCl acuoso saturado (100 mL), se secó sobre $MgSO_4$, y se concentró in vacuo. El material crudo se purificó por cromatografía instantánea en columna sobre gel de sílice eluyendo con 20% EtOAc en hexanos para dar el compuesto 260A (1.09 g, 89%) como un aceite color naranja.

B. 4-Amino-7-cloro-2-metilbenzo[b]tiofeno (260B)



Una solución de 1.09 g (4.67 mmol) de compuesto 260A en 20 mL de AcOH con 10 mL de EtOAc y 2 mL de H_2O se calentó hasta 80°C y se trató con polvo de hierro (1.3 g, 23.4 mmol). La mezcla se calentó a 80°C por 40 min. y después se dejó enfriar a temperatura ambiente. La mezcla se filtró a través de Celite eluyendo con EtOAc. El filtrado se lavó con $NaHCO_3$ saturado acuoso, se secó sobre $MgSO_4$, y se concentró in vacuo. Se agregó N,N-dietilanilina (10 mL), y la reacción se calentó a 215°C por 6 h. Después de enfriar a temperatura ambiente, se agregó HCl 1 N acuoso (20 mL), y la reacción se agitó a temperatura ambiente por 2 h. La mezcla se extrajo

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con EtOAc (3 x 30 mL). La fase orgánica se lavó con $NaHCO_3$ acuoso saturado, se secó sobre $MgSO_4$, y se concentró in vacuo. El material crudo se purificó por cromatografía instantánea en columna sobre gel de sílice eluyendo con 25% EtOAc en hexanos para dar el compuesto 260B (320 mg, 35%) como un sólido color beige.

C. (3aα,4β,7β,7aα)-2-(7-Cloro-2-metilbenzo[b]tiofen-4-il)hexahidro-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3(2H)-diona, (260C)

El compuesto 260B (49 mg, 0.25 mmol) reaccionó en un tubo sellado con el compuesto 20A (73.5 mg, 0.38 mmol), $MgSO_4$ (75 mg, 0.63 mmol) y Et_3N (170 µL, 1.25 mmol) en 250 µL de tolueno según el procedimiento descrito en el ejemplo 208C para dar, después de la purificación por CLAR preparativa de fase inversa (YMC S5 ODS 20 x 100 mm eluyendo con 30-100% metanol acuoso durante 12 min. conteniendo 0.1% TFA, 20 mL/min.), 28 mg (30%) de compuesto 260C como un sólido amarillo pálido. CLAR: 96% a 3.18 min. (tiempo de retención) (Columna YMC S5 ODS 4.6 x 50 mm eluyendo con 10-90% metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (DCI): m/z 376.0 $[M]^+$.

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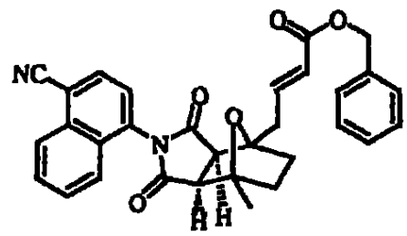
Ejemplo 261

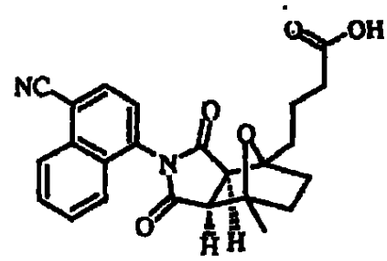
Éster de fenilmetílico del ácido [3aα,4β(E),7β,7aα]-4-[2-(4-ciano-1-naftalenil)octahidro-7-metil-1,3-dioxo-4,7-epoxi-4H-isoindol-4-il]-2-butenoico, (261)



El compuesto 247 (0.500 g, 1.34 mmol) se disolvió en THF (20 mL) y se agregó bencil(trifenilfosforanilideno) (0.55 g, 1.34 mmol). La mezcla de reacción se agitó a 67°C por 2 h y después se concentró bajo presión reducida. La purificación por cromatografía instantánea sobre SiO_2 eluyendo con 5% acetona/95% $CHCl_3$ dio 0.65 g de compuesto 261 como un sólido amarillo. CLAR: 99% a 3.717 min. (tiempo de retención) (Columna YMC S5 ODS 4.6 x 50 mm eluyendo con 10-90% metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 507.1 $[M+H]^+$.

Ejemplo 262

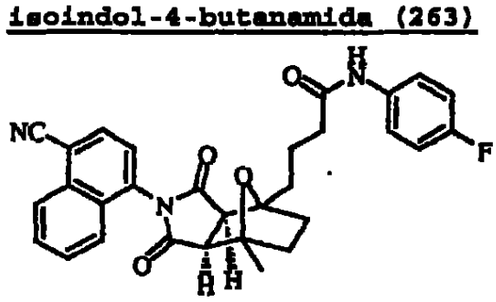
Ácido (3aα,4β,7β,7aα)-2-(4-Ciano-1-naftalenil)octahidro-7-metil-1,3-dioxo-4,7-epoxi-4H-isoindol-4-butanoico, (262)



El compuesto 261 (0.60 g, 1.19 mmol) se disolvió en EtOH/EtOAc (5mL/5mL) y se agregó 10% Pd/C (0.30 g). Se introdujo después hidrógeno por medio de un globo. Después de 8 h la reacción se filtró a través de Celite y después se concentró bajo presión reducida para dar el compuesto 262 (0.47 g) como un sólido blanco. CLAR: 98% a 2.81 min. (tiempo de retención) (Columna YMC S5 ODS 4.6 x 50 mm eluyendo con 10-90% metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 419.1 $[M+H]^+$.

Ejemplo 263

(3aα,4β,7β,7aα)-2-(4-Ciano-1-naftalenil)-N-(4-fluorofenil)octahidro-7-metil-1,3-dioxo-4,7-epoxi-4H-isoindol-4-butanamida (263)

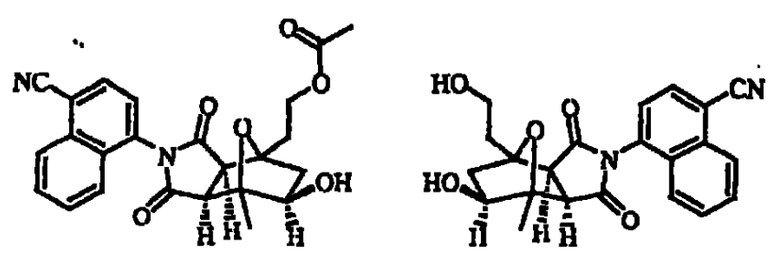


El compuesto 262 (0.030 g, 0.072 mmol) se disolvió en CH_3CN (1 mL). Se agregaron después DCC (0.014 g, 0.072 mmol)

y HOAc (0.0098 g, 0.072 mmol), seguido por 4-fluoroanilina (0.007 mL, 0.072 mmol). La mezcla de reacción se agitó bajo argón por 14 h y el material crudo se disolvió en MeOH, se purificó por CLAR preparativa de fase inversa (YMC VP-ODS columna, 20 x 100 mm, eluyendo con 20% B hasta 100% B en 15 minutos y se mantuvo @ 100% B por 10 minutos). Se aisló el compuesto 263 (0.020 g) como un sólido blanco. CLAR: 100% a 3.217 min. (tiempo de retención) (Columna YMC S5 ODS 4.6 x 50 mm eluyendo con 10-90% metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min, observando a 220 nm). EM (ES): m/z 512.1 $[M+H]^+$.

Ejemplo 264

[3aS-(3aα,4β,5β,7β,7aα)]-4-[7-[2-(Acetiloxi)etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo y [3aR-(3aα,4β,5β,7β,7aα)]-4-[Octahidro-5-hidroxi-7-(2-hidroxietil)-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo. (264 y 243Dii)



Una mezcla racémica de los compuestos 243Di y 243Dii (1.90 gramos) se disolvió en 100 mL de THF anhidro en un

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matraz de 2 L. Se transfirieron éter de metil tert-butilo anhidro (900 mL) y acetato de vinilo (40 mL) en el matraz con agitación, y se agregó lipasa (20 g, tipo II, cruda, de páncreas porcino; Sigma, Cat# L3126). La mezcla de reacción se agitó por 21 hr a temperatura ambiente, punto en el cual se agregaron 5 gramos adicionales de la lipasa y 20 mL de acetato de vinilo. La reacción se agitó a temperatura ambiente por 19 h adicionales, se almacenó a 4°C sin agitación por 36 h y después se agitó a temperatura ambiente por otras 22 h (hasta que el % ee deseado fue evidente por CLAR quiral). Para observar la reacción, se retiraron 200 uL de la mezcla y se centrifugaron. Se secó el sobrenadante (100 uL) bajo nitrógeno y el residuo resultante se disolvió en 100 uL de EtOH y se sometió a un análisis por CLAR:

1) CLAR de fase inversa: Columna, YMC-ODS AQ 150x4.6; relación de flujo, 1.2 mL/min.; tamaño de muestra, 10 uL solvente A,: HCl 1 mM en agua; solvente B, MeCN; observado a 300 nm

Gradiente:

Tiempo(min.)	0	8	8.5	9.5	10	12
B%	30	60	85	85	30	30

2) CLAR quiral: Columna, CHIRACLEL OJ 4.6 x 250 mm fase móvil, hexanos/MeOH/EtOH (8:1:1) relación de flujo, 1 mL/min.; tamaño de muestra, 20 uL observado a 220 y 300 nm

llevado a cabo a 25°C y 40°C.

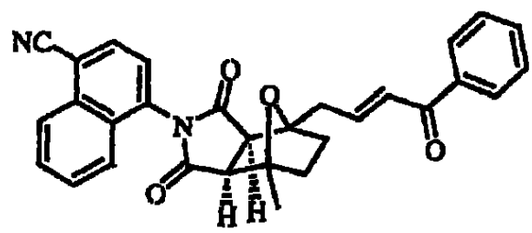
(para la determinación del %ee de la mezcla de reacción)

La enzima se separó por filtración y el filtrado se concentró bajo presión reducida. La mezcla resultante se disolvió en $CHCl_3$ y se absorbió sobre gel de sílice (63-200 micras). Estos sólidos se aplicaron a un embudo VCL (3 cm D.I., VCL es cromatografía líquida a vacío usando embudos de vidrio que tienen uniones 24/40 en el fondo) conteniendo una altura de lecho de 5 cm de gel de sílice (25-40 micras) y se llevó a cabo un gradiente por etapas. El gradiente fue de 100% $CHCl_3$ en las primeras 3 fracciones, seguido por $CHCl_3$-1% MeOH (3 fracciones), $CHCl_3$-2% MeOH (3 fracciones), $CHCl_3$-3% MeOH (3 fracciones), $CHCl_3$-4% MeOH (3 fracciones), y finalmente con $CHCl_3$-5% MeOH (3 fracciones). El volumen de las fracciones fue de 100 mL hasta aCLanzar $CHCl_3$-3% MeOH y desde ese punto fue 200 mL. El compuesto 264 eluye en al menos dos fracciones de 100% $CHCl_3$ y hasta la primera fracción de CHC_3-2% MeOH. El compuesto 243Dii eluye partiendo con la segunda fracción de $CHCl_3$-2% MeOH, y continua a la primera fracción de $CHCl_3$-5% MeOH. El compuesto crudo 243Dii contiene una cantidad pequeña de una impureza coloreada que se elimina por una columna Sephadex [LH-20 aumentada en $CHCl_3$-MeOH (2:1), columna (2.5 cm D.I. y 90 cm de largo) para dar 632 mg del compuesto 243Dii. Compuesto 264: Condiciones CLAR: 98% a 7.2 min. (tiempo de retención) (método 1),

Condiciones CLAR quiral: 29.0 min. @ 25°C (método 2). Compuesto 243Dii: Condiciones CLAR: 98% a 4.6 min. (tiempo de retención) (método 1), Condiciones CLAR quiral: 96% ee a 25.7 min. (tiempo de retención) (@ 25°C) y 19.8 min. (tiempo de retención) (@ 40°C) (método 2).

Ejemplo 265

(3aα,4β,7β,7aα(E)]-4-[Octahidro-4-metil-1,3-dioxo-7-(4-oxo-4-fenil-2-butenil)-4,7-epoxi-2H-isoindol-2-il)-1-naftalencarbonitrilo. (265)

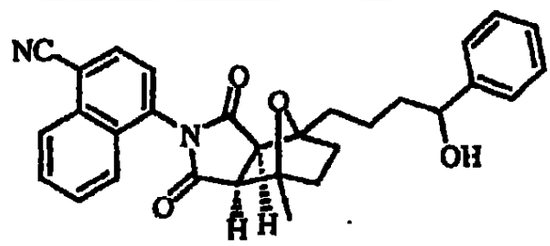


El compuesto 247 (0.050 g, 0.134 mmol) se disolvió en THF (1.5 mL) y se agregó (fenaciliden)trifenilfosforano (0.051 g, 0.134 mmol). La mezcla de reacción se agitó a 67°C por 24 h y después se enfrió hasta 23°C y se concentró in vacuo. El material crudo se purificó después por CLAR preparativa de fase inversa. (Columna YMC VP-ODS, 20 x 100 mm, eluyendo con 20% B hasta 100%B en 15 minutos y se mantiene @ 100%B por 10 minutos.) para dar el compuesto 265 (0.040 g) como un sólido blanco. CLAR: 100% a 3.503 min. (tiempo de retención) (Columna YMC S5 ODS 4.6 x 50 mm eluyendo con 10-90% metanol acuoso durante 4 minutos

conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM(ES): m/z 477.1 $[M+H]^+$.

Ejemplo 266

(3aα,4β,7β,7aα(E)]-4-Octahidro-4-metil-1,3-dioxo-7-(4-hidroxi-4-fenil-2-butil)-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo. (266)



El compuesto 265 (0.010 g, 0.021 mmol) se disolvió en EtOH (2.0 mL) y se agregó Pd/C (10% Pd, 0.005 g). Se introdujo después el hidrógeno por medio de un globo y la reacción se agitó a 25°C por 3 h. La reacción se filtró después a través de Celite enjuagando con EtOAc y se concentró in vacuo para dar el compuesto 266 como un sólido café claro (0.009 g). No fue necesaria purificación. CLAR: 100% a 3.38 min. (tiempo de retención) (Columna YMC S5 ODS 4.6 x 50 mm eluyendo con 10-90% metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 503.2 $[M+Na]^+$. (Donde esta reacción se corrió por 1 hora, el producto resultante fue el compuesto 455.)

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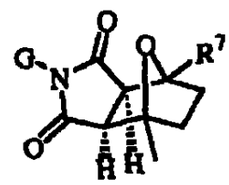
Ejemplos 267 a 378

Los compuestos adicionales de la presente invención se prepararon por procedimientos análogos a aquellos antes descritos. Los compuestos de los Ejemplos 267 al 378 tienen la siguiente estructura (L es un enlace):

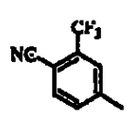
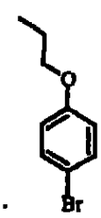
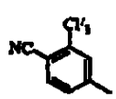
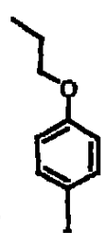


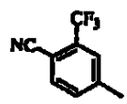
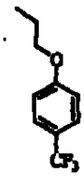
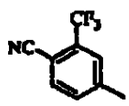
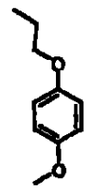
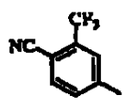
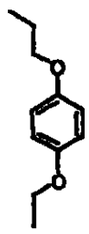
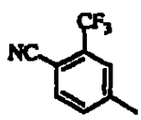
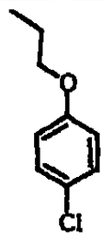
en donde G, R^7, el nombre del compuesto, tiempo de retención, masa molecular, y el procedimiento empleado, son establecidos en la Tabla 5. La configuración absoluta para los siguientes compuestos no se determinó. Por simplicidad en la nomenclatura, el compuesto 238i se designa en la presente como que tiene una configuración "R" y el compuesto 238ii como que tiene una configuración "S". Los productos enantioméricamente puros derivados de los compuestos 238i se designan en la presente por tener una configuración "R" y los productos enantioméricamente puros derivados del compuesto 238ii se designan en la presente por tener una configuración "S".

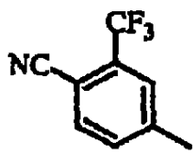
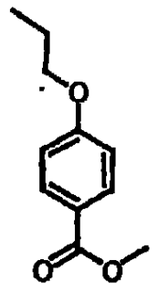
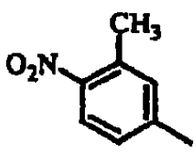
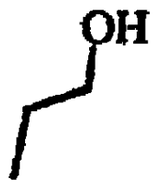
Las técnicas de cromatografía usadas para determinar los tiempos de retención de los compuestos de la Tabla 5 son como siguen: CLEM = Columna YMC S5 ODS, 4.6 X 50 mm eluyendo con 10-90% MeOH/H_2O durante 4 minutos conteniendo 0.1 % TFA; 4 mL/min., observando a 220 nm. CLEM* = Columna YMC S5 ODS, 4.6

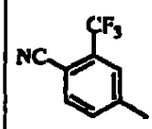
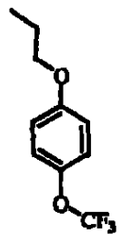
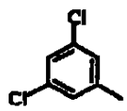
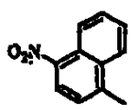
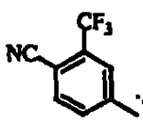
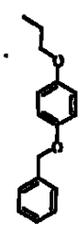
X 50 mm eluyendo con 10-90% MeOH/H_2O durante 2 minutos conteniendo 0.1% TFA; 4 mL/min., observando a 220 nm. CL = Columna YMC S5 ODS 4.6 x 50 mm eluyendo con 10-90% MeOH/H_2O durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min, observando a 220 nm. La masa molecular de los compuestos enlistados en la Tabla 5 se determinaron por EM(ES) por la fórmula m/z.

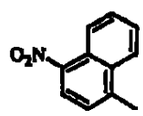
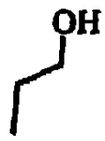
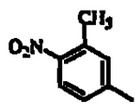
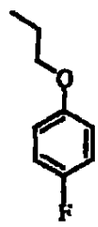
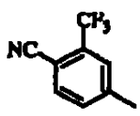
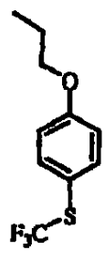
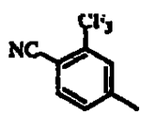
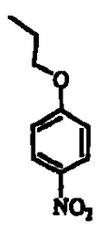
Tabla 5.

Ej. No.	G	R^7	Nombre del Compuesto	Tiempo de retención Min./Masa Molecular	Proced. del Ej.
267			(3aα,4β,7β,7aα)-(4-[7-[2-(4-bromofenoxi)etil]octahidro-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2-(trifluorometil)benzonitrilo	3.97 CLEM 549.0 $[M+H]^+$	204, 35
268			(3aα,4β,7β,7aα)-4-[octahidro-7-[2-(4-yodofenoxi)etil]-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2-(trifluorometil)benzonitrilo	4.09 CLEM 597.0 $[M+H]^+$	204, 35

Ej. No.	G	R^7	Nombre del Compuesto	Tiempo de retención Min./Masa Molecular	Proced. del Ej.
269			(3aα,4β,7β,7aα)-4-[octahidro-4-metil-1,3-dioxo-7-]2-[4-(trifluorometil)fenoxi]etil]-4,7-epoxi-2H-isoindol-2-il]-2-(trifluorometil)benzonitrilo	395 CL	204, 35
270			(3aα,4β,7β,7aα)-4-[octahidro-7-[2-(4-metoxifenoxi)etil]-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2-(trifluorometil)benzonitrilo	3.66 CL	204, 35
271			(3aα,4β,7β,7aα)-4-[7-[2-(4-etoxifenoxi)etil]octahidro-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2-(trifluorometil)benzonitrilo	3.81 CL	204, 35
272			(3aα,4β,7β,7aα)-4-[7-[2-(4-clorofenoxi)etil]octahidro-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2-(trifluorometil)benzonitrilo	3.97 CLEM 522.2 $[M+H]^+$	204, 35

Ej. No.	G	R^7	Nombre del Compuesto	Tiempo de retención Min./Masa Molecular	Proced. del Ej.
273			Éster de metilo del ácido (3aα,4β,7β,7aα)-4-[2-[2-[4-ciano-3-(trifluorometil)fenil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-4H-isoindol-4-il]-etoxi]benzóico	3.77 CLEM 529.12 $[M+H]^+$	204, 35
274			(3aα,4β,7β,7aα)-hexahidro-4-(2-hidroxietil)-7-metil-2-(3-metil-4-nitrofenil)- 4,7-epoxi-1H-isoindol-1,3(2H)-diona	2.44 CL	204, 35

Ej. No.	G	R^7	Nombre del Compuesto	Tiempo de retención Min./Masa Molecular	Procad. del Ej.
275			(3aα,4β,7β,7aα)-4-[octahidro-4-metil-1,3-dioxo-7-[2-[4-(trifluorometoxi)fenoxi]etil]-4,7-epoxi-2H-isoindol-2-il]-2-(trifluorometil)benzonitrilo	3.97 CL	204, 35
276		CH_3	(3aα,4β,7β,7aα)-2-(3,5-diclorofenil)hexahidro-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3(2H)-diona	3.31 CLEM 341.2 $[M+H]^+$	20
277		CH_3	(3aα,4β,7β,7aα)-hexahidro-4,7-dimetil-2-(4-nitro-1-naftalenil)-4,7-epoxi-1H-isoindol-1,3(2H)-diona	3.04 CLEM	20
278			(3aα,4β,7β,7aα)-4-[octahidro-4-metil-1,3-dioxo-7-[2-[4-(fenilmetoxi)fenoxi]etil]-4,7-epoxi-2H-isoindol-2-il]-2-(trifluorometil)benzonitrilo	4.06 CL	204, 35

Ej. No.	G	R^7	Nombre del Compuesto	Tiempo de retención Min./Masa Molecular	Proced. del Ej.
279			(3aα,4β,7β,7aα)-hexahidro-4-(2-hidroxietil)-7-metil-2-(4-nitro-1-naftalenil)-4,7-epoxi-1H-isoindol-1,3(2H)-diona	2.607 y 2.743 isómeros rotacionales CL	204, 35
280			(3aα,4β,7β,7aα)-4-[2-(4-fluorofenoxi)etil]hexahidro-7-metil-2-(3-metil-4-nitrofenil)-4,7-epoxi-1H-isoindol-1,3(2H)-diona	3.68 CL	204, 35
281			(3aα,4β,7β,7aα)-4-[octahidro-4-metil-1,3-dioxo-7-[2-[4-[(trifluorometil)tio]fenoxi]etil]-4,7-epoxi-2H-isoindol-2-il]-2-(trifluorometil)benzonitrilo	4.11 CL	204, 35
282			(3aα,4β,7β,7aα)-4-[octahidro-4-metil-7-[2-(4-nitrofenoxi)etil]-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2-(trifluorometil)benzonitrilo	3.68 CL	204, 35

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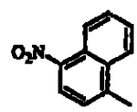
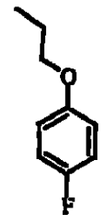
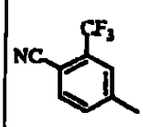
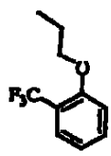
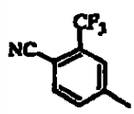
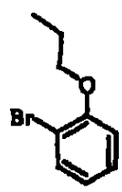
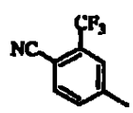
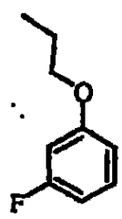
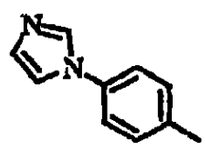
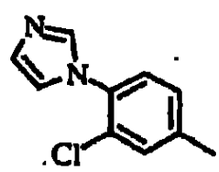
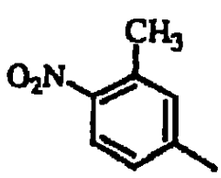
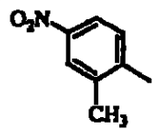
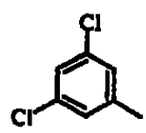
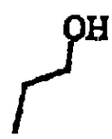
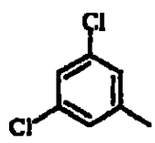
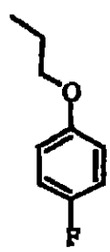
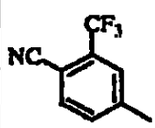
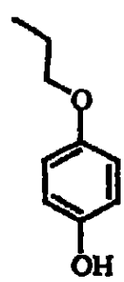
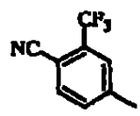
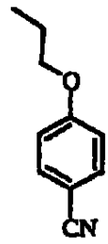
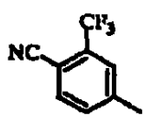
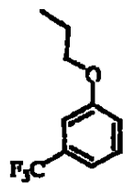
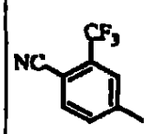
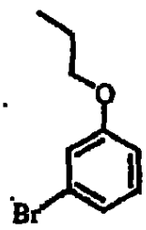
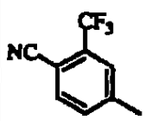
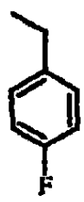
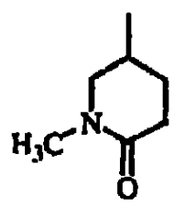
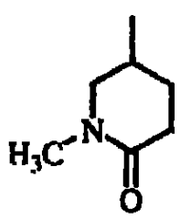
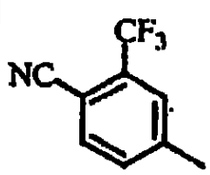
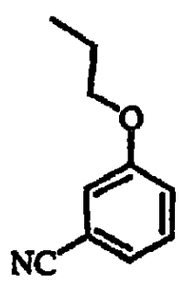
Ej. No.	G	R^7	Nombre del Compuesto	Tiempo de retención Min./Masa Molecular	Proced. del Ej.
283			(3aα,4β,7β,7aα)-4-[2-(4-fluorofenoxi)etil]hexahidro-7-metil-2-(4-nitro-1-naftalenil)-4,7-epoxi-1H-isoindol-1,3(2H)-diona	3.68 y 3.80 isómeros rotacionales CL	204, 35
284			(3aα,4β,7β,7aα)-4-[octahidro-7-metil-1,3-dioxo-7-[2-[2-(trifluorometil)fenoxi]etil]-4,7-epoxi-2H-isoindol-2-il]-2-(trifluorometil)benzonitrilo	3.89 CL	204, 35
285			(3aα,4β,7β,7aα)-4-[4-[2-(2-bromofenoxi)etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2-(trifluorometil)benzonitrilo	3.91 CL	204, 35
286			(3aα,4β,7β,7aα)-4-[4-[2-(3-fluorofenoxi)etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2-(trifluorometil)benzonitrilo	3.78 CL	204, 35

Ej. No.	G	R^7	Nombre del Compuesto	Tiempo de retención Min./Masa Molecular	Proced. del Ej.
287		H	(3aα,4β,7β,7aα)-hexahidro-2-[4-(1H-imidazol-1-il)fenil]-4-metil-4,7-epoxi-1H-isoindol-1,3(2H)-diona	1.16 CL	3
288		H	(3aα,4β,7β,7aα)-2-[3-cloro-4-(2-tiazolil)fenil]hexahidro-4-metil-4,7-epoxi-1H-isoindol-1,3(2H)-diona	2.81 CL	3
289		CH_3	(3aα,4β,7β,7aα)-hexahidro-4,7-dimetil-2-(3-metil-4-nitrofenil)-4,7-epoxi-1H-isoindol-1,3(2H)-diona	2.74 CL	20

Ej. No.	G	R^7	Nombre del Compuesto	Tiempo de retención Min./Masa Molecular	Proced. del Ej.
290		CH_3	(3aα,4β,7β,7aα)-hexahidro-4,7-dimetil-2-(2-metil-4-nitrofenil)-4,7-epoxi-1H-isoindol-1,3(2H)-diona	2.71 CL	20
291			(3aα,4β,7β,7aα)-2-(3,5-diclorofenil)hexahidro-4-(2-hidroxietil)-7-metil-4,7-epoxi-1H-isoindol-1,3(2H)-diona	2.98 CL	204
292			(3aα,4β,7β,7aα)-2-(3,5-diclorofenil)-4-[2-(4-fluorofenoxi)etil]hexahidro-7-metil-4,7-epoxi-1H-isoindol-1,3(2H)-diona	4.03 CL	204, 35
293			(3aα,4β,7β,7aα)-4-[octahidro-4-[2-(4-hidroxifenoxi)etil]-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2-(trifluorometil)benzonitrilo	3.25 CL	204, 35

Ej. No.	G	R^1	Nombre del Compuesto	Tiempo de retención Min./Masa Molecular	Proced. del Ej.
294			(3aα,4β,7β,7aα)-4-[4-[2-(4-cianofenoxi)etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2-(trifluorometil)benzonitrilo	3.51 CL	204, 35
295			(3aα,4β,7β,7aα)-4-[octahidro-4-metil-1,3-dioxo-7-[2-[3-(trifluorometil)fenoxi]etil]-4,7-epoxi-2H-isoindol-2-il]-2-(trifluorometil)benzonitrilo	3.85 CL	204, 35
296			(3aα,4β,7β,7aα)-4-[4-[2-(3-bromofenoxi)etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2-(trifluorometil)benzonitrilo	3.84 CL	204, 35
297			(3aα,4β,7β,7aα)-4-[4-[(4-fluorofenil)metil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2-(trifluorometil)benzonitrilo	3.73 CL	205

Ej. No.	G	R^7	Nombre del Compuesto	Tiempo de retención Min./Masa Molecular	Proced. del Ej.
298		CH_3	(3aα,4β,7β,7aα)-2-(1,6-dihidro-1-metil-6-oxo-3-piridinil)hexahidro-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3(2H)-diona	1.61 CL	20
299		CH_3	(3aα,4β,7β,7aα)-hexahidro-4,7-dimetil-2-(1-metil-6-oxo-3-piperidinil)-4,7-epoxi-1H-isoindol-1,3(2H)-diona	1.73 CL	20
300			(3aα,4β,7β,7aα)-4-[4-[2-(3-cianofenoxi)etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2-(trifluorometil)benzonitrilo	3.46 CL	204, 35

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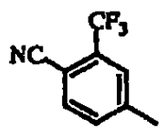
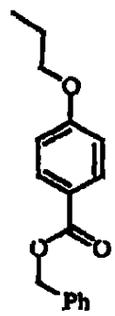
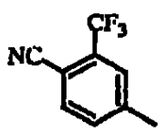
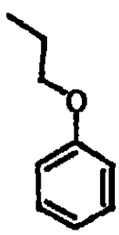
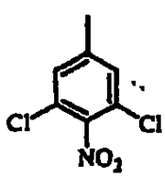
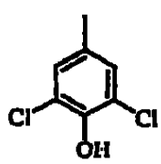
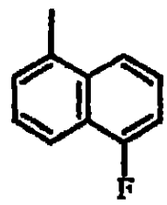
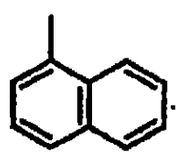
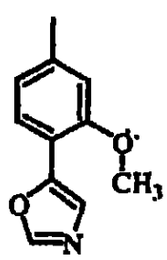
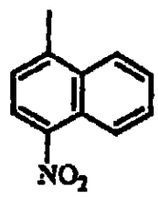
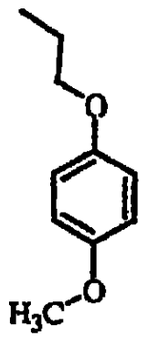
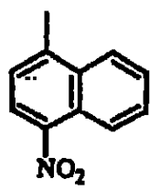
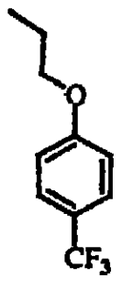
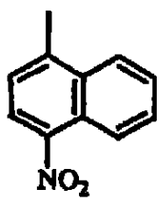
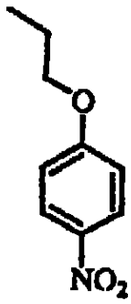
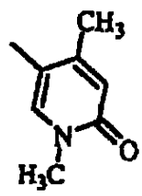
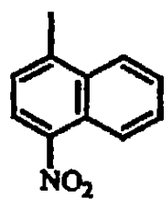
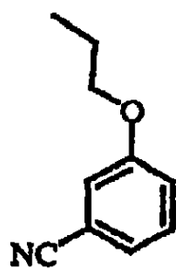
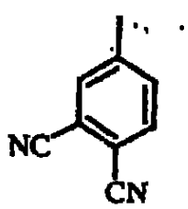
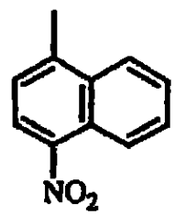
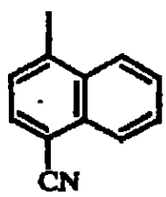
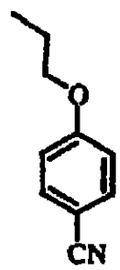
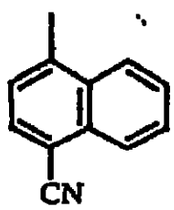
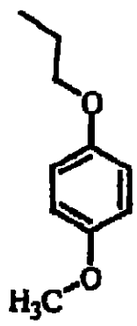
Ej. No.	G	R^7	Nombre del Compuesto	Tiempo de retención Min./Masa Molecular	Proced. del Ej.
301			Éster de fenilmetilo del ácido (3aα,4β,7β,7aα)-4-[2-[4-ciano-3-(trifluorometil)fenil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-4H-isoindol-4-il]etoxi]benzóico	4.01 CL	204, 35
302			(3aα,4β,7β,7aα)-4-[octahidro-4-metil-1,3-dioxo-7-(2-fenoxietil)-4,7-epoxi-2H-isoindol-2-il]-2-(trifluorometil)benzonitrilo	3.57 CL	204, 35
303		CH_3	(3aα,4β,7β,7aα)-2-(3,5-dicloro-4-nitrofenil)hexahidro-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3(2H)-diona	3.40 CL	20
304		CH_3	(3aα,4β,7β,7aα)-2-(3,5-dicloro-4-hidroxifenil)hexahidro-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3(2H)-diona	2.58 CL	20

Ej. No.	G	R^7	Nombre del Compuesto	Tiempo de retención Min./Masa Molecular	Proced. del Ej.
305		CH_3	(3aα,4β,7β,7aα)-2-(5-fluoro-1-naftalenil)hexahidro-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3(2H)-diona	2.96 y 3.06 isómeros rotacionales CL	20
306		CH_3	(3aα,4β,7β,7aα)-hexahidro-4,7-dimetil-2-(1-naftalenil)-4,7-epoxi-1H-isoindol-1,3(2H)-diona	2.60 y 2.73 isómeros rotacionales CL	20
307		CH_3	(3aα,4β,7β,7aα)-hexahidro-2-[3-metoxi-4-(5-oxazolil)fenil]-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3(2H)-diona	2.62 CL	20

Ej. No.	G	R^7	Nombre del Compuesto	Tiempo de retención Min./Masa Molecular	Proced. del Ej.
308			(3aα,4β,7β,7aα)-hexahidro-4-[2-(4-metoxifenoxi)etil]-7-metil-2-(4-nitro-1-naftalenil)-4,7-epoxi-1H-isoindol-1,3(2H)-diona	3.42 y 3.55 isómeros rotacionales CL	204, 35
309			(3aα,4β,7β,7aα)-hexahidro-4-metil-2-(4-nitro-1-naftalenil)-7-[2-[4-(trifluorometil)fenoxi]etil-4,7-epoxi-1H-isoindol-1,3(2H)-diona	3.81 y 3.93 isómeros rotacionales CL	204, 35
310			(3aα,4β,7β,7aα)-hexahidro-4-metil-2-(4-nitro-1-naftalenil)-7-[2-(4-nitrofenoxi)etil]-4,7-epoxi-1H-isoindol-1,3(2H)-diona	3.48 y 3.61 isómeros rotacionales CL	204, 35

Ej. No.	G	R^7	Nombre del Compuesto	Tiempo de retención Min./Masa Molecular	Proced. del Ej.
311		CH_3	(3aα,4β,7β,7aα)-2-(1,6-dihidro-1,4-dimetil-6-oxo-3-piridinil)hexahidro-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3(2H)-diona	1.89 CL	20
312			(3aα,4β,7β,7aα)-4-[octahidro-7-metil-2-(4-nitro-1-naftalenil)-1,3-dioxo-4,7-epoxi-4H-isoindol-4-il]etoxi]benzonitrilo	3.63 CL	204, 35
313		CH_3	(3aα,4β,7β,7aα)-4-(octahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-1,2-bencendicarbonitrilo	2.38 CL	20

Ej. No.	G	R^7	Nombre del Compuesto	Tiempo de retención Min./Masa Molecular	Proced. del Ej.
314			(3aα,4β,7β,7aα)-4-(2-bromoetil)hexahidro-7-metil-2-(4-nitro-1-naftalenil)-4,7-epoxi-1H-isoindol-1,3(2H)-diona	3.52 CL	36
315			(3aα,4β,7β,7aα)-4-[4-[2-(4-cianofenoxi)etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftaleno carbonitrilo	3.19 y 3.35 isómeros rotacionales CL	223, 35
316			(3aα,4β,7β,7aα)-4-[octahidro-4-[2-(4-metoxifenoxi)etil]-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftaleno carbonitrilo	3.34 y 3.50 isómeros rotacionales CL	223, 35

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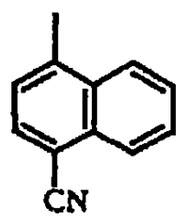
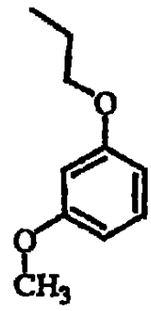
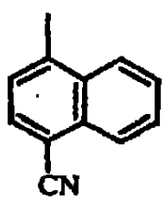
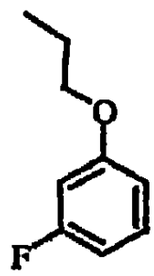
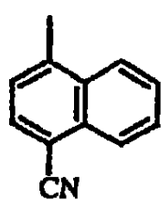
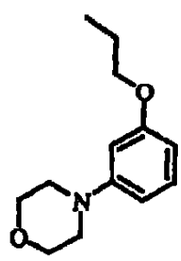
Ej. No.	G	R^7	Nombre del Compuesto	Tiempo de retención Min./Masa Molecular	Proced. del Ej.
317			(3aα,4β,7β,7aα)-4-[octahidro-4-[2-(3-metoxifenoxi)etil]-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftaleno carbonitrilo	3.34 y 3.50 isómeros rotacionales CL	223, 35
318			(3aα,4β,7β,7aα)-4-[4-[2-(3-fluorofenoxi)etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftaleno carbonitrilo	3.46 y 3.61 isómeros rotacionales CL	223, 35
319			(3aα,4β,7β,7aα)-4-[octahidro-4-metil-7-[2-[3-(4-morfolinil)fenoxi]etil]-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftaleno carbonitrilo	3.01 y 3.18 isómeros rotacionales CL	223, 35

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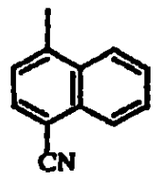
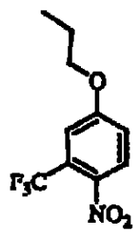
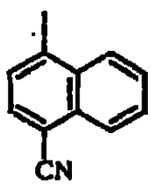
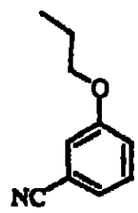
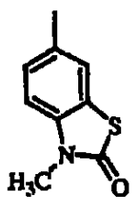
Ej. No.	G	R^7	Nombre del Compuesto	Tiempo de retención Min./Masa Molecular	Proced. del Ej.
320			(3aα,4β,7β,7aα)-4-[octahidro-4-metil-7-[2-[4-nitro-3-(trifluorometil)fenoxi]etil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftaleno carbonitrilo	3.70 y 3.83 isómeros rotacionales CL	223, 35
321			(3aα,4β,7β,7aα)-4-[4-[2-(3-cianofenoxi)etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftaleno carbonitrilo	3.39 y 3.55 isómeros rotacionales CL	223, 35
322		CH_3	(3aα,4β,7β,7aα)-2-(2,3-dihidro-3-metil-2-oxo-6-benzotiazolil)hexahidro-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3(2H)-diona	2.34 CL	20

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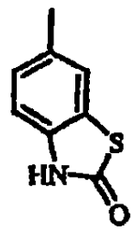
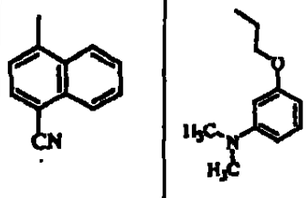
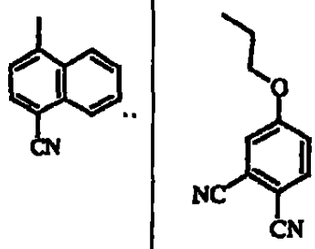
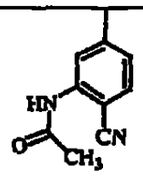
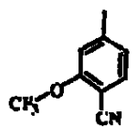
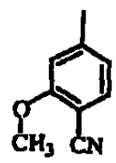
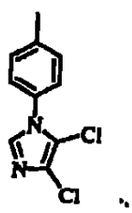
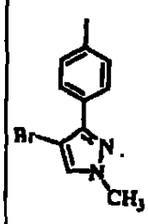
Ej. No.	G	R^7	Nombre del Compuesto	Tiempo de retención Min./Masa Molecular	Proced. del Ej.
323		CH_3	(3aα,4β,7β,7aα)-2-(2,3-dihidro-2-oxo-6-benzotiazolil)hexahidro-4,7-epoxi-1H-isoindol-1,3(2H)-diona	2.16 CL	20
324			(3aα,4β,7β,7aα)-4-[4-[2-[3-(dimetilamino)fenoxi]etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftaleno carbonitrilo	2.63 y 2.79 isómeros rotacionales CL	223, 35
325			(3aα,4β,7β,7aα)-4-[2-[4-ciano-3-(trifluorometil)fenil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-4H-isoindol-4-il]-1-etoxi]-1,2-bencendicarbonitrilo	3.42 CL	223, 35

Ej. No.	G	R^7	Nombre del Compuesto	Tiempo de retención Min./Masa Molecular	Proced. del Ej.
326		CH_3	(3aα,4β,7β,7aα)-N-[2-ciano-5-(octahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-fenil]acetamida	1.94 CL	20
327		CH_3	(3aα,4β,7β,7aα)-4-(octahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometoxi)benzonitrilo	3.52 CL	20
328		CH_3	(3aα,4β,7β,7aα)-2-metoxi-4-(octahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)benzonitrilo	2.47 CL	20
329		CH_3	(3aα,4β,7β,7aα)-2-[4-(4,5-dicloro-1H-imidazol-1-il)fenil]hexahidro-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3(2H)-diona	3.09 CL	20
330		CH_3	(3aα,4β,7β,7aα)-2-[4-(4-bromo-1-metil-1H-pirazol-3-il)fenil]hexahidro-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3(2H)-diona	3.04 CL	20

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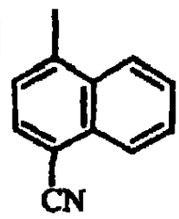
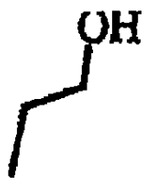
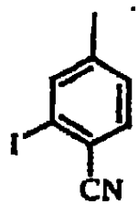
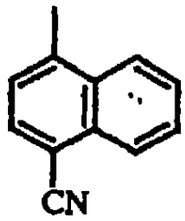
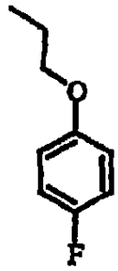
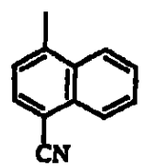
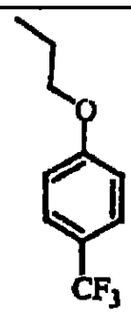
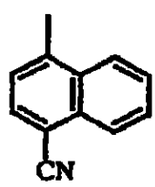
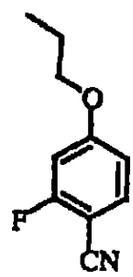
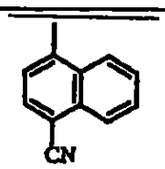
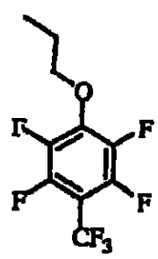
Ej. No.	G	R^7	Nombre del Compuesto	Tiempo de retención Min./Masa Molecular	Proced. del Ej.
331			(3aα,4β,7β,7aα)-4-[octahidro-4-(2-hidroxietil)-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftaleno carbonitrilo	2.44 y 2.60 isómaros rotacionales CL	223
332		CH_3	(3aα,4β,7β,7aα)-2-yodo-4-(octahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)benzonitrilo	2.78 CL	20
333			(3aα,4β,7β,7aα)-4-[4-[2-(4-fluorofenoxi)etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalenocarbonitrilo	3.39 y 3.53 isómeros rotacionales CL	223, 35

Ej. No.	G	R^7	Nombre del Compuesto	Tiempo de retención Min./Masa Molecular	Proced. del Ej.
334			(3aα,4β,7β,7aα)-4-[octahidro-4-metil-1,3-dioxo-7-[2-[4-(trifluorometil)fenoxi]etil]-4,7-epoxi-2H-isoindol-2-il]-1-naftalenocarbonitrilo	3.66 y 3.78 isómeros rotacionales CL	223, 35
335			(3aα,4β,7β,7aα)-4-[4-[2-(4-ciano-3-fluorofenoxi)etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftaleno carbonitrilo	3.26 y 3.41 isómeros rotacionales CL	223, 35
336			(3aα,4β,7β,7aα)-4-[octahidro-4-metil-1,3-dioxo-7-[2-[2,3,5,6-tetrafluoro-4-(trifluorometil)fenoxi]etil]-4,7-epoxi-2H-isoindol-2-il]-1-naftaleno carbonitrilo	3.94 y 4.01 isómeros rotacionales CL	223, 35

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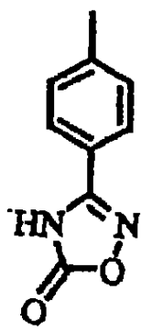
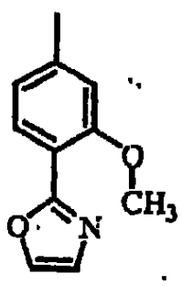
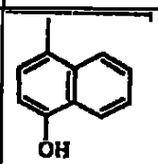
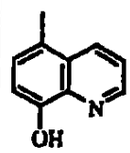
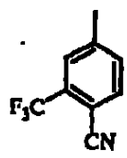
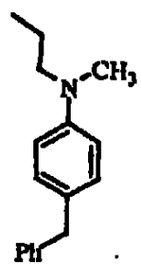
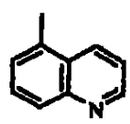
Ej. No.	G	R^7	Nombre del Compuesto	Tiempo de retención Min./Masa Molecular	Procad. del Ej.
337		CH_3	(3aα,4β,7β,7aα)-hexahidro-4,7-dimetil-2-[4-(1H-1,2,4-triazol-3-il)fenil]-4,7-epoxi-1H-isoindol-1,3(2H)-diona	2.06 CL	20
338		CH_3	(3aα,4β,7β,7aα)-2-[4-(4,5-dihidro-5-oxo-1,2,4-oxadiazol-3-il)fenil]hexahidro-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3(2H)-diona	2.42 CL	20
339		CH_3	(3aα,4β,7β,7aα)-hexahidro-2-[3-metoxi-4-(2-oxazolil)fenil]-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3(2H)-diona	2.51 CL	20

Ej. No.	G	R^7	Nombre del Compuesto	Tiempo de retención Min./Masa Molecular	Proced. del Ej.
340		CH_3	(3aα,4β,7β,7aα)-hexahidro-2-(4-hidroxi-1-naftalenil)-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3(2H)-diona	2.30 CL	20
341		CH_3	(3aα,4β,7β,7aα)-hexahidro-2-(8-hidroxi-5-quinolinil)-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3-(2H)-diona, trifluoroacetato(1:1)	1.49 CL	20
342			(3aα,4β,7β,7aα)-4-[octahidro-4-metil-1,3-dioxo-7-[2-[metil(fenilmetil)amino]etil-4,7-epoxi-2H-isoindol-2-il]-2-(trifluorometil)benzonitrilo	2.42 CL	204, 35
343		CH_3	(3aα,4β,7β,7aα)-hexahidro-4,7-dimetil-2-(5-quinolinil)-4,7-epoxi-1H-isoindol-1,3(2H)-diona	1.69 CL	20

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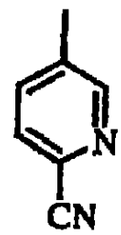
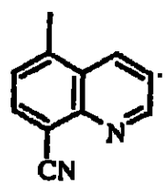
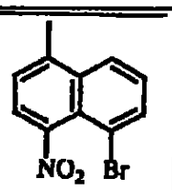
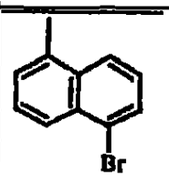
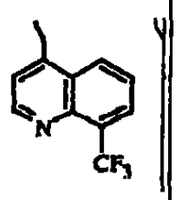
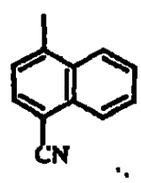
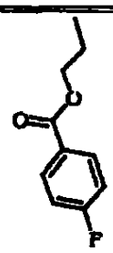
Ej. No.	G	R^7	Nombre del Compuesto	Tiempo de retención Min./Masa Molecular	Proced. del Ej.
344		CH_3	(3aα,4β,7β,7aα)-5-(octahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-piridincarbonitrilo	2.18 CL	20
345		CH_3	(3aα,4β,7β,7aα)-5-(octahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-8-quino carbonitrilo	2.31 CL	20
346		CH_3	(3aα,4β,7β,7aα)-2-(5-bromo-4-nitro-1-naftalenil)hexahidro-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3(2H)-diona	3.10 y 3.29 isómeros rotacionales CL	20

Ej. No.	G	R^7	Nombre del Compuesto	Tiempo de retención Min./Masa Molecular	Proced. del Ej.
347		CH_3	(3aα,4β,7β,7aα)-2-(5-bromo-1-naftalenil)hexahidro-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3(2H)-diona	3.28 y 3.40 isómeros rotacionales CL	20
348		CH_3	(3aα,4β,7β,7aα)-hexahidro-4,7-dimetil-2[8-(trifluorometil)-4-quinolinil]-4,7-epoxi-1H-isoindol-1,3(2H)-diona	3.08 CL	20
349			Éster de 2-[(3aα,4β,7β,7aα)-2-(4-ciano-1-naftalenil)octahidro-7-metil-1,3-dioxo-4,7-epoxi-4H-isoindol-4-il]etilo del ácido 4-fluorobenzóico	3.64 y 3.77 isómeros rotacionales CL	223

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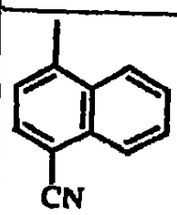
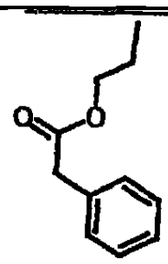
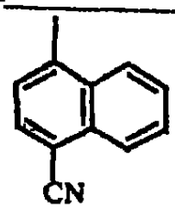
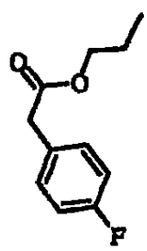
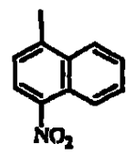
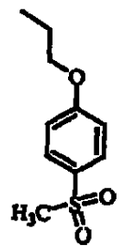
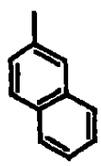
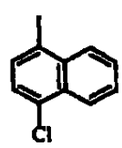
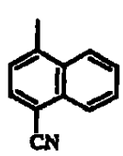
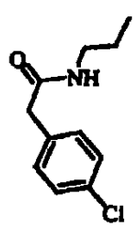
Ej. No.	G	R^7	Nombre del Compuesto	Tiempo de retención Min./Masa Molecular	Procad. del Ej.
350			Éster 2-[(3aα,4β,7β,7aα)-2-(4-ciano-1-naftalenil)octahidro-7-metil-1,3-dioxo-4,7-epoxi-4H-isoindol-4-il]etil del ácido bencenacético	3.53 y 3.67 isómeros rotacionales CL	223
351			Éster de 2-[(3aα,4β,7β,7aα)-2-(4-ciano-1-naftalenil)octahidro-7-metil-1,3-dioxo-4,7-epoxi-4H-isoindol-4-il]etilo del ácido 4-fluorobencenacético	3.53 y 3.66 isómeros rotacionales CL	223

Ej. No.	G	R^7	Nombre del Compuesto	Tiempo de retención Min./Masa Molecular	Proced. del Ej.
352			(3aα,4β,7β,7aα)-hexahidro-4-metil-7-[2-[4-(metilsulfonil)fenoxi]etil]-2-(4-nitro-1-naftalenil)-4,7-epoxi-1H-isoindol-1,3(2H)-diona	3.31 CL	204, 35
353		CH_3	(3aα,4β,7β,7aα)-hexahidro-2-(2-naftalenil)-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3(2H)-diona	2.94 CL	20
354		CH_3	(3aα,4β,7β,7aα)-2-(4-cloro-1-naftalenil)hexahidro-4,7-dimetil- 4,7-epoxi-1H-isoindol-1,3(2H)-diona	3.22 y 3.34 isómeros rotacionáles CL	20
355			(3aα,4β,7β,7aα)-N-[(4-clorofenil)metil]-2-(4-ciano-1-naftalenil)octahidro-7-metil-1,3-dioxo-4,7-epoxi-4H-isoindol-4-acetamida.	3.52 CL	237

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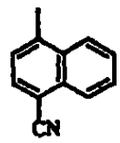
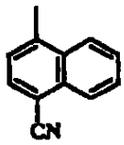
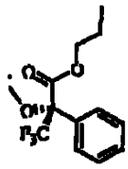
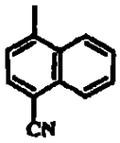
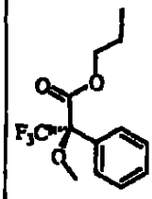
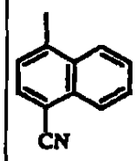
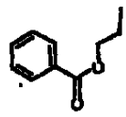
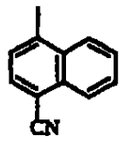
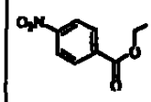
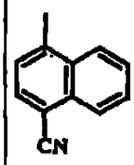
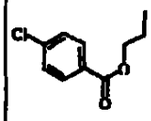
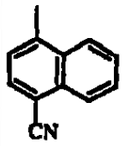
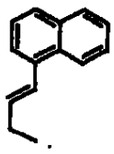
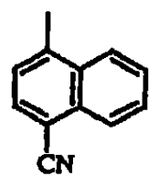
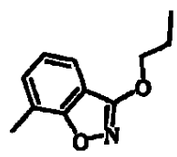
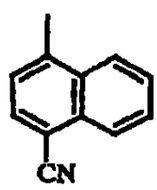
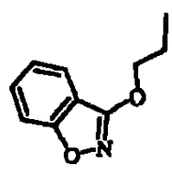
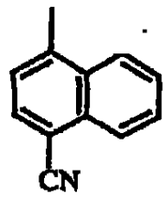
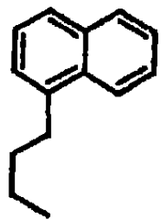
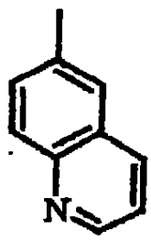
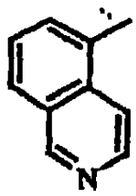
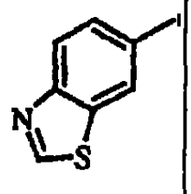
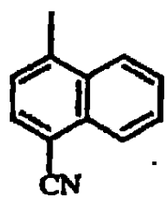
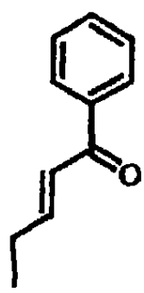
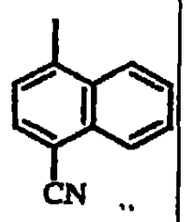
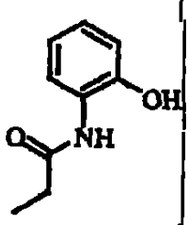
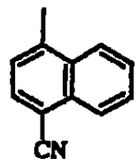
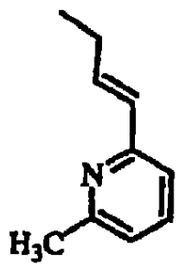
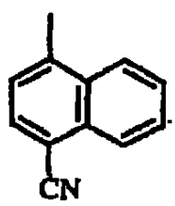
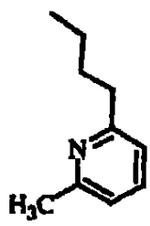
Ej. No.	G	R^7	Nombre del Compuesto	Tiempo de retención Min./Masa Molecular	Proced. del Ej.
356			Éster de 2-[(3aα,4β,7β,7aα)-2-(4-ciano-1-naftalenil)octahidro-7-metil-1,3-dioxo-4,7-epoxi-4H-isoindol-4-il]etilo del ácido 4,7,7-trimetil-3-oxo-2-oxabiciclo[2.2.1]heptano-1-carboxilico	3.45 CL	223
357			Éster 2-[(3aα,4β,7β,7aα)-2-(4-ciano-1-naftalenil)octahidro-7-metil-1,3-dioxo-4,7-epoxi-4H-isoindol-4-il]etilico del ácido (αS-α-metoxi-α-(trifluorometil)bencenacético	3.91 CL	223
358			Éster de 2-[(3aα,4β,7β,7aα)-2-(4-ciano-1-naftalenil)octahidro-7-metil-1,3-dioxo-4,7-epoxi-4H-isoindol-4-il]etilo del ácido (αR)-α-metoxi-α-(trifluorometil)bencenacético	2.00 CL	223

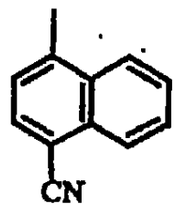
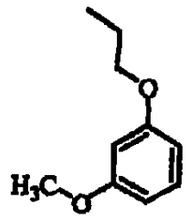
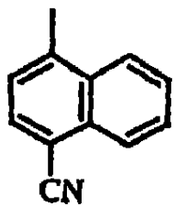
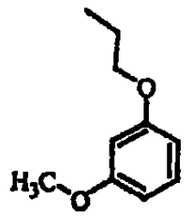
Ej. No.	G	R^7	Nombre del Compuesto	Tiempo de retención Min./Masa Molecular	Proced. del Ej.
361			(3aα,4β,7β,7aα)-4-[2-(benzoiloxi)etil]-2-(4-ciano-1-naftalenil)hexahidro-7-metil-4,7-epoxi-1H-isoindol-1,3(2H)-diona	3.51 y 3.66 isómeros rotacionales CL	223
362			(3aα,4β,7β,7aα)-2-(4-ciano-1-naftalenil)-4-[2-[(4-nitrobenzoil)oxi]etil]hexahidro-7-metil-4,7-epoxi-1H-isoindol-1,3(2H)-diona	3.52 y 3.67 isómeros rotacionales CL	223
363			Éster de 2-[(3aα,4β,7β,7aα)-2-(4-ciano-1-naftalenil)octahidro-7-metil-1,3-dioxo-4,7-epoxi-4H-isoindol-4-il]etílico del ácido 4-clorobenzóico	3.79 CL	223
364			[3aα,4β,7β,7aα(E)]-4-[octahidro-4-metil-7-[3-(1-naftalenil)-2-propenil]-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftaleno carbonitrilo	4.14 CL 499.13 $[M+H]^+$	248

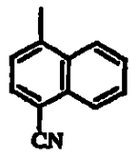
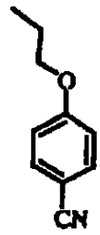
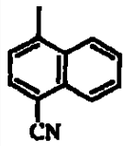
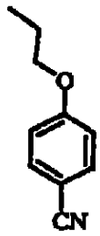
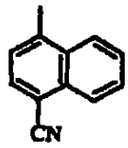
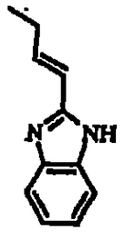
Ej. No.	G	R^7	Nombre del Compuesto	Tiempo de retención Min./Masa Molecular	Proced. del Ej.
359			(3aα,4β,7β,7aα)-4-[octahidro-4-metil-7-[2-[(7-metil-1,2-bencisoxazol-3-il)oxi]etil]-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftaleno carbonitrilo	3.79 y 3.92 isómeros rotacionales CL	250
360			(3aα,4β,7β,7aα)-4-[4-[2-(1,2-bencisoxazol-3-iloxi)etil[octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftaleno carbonitrilo	3.55 y 3.70 isómeros rotacionales CL	250

Ej. No.	G	R^7	Nombre del Compuesto	Tiempo de retención Min./Masa Molecular	Proced. del Ej.
365			(3aα,4β,7β,7aα)-4-[octahidro-4-metil-7-[3-(1-naftalenil)propil]-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftaleno carbonitrilo	4.14 CL 501.14 $[M+H]^+$	248, 249
366		CH_3	(3aα,4β,7β,7aα)-hexahidro-4,7-dimetil-2(2-metil-6-quinolinil)-4,7-epoxi-1H-isoindol-1,3(2H)-diona	1.25 CL 337.0 $[M+H]^+$	20
367		CH_3	(3aα,4β,7β,7aα)-hexahidro-2-(5-isoquinolinil)-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3(2H)-diona	1.06 y 1.29 isómeros rotacionales CL 323.0 $[M+H]^+$	20

Ej. No.	G	R^7	Nombre del Compuesto	Tiempo de retención Min./Masa Molecular	Proced. del Ej.
368		CH_3	(3aα,4β,7β,7aα)-2-(6-benzotiazolil)hexahidro-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3(2H)-diona	2.15 CL 329.0 $[M+H]^+$	20
369			[3aα,4β,7β,7aα(E)]-4-[octahidro-4-metil-1,3-dioxo-7-(4-oxo-4-fenil-2-butenil)-4,7-epoxi-2H-isoindol-2-il]-1-naftaleno carbonitrilo	3.50 CL 477.1 $[M+H]^+$	265
370			(3aα,4β,7β,7aα)-2-(4-ciano-1-naftalenil)octahidro-N-(2-hidroxifenil)-7-metil-1,3-dioxo-4,7-epoxi-4H-isoindol-4-acetamida	3.07 CL 482.14 $[M+H]^+$	236

Ej. No.	G	R^7	Nombre del Compuesto	Tiempo de retención Min./Masa Molecular	Proced. del Ej.
371			[3aα,4β(E),7β,7aα]-4-[octahidro-4-metil-7-[3-(6-metil-2-piridinil)-2-propenil]-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalenocarbonitrilo	2.28 CL 464.19 $[M+H]^+$	248
372			(3aα,4β,7β,7aα)-4-[octahidro-4-metil-7-[3-(6-metil-2-piridinil)propil]-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftaleno carbonitrilo	2.19 CL 466.32 $[M+H]^+$	248, 249

Ej. No.	G	R^7	Nombre del Compuesto	Tiempo de retención Min./Masa Molecular	Proced. del Ej.
373			[3aR-(3aα,4β,7β,7aα)-]-4-[octahidro-4-[2-(3-metoxifenoxi)etil]-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftaleno carbonitrilo	3.73 CL 483.65 $[M+H]^+$	238i, 239i
374			[3aS-(3aα,4β,7β,7aα)]-4-[octahidro-4-[2-(3-metoxifenoxi)etil]-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftaleno carbonitrilo	3.73 CL	238ii, 239ii

Ej. No.	G	R^7	Nombre del Compuesto	Tiempo de retención Min./Masa Molecular	Proced. del Ej.
375			[3aR-(3aα,4β,7β,7aα)]-4-[4-[2-(4-cianofenoxi)etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftaleno carbonitrilo	3.33 y 3.49 isómeros rotacionales CL	238i, 239i
376			[3aS-(3aα,4β,7β,7aα)]-4-[4-[2-(4-cianofenoxi)etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalenocarbonitrilo	3.73 CL 483.65 $[M+H]^+$	238ii, 239ii
377			[3aα,4β(E),7β,7aα]-4-[4-[3-(1H-bencimidazol-2-il)-2-propenil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftaleno carbonitrilo	2.48 CL 489.26 $[M+H]^+$	248

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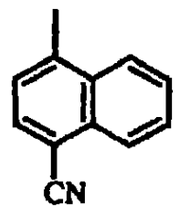
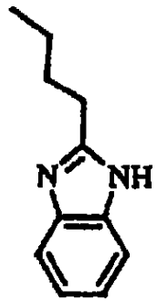
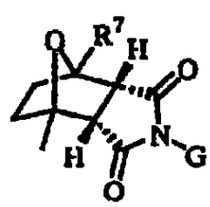
Ej. No.	G	R^7	Nombre del Compuesto	Tiempo de retención Min./Masa Molecular	Procad. del Ej.
378			(3aα,4β,7β,7aα)-4-[4-[3-(1H-bencimidazol-2-il)propil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftaleno carbonitrilo	2.37 CL 491.26 $[M+H]^+$	249

Ejemplos 379 a 381

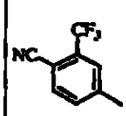
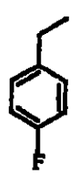
Los compuestos adicionales de la presente invención se prepararon por procedimientos análogos a aquellos antes descritos. Los compuestos de los Ejemplos 379 al 381 tienen la siguiente estructura (L es un enlace):

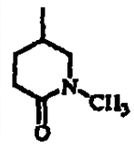
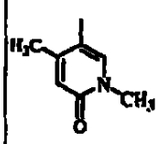


en donde G, R^7, el nombre del compuesto, tiempo de retención, masa molecular, y el procedimiento empleado, son establecidos en la Tabla 6. Las técnicas de cromatografía usadas para determinar los tiempos de retención de los compuestos de la Tabla 6 son como siguen: CLEM = Columna YMC S5 ODS, 4.6 X 50 mm eluyendo con 10-90% MeOH/H_2O durante 4 minutos conteniendo 0.1 % TFA; 4 mL/min., observando a 220 nm. CLEM* = Columna YMC S5 ODS, 4.6 X 50 mm eluyendo con 10-90% MeOH/H_2O durante 2 minutos conteniendo 0.1% TFA; 4 mL/min., observando a 220 nm. CL = Columna YMC S5 ODS 4.6 x 50 mm eluyendo con 10-90% MeOH/H_2O durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm.

La masa molecular de los compuestos enlistados en la Tabla 6 se determinó por EM(ES) por la fórmula m/z.

Tabla 6

Ej. No.	G	R^7	Nombre del Compuesto	Tiempo de retención Min./Masa Molecular	Procedimiento del Ej.
379			(3aα,4α,7α,7aα)-4-[4-[(4-fluorofenil)metil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2-(trifluorometil)benzonitrilo	3.75 CL	205

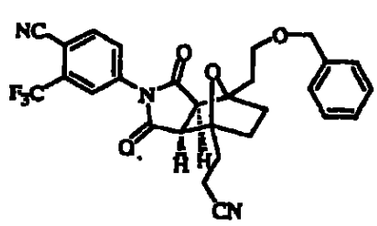
Ej. No.	G	R'	Nombre del Compuesto	Tiempo de retención Min./Masa Molecular	Procedimiento del Ej.
380		CH_3	(3aα,4α,7α,7aα)-hexahidro-4,7-dimetil-2-(1-metil-6-oxo-3-piperidinil)-4,7-epoxi-1H-isoindol-1,3(2H)-diona	1.88 CL	27
381		CH_3	(3aα,4α,7α,7aα)-2-(1,6-dihidro-1,4-dimetil-6-oxo-3-piridinil)hexahidro-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3(2H)-diona	1.91 CL	27

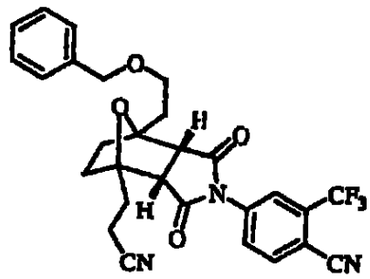
Ejemplos 382 a 383

Los compuestos adicionales de la presente invención se prepararon por procedimientos análogos a aquellos antes descritos. Los compuestos de los Ejemplos 382 al 383 tienen la estructura, el nombre del compuesto, tiempo de retención, masa molecular, y se prepararon por el procedimiento empleado, establecido en la Tabla 7. Las técnicas de cromatografía usadas para determinar los tiempos de retención de los compuestos de la Tabla 7 son como siguen: CLEM =

Columna YMC S5 ODS, 4.6 X 50 mm eluyendo con 10-90% MeOH/H_2O durante 4 minutos conteniendo 0.1 % TFA; 4 mL/min., observando a 220 nm. CLEM* = Columna YMC S5 ODS, 4.6 X 50 mm eluyendo con 10-90% MeOH/H_2O durante 2 minutos conteniendo 0.1% TFA; 4 mL/min., observando a 220 nm. CL = Columna YMC S5 ODS 4.6 x 50 mm eluyendo con 10-90% MeOH/H_2O durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm. La masa molecular de los compuestos enlistados en la Tabla 7 se determinó por EM(ES) por la fórmula m/z.

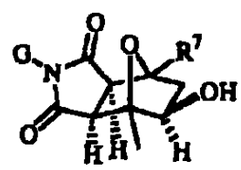
Tabla 7

Ej. No.	Estructura	Nombre del Compuesto	Tiempo de Retención Min.	Procedimiento del Ejemplo
382		(3aα,4α,7α,7aα)-2-[4-ciano-3-(trifluorometil)fenil]octahidro-1,3-dioxo-7-[2-(fenilmetoxi-etil]-4,7-epoxi-4H-isoindol-4-propanonitrilo	3.63 CL	255

383		(3aα,4α,7α,7aα)-2-[4-ciano-3-(trifluorometil)fenil]octahidro-1,3-dioxo-7-[2-(fenilmetoxi-etil]-4,7-epoxi-4H-isoindol-4-propanonitrilo	3.64 CL	255

Ejemplos 384 a 418

Los compuestos adicionales de la presente invención se prepararon por procedimientos análogos a aquellos antes descritos. Los compuestos de los Ejemplos 384 al 418 tienen la siguiente estructura (L es un enlace):



en donde G, R^7, el nombre del compuesto, tiempo de retención, masa molecular, y el procedimiento empleado, son establecidos en la Tabla 8. La configuración absoluta para los siguientes compuestos no se determinó. Por simplicidad en la nomenclatura, el compuesto 243Di se designa en la presente como que tiene una configuración "S" y el compuesto 243Dii

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como que tiene una configuración "R". Los productos enantioméricamente puros derivados de los compuestos 243Di se designan en la presente por tener una configuración "S" y los productos enantioméricamente puros derivados del compuesto 243Dii se designan en la presente por tener una configuración "R".

Las técnicas de cromatografía usadas para determinar los tiempos de retención de los compuestos de la Tabla 8 son como siguen: CLEM = Columna YMC S5 ODS, 4.6 X 50 mm eluyendo con 10-90% MeOH/H_2O durante 4 minutos conteniendo 0.1 % TFA; 4 mL/min., observando a 220 nm. CLEM* = Columna YMC S5 ODS, 4.6 X 50 mm eluyendo con 10-90% MeOH/H_2O durante 2 minutos conteniendo 0.1% TFA; 4 mL/min., observando a 220 nm. CL = Columna YMC S5 ODS 4.6 x 50 mm eluyendo con 10-90% MeOH/H_2O durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm.

La masa molecular de los compuestos enlistados en la Tabla 8 se determinó por EM(ES) por la fórmula m/z.

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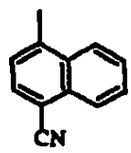
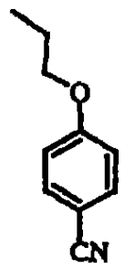
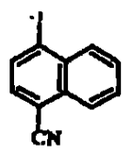
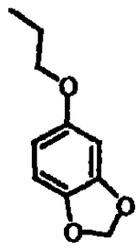
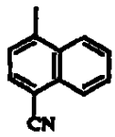
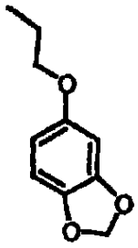
Tabla 8

Ej. No.	G	R'	Nombre del Compuesto	Tiempo de retención Min./Masa Molecular	Procedimiento del Ej.
384			(3aα,4β,7β,7aα)-4-[7-[2-(4-cianofenoxi)etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalenocarbonitrilo	3.18 CL 494.40 $[M+H]^+$	227, 228, 229
385			[3aS-(3aα,4β,7β,7aα)]-4-[7-[2-(1,3-benzodioxol-5-iloxi)etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalenocarbonitrilo	3.19 CL 571.3 $[M+H+OAc]^-$	243Di, 244i
386			[3aR-(3aα,4β,7β,7aα)]-4-[7-[2-(1,3-benzodioxol-5-iloxi)etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalenocarbonitrilo	3.22 CL 571.2 $[M+H+OAc]^-$	234Dii, 244ii

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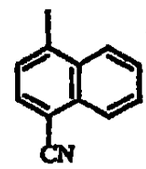
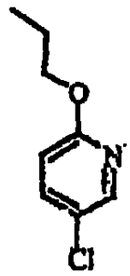
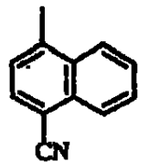
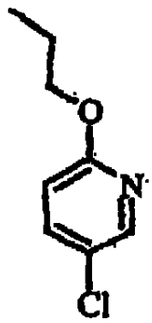
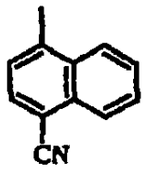
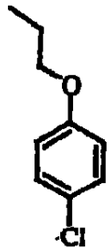
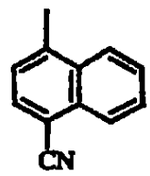
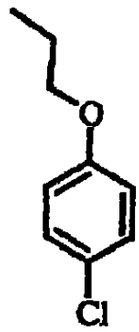
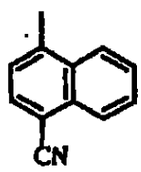
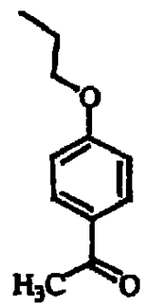
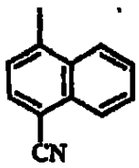
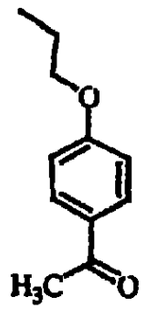
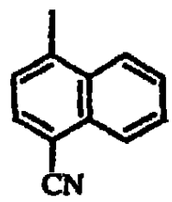
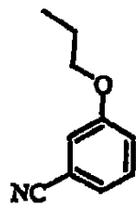
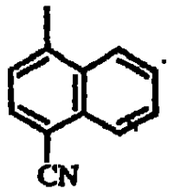
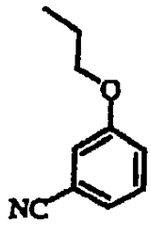
Ej. No.	G	R'	Nombre del Compuesto	Tiempo de retención Min./Masa Molecular	Procedimiento del Ej.
387			[3aS-(3aα,4β,7β,7aα)]-4-[7-[2-[(5-cloro-2-piridinil)oxi]etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalenocarbonitrilo	3.37 CL 562.2 $[M+H+OAc]^-$	243Di, 244i
388			[3aR-(3aα,4β,7β,7aα)]-4-[7-[2-[(5-cloro-2-piridinil)oxi]etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalenocarbonitrilo	3.37 CL 504.0 $[M+H]^+$	243Dii, 244ii
389			[3aS-(3aα,4β,7β,7aα)]-4-[7-[2-(4-clorofenoxi)etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalenocarbonitrilo	3.51 CL 503.08 $[M+H]^+$	243Di, 244i

817

Ej. No.	G	R'	Nombre del Compuesto	Tiempo de retención Min./Masa Molecular	Procedimiento del Ej.
390			[3aR-(3aα,4β,7β,7aα)]-4-[7-[2-(4-clorofenoxi)etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalenocarbonitrilo	3.51 CL 503.08 $[M+H]^+$	243Dii, 244ii
391			[3aS-(3aα,4β,7β,7aα)]-4-[7-[2-(4-acetilfenoxi)etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalenocarbonitrilo	3.05 CL 511.13 $[M+H]^+$	243Di, 244i
392			[3aR-(3aα,4β,7β,7aα)]-4-[7-[2-(4-acetilfenoxi)etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalenocarbonitrilo	3.05 CL 503.13 $[M+H]^+$	243Dii, 244ii

Ej. No.	G	R'	Nombre del Compuesto	Tiempo de retención Min./Masa Molecular	Procedimiento del Ej.
393			[3aS-(3aα,4α,7α,7aα)]-4-[7-[2-(3-cianofenoxi)-etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalenocarbonitrilo	3.09 CL 494.13 $[M+H]^+$	243Di, 244i
394			[3aR-(3aα,4β,7β,7aα)]-4-[7-[2-(3-cianofenoxi)etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalenocarbonitrilo	3.09 CL 494.13 $[M+H]^+$	243Dii, 244ii

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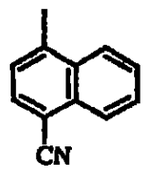
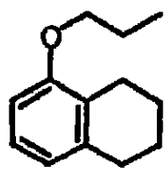
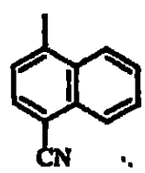
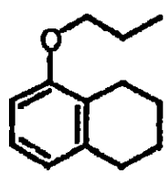
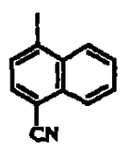
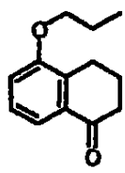
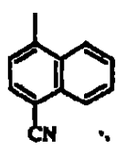
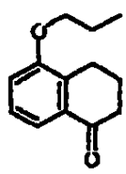
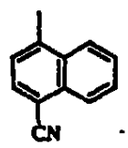
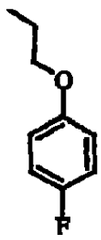
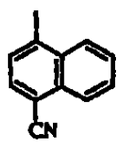
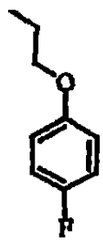
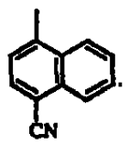
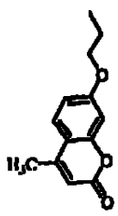
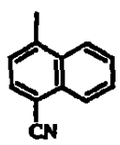
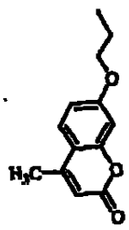
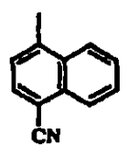
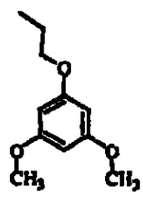
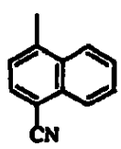
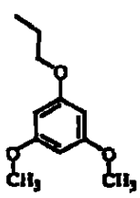
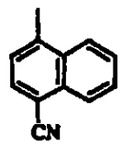
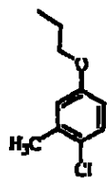
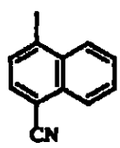
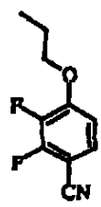
Ej. No.	G	R'	Nombre del Compuesto	Tiempo de retención Min./Masa Molecular	Procedimiento del Ej.
395			[3aS-(3aα,4β,7β,7aα)]-4-[octahidro-5-hidroxi-4-metil-1,3-dioxo-7-[2-[(5,6,7,8-tetrahidro-1-naftalenil)oxi]etil]-4,7-epoxi-2H-isoindol-2-il]-1-naftalenocarbonitrilo	3.85 CL 523.17 $[M+H]^+$	243Di, 244i
396			[3aR-(3aα,4β,7β,7aα)]-4-[octahidro-5-hidroxi-4-metil-1,3-dioxo-7-[2-[(5,6,7,8-tetrahidro-1-naftalenil)oxi]etil]-4,7-epoxi-2H-isoindol-2-il]-1-naftalenocarbonitrilo	3.85 CL 523.17 $[M+H]^+$	243Dii, 244ii

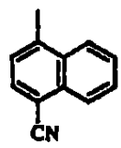
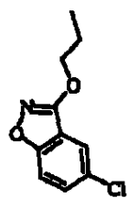
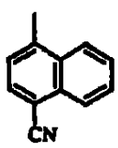
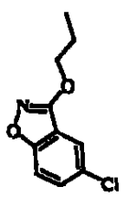
Ej. No	G	R'	Nombre del Comp.	Tiempo de retención Min./Masa molecular	Procedimiento del Ej.
397			[3aS-(3aα,4β,7β,7aα)]-4-[Octahidro-5-hidroxi-4-metil-1,3-dioxo-7-[2-[(5,6,7,8-tetrahidro-5-oxo-1-naftalenil)oxi]etil]-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo.	3.39 CL 537.13 $[M+H]^+$	243Di, 244i
398			[3aR-(3aα,4β,7β,7aα)]-4-[Octahidro-5-hidroxi-4-metil-1,3-dioxo-7-[2-[(5,6,7,8-tetrahidro-5-oxo-1-naftalenil)oxi]etil]-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo.	3.29 CL 537.13 $[M+H]^+$	243Dii, 244ii

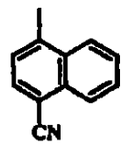
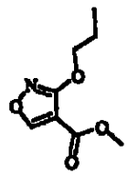
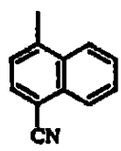
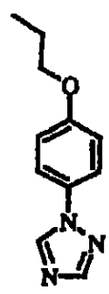
Ej. No	G	R^7	Nombre del Comp.	Tiempo de retención Min./Masa molecular	Procedimiento del Ej.
399			[3aS-(3aα,4β,7β,7aα)]-4-[7-[2-(4-Fluorofenoxi)etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo.	3.28 CL 487.11 $[M+H]^+$	243Di, 244i
400			[3aR-(3aα,4β,7β,7aα)]-4-[7-[2-(4-Fluorofenoxi)etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo.	3.27 CL 487.11 $[M+H]^+$	243Dii, 244ii

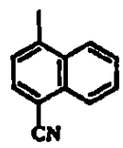
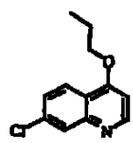
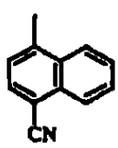
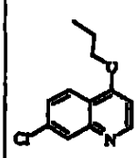
Ej. No	G	R'	Nombre del Comp.	Tiempo de retención Min./Masa molecular	Procedimiento del Ej.
401			[3aS-(3aα,4β,7β,7aα)]-4-[Octahidro-5-hidroxi-4-metil-7-[2-[(4-metil-2-oxo-2H-1-benzopiran-7-il)oxi]etil]-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo.	3.15 CL 551.15 $[M+H]^+$	243Di, 244i
402			[3aR-(3aα,4β,7β,7aα)]-4-[Octahidro-5-hidroxi-4-metil-7-[2-[(4-metil-2-oxo-2H-1-benzopiran-7-il)oxi]etil]-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo.	3.16 CL 551.10 $[M+H]^+$	243Dii, 244ii

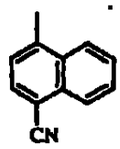
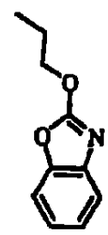
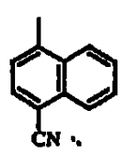
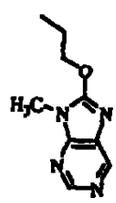
Ej. No	G	R^7	Nombre del Comp.	Tiempo de retención Min./Masa molecular	Procedimiento del Ej.
403			[3aS-(3aα,4β,7β,7aα)]-4-[7-[2-(3,5-Dimetoxifenoxi)etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo.	3.28 CL 529.19 $[M+H]^+$	243Di, 244i
404			[3aR-(3aα,4β,7β,7aα)]-4-[7-[2-(3,5-Dimetoxifenoxi)etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo.	3.26 CL 529.12 $[M+H]^+$	243Dii, 244ii

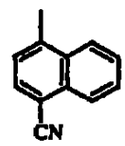
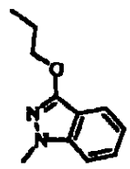
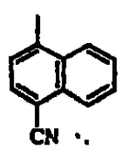
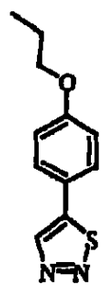
Ej. No	G	R'	Nombre del Comp.	Tiempo de retención Min./Masa molecular	Procedimiento del Ej.
405			[3aR-(3aα,4β,7β,7aα)]-4-[7-[2-(4-Cloro-3-metilfenoxi)etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo.	3.68 CL 517.33 $[M+H]^+$	243Dii, 244ii
406			[3aR-(3aα,4β,7β,7aα)]-4-[7-[2-(4-Ciano-2,3-difluorofenoxi)etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo.	3.23 CL 530.13 $[M+H]^+$	243Dii, 244ii

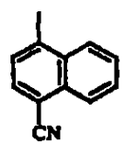
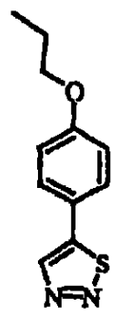
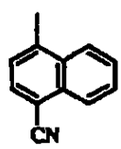
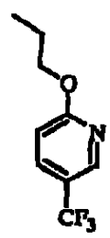
Ej. No	G	R^7	Nombre del Comp.	Tiempo de retención Min./Masa molecular	Procedimiento del Ej.
407			[3aS-(3aα,4β,7β,7aα)]-4-[7-[2-[(5-Cloro-1,2-benzisoxazol-3-il)oxi]etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo.	3.59 CL 602.1 [M-H+OAc]$^-$	243Di, 252
408			[3aR-(3aα,4β,7β,7aα)]-4-[7-[2-[(5-Cloro-1,2-benzisoxazol-3-il)oxi]etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo.	3.57 CL 602.0 [MH+OAc]$^-$	243Dii, 253.

Ej. No	G	R'	Nombre del Comp.	Tiempo de retención Min./Masa molecular	Procedimiento del Ej.
409			Ester de metilo del ácido [3aR-(3aα,4β,7β,7aα)]-3-[2-[2-(4-Ciano-1-naftalenil)octahidro-6-hidroxi-7-metil-1,3-dioxo-4,7-epoxi-4H-isoindol-4-il]etoxi]-5-isoxazoCLarboxilico	2.90 CL 518.27 $[M+H]^+$	243Dii, 253
410			[3aR-(3aα,4β,7β,7aα)]-4-[Octahidro-5-hidroxi-4-metil-1,3-dioxo-7-[2-[4-(1H-1,2,4-triazol-1-il)fenoxi]etil]-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo.	2.93 CL 536.30 $[M+H]^+$	243Dii, 244ii

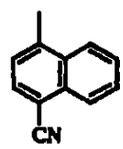
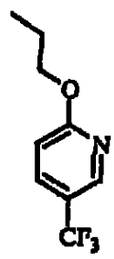
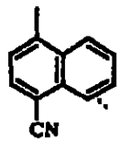
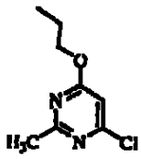
Ej. No	G	R'	Nombre del Comp.	Tiempo de retención Min./Masa molecular	Procedimiento del Ej.
411			[3aS-(3aα,4β,7β,7aα)]-4-[7-[2-[(7-Cloro-4-quinolinil)oxi]etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo, trifluoroacetato (1:1)	2.52 CL 554.13 $[M+H]^+$	243Di, 244i
412			[3aR-(3aα,4β,7β,7aα)]-4-[7-[2-[(7-Cloro-4-quinolinil)oxi]etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo, trifluoroacetato (1:1)	2.53 CL 554.27 $[M+H]^+$	243Dii, 244ii

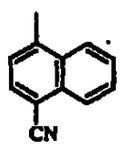
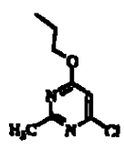
Ej. No	G	R'	Nombre del Comp.	Tiempo de retención Min./Masa molecular	Procedimiento del Ej.
413			[3aR-(3aα,4β,5β,7β,7aα)]-4-[7-[2-(2-Benzoxazoliloxi)etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.13 CL 568.1 $[M-H+OAc]^-$	243Dii, 244ii
414			[3aR-(3aα,4β,5β,7β,7aα)]-4-[Octahidro-5-hidroxi-4-metil-7-[2-[(9-metil-9H-purin-8-il)oxi]etil]-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	2.34 CL 525.2 $[M+H]^+$	243Dii, 244ii

Ej. No	G	R'	Nombre del Comp.	Tiempo de retención Min./Masa molecular	Procedimiento del Ej.
415			[3aR-(3aα,4β,5β,7β,7aα)]-4-[Octahidro-5-hidroxi-4-metil-7-[2-[(1-metil-1H-indazol-3-il)oxi]etil]-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.33 CL	251, 253
416			[3aS-(3aα,4β,5β,7β,7aα)]-4-[Octahidro-5-hidroxi-4-metil-7-[2-[4-(1,2,3-tiadiazol-5-il)fenoxi]etil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.17 CL 553.10 $[M+H]^+$	243Dii, 244ii

Ej. No	G	R'	Nombre del Comp.	Tiempo de retención Min./Masa molecular	Procedimiento del Ej.
417			[3aR-(3aα,4β,5β,7β,7aα)]-4-[Octahidro-5-hidroxi-4-metil-7-[2-[4-(1,2,3-tiadiazol-5-il)fenoxi]etil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.20 CL 553.25 $[M+H]^+$	243Dii, 244ii
418			[3aS-(3aα,4β,5β,7β,7aα)]-4-[Octahidro-5-hidroxi-4-metil-1,3-dioxo-7-[2-[[5-(trifluorometil)-2-piridinil]oxi]etil]-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.45 CL 538.23 $[M+H]^+$	243Dii, 244ii

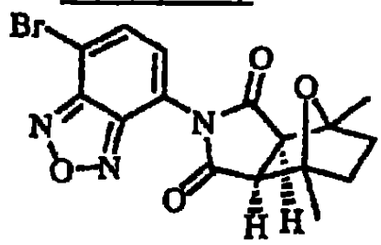
831

Ej. No	G	R'	Nombre del Comp.	Tiempo de retención Min./Masa molecular	Procedimiento del Ej.
419			[3aR-(3aα,4β,5β,7β,7aα)]-4-[Octahidro-5-hidroxi-4-metil-1,3-dioxo-7-[2-[[5-(Trifluorometil)-2-piridinil]oxi]etil]-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.45 CL 538.23 $[M+H]^+$	243Dii, 244ii
420			[3aS-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[(6-Cloro-2-metil-4-pirimidinil)oxi]etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.02 CL	243Dii, 244ii

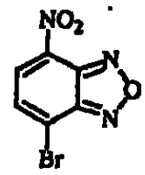
Ej. No	G	R'	Nombre del Comp.	Tiempo de retención Min./Masa molecular	Procedimiento del Ej.
421			[3aR-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[(6-Cloro-2-metil-4-pirimidinil)oxi]etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.02 CL	243Dii, 244ii

Ejemplo 422

(3aα,4β,7β,7Aα)-2-(7-bromo-2,1,3-benzoxadiazol-4-il)hexahidro-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3(2H)-diona(422C)



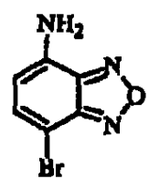
A. 4-Bromo-7-nitrobenzofurazan (422A)



A una solución de 2,6-dibromoanilina (1.0 g, 4.0 mmol) en $CHCl_3$, (8 mL) se agregó una suspensión de *m*CPBA (70% por HPCL, 1.4 g, 8.0 mmol) en $CHCl_3$, (8 mL) y la mezcla resultante se agitó por 24 h a temperatura ambiente. La mezcla de reacción se diluyó con $CHCl_3$, y se lavó sucesivamente con una solución de 2% $Na_2S_2O_3$, solución de 5% Na_2CO_3 y salmuera. La capa orgánica se secó sobre Na_2SO_4 y se concentró bajo presión reducida para dejar un sólido que se suspendió en DEMO (15 mL). A esta suspensión se le agregó una solución de NaN_3 (272 mg, 4.19 mmol) en DEMO (15 mL) a temperatura ambiente. La mezcla resultante se agitó a temperatura ambiente hasta que la mayoría del nitrógeno había evolucionado y después se calentó rápidamente hasta 120°C por 3 min. La mezcla de reacción se enfrió y se vació en hielo triturado (100 g). Después de reposar por 1 h los precipitados se filtraron, se secaron in vacuo y se volvieron a disolver en H_2SO_4 concentrado (5 mL). A esta solución se le agregó una solución de $NaNO_3$ (400 mg, 4.7 mmol) en 50% H_2SO_4 (1.6 mL) y la temperatura se mantuvo a 60°C. Después de que la adición se terminó, la mezcla se calentó a 85°C por 30

min, se enfrió a temperatura ambiente y se vació sobre hielo triturado (40 g). Se agregó EtOAc, se separaron las capas y se extrajo la capa acuosa con EtOAc. Las capas orgánicas combinadas se secaron sobre Na_2SO_4 y se concentraron bajo presión reducida para dejar un sólido que se purificó por cromatografía instantánea (gel de sílice, EtOAc (20%) en hexanos) resultando el compuesto 422A (785 mg, 81%) como un sólido café claro.

B. 4-Bromo-7-aminobenzofurazan (422B)



Una solución del compuesto 422A (563 mg, 2.31 mmol) en AcOH (5 mL), se calentó a 70°C y se agregó polvo de Fe^0 (258 mg, 4.62 mmol) en una porción. La mezcla de reacción oscura resultante se agitó por 15 min., se enfrió a temperatura ambiente y se concentró bajo presión reducida. Se recuperó el residuo en EtOAc y la solución resultante se lavó con solución saturada de Na_2CO_3. La capa orgánica se secó sobre Na_2SO_4, se concentró in vacuo y se purificó por cromatografía instantánea en gel de sílice eluyendo con 10-60% EtOAc en hexanos para dar 470 mg (95%) del compuesto 422B como un sólido rojo.

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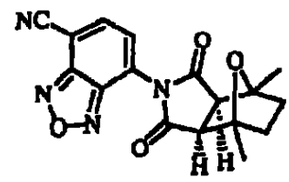
C. (3aα,4β,7β,7aα)-2-(7-Bromo-2,1,3-benzoxadiazol-4-il)hexahidro-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3(2H)-diona (422C)

Se colocó una mezcla del compuesto 422B (43 mg, 0.20 mmol), compuesto 20A (45 mg, 0.23 mmol), $MgSO_4$ (60 mg, 0.50 mmol), Et_3N (139 µL, 1.0 mmol) y 1,2-dimetoxietano (300 µL), en un tubo sellado y se calentó a 135°C por 14 h. Después de enfriar a temperatura ambiente, se filtró la mezcla a través de Celite eluyendo con MeOH, para producir un sólido oscuro que se purificó por cromatografía instantánea en gel de sílice eluyendo con 5-40% EtOAc en hexanos para dar 42 mg (54%) del compuesto 422C como un sólido amarillo. CLAR: 99% a 2.96 min. (tiempo de retención) (YMC S5 ODS columna 4.6 x 50 mm Ballistic, metanol acuoso 10-90% durante 4 minutos que contenían 0.2% H_3PO_4, 4 mL/min., monitoreando a 220 nm). ^1H RMN (acetona-d_6, 400 MHz): δ = 8.00 (d, J = 7.5 Hz, 1H), 7.45 (d, J = 7.5 Hz, 1H), 3.31 (s, 2H), 1.98-1.93 (m, 2H), 1.74-1.69 (m, 2H), 1.57 (s, 6H).

Ejemplo 423

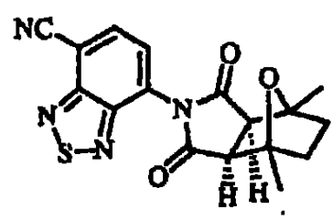
(3aα,4β,7β,7aα)-7-[Octahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2,1,3-benzoxadiazol-4-carbonitrilo (423)



A una solución de compuesto 422C (42 mg, 0.11 mmol) en DMA (1 mL) se agregó CuCN (20 mg, 0.22 mmol) y la mezcla resultante se calentó a 150°C por 5 h. La mezcla se dejó enfriar a temperatura ambiente y se dividió entre EtOAc y solución acuosa de NaCN (5 g/50 mL). Las capas se separaron y se extrajo la capa acuosa una vez con EtOAc. Se secaron las fases orgánicas combinadas sobre Na_2SO_4, se concentraron in vacuo y se purificaron por cromatografía instantánea en gel de sílice eluyendo con 20-70% EtQAc en hexanos para dar 13 mg (35%) del compuesto 423 como un aceite amarillo. CLAR: 99% a 2.66 min. (tiempo de retención) (YMC S5 ODS columna 4.6 x 50 mm Ballistic, metanol acuoso 10-90% durante 4 minutos conteniendo 0.2% H_3PO_4, 4 mL/min., monitoreado a 220 nm). EM (ES): m/z 396.9 $[M-H+OAc]^-$.

Ejemplo 424

(3aα,4β,7β,7aα)-7-Octahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2,1,3-benzotiadiazol-4-carbonitrilo (424B)



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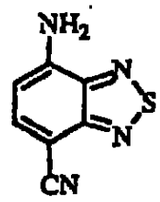
A. 4-Ciano-7-amino-benzotiadiazol (424A)



Una solución de 2-ciano-5-nitrofenilendiamina (78 mg, 0.44 mmol, preparada como se describe en WO 0076501) en $SOCl_2$ (2 mL), se calentó a reflujo por 3 h. La mezcla resultante se dejó enfriar a temperatura ambiente y se vació después en hielo/agua. Se agregó CH_2CL_2, se separaron las capas y la capa acuosa se extrajo dos veces con CH_2Cl_2. Las fases orgánicas combinadas se secaron sobre $MgSO_4$, se concentraron in vacuo y se purificaron por cromatografía instantánea sobre gel de sílice eluyendo con 50% EtOAc en hexanos para dar 4-ciano-7-nitrobenzotiadiazol. Este material se disolvió en AcOH (2 mL) conteniendo EtOAc (1 mL) y H_2O (0.2 mL) y calentado a 70°C. Se agregó a esta temperatura polvo de Fe^0 (78 mg, 1.41 mmol) en una porción sólida y la mezcla oscura se agitó por 20 min. y después se enfrió a temperatura ambiente. La mezcla de reacción se filtró a través de Celite eluyendo con EtOAc, se lavó con una solución sat. de Na_2CO_3, se secó sobre $MgSO_4$ y se concentró in vacuo. La purificación por cromatografía instantánea sobre gel de sílice eluyendo con 20-70% EtOAc en hexanos para dar 47 mg (67%) del compuesto 424A como un sólido café.

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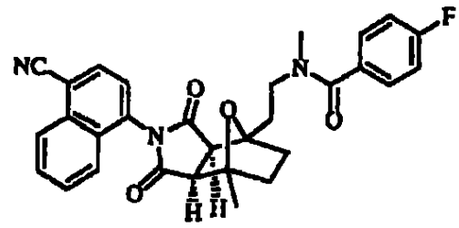
B. (3aα,4β,7β,7aα)-7-[Octahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2,1,3-benzotiadiazol-4-carbonitrilo (424B)

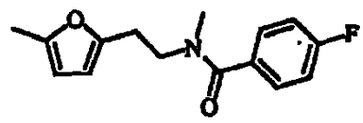
Una mezcla del compuesto 424A (35 mg, 0.20 mmol), compuesto 20A (45 mg, 0.23 mmol), $MgSO_4$ (60 mg, 0.50 mmol), Et_3N (139 µL, 1.0 mmol) y DME (200 µL), se colocó en un tubo sellado y calentó a 135°C por 14 h. Después de enfriar a temperatura ambiente, se filtró la mezcla a través de Celite eluyendo con MeOH para resultar un sólido oscuro que se purificó por una combinación de cromatografía instantánea sobre gel de sílice eluyendo con 10-50% EtOAc en hexanos, CLAR preparativa de fase inversa (YMC S5 ODS 20 x 100 mm eluyendo con metanol acuoso 27-100% sobre 10 min. que contenía 0.1% TFA, 20 mL/min.) para dar 36 mg (51%) del compuesto 424B como un sólido amarillo. CLAR: 98% a 2.45 min. (tiempo de retención) (YMC S5 ODS columna 4.6 x 50 mm Balístico, metanol acuoso 10-90% durante 4 minutos que contenían 0.2% H_3PO_4, 4 mL/min., monitoreando a 220 nm). EM (DCI): m/z 355.0 $[M+H]^+$.

Ejemplo 425

(3aα,4β,7β,7aα)-N-[2-[2-(4-Ciano-1-naftalenil)octahidro-7-metil-1,3-dioxo-4,7-epoxi-4H-isoindol-4-il]etil]-4-fluoro-N-metilbenzamida (425B)



A. 4-Fluoro-N-metil-N-[2-(5-metil-furan-2-il)-etil]-benzamida (425A)



Se agregó en porciones NaH (dispersión al 60% en aceite, 65 mg, 1.63 mmol) a una solución de 4-fluoro-N-[2-(5-metil-2-furanil)etil]benzamida (269 mg, 1.09 mmol, 237A) en THF (5 mL). Después de que cesó la evolución de gas, se agregó gota a gota yodometano (0.14 mL, 2.18 mmol). Una vez que el análisis CLAR mostró que la reacción estaba completa al 50%, se concentró la mezcla bajo presión reducida y se volvió a someter a las condiciones anteriores. Después de que se consumió todo el material de partida, se agregó H_2O y la mezcla resultante se extrajo con EtOAc (2X5 mL). Las capas orgánicas combinadas se secaron sobre Na_2SO_4 y se concentraron bajo presión reducida. La purificación por cromatografía instantánea en gel de sílice eluyendo con 20% acetona/$CHCl_3$ dio 238 mg (84%) del compuesto 425A. CLAR: 98% a 2.94 min. (tiempo de retención) (columna Phenomenex-prime S5-C18 4.6 x 50 mm eluyendo con metanol acuoso al 10-90% durante 4

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minutos conteniendo ácido fosfórico al 0.2%, 4 mL/min., monitoreando a 220 nm). EM (ES): m/z [M+H] = 262.38.

B. (3aα,4β,7β,7aα)-N-[2-[2-(4-Ciano-1-naftalenil)octahidro-7-metil-1,3-dioxo-4,7-epoxi-4H-isoindol-4-il]etil]-4-fluoro-N-metilbenzamida (425B)

Una solución del compuesto 425A (183 mg, 0.75 mmol) y 4-(2,5-dihidro-2,5-dioxo-1H-1-il)-1-naftalencarbonitrilo (174 mg, 0.75 mmol) en benceno (1 mL) se calentó a 60°C por 15 hr. Se concentró la mezcla de reacción bajo presión reducida para dar 357 mg de intermediario crudo. El intermediario crudo (156 mg) se disolvió en EtOAc (6 mL) y 10% Pd/C (16 mg) se agregó y la mezcla se agitó bajo un globo de hidrógeno durante la noche. La mezcla de reacción se filtró a través de una almohadilla de Celite y se concentró bajo presión reducida. La purificación por CLAR de fase inversa preparativa (YMC S5 ODS 20 X 100 mm, metanol acuoso 20-100% durante 15 minutos que contenía 0.1% TFA, 20 mL/min., observando a 220 nm) dio 160.3 mg (72%) del compuesto 425B como un sólido blanco apagado. CLAR: 99% a 3.23 min. (tiempo de retención) (columna Phenomenex-prime S5-C18 4.6 x 50 mm eluyendo con metanol acuoso al 10-90% durante 4 minutos conteniendo ácido fosfórico al 0.2%, 4 mL/min., observando a 220 nm). EM (ES): m/z [M+H] = 512.19.

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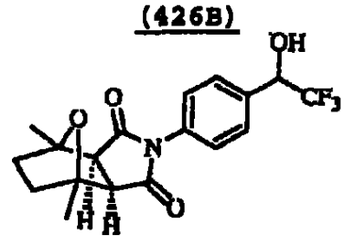
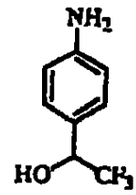
Ejemplo 426

(3aα,4β,7β,7aα)-Hexahidro-4,7-dimetil-2-[4-(2,2,2-trifluoro-1-hidroxietil)fenil]-4,7-epoxi-1H-isoindol-1,3(2H)-diona

(426B)



A. 1-(4-Amino-fenil)-2,2,2-trifluoro-etanol (426A)



El compuesto 426A se preparó según el procedimiento descrito en Stewart, R. et al. Can. J. Chem. 58, 2491-2496 (1980). Se agregó $NaBH_4$ (47 mg, 1.235 mmol) a una solución de p-aminotrifluoroacetofenona (155.7 mg, 0.823 mmol, sintetizada como se describe por Klabunde, K. J. et al. J. Org. Chem. 35, 1711-1712 (1970)) en isopropanol (3 mL) a temperatura ambiente. Después de 30 min., se apagó la reacción con solución amortiguadora de fosfato (pH 7.2), se diluyó con H_2O y se extrajo con EtOAc (2 X 10 mL). Las capas orgánicas combinadas se secaron sobre Na_2SO_4 y se concentraron bajo presión reducida para dar 154 mg (98%) del compuesto 426A como un sólido café claro. El material se utilizó directamente en la siguiente etapa sin purificación. CLAR: 99% a 0.42 min. (tiempo de retención) (columna YMC S5 ODS 4.6

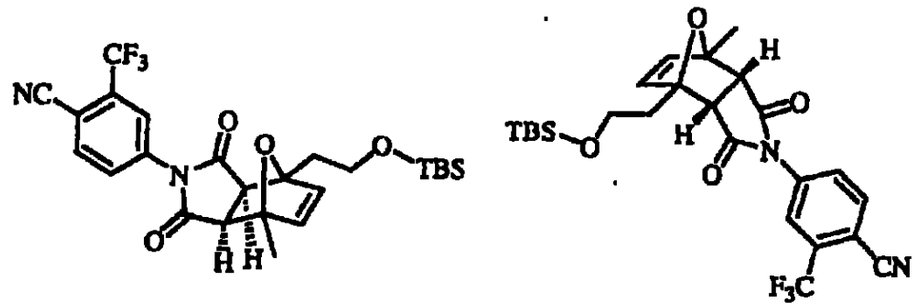
x 50 mm eluyendo con metanol acuoso al 10-90% durante 4 minutos que contenían ácido fosfórico al 0.2%, 4 mL/min., observando a 220 nm). EM (ES): m/z [M+H] = 192.13.

B. (3aα,4β,7β,7aα)-Hexahidro-4,7-dimetil-2-[4-(2,2,2-trifluoro-1-hidroxietil)fenil]-4,7-epoxi-1H-isoindol-1,3(2H)-diona (426B)

Una mezcla del compuesto 426A (75.3 mg, 0.394), compuesto 20A (51.5 mg, 0.262 mmol), trietilamina (0.15 mL) y $MgSO_4$ (50 mg) en tolueno (1 mL) se calentó en tubo sellado hasta 135°C por 15 hr. La mezcla se filtró y se concentró bajo presión reducida. La purificación por CLAR preparativa de fase inversa (YMC S5 ODS 20 X 100 mm, metanol acuoso al 20-100% sobre 15 minutos que contenían 0.1% TFA, 20 mL/min., se observó a 220 nm) dando 63.1 mg (65%) del compuesto 426B como un sólido blanco. CLAR: 98% a 2.49 min. (tiempo de retención) (columna Phenomenex-prime S5-C18 4.6 x 50 mm eluyendo con metanol acuoso al 10-90% durante 4 minutos conteniendo ácido fosfórico al 0.2%, 4 mL/min., observando a 220 nm). EM (ES): m/z [M+H] = 370.16.

Ejemplo 427

(3aα,4β,7β,7aα)-4-[4-[2-[[(1,1-Dimetiletil)dimetilsilil]oxi]etil]-1,3,3a,4,7,7a-hexahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2-(trifluorometil)benzonitrilo y (3aα,4α,7α,7aα)-4-[4-[2-[[1,1-Dimetiletil)dimetilsilil]oxi]etil]-1,3,3a,4,7,7a-hexahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2-(trifluorometil)benzonitrilo (427i y 427ii)

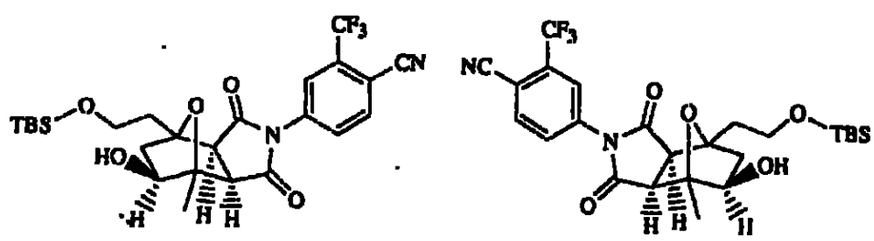


El compuesto 204A (2.00 g, 8.50 mmol) y 4-(2,5-dihidro-2,5-dioxo-1H-pirrol-1-il)-2-trifluorometilbenzonitrilo (1.50 g, 5.60 mmol) se mezclaron en benceno (5.0 mL) y se calentaron a 60°C por 14 h, después se enfriaron a 25°C. Se separó el solvente a 40°C bajo vacío por 1 h para dar el material crudo que se purificó por cromatografía instantánea en SiO_2 eluyendo con 0.5% $EtOAc/CH_2Cl_2$ para dar 2.0 g del compuesto 427i y 1.3 g del compuesto 427ii, ambos como sólidos café claro. Compuesto 427i: CLAR: 95% a 4.200 min. (tiempo de retención) (columna YMC S5 ODS de 4.6 x 50 mm eluyendo con metanol acuoso al 10-90% durante 4 minutos que

contenía ácido fosfórico al 0.2%, 4 mL/min., observando a 220 nm). EM (ES): m/z 507.1 $[M+H]^+$. Compuesto 427ii: CLAR: 95% a 4.20 min. (tiempo de retención) (columna YMC S5 ODS de 4.6 x 50 mm eluyendo con metanol acuoso al 10-90% durante 4 minutos que contenía ácido fosfórico al 0.2%, 4 mL/min., observando a 220 nm). EM (ES):m/z 507.1 $[M+H]^+$.

Ejemplo 428

[3aR-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[[(1,1-Dimetiletil)dimetilsilil]oxi]etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2-(trifluorometil)benzonitrilo y [3aS-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[[(1,1-Dimetiletil)dimetilsilil]oxi]etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2-(trifluorometil)benzonitrilo (428i y 428ii)



El compuesto 427i (1.40 g, 2.77 mmol) y $RhCl(PPh_3)_3$ (0.128 g, 0.14 mmol) se mezclaron en un matraz. El matraz se evacuó después y se llenó con argón tres veces, seguido por la adición con una jeringa de THF (3.0 mL). Una vez que se disolvieron todos los materiales en partículas, se agregó

gota a gota catecolborano (0.59 mL, 5.54 mmol). Se agitó la mezcla de reacción a 25°C bajo argón por 30 min., después se enfrió a 0°C. Se agregó solución amortiguadora de fosfato (pH 7, 20 mL), seguida por EtOH (10 mL), 30% H_2O_2/H_2O (2 mL). La mezcla de reacción se agitó a 0°C por 3 h, se extrajo después con diclorometano (3 x 25 mL). Se lavaron las capas orgánicas combinadas con NaOH 1 N (25 mL), 10% Na_2SO_3 (25 mL) y salmuera (25 mL). Se concentró después el material crudo in vacuo y se purificó por cromatografía instantánea sobren SiO_2 eluyendo con 2% EtOAc/CH_2Cl_2 hasta 10% EtOAc/CH_2Cl_2 para dar 0.63 g de una mezcla racémica de los compuestos 428i y 428ii como un sólido amarillo claro. CLAR: 99% a 3.867 min. (tiempo de retención) (columna YMC S5 ODS de 4.6 x 50 mm eluyendo con metanol acuoso al 10-90% durante 4 minutos que contenía ácido fosfórico al 0.2%, 4 mL/min., observando a 220 nm). EM (ES): m/z 525.1 [M+H]

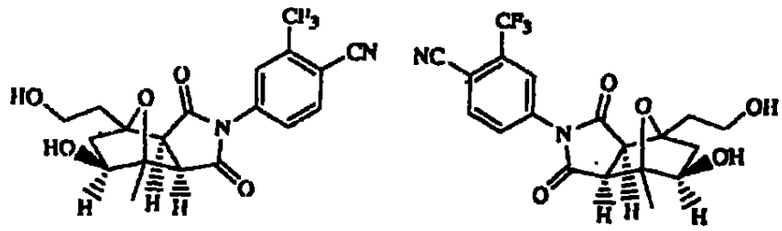
La mezcla racémica de los compuestos 428i y 428ii se separó por CLAR quiral preparativa de fase normal usando una columna Chiracel OD (5 cm x 50 cm), eluyendo con 13% de solvente B (EtOH) en solvente A (hexanos), relación de flujo: 50 mL/min. El compuesto 428i se eluyó por 34 min. a 38 min. y el compuesto 428ii se eluyó desde 44 min. a 49 min. Se determinó el exceso enantiomérico por CLAR quiral. El compuesto 428i: >99% ee (12.576 min. (tiempo de retención) (columna ChiraCLel OJ de 4.6 x 250 mm eluyendo con 85% de

heptano isocrático/15% de MeOH/etanol (1:1), 1 mL/min., observando a 220 nm, 40°C). Compuesto 428ii: 99% ee (18.133 min. (tiempo de retención) (columna ChiraCLel OJ 4.6 x 250 mm eluyendo con 85% de heptano /15% MeOH/etanol (1:1) isocrático, 1 mL/min., observando a 220 nm, 40°C).

No se establecieron las configuraciones absolutas para los compuestos 428i y 428ii. Por simplicidad en la nomenclatura, se designa el compuesto 428i como que tiene una configuración "R" y el compuesto 428ii como que tiene una configuración "S". Los productos enantioméricamente puros derivados del compuesto 428i se designan en la presente como que tienen una configuración "R" y los productos enantioméricamente puros derivados del compuesto 428ii se designan en la presente como que tiene una configuración "S".

Ejemplo 429

[3aR-(3aα,4β,5β,7β,7aα)]-4-[Octahidro-5-hidroxi-7-(2-hidroxietil)-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2-(trifluorometil)benzonitrilo y [3aS-(3aα,4β,5β,7β,7aα)]-4-[Octahidro-5-hidroxi-7-(2-hidroxietil)-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2-(trifluorometil)benzonitrilo (429i y 429ii)

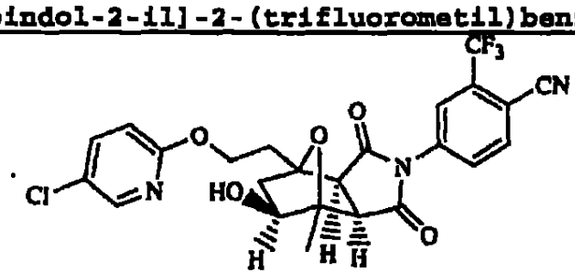


El compuesto 428i (180 mg, 0.34 mmol) se disolvió en 2% HCl/EtOH (5.0 mL). Después de 30 min., se agregó $NaHCO_3$ saturado y la capa acuosa se extrajo con diclorometano (20 mL x 3), se lavó con salmuera y se secó sobre Na_2SO_4 para dar 135 mg del compuesto 429i como un sólido blanco. CLAR: 99% a 2.257 min. (tiempo de retención) (columna YMC S5 ODS de 4.6 x 50 mm eluyendo con metanol acuoso al 10-90% durante 4 minutos que contenía ácido fosfórico al 0.2%, 4 mL/min., observando a 220 nm). EM (ES): m/z 411.1 $[M+H]^+$.

El procedimiento anterior se repitió con el compuesto 428ii para producir el compuesto deseado de diol 429ii en un rendimiento similar.

Ejemplo 430

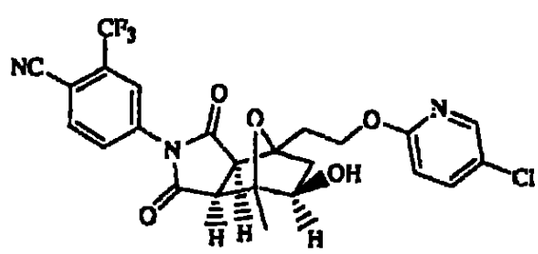
[3aR-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[5-Cloro-2-piridinil)oxi]etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2-(trifluorometil)benzonitrilo(430)



Se mezcló trifenilfosfina (0.026 g, 0.098 mmol) y DBAD (0.023 g, 0.098 mmol) en THF (0.5 mL). Después de permitir que reaccionara la mezcla previa por 15 min., se agregó 2-hidroxi-6-cloropiridina (0.016 g, 0.100 mmol), se dejó agitar la mezcla por 10 min. y se agregó el compuesto 429i (0.020 g, 0.049 mmol). La mezcla de reacción se agitó a 25°C por 2 h, y después el material crudo se purificó por CCD preparativa, eluyendo con 10% acetona/CHC_3, para dar 0.014 g del compuesto 430 como un sólido café claro. CLAR: 100% a 3.370 min. (tiempo de retención) (columna YMC S5 ODS de 4.6 x 50 mm eluyendo con metanol acuoso al 10-90% durante 4 minutos que contenía 0.1% de TFA, 4 mL/min., observando a 220 nm). EM (ES): m/z 522.08 $[M+H]^+$.

Ejemplo 431

[3aS-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[(5-Cloro-2-piridinil)oxi]etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2-(trifluorometil)benzonitrilo (431)

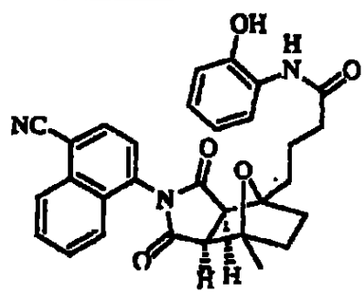


Se mezclaron trifenilfosfina (0.026 g, 0.098 mmol) y DBAD (0.023 g, 0.098 mmol) en THF (0.5 mL). Después de permitir que la mezcla previa reaccionara por 15 min., se

agregaron 2-hidroxi-6-cloropiridina (0.016 g, 0.100 mmol), la mezcla se dejó agitar por 10 min. y el compuesto 429ii (0.020 g, 0.049 mmol) se agregó. Se agitó la mezcla de reacción a 25°C por 2 h y después se purificó el material crudo por CCD preparativa, eluyendo con 10% acetona/$CHCl_3$, para dar 0.015 g del compuesto 431 como un sólido café claro. CLAR: 100% a 3.370 min. (tiempo de retención) (columna YMC S5 ODS de 4.6 x 50 mm eluyendo con metanol acuoso al 10-90% durante 4 minutos conteniendo TFA al 0.1%, 4 mL/min., observando a 220 nm). EM (ES): m/z 522.08 $[M+H]^+$.

Ejemplo 432

(3aα,4β,7β,7aα)-2-(4-Ciano-1-naftalenil)octahidro-N-(2-hidroxifenil)-7-metil-1,3-dioxo-4,7-epoxi-4H-isoindol-4-butanamida (432)

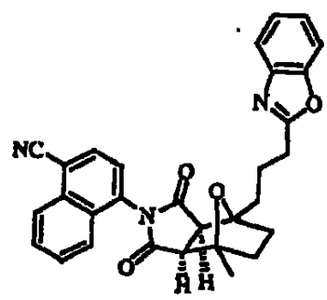


Se disolvió el compuesto 262 (0.100 g, 0.239 mmol) en DMF (anhidro, 1.5 mL), se agregó BOP (0.211 g, 0.478 mmol) seguido por 2-aminofenol (0.052 g, 0.478 mmol) y N-metil morfolina (0.052 mL, 0.478 mmol). La mezcla de reacción se agitó a 25°C bajo argón por 3 h, después se purificó el

material crudo por CLAR preparativa de fase inversa (YMC S5 ODS 20 X 100 mm, metanol acuoso 20-100% durante 15 minutos conteniendo 0.1% TFA, 20 mL/min., observando a 220 nm) para dar 0.060 g del compuesto 432 como un sólido café claro. CLAR: 100% a 3.037 min. (tiempo de retención) (columna YMC S5 ODS de 4.6 x 50 mm eluyendo con metanol acuoso al 10-90% durante 4 minutos conteniendo 0.1% TFA, 4 mL/min.; observando a 220 nm). EM (ES): m/z 510.34 $[M+H]^+$.

Ejemplo 433

(3aα,4β,7β,7aα)-4-[4-[3-(2-Benzoxazolil)propil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo (433)



Se mezclaron trifenilfosfina (0.031 g, 0.118 mmol) y DBAD (0.027 g, 0.118 mmol) en THF (0.5 mL). Después de permitir que la mezcla previa reaccionara por 15 min., se agregó el compuesto 432 (0.030 g, 0.059 mmol). Se agitó la mezcla de reacción a 25°C por 2 h y después se purificó el material crudo por CLAR preparativa de fase inversa (YMC S5 ODS 20 X 100 mm, metanol acuoso al 20-100% durante 15 minutos

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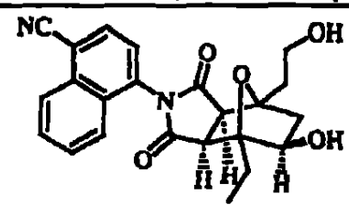
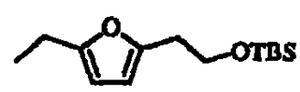
conteniendo 0.1% TFA, 20 mL/min., observando a 220 nm) para dar 0.018 g del compuesto 433 como un sólido café claro. CLAR: 100% a 3.357 min. (tiempo de retención) (columna YMC S5 ODS de 4.6 x 50 mm eluyendo con metanol acuoso al 10-90% durante 4 minutos conteniendo 0.1% TFA, 4 mL/min., observando a 220 nm). EM (ES): m/z 492.37 $[M+H]^+$.

Ejemplo 434

(3aα,4β,5β,7β,7aα)-4-[4-Etiloctahidro-5-hidroxi-7-(2-hidroxietil)-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo (434C)



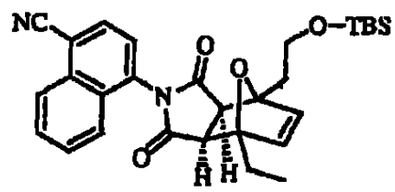
A. Tert-Butil-[2-(5-etil-furan-2-il)-etoxi]-dimetil-silano (434A)



Se agregaron imidazol (255 mg, 3.75 mmol) y TBSCl (414 mg, 2.75 mmol) a una solución de 245A (350 mg, 2.5 mmol) en DMF (4 mL). La mezcla se agitó a temperatura ambiente por 15 hr y después se agregaron 100 mg (0.66 mmol) de TBSCl adicional para llevar la reacción hasta su terminación. Después de agitar por una hora adicional, se diluyó la mezcla de reacción con éter de dietilo (100 mL) y se lavó con agua

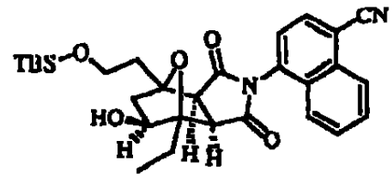
(20 mL), HCl 1N (20 mL), agua (20 mL) y salmuera (20 mL). La capa orgánica se secó sobre Na_2SO_4 y se concentró bajo presión reducida para dar 509 mg del compuesto 434A (80.3%) como un aceite amarillo.

B. (3aα,4β,7β,7aα)-4-[4-[2-[[(1,1-Dimetiletil)-dimetilsilil]oxi]etil]-4-etil-1,3,3a,4,7,7a-hexahidro-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo (434B)



Una solución del compuesto 434A (509 mg, 2.00 mmol) y 4-(2,5-dihidro-2,5-dioxo-1H-1-il)-1-naftalencarbonitrilo (498 mg, 2.00 mmol) en benceno (2 mL) se calentó a 60°C por 18 h. Se concentró la mezcla de reacción bajo presión reducida para dar 992 mg (99%) del compuesto crudo 434B, que se usó directamente en la siguiente etapa sin purificación adicional.

C. (3aα,4β,5β,7β,7aα)-4-[7-[2-[[(1,1-Dimetiletil)-dimetilsilil]oxi]etil]-4-etiloctahidro-5-hidroxi-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo (434C)



Se evacuó una mezcla del compuesto 434B (992 mg, 1.98 mmol) y $RhCl_2(PPh_3)_3$ (183 mg, 0.198 mmol) y se llenó con argón (3X). Se agregó THF (20 mL) y una vez que todos los materiales particulados se habían disuelto, se agregó lentamente gota a gota el catecolborano (0.42 mL, 3.96 mmol). Cuando terminó la formación de producto, como se determina por CLAR, se enfrió la mezcla de reacción a 0°C y se apagó con solución amortiguadora de fosfato (34 mL, pH 7.2), seguida por la adición de EtOH (19 mL) y 30% H_2O_2 (2.9 mL). Después de 2 h, se agregaron una solución adicional amortiguadora de fosfato (6.8 mL, pH 7.2), EtOH (3.8 mL) y H_2O_2 (0.6 mL). La mezcla de reacción se agitó a temperatura ambiente por 3 h. Una vez que se consumió el intermediario de boronato, se extrajo la mezcla con CH_2Cl_2 (300 mL) y las capas orgánicas combinadas se lavaron con NaOH 1N, $NaHSO_3$ al 10% ac. y salmuera y después se secaron sobre Na_2SO_4. La purificación por cromatografía instantánea sobre gel de sílice eluyendo con 10% $MeOH/CH_2Cl_2$ dio 75 mg (9.3%) del compuesto 434C como un sólido gris. Condiciones CLAR: 97% a 2.43 min. (tiempo de retención) (columna Phenomenex-prime S5-C18 de 4.6 x 50 mm, metanol acuoso al 10%-90% sobre un

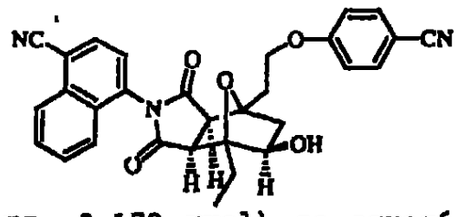
gradiente de 4 minutos con 0.2% HL_3PO_4, detectando a 220 nm). EM (ES): m/z 407.18 $[M+H]^+$.

D. (3aα,4β,5β,7β,7aα)-4-[4-Etiloctahidro-5-hidroxi-7-(2-hidroxietil)-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo (434D)

Se disolvió el compuesto 434C (24 mg, 0.046 mmol) en 2% de HCl/EtOH (0.8 mL) concentrado y la mezcla se agitó a temperatura ambiente por 20 min. Se agregó $NaHCO_3$ frío saturado a la mezcla, hasta que se hizo básica la solución (pH 8). Se extrajo la reacción con EtOAc (3x2 mL) y las capas orgánicas combinadas se lavaron con salmuera (2x5 mL) y se secaron sobre sulfato de sodio anhidro. La concentración in vacuo dio 14 mg (75%) del compuesto 434D como un sólido blancó. CLAR: 95% a 2.40 min. (tiempo de retención) (YMC S5 ODS 4.6 x 50 mm, metanol acuoso al 10%-90% sobre un gradiente de 4 minutos con 0.2% H_3PO_4, observando a 220 nm).

Ejemplo 435

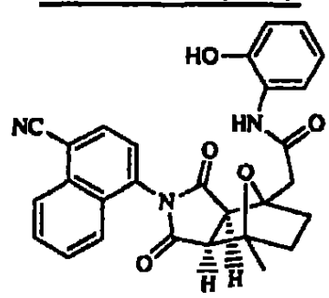
(3aα,4β,5β,7β,7aα)-4-[7-[2-(4-Cianofenoxi)etil-4-etiloctahidro-5-hidroxi-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo (435)



DBAD (39.6 mg, 0.172 mmol) se agregó a una solución de PPh_3 (45.1 mg, 0.172 mmol) en THF (0.8 mL). Después de agitar por 10 min., se agregó 4-cianofenol (20.5 mg, 0.172 mmol) y se agitó la mezcla de reacción por 5 min. adicionales. El compuesto 434C (25.0 mg, 0.062 mmol) se agregó y la mezcla se agitó a temperatura ambiente por 2 h. La reacción se concentró bajo presión reducida. La purificación por CCD preparativa eluída con 10% acetona/$CHCl_3$ dio 18.1 mg (0.036 mmol, 57.6%) del compuesto 435. condiciones CLAR: 96% a 3.15 min. (tiempo de retención) (YMC S5 ODS 4.6 X 50 mm, metanol acuoso al 10%-90% sobre un gradiente de 4 minutos con 0.2% H_3PO_4, detectado a 220 nm). EM (ES): m/z 508.14 $[M+H]^+$.

Ejemplo 436

(3aα,4β,7β,7aα)-2-(4-Ciano-1-naftialenil)octahidro-N-(2-hidroxifenil)-7-metil-1,3-dioxo-4,7-expoxi-4H-isoindol-4-etanamida (436)



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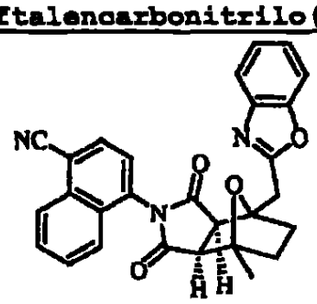
El compuesto 234B (0.100 g, 0.256 mmol) se disolvió en DMF (anhidro, 1.5 mL), BOP (0.225 g, 0.51 mmol) se agregó seguido por 2-aminofenol (0.056 g, 0.51 mmol) y N-metil morfolina (0.056 mL, 0.51 mmol). Se agitó la mezcla de reacción a 25°C bajo argón por 3 h, después se purificó el material crudo por CLAR preparativa de fase inversa (YMC S5 ODS 20 X 100 mm, metanol acuoso al 20-100% durante 15 minutos conteniendo 0.1% TFA, 20 mL/min., observando a 220 nm) para dar 0.078 g del compuesto 436 como un sólido café claro. CLAR: 100% a 3.037 min. (tiempo de retención) (columna YMC S5 ODS de 4.6 x 50 mm eluyendo con metanol acuoso al 10-90% durante 4 minutos conteniendo 0.1% TFA, 4 mL/min., observando a 220 nm). EM (ES): m/z 482.34 $[M+H]^+$.

Ejemplo 437

(3aα,4β,7β,7aα)-4-[4-(2-Benzoxazolilmetil)octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo(437)

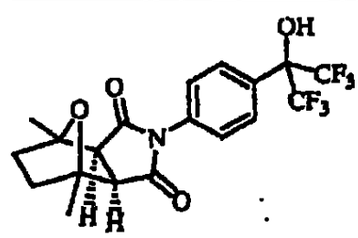


Se mezclaron trifenilfosfina (0.082 g, 0.312 mmol) y DBAD (0.072 g, 0.312 mmol) en THF (0.5 mL). Después de permitir que la mezcla previa reaccionara por 15 min., se

agregó el compuesto 436 (0.075 g, 0.156 mmol). Se agitó la mezcla de reacción a 25°C por 2 h y después se purificó el material crudo por CLAR preparativa de fase inversa (YMC S5 ODS 20 X 100 mm, metanol acuoso al 20-100% durante 15 minutos conteniendo 0.1% TFA, 20 mL/min., observando a 220 nm) para dar 0.052 g del compuesto 437 como un sólido café claro. CLAR: 100% a 3.443 min. (tiempo de retención) (columna YMC S5 ODS de 4.6 x 50 mm eluyendo con metanol acuoso al 10-90% durante 4 minutos conteniendo 0.1% TFA, 4 mL/min., observando a 220 nm). EM (ES): m/z 464.18 $[M+H]^+$.

Ejemplo 438

(3aα,4β,7β,7aα)-Hexahidro-4,7-dimetil-2-[4-[2,2,2-trifluoro-1-hidroxi-1-(trifluorometil)etil]fenil]-4,7-epoxi-1H-isoindol-1,3(2H)-diona (438)

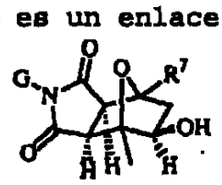


Se calentó una mezcla de 2-(4'-aminofenil)-1,1,1,3,3,3-hexafluoro-2-propanol (95.7 mg, 0.369), compuesto 20A (48.3 mg, 0.246 mmol), trietilamina (0.15 mL) y $MgSO_4$ (50 mg) en tolueno (1 mL) en un tubo sellado a 135°C durante la noche. La mezcla se filtró y se concentró bajo presión reducida. La purificación por CLAR preparativa de fase inversa (YMC S5 ODS

20 X 100 mm, metanol acuoso al 20-100% durante 15 minutos conteniendo 0.1% TFA, 20 mL/min., observando a 220 nm) dio 44.0 mg (41%) del compuesto 438 como un sólido blanco. CLAR: 99% a 3.10 min. (tiempo de retención) (columna Phenomenex-prime S5-C18 de 4.6 x 50 mm eluyendo con metanol acuoso al 10-90% durante 4 minutos conteniendo ácido fosfórico 0.2%, 4 mL/min., observando a 220 nm). EM (ES): m/z [M+H] = 438.14.

Ejemplos 439 al 454

Los compuestos adicionales de la presente invención se prepararon por procedimientos análogos a aquellos antes descritos. Los compuestos de los Ejemplos 439 a 454 tienen la siguiente estructura (L es un enlace):

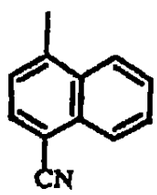
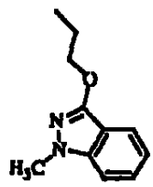
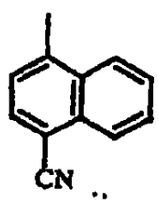
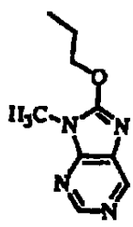


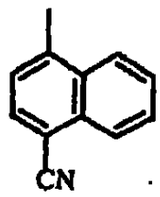
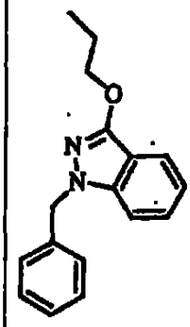
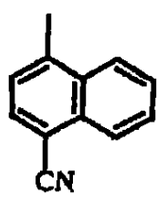
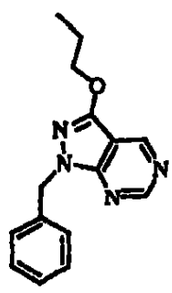
en donde G, R^7, el nombre del compuesto, tiempo de retención, masa molecular, y el procedimiento empleado, se establecen en la Tabla 9. La configuración absoluta para los siguientes compuestos no se determinó. Por simplicidad en la nomenclatura, el compuesto 243Di se designa en la presente como que tiene una configuración "S" y el compuesto 243Dii como que tiene una configuración "R". Los productos enantioméricamente puros derivados del compuesto 243Di se designan en la presente como que tienen una configuración "S" y los productos enantioméricamente puros derivados del

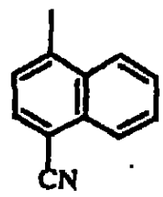
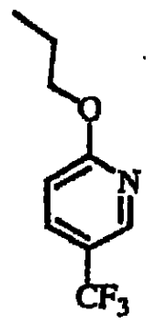
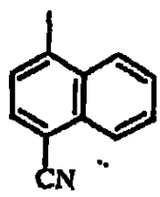
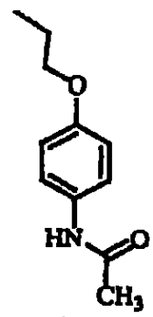
compuesto 243Dii se designan en la presente como que tiene una configuración "R". Similarmente, el compuesto 428i se designa como que tiene una configuración "S" y el compuesto 428ii como que tiene una configuración "R". Los productos enantioméricamente puros derivados del compuesto 428i se designan en la presente como que tienen una configuración "S", y los productos enantioméricamente puros derivados del compuesto 428ii se designan en la presente como que tienen una configuración "R".

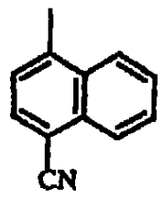
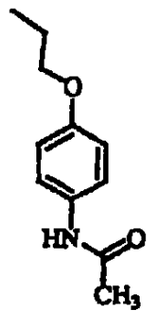
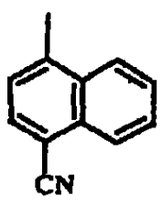
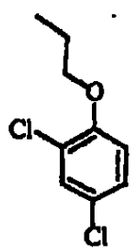
Las técnicas de cromatografía usadas para determinar los tiempos de retención del compuesto de la Tabla 9 son como sigue: columna CLEM = YMC S5 ODS, 4.6 X 50 mm eluyendo con 10-90% MeOH/H_2O durante 4 minutos que contiene 0.1% TFA; 4 mL/min., observando a 220 nm. CLEM* = columna YMC S5 ODS, 4.6 X 50 mm eluyendo con 10-90% MeOH/H_2O durante 2 minutos que contiene 0.1% TFA; 4 mL/min., observando a 220 nm. CL = columna YMC S5 ODS de 4.6 x 50 mm eluyendo con 10-90% MeOH/H_2O durante 4 minutos conteniendo ácido fosfóriço al 0.2%, 4 mL/min., observando a 220 nm. El peso molecular de los compuestos enlistados en la Tabla 9, se determinaron por EM (ES) por la fórmula m/z.

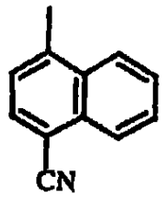
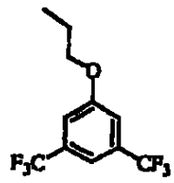
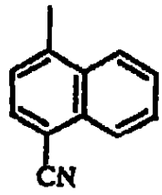
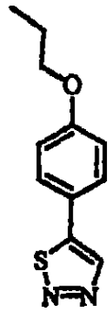
Tabla 9

Ej. No	G	R^7	Nombre del Comp.	Tiempo de retención Min./Masa molecular	Procedimiento del Ej.
439			[3aR-(3aα,4β,5β,7β,7aα)]-4-[Octahidro-5-hidroxi-4-metil-7-[2-[(1-metil-1H-indazol-3-il)oxi]etil]-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.33 CL 523.3 $[M+H]^+$	251, 253
440			[3aR-(3aα,4β,5β,7β,7aα)]-4-[Octahidro-5-hidroxi-4-metil-7-[2-[(9-metil-9H-purin-8-il)oxi]etil]1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	2.34 CL 525.2 $[M+H]^+$	251, 253

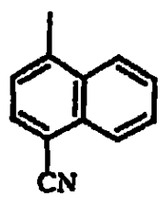
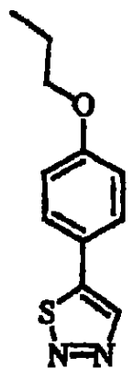
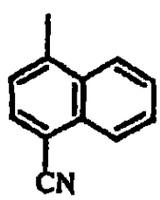
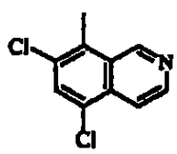
Ej. No	G	R'	Nombre del Comp.	Tiempo de retención Min./Masa molecular	Procedimiento del Ej.
441			[3aR-(3aα,4β,5β,7β,7aα)]-4-[Octahidro-5-hidroxi-4-metil-1,3-dioxo-7-[2-[[1-(fenilmetil)-1H-indazol-3-il]oxi]etil]-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.73 CL	251, 253
442			[3aR-(3aα,4β,5β,7β,7aα)]-4-[Octahidro-5-hidroxi-4-metil-1,3-dioxo-7-[2-[[1-(fenilmetil)-1H-pirazolo[3,4-d]pirimidin-3-il]oxi]etil]-4,7-epoxi-2H-isoindol-2il]-1-naftalencarbonitrilo	3.37 CL	251, 253

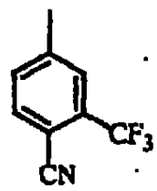
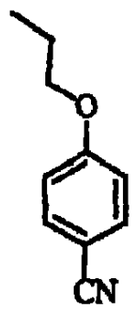
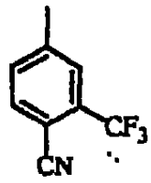
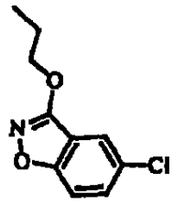
Ej. No	G	R'	Nombre del Comp.	Tiempo de retención Min./Masa molecular	Procedimiento del Ej.
443			[3aS-(3aα,4β,5β,7β,7aα)]-4-[Octahidro-5-hidroxi-4-metil-1,3-dioxo-7-[2-[[5-(trifluorometil)-2-piridinil]oxi]etil]-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.45 CL 538.23 $[M+H]^+$	243Di, 244i
444			[3aR-(3aα,4β,5β,7β,7aα)]-4-[Octahidro-5-hidroxi-4-metil-1,3-dioxo-7-[2-[[5-(trifluorometil)-2-piridinil]oxi]etil]-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.46 CL 538.24 $[M+H]^+$	243Dii, 244ii

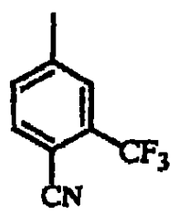
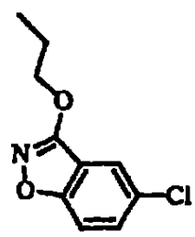
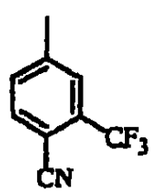
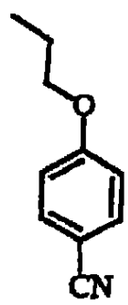
Ej. No	G	R^7	Nombre del Comp.	Tiempo de retención Min./Masa molecular	Procedimiento del Ej.
445			[3aR-(3aα,4β,5β,7β,7aα)]-N-[4-[2-[2-(4-Ciano-1-naftalenil)octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-7H-isoindol-7-il]etoxi]fenil]acetamida	2.747 CL 526.28 $[M+H]^+$	243Dii, 244ii
446			[3aR-(3aα,4β,5β,7β,7aα)]-4-[7-[2-(2,4-Diclorofenoxi)etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.71 CL 537.17 $[M+H]^+$	243Dii, 244ii

Ej. No	G	R'	Nombre del Comp.	Tiempo de retención Min./Masa molecular	Procedimiento del Ej.
447			[3aR-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[3,5-Bis(trifluorometil)fenoxi]etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.89 CL 605.25 $[M+H]^+$	243Dii, 244ii
448			[3aS-(3aα,4β,5β,7β,7aα)]-4-[Octahidro-5-hidroxi-4-metil-1,3-dioxo-7-[2-[4-(1,2,3-tiadiazol-5-il)fenoxi]etil]-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.14 CL 553.1 $[M+H]^+$	243Di, 244i

865

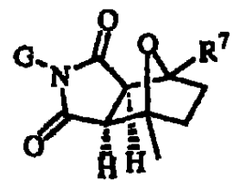
Ej. No	G	R'	Nombre del Comp.	Tiempo de retención Min./Masa molecular	Procedimiento del Ej.
449			[3aR-(3aα,4β,5β,7β,7aα)]-4-[Octahidro-5-hidroxi-4-metil-1,3-dioxo-7-[2-[4-(1,2,3-tiadiazol-5-il)fenoxi]etil]-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.15 CL 553.23 $[M+H]^+$	243Dli, 244ii
450			[3aR-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[(5,7-Dicloro-8-quinolinil)oxi]etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo, trifluoroacetato (1:1)	3.70 CL 588.26 $[M+H]^+$	243Dli, 244ii

Ej. No	G	R'	Nombre del Comp.	Tiempo de retención Min./Masa molecular	Procedimiento del Ej.
451			[3aS-(3aα,4β,5β,7β,7aα)]-4-[7-[2-(4-cianofenoxi)etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2-(trifluorometil)benzonitrilo	3.087 CL 512.13 $[M+H]^+$	431
452			[3aS-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[(5-Cloro-1,2-benzisoxazol-3-il)oxi]etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2-(trifluorometil)benzonitrilo	3.563 CL 562.08 $[M+H]^+$	431

Ej. No	G	R'	Nombre del Comp.	Tiempo de retención Min./Masa molecular	Procedimiento del Ej.
453			[3aR-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[(5-Cloro-1,2-benzisoxazol-3-il)oxi]etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2-(trifluorometil)benzonitrilo	3.57 Cl 562.08 $[M+H]^+$	430
454			[3aR-(3aα,4β,5β,7β,7aα)]-4-[7-[2-(4-Cianofenoxi)etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2-(trifluorometil)benzonitrilo	3.087 CL 512.08 $[M+H]^+$	430

Ejemplos 455 a 457

Los compuestos de la presente invención se prepararon por procedimientos análogos a aquellos antes descritos. Los compuestos de los Ejemplos 455 a 457 tienen la siguiente estructura (L es un enlace):

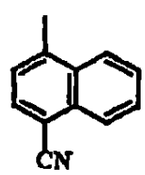
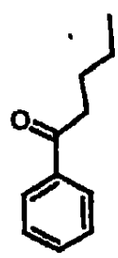
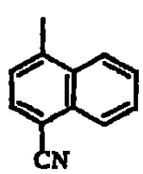
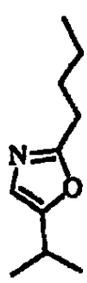


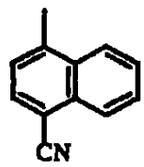
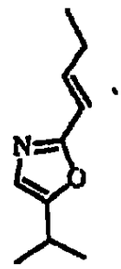
en donde G, R^7, el nombre del compuesto, tiempo de retención, masa molecular, y el procedimiento empleado, se establecen en la Tabla 10. No se determinó la configuración absoluta para los siguientes compuestos. Para simplicidad en la nomenclatura, el compuesto 238i se designa en la presente como que tiene una configuración "R" y el compuesto 238ii como que tiene una configuración "S". Los productos enantioméricamente puros derivados del compuesto 238i se designan en la presente como que tienen una configuración "R" y los productos enantioméricamente puros derivados del compuesto 238ii se designan en la presente como que tienen una "S".

Las técnicas de cromatografía usadas para determinar los tiempos de retención del compuesto en la Tabla 10 son como sigue: CLEM = columna YMC S5 ODS, 4.6 X 50 mm eluyendo con 10-90% MeOH/H_2O durante 4 minutos que contiene 0.1 % TFA; 4 mL/min, observando a 220 nm. CLEM* = columna YMC S5 ODS, 4.6

X 50 mm eluyendo con 10-90% MeOH/H_2O durante 2 minutos conteniendo 0.1 % TFA; 4 mL/min, observando a 220 nm. CL = columna YMC S5 ODS 4.6 x 50 mm eluyendo con 10-90% MeOH/H_2O durante 4 minutos que contiene ácido fosforico al 0.2%, 4 mL/min, observando a 220 nm. La masa molecular de los compuestos enlistados en la Tabla 10 se determina por EM(ES) por la fórmula m/z.

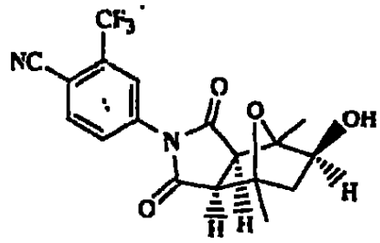
Tabla 10

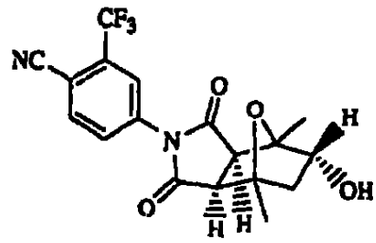
Ej. No	G	R'	Nombre del Comp.	Tiempo de retención Min./Masa molecular	Procedimiento del Ej.
455			(3aα,4β,5β,7β,7aα)-4-[Octahidro-4-metil-1,3-dioxo-7-(4-oxo-4-fenilbutil)-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.53 CL 479.35 $[M+H]^+$	265, 266
456			(3aα,4β,5β,7β,7aα)-4-[Octahidro-4-metil-7-[3-[5-(1-metiletil)-2-oxazolil]-2-propil]-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.547 CL 482.28 $[M+H]^+$	248, 249

Ej. No	G	R'	Nombre del Comp.	Tiempo de retención Min./Masa molecular	Procedimiento del Ej.
457			(3aα,4β,5β,7β,7aα(E)]-4-[Octahidro-4-metil-7-[3-[5-(1-metiletil)-2-oxazolil]-2-propenil]-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.66 CL 482.28 $[M+H]^+$	248, 249

Ejemplo 458

(3aα,4β,5β,7β,7aα)-4-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7,epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo y (3aα,4β,5α,7β,7aα)-4-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo (221B y 222D)





El compuesto 20B se convirtió a los compuestos 221B y 222D (también sintetizados como compuestos 221B y 222D) por biotransformación.

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El compuesto 20B se hidroxiló por *Amycolatopsis orientalis* (ATCC 43491). Se utilizó un cultivo de 1 mL de un vial congelado, para inocular 100 mL de medio en un matraz Erlenmeyer en porciones de 500 mL, y el matraz se incubó a 28°C, a 200 rpm por 3 días. Se utilizó una porción de 10 mL de este cultivo para inocular 100 mL de medio en un matraz Erlenmeyer de 500 mL, y el matraz se incubó a 28°C, a 200 rpm por 1 día. Se distribuyeron porciones de 10 mL del cultivo de 1 día en cada uno de los tres matraces de 50 mL. Se agregó el compuesto 20B (3 mg en 0.1 mL de metanol) a cada cultivo y se continuaron las incubaciones por 3 días. El caldo de cultivo en cada matraz se extrajo con 20 mL de acetato de etilo, y los extractos acumulados de acetato de etilo se evaporaron hasta sequedad a 40°C bajo una corriente de nitrógeno. El residuo se disolvió en 1.2 mL de metanol y se analizó por CLAR, CL/EM y CL/RMN. La solución contenía 2.5 mg del compuesto restante 20B, 1.6 mg del compuesto 221B, y 1.3 mg del compuesto 222D. Los análisis EM y RMN estuvieron de acuerdo con las estructuras antes mostradas.

<u>Medio</u>: nutrisoya tostada 0.5%, glucosa al 2%, extracto de levadura 0.5%, K_2HPO_4 al 0.5%, NaCl al 0.5%, ajustado hasta un pH de 7 con HCl (R. V. Smith y J. P. Rosazza, Arch. Biochem. Biophys., 161, 551-558 (1974)

<u>Análisis CLAR</u>

Columna: Fenomenex Luna C18, 150x2 mm, 5µ

Fase móvil: solvente A: 95% de acetato de amonio 20 mM pH 5.1, acetonitrilo al 5%

solvente B: acetonitrilo al 95%, 5% de acetato de amonio 20 mM pH 5.1.

El gradiente lineal va desde el solvente A al 100% hasta el solvente A al 5% en 25 minutos, seguido por equilibrio en el solvente A al 100% por 8 minutos.

temperatura: 40°C

Detección: 250 nm

Volumen de inyección: 1 µL

Tiempos de retención: compuesto 20B, 20.8 min; compuesto 221B, 16.5 min; compuesto 222D, 17.8 min.

Condiciones CLAR

Las condiciones quirales de CLAR se emplearon para la separación de los enantiómeros y las condiciones no quirales de CLAR se emplearon para la separación de los diastereómeros de los análogos hidroxilados del compuesto 20B (esto es, compuestos 221B y 222D y compuestos 254i y 254ii)

Se utilizaron dos métodos bajo condiciones quirales de CLAR, fase inversa (RP) para el análisis quiral de los productos de biotransformación en muestras biológicas y de fase normal (NP) para muestras no biológicas.

Condición quiral RP-CLAR

Columna: CHIRALPAK AD-R

4.6 x 250 mm, 10 µ

Temperatura: 40°C

Volumen de inyección: 5 o 20 µL

Fase Móvil: A: MeCN

B: H_2O

Isocrático, 30% de A, 18 min.

Relación de flujo: 1mL/min.

Detección UV: 242 nm

Condición quiral NP-CLAR

Columna: CHIRALPAK AD

4.6 x 250 mm, 10 µ

Temperatura: 25°C

Volumen de inyección: 5 ó 20 µL

Fase Móvil: A: Heptano

B: MeOH/Etanol

(1:1)

Isocrático, 80% de A, 20 min.

Relación de flujo: 1 mL/min.

Detección UV: 242 nm

Bajo estas condiciones, los compuestos 254i y 254ii tuvieron tiempo de retención de 8.5 minutos y 9.85 minutos, respectivamente.

La CLAR de fase inversa se empleo para la separación de los compuestos diastereoméricos 221B y 222D:

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Fase Móvil:

Solvente A: Acetato de amonio 20 mM al 95% pH 5.1,5% acetonitrilo

Solvente B: Acetonitrilo al 95%, acetato de amonio 20 mM al 5% pH 5.1

Gradiente:

El gradiente lineal va desde un solvente A al 100% hasta un solvente A al 5% en 25 minutos, seguido por un equilibrio en el solvente A al 100% por 8 minutos. El tiempo total de la corrida de 36 minutos.

Relación de flujo:

0.2 mL/min

Columna:

Fenomenex Luna 5 micron C_{18} 150 X 2.0 mm id

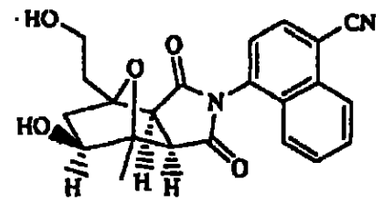
Detección:

detección UV a 242 nm

Bajo estas condiciones los compuestos 221B y 222D tuvieron tiempos de retención de 18.983 min y 20.362 min, respectivamente.

Ejemplo 459

(3aα,4β,5β,7β,7aα)-4-[Octahidro-5-hidroxi-7-(2-hidroxietil)-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo (459)



Los compuestos 223A y 331 se convirtieron al compuesto 459 por biotransformación.

Hidroxilación microbiana del compuesto 223A

1. Reacción

A un matraz de 500 mL conteniendo 100 mL del medio de transformación se le agregó un vial congelado (aproximadamente 2 mL) de *Streptomyces griseus* ATCC 10137. El medio de transformación se preparó como sigue: a una cuba de plástico de 2 L se le agregó 20 g de dextrosa, 5.0 g de extracto de levadura, 5.0 g harina de soya, 5.0 g de cloruro de sodio, 5.0 g de fosfato de potasio (dibásico) y 1 L de agua desionizada, y la mezcla se agitó a temperatura ambiente durante 3 hasta 30 min. El pH de la mezcla se ajustó después hasta 7.0 con HCl 1N o NaOH 1N. La mezcla resultante se dispensó en matraces de 500 mL (100 mL por matraz). Los matraces se cubrieron con Bio/Wrap y se colocraron en autoclave a 121°C durante 15 min. y se enfriaron hasta temperatura ambiente antes de usarse.

El cultivo se incubó a 28°C y a 250 rpm durante 24 horas. Se transfirieron diez mL del cultivo resultante a un matraz de 50 mL, al cual se le agregó 1 mg del compuesto 223A

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en 0.2 mL de etanol. El matraz se incubó a 28°C y 250 rpm durante 24 horas, y el cultivo de reacción se extrajo con EtOAc (10 mL). El extracto de EtOAc se secó bajo N_2 y el residuo se disolvió en 1 mL de MeOH (extracto de reacción).

2. Análisis del Producto

CLAR:

Se inyectaron 10 µL del extracto de la reacción en la Columna CLAR (Columna YMC ODS-AQ C-18, 160 x 6.0 mm d.i.). La columna se eluyó con 1 mM HCl en agua/CH_3CN a una relación de flujo de 1.2 mL/min.: 30 hasta 60% CH_3CN durante 8 min., 60 hasta 85% CH_3CN durante 0.5 min., 85% CH_3CN por 1 min., 85 hasta 30% CH_3CN durante 0.5 min. Los eluyentes se observaron a 300 mn. Se observaron dos picos principales con un área de alrededor de 1 a 1, que tenían los mismos espectros UV que aquellos de los compuestos 459 y 331, y tuvieron tiempos de retención de 4.55 min. y 7.23 min., respectivamente, acoplando el tiempo de retención de las muestras auténticas del compuesto 459 (4.53 min.) y del compuesto 331 (7.2 min.).

CL/EM

El extracto de la reacción: dos picos principales UV.

Pico 1, Tr 4.68 min.: 391 $[M+H]^+$, 343, 319, 303, 289

Pico 2, Tr 5.35 min.: 375 $[M+H]^+$, 345

Muestras Auténticas

Compuesto 459, Tr 4.82 min.: 391 $[M+H]^+$, 343, 319, 289

Compuesto 331, Tr 5.48 min.: 375 $[M+H]^+$, 345

Hidroxilación microbiana del Compuesto 331

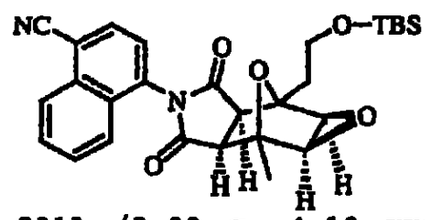
Se agregó a un matraz de 500 mL conteniendo 100 mL del medio de transformación, un vial congelado (aproximadamente 2 mL) de *Streptomyces griseus* ATCC 10137. El medio de transformación se preparó como sigue: a un vaso de precipitados de plástico de 2 L, se agregaron 20 g de dextrosa, 5.0 g de extracto de levadura, 5.0 g de harina de soya, 5.0 g de cloruro de sodio, 5.0 g de fosfato de potasio (dibásico) y un L de agua desionizada, y la mezcla se agitó a temperatura ambiente por 3 hasta 30 min. El pH de la mezcla se ajustó después hasta 7.0 con HCl 1N o NaOH 1N. La mezcla resultante se dosificó en matraces de 500 mL (100 mL por matraz). Se cubrieron los matraces con Bio/Wrap y se procesaron en autoclave a 121°C por 15 min. y se enfriaron hasta temperatura ambiente antes de su uso.

El cultivo se incubó a 28°C y 250 rpm por 3 días. Se agregó un mL del cultivo resultante a un matraz de 500 mL conteniendo 100 mL del medio de transformación y el matraz se incubó a 28°C y 250 rpm por 24 horas. Se transfirieron diez mL del cultivo resultante a un matraz de 50 mL, al cual se agregó 1 mg del compuesto 331 en 0.2 mL de etanol. El matraz

se incubó a 28°C y 250 rpm por 23 horas. El análisis CLAR mostró que la relación de área pico del compuesto 459 al compuesto 331 en el cultivo de reacción fue de alrededor de 1.1/1.

Ejemplo 460

(1aα,2β,2aα,5aα,6βb,6aα)-4-[2-[2-[[(1,1-Dimetiletil)dimetilsilil]oxi]etil]octahidro-6-metil-3,5-dioxo-2,6-epoxi-4H-oxireno[f]isoindol-4-il]-1-naftalencarbonitrilo (460)

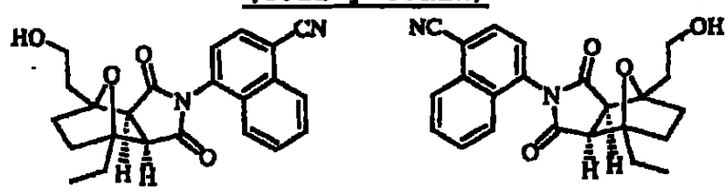


El compuesto 231A (2.00 g, 4.10 mmol) se disolvió en diclorometano (40 mL) y se enfrió hasta 0°C. Se agregó mCPBA (2.36 g, 8.20 mmol). La mezcla de reacción se calentó después hasta temperatura ambiente y se agitó bajo argón por 18 horas, seguido por la adición de 10% Na_2SO_3 (25 mL) y de $NaHCO_3$ saturado (25 mL). Después de agitar por 20 minutos, la capa orgánica se separó y la capa acuosa se extrajo con diclorometano (3 x 50 mL). Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre Na_2SO_4 y se concentraron bajo presión reducida para dar 2.0 g del compuesto 460 como un sólido amarillo ligero. CLAR: 99% a 4.00 min. (tiempo de retención) (Columna Phenomenex-prime S5-

C18 4.6 x 50 mm eluyendo con 10-90% metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z [M+H]=505.19.

Ejemplo 461

[3aR-(3aα,4β,7β,7aα)]-4-[4-Etiloctahidro-7-(2-hidroxietil)-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo y [3aS-(3aα,4β,7β,7aα)]-4-[4-Etiloctahidro-7-(2-hidroxietil)-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo (461i y 461ii)



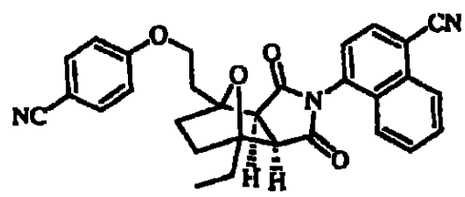
La mezcla racémica de compuestos 245C se separó por CLAR quiral preparativa en fase normal usando una columna Chiracel AD (5 cm x 50 cm), eluyendo con 20% del solvente B (50% MeOH/EtOH) en solvente A (Heptano), relación de flujo: 50 mL/min. El compuesto 461i se eluyó desde 80 min. hasta 100 min. y el compuesto 461ii se eluyó desde 125 min. hasta 150 min.

La conformación absoluta de los compuestos 461i y 461ii no se determinó. Por simplicidad en la nomenclatura, el compuesto 461i se designa en la presente como que tiene una configuración "R" y el compuesto 461ii como que tiene una

configuración "S". Los productos enantioméricamente puros derivados de los compuestos 461i se designan en la presente por tener una configuración "R" y los productos enantioméricamente puros derivados del compuesto 461ii se designan en la presente por tener una configuración "S".

Ejemplo 462

[3aR-(3aα,4β,7β,7aα)]-4-[4-[2-(4-Cianofenoxi)etil]-7-etiloctahidro-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo (462)



Se agregó DBAD (29.5 mg, 0.128 mmol) a una solución de PPh_3 (33.6 mg, 0.128 mmol) en THF (0.5 mL). Después de agitar por 10 min., se agregó 4-cianofenol (15.2 mg, 0.128 mmol) y la mezcla de reacción se agitó por 5 min., adicionales. Se agregó el compuesto 461i (18.3 mg, 0.047 mmol) y la mezcla se agitó a temperatura ambiente por 2 h. La reacción se concentró bajo presión reducida. La purificación por cromatografía instantánea sobre gel de sílice eluyendo con 40% EtOAc/hexano dio 16.9 mg (0.034 mmol, 73.2%) de compuesto 462. Condiciones CLAR: 98% a 3.64 min. (tiempo de retención) (YMC S5 ODS 4.6 X 50 mm, 10%-90% metanol acuoso durante un gradiente de 4 minutos con 0.2% H_3PO_4, detectando a 220 mn). EM (ES): m/z 492.23 $[M+H]^+$.

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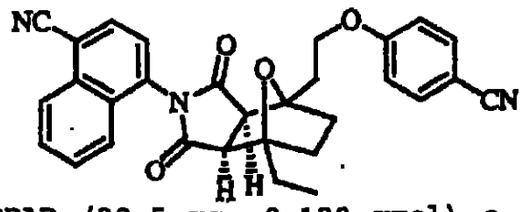
Ejemplo 463

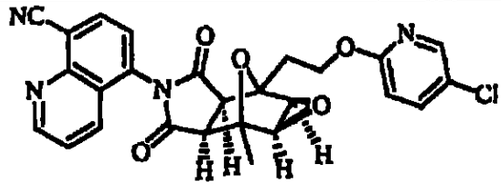
[3aS-(3aα,4β,7β,7aα)]-4-[4-[2-(4-Cianofenoxi)etil]-7-etiloctahidro-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo (463)



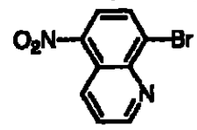
Se agregó DBAD (29.5 mg, 0.128 mmol) a una solución de PPh_3 (33.6 mg, 0.128 mmol) en THF (0.5 mL). Después de agitar por 10 min., se agregó 4-cianofenol (15.2 mg, 0.128 mmol) y la mezcla de reacción se agitó por 5 min. adicionales. Se agregó el compuesto 461ii (18.3 mg, 0.047 mmol) y la mezcla se agitó a temperatura ambiente por 2 h. La reacción se concentró bajo presión reducida. La purificación por cromatografía instantánea sobre gel de sílice eluyendo con 40% EtOAc/hexano dio 18.1 mg (0.037 mmol, 78.4%) de compuesto 463. Condiciones CLAR: 97% a 3.63 min. (tiempo de retención) (YMC S5 ODS 4.6 X 50 mm, 10%-90% metanol acuoso durante un gradiente de 4 minutos con 0.2% H_3PO_4, detectando a 220 nm). EM (ES): m/z 492.17 $[M+H]^+$.

Ejemplo 464

(1aα,2β,2aα,5aα,6β,6aα)-5-[2-[2-[(5-Cloro-2-piridinil)oxi]etil]octahidro-6-metil-3,5-dioxo-2,6-epoxi-4H-oxireno[f]isoindol-4-il]-8-quinolinocarbonitrilo (464H)

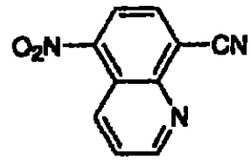


A. 8-Bromo-5-nitro-quinolina (464A)



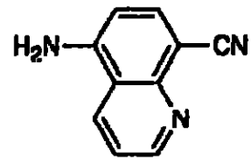
La 8-bromoquinolina (25.00 g, 120.2 mmol) se disolvió en ácido sulfúrico (82.5 mL) a temperatura ambiente y se enfrió después hasta 0°C. Se agregó después lentamente HNO_3 (fumante, 32.5 mL) durante un periodo de 10 minutos. La reacción se calentó después a temperatura ambiente y después hasta 65°C. Después de 48 h a 65°C, la reacción se enfrió hasta temperatura ambiente y se vació sobre 500 g de hielo. Esta solución se extrajo con cloruro de metileno (5 x 200 mL). Las capas orgánicas se lavaron una vez con salmuera y se secaron sobre sulfato de sodio anhidro. La concentración dio el compuesto crudo 464A como un sólido amarillo ligero (28.6 g, 94%). CLAR: 98% a 2.717 min. (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso durante 4 min. conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm).

B. 5-Nitro-quinolino-8-carbonitrilo (464B)



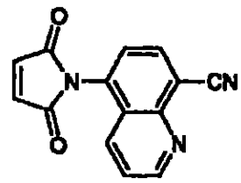
El compuesto 464A (15.0 g, 59.3 mmol) se disolvió en DMF (120 mL) y se agregó cianuro de zinc (4.20 g, 35.9 mmol). Se agregaron después bis(difenilfosfino)ferroceno (3.00 g, 5.40 mmol) y tris(bencilidinacetona)dipaladio (3.00 g, 3.30 mmol) y la reacción se calentó a 100°C por 1.5 h. La reacción se enfrió hasta 22°C y después se vació en hidróxido de amonio concentrado (900 mL) resultando en un precipitado color naranja que se filtró y enjuagó en agua fría (1 L). El precipitado resultante se disolvió en cloruro de metileno, se lavó con salmuera (1 x 300 mL) y después se secó sobre sulfato de sodio anhidro. La concentración in vacuo dio el material crudo como un sólido color naranja que fue purificado por cromatografía instantánea sobre gel de sílice eluyendo con cloruro de metileno para dar 6.01 g (51%) de compuesto 464B como un sólido amarillo. CLAR: 99% a 1.900 min. (tiempo de retención) (Columna YMC S5 ODS. 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso durante 4 min. conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm).

C. 5-Amino-quinolino-8-carbonitrilo (464C)



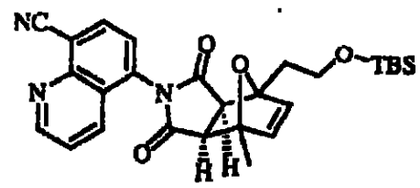
El compuesto 464B (6.00 g, 30.1 mmol) se disolvió en THF (150 mL) a reflujo con agitación mecánica. Se agregó después EtOH (150 mL) seguido por cloruro de amonio acuoso (2.4 g/225 mL agua). La mezcla se calentó a 70°C y después se agregó polvo de hierro (malla 325, 6.75 g, 120 mmol) con agitación mecánica vigorosa. Después de 1 h, la reacción se enfrió hasta 22°C y se filtró a través de Celite enjuagando con cloruro de metileno. El filtrado se concentró después hasta ~250 mL y se ajustó el pH hasta 10 por la adición de 1N NaOH. La solución se extrajo después con acetato de etilo (5 x 150 mL). Las capas orgánicas combinadas se lavaron una vez con salmuera (250 mL) y después se secaron sobre sulfato de magnesio anhidro. La concentración in vacuo dio 5.09 g (100%) de compuesto 464C como un sólido amarillo. CLAR: 99% a 1.143 min. (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso durante 4 min. conteniendo 0,2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 170.16 $[M+H]^+$.

D. 5-(2,5-Dioxo-2,5-dihidro-pirrol-1-il)-quinolino-8-carbonitrilo(464D)



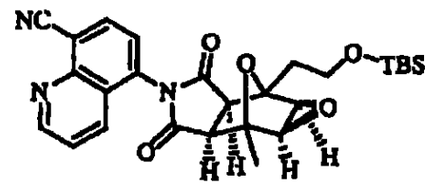
El compuesto 464C (7.00 g, 41.4 mmol) y anhídrido maléico (6.00 g, 62.1 mmol) se combinaron en un tubo sellado y se agregó THF (10 mL). La mezcla de reacción se calentó a 115°C por 15 min. después se enfrió hasta temperatura ambiente, resultando en la precipitación de la amida ácida intermediaria. El sólido se filtró y se enjuagó con THF frío para dar 11.0 g del ácido como un sólido amarillo. A la amida ácida anterior, se agregó Ac_2O (25 mL) en un tubo sellado y la mezcla se calentó a 100°C por 15 min., después se enfrió hasta temperatura ambiente. El sólido resultante se filtró y se enjuagó con éter de dietilo frío para dar 8.30 g (80%) de compuesto 464D como un sólido amarillo. CLAR: 97% a 1.783 min. (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso durante 4 min. conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm).

E. (3aα,4β,7β,7aα)-5-[4-[2-[[(1,1-Dimetiletil)dimetilsilil]oxi]etil]-1,3,3a,4,7,7a-hexahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-8-quinolinocarbonitrilo (464E)



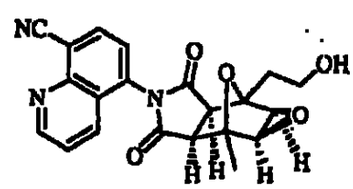
El compuesto 464D (6.00 g, 24.1 mmol) se disolvió en una mezcla de benceno (80 mL) y acetona (20 mL) seguido por la adición del compuesto 204A (14.46 g, 60.15 mmol). La mezcla se calentó a 80°C por 14 h y después se enfrió hasta 22°C. La concentración in vacuo a 40°C seguida por la adición de acetona (40 mL) y concentración nuevamente a 40°C. El aceite amarillo resultante fue purificado por cromatografía instantánea en columna sobre gel de sílice eluyendo con 0-10% acetona en cloroformo para dar 9.98 g (85%) de compuesto 464E como un aceite amarillo. El compuesto 464E demostró ser un isómero sencillo por espectroscopia RMN. CLAR: 97% a 3.853 min. (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso durante 4 min. conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 490.35 $[M+H]^+$.

F. (1aα,2β,2aα,5aα,6β,6aα)-5-[2-[2-[[(1,1-Dimetiletil)dimetilsilil]oxi]etil]octahidro-6-metil-3,5-dioxo-2,6-epoxi-4H-oxireno[f]isoindol-4-il]-8-quinolincarbonitrilo(464F)



A una solución de compuesto 464E (0.050 g, 0.10 mmol) en diclorometano (2 mL), se agregó mCPBA (mezcla al 60%, 0.063 g, 0.22 mmol). La mezcla de reacción se agitó a temperatura ambiente por 16 h y después se agregaron adicionalmente diclorometano (20 mL), $NaHCO_3$ saturado (10 mL) y 10% de Na_2SO_3 (10 mL). La mezcla se agitó vigorosamente por 40 min., la capa orgánica se separó después, se lavó una vez con salmuera, y se secó sobre Na_2SO_4. La concentración in vacuo dio 48 mg (96%) de compuesto 464F como un sólido amarillo claro. CLAR: 98% a 3.783 min. (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso durante 4 min. conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 506.25 $[M+H]^+$.

G. (1aα,2β,2aα,5aα,6β,6aα)-5-[Octahidro-2-(2-hidroxietil)-6-metil-3,5-dioxo-2,6-epoxi-4H-oxireno[f]isoindol-4-il]-8-quinolincarbonitrilo (464G)



El compuesto 464F (1.30 g, 2.57 mmol) se disolvió en HCl al 2% concentrado/EtOH (50 mL). La mezcla de reacción se agitó a temperatura ambiente por 1 h y después se agregaron $NaHCO_3$ saturado (50 mL) y diclorometano (100 mL). La capa orgánica se separó, se lavó una vez con salmuera y se secó sobre Na_2SO_4. La concentración in vacuo dio 930 mg (93%) de compuesto 464G como un sólido amarillo. CLAR: 98% a 1.863 (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso durante 4 min. conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 392.20 $[M+H]^+$.

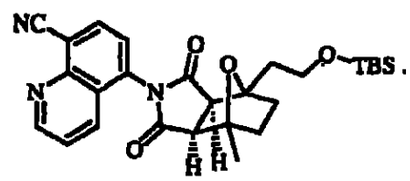
H. (1aα,2β,2aα,5aα,6β,6aα)-5-[2-[2-[(5-cloro-2-piridinil)oxi]etil]octahidro-6-metil-3,5-dioxo-2,6-dioxo-2,6-epoxi-4H-oxireno[f]isoindol-4-il]-8-quinolincarbonitrilo (464H)

Se mezclaron trifenilfosfina (25 mg, 0.096 mmol) y DBAD (22 mg, 0.096 mmol) en THF (0.5 mL) bajo argón. Después de 5 min., se agregó 5-cloro-2-piridinol (13 mg, 0.096 mmol). La mezcla de reacción se agitó a 22°C por otros 10 min., después se agregó el compuesto 464G (25 mg, 0.064 mmol). La mezcla de reacción se agitó a 22°C bajo argón por 3 h, y después se concentró in vacuo. El material crudo fue purificado por CCD preparativa sobre gel de sílice eluyendo con 10% acetona en cloroformo para dar 11 mg (23%) de compuesto 464H como un

sólido blanco. CLAR: 100% a 3.177 (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso durante 4 min. conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 503.14 $[M+H]^+$.

Ejemplo 465

(3aα,4β,7β,7aα)-5-[4-[2-[[(1,1-Dimetiletil)dimetilsilil]oxi]etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-8-quinolincarbonitrilo(465)



El compuesto 464E (2.40 g, 4.91 mmol) se disolvió en acetato de etilo y se agregó Pd/C (10% Pd, 0.50 g). El hidrógeno se introdujo después por medio de un globo. Después de 3 h, la reacción se purgó con nitrógeno y se filtró a través de Celite, enjuagando con acetato de etilo. La concentración in vacuo dio 2.39 g (99%) de compuesto 465 como un aceite amarillo. CLAR: 95% a 4.013 min. (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso durante 4 min. conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 492.22 $[M+H]^+$.

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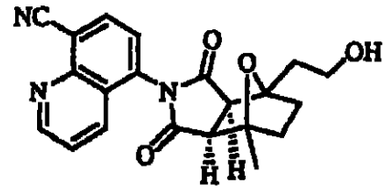
Ejemplo 466

(3aα,4β,7β,7aα)-5-[Octahidro-4-(2-hidroxietil)-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-8-quinolincarbonitrilo(466)



El compuesto 465 (1.40 g, 2.85 mmol) se disolvió en HCl concentrado al 2%/MeOH (20 mL) y se agitó a 22°C por 3 h. La reacción se concentró después hasta ~5 mL de volumen y se apagó con una cantidad mínima de bicarbonato de sodio acuoso saturado. Esta solución se extrajo después con cloruro de metileno (3 x 30 mL) y las capas orgánicas combinadas se secaron sobre sulfato de sodio anhidro. La concentración in vacuo dio 0.893 g (93%) del compuesto 466 como un sólido amarillo. Este material se llevó sin purificación adicional. CLAR: 98% a 2.140 min. (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso durante 4 min. conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 378.25 $[M+H]^+$.

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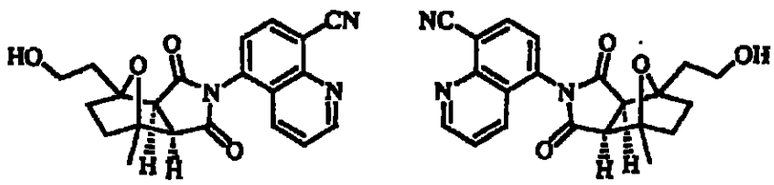
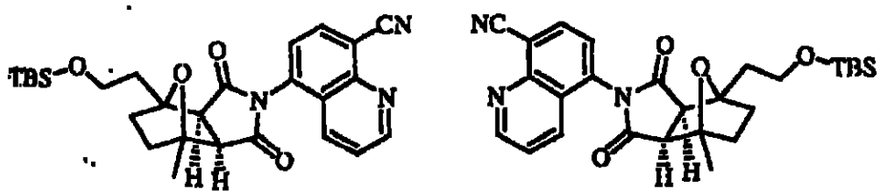
Ejemplo 467

[3aR-(3aα,4β,7β,7aα)]-5-[Octahidro-4-(2-hidroxietil)-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-8-quinolincarbonitrilo (467Bi) y [3aS-(3aα,4β,7β,7aα)]-5-[Octahidro-4-(2-hidroxietil)-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-8-quinolincarbonitrilo (467Bii)



A. [3aR-(3aα,4β,7β,7aα)]-5-[4-[2-[[(1,1-Dimetiletil)dimetilsilil]oxi]etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-8-quinolincarbonitrilo (467Ai) y [3aS-(3aα,4β,7β,7aα)]-5-[4-[2-[[(1,1-Dimetiletil)dimetilsilil]oxi]etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-8-quinolincarbonitrilo(467Aii)



El compuesto 465 se separó en sus antípodos individuales por CLAR quiral preparativa en fase normal. Se usó la columna A ChiraCLel OD (50 x 500 mm) con una relación de flujo de 50 mL/min. (16% EtOH/hexanos) observando a 220 nm. El compuesto antípodo de elución más rápida 467Ai tuvo un tiempo de

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retención de 40.85 min. (>99% ee) y el compuesto antípodo más lento 467AU tuvo un tiempo de retención de 62.81 min. (>99% ee). Se aislaron ambos antípodos como sólidos blancos después de la separación. La conformación absoluta de los compuestos 467Ai y 467Aii no se determinó. Por simplicidad en la nomenclatura, el compuesto 467Ai se designa en la presente como que tiene una configuración "R" y el compuesto 467Aii como que tiene una configuración "S". Los productos enantioméricamente puros derivados de los compuestos 467Ai se designan en la presente por tener una configuración "R" y los productos enantioméricamente puros derivados del compuesto 467Aii se designan en la presente por tener una configuración "S".

B. [3aR-(3aα,4β,7β,7aα)]-5-[Octahidro-4-(2-hidroxietil)-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-8-quinolincarbonitrilo (467Bi) y [3aS-(3aα,4β,7β,7aα)]-5-[Octahidro-4-(2-hidroxietil)-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-8-quinolincarbonitrilo(467Bii)

Se desprotegieron ambos antípodos como se describen en el Ejemplo 464G para dar los alcoholes correspondientes, compuestos 467Bi y 467Bii como sólidos blancos:

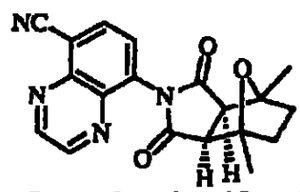
El compuesto 467Bi: CLAR: 98% a 2.110 min. (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, eluyendo con 10-

90% metanol acuoso durante 4 min. conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 378.21 $[M+H]^+$.

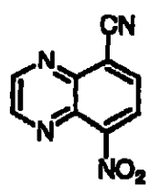
El compuesto 467Bii: CLAR: 98% a 2.117 min. (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso durante 4 min. conteniendo 0.2% ácid fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 378.20 $[M+H]^+$.

Ejemplo 468

(3aα,4β,7β,7aα)-8-[Octahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-5-quinoxalincarbonitrilo (468C)



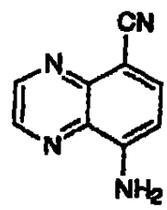
A. 8-Nitro-quinoxalin-5-carbonitrilo (468A)



Se agregó 2,3-Diamino-4-nitro-benzonitrilo (0.050 g, 0.28 mmol, como se preparó en WO-98/32439) a una solución de glioxal (40% en agua, 0.032 mL, 0.28 mmol) en ácido acético (0.75 mL) y se agitó a 22°C por 3 h. La reacción se enfrió hasta 0°C y se agregó agua (2.0 mL) y se ajustó el pH hasta 9.0 por la adición de hidróxido de amonio, que provocó que se

precipitara el producto. La mezcla se filtró después y se enjuagó con agua fría. El secado in vacuo dio 0.039 g (70%) de compuesto 468A como un sólido color naranja. CLAR: 100% a 2.037 min. (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso durante 4 min. conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm).

B. 8-Amino-quinoxalin-5-carbonitrilo (468B)



El compuesto 468A (0.200 g, 1.00 mmol) se suspendió en ácido acético (5.0 mL) y se agregó polvo de hierro (malla 325, 0.112 g, 2.00 mmol). La reacción se calentó después a 70°C por 20 min. y después se enfrió hasta 22°C. La reacción se filtró a través de Celite, enjuagando con acetato de etilo. El enjuague de acetato de etilo se recolectó y se lavó con K_2CO_3 acuoso saturado. La capa acuosa se extrajo con acetato de etilo (3 x 20 mL) y las capas orgánicas combinadas se secaron sobre sulfato de magnesio anhidro. La concentración in vacuo dio 0.170 g (100%) de compuesto 468B como un sólido amarillo. CLAR: 88% a 1.677 min. (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, eluyendo con 10-

90% metanol acuoso durante 4 min. conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 171.29 $[M+H]^+$.

C. (3aα,4β,7β,7aα)-8-[Octahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-5-quinoxalincarbonitrilo (468C)

El compuesto 468B (0.060 g, 0.35 mmol) se suspendió en tolueno (1.0 mL) con sulfato de magnesio (0.060 g) y el compuesto 20A (0.104 g, 0.529 mmol). TEA (0.2 mL) se agregó después y la mezcla se calentó a 145°C en un tubo sellado. Después de 16 h la reacción se enfrió hasta 22°C y se filtró a través de Celite, enjuagando con acetona. La mezcla se concentró in vacuo y después purificada por CCD preparativa sobre gel de sílice eluyendo con 7% acetato de etilo/cloruro de metileno. Esto dio 0.018 g (15%) de compuesto 468C como un sólido amarillo. CLAR: 100% a 2.040 y 2.133 min. (atropisómeros, tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso durante 4 min. conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 349.33 $[M+H]^+$.

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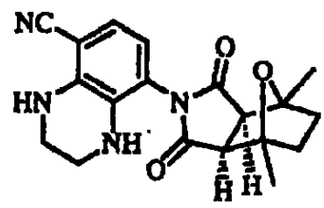
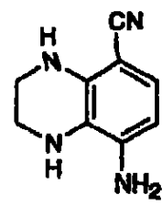
Ejemplo 469

(3aα,4β,7β,7aα)-1,2,3,4-Tetrahidro-8-(octahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-5-quinoxalincarbonitrilo(469B)



A. 8-Amino-1,2,3,4-tetrahidro-quinoxalin-5-carbonitrilo (469A)



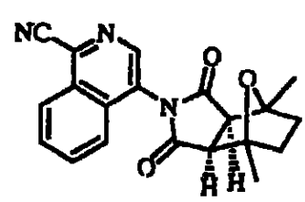
El compuesto 468A (0.037 g, 0.18 mmol) se disolvió en una mezcla de acetato de etilo (1.0 mL)/etanol (1.0 mL) y se agregó 10% Pd/C (0.050 g). Se introdujo después hidrógeno por medio de un globo. Después de 2 h, la reacción se purgó con nitrógeno y se filtró a través de Celite, se enjuagó con acetato de etilo. La concentración in vacuo dio 0.029 g (90%) de compuesto 469A como un aceite rojo, que se llevó sin purificación adicional. CLAR: 97% a 3.217 min. (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso durante 4 min. conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm).

B. (3aα,4β,7β,7aα)-1,2,3,4-Tetrahidro-8-(octahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-5-quinoxalincarbonitrilo(469B)

El compuesto 469A (0.029 g, 0.17 mmol) se suspendió en tolueno (1.0 mL) con sulfato de magnesio (0.030 g) y compuesto 20A (0.050 g, 0.256 mmol). Se agregó después TEA (0.2 mL) y la mezcla se calentó a 145°C en un tubo sellado. Después de 48 h la reacción se enfrió hasta 22°C y se filtró a través de Celite, enjuagando con acetona. La mezcla se concentró in vacuo y después fue purificada por CCD preparativa eluyendo con 20% acetona en cloroformo. Esto dio 0.014 g (24%) de compuesto 469B como un sólido amarillo. CLAR: 85% a 2.267 min. (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso durante 4 min. conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 353.19 $[M+H]^+$.

Ejemplo 470

(3aα,4β,7β,7aα)-4-(Octahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-1-isoquinolincarbonitrilo (470E)



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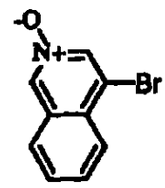
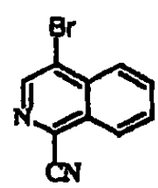
A. 2-óxido de 4-Bromo-isoquinolina (470A)



Una solución de 4-bromoisoquinolina (4.16 g, 18.6 mmol) en 100 mL de cloroformo, se agregó gota a gota durante 1 h a una solución de 70% mCPBA (12.4 g, 50.3 mmol) en 100 mL de cloroformo a temperatura ambiente. Después de agitar 18 h, La mezcla de reacción se lavó con NaOH 1N (2 x 150 mL), se secó sobre sulfato de magnesio y se concentró in vacuo para resultar 4.23 g (94%) de compuesto 470A como un sólido blanco apagado. ^{1}H NMR-400 MHz ($CDCl_3$): δ 8.71 (s, 1H), 8.43 (s, 1H), 8.09 (d, 1H, J=8 Hz), 7.70 (m, 3H).

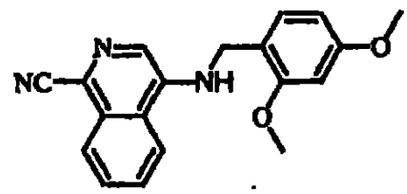
B. 4-Bromo-isoquinolin-1-carbonitrilo (470B)



Se agregó 1,8-Diazabiciclo[5.4.0]undec-7-eno (1.67 mL, 11.2 mmol) a una mezcla de compuesto 470A (1.12 g, 5.00 mmol) y cianotrimetilsilano (0.75 mL, 5.5 mmol) en 35 mL de THF. La mezcla homogénea resultante se puso a reflujo por 20 min. Después de concentrarse in vacuo, el residuo fue purificado por cromatografía instantánea sobre una columna de 5 x 15 cm de gel de sílice, eluyendo con 3:1 hexano: acetato de etilo

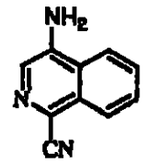
para dar 0.95 g (82%) de compuesto 470B como un polvo blanco. ^{1}H RMN (400 MHz, $CDCl_3$): δ 8.85 (s, 1H). 8.36 (d, 1H, J = 8.5 Hz), 8.28 (d, 1H, J = 8.5 Hz), 7.96 (t, 1H, J = 8.5 Hz), 7.89 (t, 1H, J = 8.5 Hz).

C. 4-(2,4-Dimetoxi-bencilamino)-isoquinolino-1-carbonitrilo (470C)



Una mezcla de compuesto 470B (699 mg, 3.00 mmol) y 2,4-dimetoxibencilamina (4.8 mL, 30 mmol) en 15 mL de acetonitrilo se puso a reflujo por 16 h. Después de la concentración in vacuo, el residuo se purificó en una columna de 5 x 15 cm de gel de sílice, eluyendo con 3:2 hexano:acetato de etilo para resultar 290 mg (30%) de 470C como un sólido amarillo claro. CLAR: 1.76 min. (tiempo de retención) (Phenomenex C-18, columna de 5 micras, 4.6 x 30 mm, eluyendo con 10-90% metanol acuoso durante 2 min. conteniendo 0.1% TFA, 4 mL/min., observando a 254 nm).

D. 4-Amino-isoquinolin-1-carbonitrilo (470D)



El compuesto 470C (50 mg, 0.16 mmol) se trató con ácido trifluoroacético (0.5 mL) por 1 h. La mezcla altamente coloreada se dividió entre acetato de etilo (30 mL) y NaOH 1N (30 mL). Después de lavar con salmuera (15 mL), la capa orgánica se secó sobre sulfato de magnesio y se concentró in vacuo para resultar 24 mg (92%) de compuesto 470D como un sólido amarillo. CLAR: 99% a 1.09 min. (tiempo de retención) (Phenomenex C-18, columna de 5 micras, 4.6 x 30 mm, eluyendo con 10-90% metanol acuoso durante 2 min. conteniendo 0.1% TFA, 4 mL/min., observando a 254 nm). EM (ES^+): m/z 170.2 $[M+H]^+$.

Una ruta alternativa para la síntesis del compuesto 470D es como sigue. Una mezcla de compuesto 470B (1.17 g, 5.02 mmol), benzofenona imina (1.05 mL, 6.26 mmol), acetato de paladio (25 mg, 0.11 mmol), rac-2,2'-bis(difenilfosfino)-1,1' binaftil (100 mg, 0.161 mmol) y carbonato de cesio (2.30 g, 7.06 mmol) en 20 mL de tolueno se calentó a 100°C por 20 h. La mezcla de reacción se diluyó con éter de etilo (200 mL) y se filtró a través de Celite. Después de concentrar el filtrado, el residuo se disolvió en 120 mL de THF y se trató con 40 mL de HCl 1N. Después de reposar por 2 h a temperatura ambiente, la mezcla se dividió entre acetato de etilo (150 mL) y 0.25 N NaOH (160 mL). Después de lavar con salmuera (100 mL), la capa orgánica se secó sobre sulfato de magnesio. La capa orgánica se filtró y ~ 50 g de celite se agregaron al

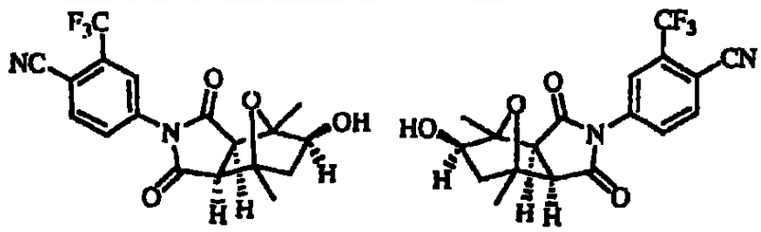
filtrado. Después de la concentración in vacuo, el residuo en polvo fue purificado por cromatografía instantánea sobre una columna de 5 x 15 cm de gel de sílice eluyendo con 1 L de cada uno de 1:1 acetato de etilo:hexano, 6:4 acetato de etilo: hexano y 8:2 acetato de etilo: hexano para dar 450 mg (53%) de 470D como un polvo amarillo.

E. (3aα,4β,7β,7aα)-4-(Octahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-1-isoquinolincarbonitrilo (470E)

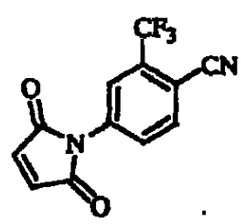
Una mezcla de compuesto 470D (24 mg, 0.14 mmol), compuesto 20A (55 mg, 0.28 mmol), trietilamina (0.1 mL), sulfato de magnesio (100 mg), 2-metoxietiléter (0.5 mL) y DMF (0.1 mL) se calentó en un recipiente sellado hasta 250°C por un total de 2.5 h usando un dispositivo de calentamiento por microondas. Después de dividir la mezcla de reacción entre el acetato de etilo (25 mL) y agua (25 mL), la capa orgánica se secó sobre sulfato de magnesio y se concentró in vacuo. Aproximadamente la mitad del residuo fue purificado por CLAR preparativa de fase inversa (YMC S5 ODS 20 x 50 mm, eluyendo con 10-100% metanol acuoso durante 10 min. conteniendo 0.1% TFA, 20 mL/min.). La concentración de la fracción pura resultó en 6 mg (12%) de compuesto 470E como un polvo blanco. CLAR: 99% a 1.42 min. (tiempo de retención) (Phenomenex C-18,columna de 5 micras, 4.6 x 30 mm, eluyendo con 10-90% metanol acuoso durante 2 min. conteniendo 0.1% TFA, 4 mL/min., observando a 254 nm). EM (ES^+): m/z 348.23 $[M]^+$.

Ejemplo 471

[3aR-(3aα,4β,5β,7β,7aα)]-4-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-trifluorometil)benzonitrilo (471Di) y [3aS-(3aα,4β,5β,7β,7aα)]-4-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo (471Dii)



A. 4-(2,5-Dioxo-2,5-dihidro-pirrol-1-il)-2-trifluorometil-benzonitrilo (471A)



Una mezcla de 3-trifluorometil-4-ciano-anilina (24.0 g, 129 mmol) y anhídrido maleico (14.0 g, 143 mmol) en 50 mL de ácido acético se calentó a 115°C durante la noche. Se obtuvo un precipitado durante el periodo de calentamiento. La reacción se dejó reposar a temperatura ambiente por un periodo adicional durante la noche. Se separó el sólido por filtración, se lavó la torta filtro con éter de dietilo y se secó para dar 21 g (79 mmol, 61%) de compuesto 471A como un

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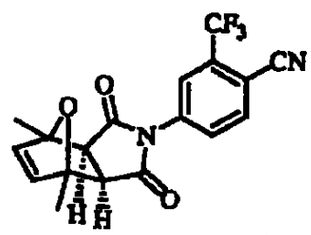
sólido blanco apagado. CLAR: 100% a 2.11 min. (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso durante 4 min. conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm).

B. (3aα,4β,7β,7aα)-4-(1,3,3a,4,7,7a-Hexahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo (471B)



Una suspensión del compuesto 471A (13.0 g, 48.8 mmol) y 2,5-dimetilfurano (10.5 mL, 98.6 mmol) en 50 mL de tolueno se calentó a 60°C, bajo argón. Se obtuvo una solución con el calentamiento inicial y se observó un precipitado después de aproximadamente 1 h. El calentamiento continuó durante la noche. Después de enfriarla, la suspensión se dejó reposar a 4°C durante la noche. El sólido resultante se filtró y la torta filtro se lavó con tolueno frío, seguido por secado con aire para dar 13.2 g del compuesto puro 471B como un sólido blanco. El volumen de filtrado se redujo in vacuo por la mitad y se trató la solución resultante como arriba para resultar en 2.8 g adicionales de compuesto puro 471B (total 16.0 g, 90%). CLAR: 90% a 3.65 min. (tiempo de retención)

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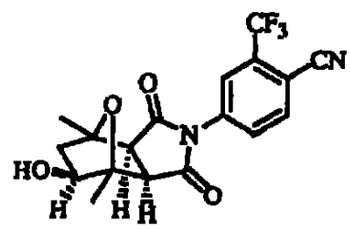
(Columna YMC S5 ODS, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso durante 4 min. conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm).

C. (3aα,4βp,5β,7β,7aα)-4-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo (471C)



Una solución de compuesto 471B (25 g, 69 mmol) en 125 mL de THF, en un matraz seco bajo nitrógeno, se enfrió hasta 10°C con un baño de hielo. A esta solución se le agregó un complejo puro borano-dimetilsulfuro (13.0 mL, 138 mmol) gota a gota durante 10 min., mientras se mantiene una temperatura de reacción de <15°C. La mezcla de reacción se agitó por 30 min. a temperatura ambiente y después en un baño de hielo se enfrió hasta 10°C. A la solución fría se le agregó lentamente 480 mL de una solución amortiguadora de fosfato de pH 7, que resultó en una reacción exotérmica fuerte y evolución vigorosa del gas. La solución se mantuvo a <21°C a través de la adición por medio de un baño de hielo. A la solución resultante se le agregaron 240 mL de etanol y la mezcla resultante se enfrió hasta 5°C con un baño de hielo. A la

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solución enfriada se le agregaron 50 mL de peróxido de hidrógeno al 30% y la mezcla resultante se agitó a 10-20°C por 1.5 h. La mezcla se extrajo con acetato de etilo (2 x 1 L) y las capas orgánicas combinadas se lavaron con sulfito de sodio al 10% (1 x 500 mL) y salmuera (2 x 300 mL) y se secaron sobre $MgSO_4$. La concentración in vacuo resultó en 29 g de producto crudo como un sólido blanco. Este material se sometió a cromatografía instantánea en una columna de 1.2 L de gel de sílice equilibrada con 100% CH_2Cl_2. El material se aplicó a la columna como una solución que consiste de 100 mL de EtOAc (caliente) y 400 mL CH_2Cl_2. La elución inicial con CH_2Cl_2 (3 L), seguida por 25% EtOAc/75% CH_2Cl_2 (3 L) y finalmente 50% EtOAc/50% CH_2Cl_2 (6 L) dio 11.8 g (45%) de compuesto 471C que es una mezcla racémica.

Alternativamente el compuesto 471C se puede hacer por el siguiente método: Se desgasificó un matraz seco conteniendo el compuesto 471B (8.90 g, 24.6 mmol) y catalizador de Wilkinson (0.57 mg, 0.62 mmol) 4x con vacío/argón. Se agregó THF (40 mL) al matraz y la mezcla se agitó hasta que se obtuvo una solución café claro. Se agregó después catecolborano (49 mL, 49 mmol, 1 M en THF) gota a gota durante 20 min. y se observó una ligera exotermia. Se continuó la agitación por 45 min. seguida por enfriamiento de la mezcla de reacción con un baño de hielo. Se agregó lentamente una solución amortiguadora de

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fosfato con un pH 7 (175 mL), seguido por la adición consecutiva de etanol (87 mL) y peróxido de hidrógeno al 30% (18 mL). Se continuó la agitación con enfriamiento y el avance de la reacción se observó por CLAR por 4 h. La reacción se extrajo con CH_2Cl_2; (3 x 250 mL). Los extractos combinados se lavaron con 1:1 NaOH 1N:15% de sulfito de sodio (300 mL) y salmuera, se secaron sobre $MgSO_4$, y el solvente se eliminó in vacuo para dar 8.5 g de un sólido café claro. El producto crudo se sometió a cromatografía instantánea en una columna de gel de sílice de 500 cm^3 eluyendo con un gradiente de 25-50% EtOAc/CH_2Cl_2 para dar 6.00 g del compuesto 471C (15.8 mmol, 64%) como un sólido blanco. CLAR: 90% a 2.45 min. (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso durante 4 min. conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 381.11 $[M+H]^+$.

D. [3aR-(3aα,4β,5β,7β,7aα)]-4-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo (471Di) y [3aS-(3aα,4β,5β,7β,7aα)]-4-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo (471Dii).

Los antípodos individuales del compuesto 471C se separaron por CLAR quiral preparativa en fase normal (columna CHIRALPAK AD, 5 x 50 cm). Una porción de 2.5 g de 471C se disolvió en 25 mL de acetona caliente y se diluyó hasta 50-75 mL con hexano por inyección. La elución isocrática con 20% MeOH/EtOH (1:1) en heptano a 50 mL/min. dio el compuesto de elución más rápida 471Di (CLAR quiral: 10.02 min.; columna CHIRALPAK AD 4.6 x 250 mm; elución isocrática con 20% MeOH/EtOH (1:1) en heptano a 1 mL/min.) y el compuesto de elución más lenta 471Dii (CLAR quiral: 14.74 min.; columna CHIRALPAK AD 4.6 x 250 mm; elución isocrática con 20% MeOH/EtOH (1:1) en heptano a 1 mL/min.). Compuestos 471Di y 471Dii: CLAR: 90% a 2.45 min. (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso durante 4 min. conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 381.11 $[M+H]^+$. La estereoquímica absoluta de los compuestos 471Di y 471Dii se determinó por estudios de difracción de rayos X de cristal sencillo y es como se describe para la nomenclatura designada.

Las fracciones purificadas resultantes de la CLAR de los compuestos 471Di y 471Dii se purificaron además por cristalización usando cualesquiera de los procedimientos abajo descritos.

1) A partir de Acetato de etilo

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Una porción de 700 mg del compuesto 471Di, obtenida después de cromatografía quiral como se describe arriba, se disolvió en acetato de etilo (10 mL) a temperatura ambiente. La solución se diluyó en porciones pequeñas de hexano (20 mL) hasta que se observó turbidez. La solución se dejó reposar durante la noche a temperatura ambiente. El sólido blanco resultante se filtró y se secó con aire para dar 430 mg de compuesto 471Di como un polvo blanco. Esta muestra se secó además a 60°C (3 h, 0.5 Torr), después a 70°C, (12 h, 0.5 Torr).

2) A partir de Acetona

Una porción de 500 mg de compuesto 471Di, obtenida después de cromatografía quiral como se describe arriba, se disolvió en una cantidad mínima de acetona (3 mL) y se diluyó lentamente con hexano (1 mL). La solución incolora transparente se dejó reposar durante la noche a temperatura ambiente. El sólido blanco resultante se filtró y se secó en aire para dar 440 mg de compuesto 471Di como un polvo blanco. Esta muestra se secó además a 60°C, (3 h, 0.5 Torr) después a 70°C, (12 h, 0.5 Torr).

3) A partir de Metanol

Una porción de 500 mg de compuesto 471Di, obtenida después de cromatografía quiral como se describe arriba, se

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disolvió en 5 mL de metanol caliente (baño de vapor). La solución transparente incolora, se dejó reposar a temperatura ambiente por 2 h, después a 4°C durante la noche. El sólido resultante se filtró, se lavó con un mínimo de metanol frío y se secó con aire para resultar 360 mg de compuesto 471Di como un polvo blanco. Esta muestra se secó además a 70°C, (12 h, 0.5 Torr).

4) A partir de CH_2Cl_2

Una porción de 7.00 g del compuesto 471Di, obtenido después de cromatografía quiral como se describe arriba, se disolvió en 75 mL de CH_2Cl_2 a temperatura ambiente. La solución transparente e incolora, se diluyó lentamente con hexano (48 mL) hasta que se observó la cristalización. La solución se dejó reposar a temperatura ambiente por 1 h, después a 4°C durante la noche. El material cristalino resultante se filtró y después se lavó con una cantidad mínima de 2:1 CH_2Cl_2:hexano frío. Los cristales grandes se molieron hasta un polvo fino y se secaron a 50°C (12 h, 0.5 Torr) para dar 5.96 g de compuesto 471Di como un polvo blanco.

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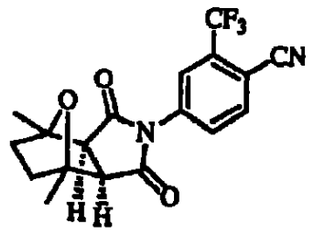
Ejemplo 472

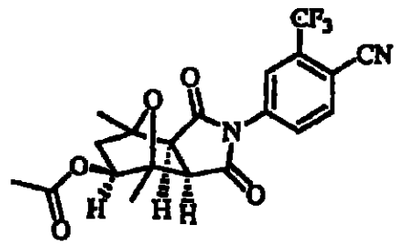
(3aα,4β,7β,7aα)-4-(Octahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo (472)



Una solución de compuesto 471B (500 mg, 1.38 mmol) en acetato de etilo (10 mL), conteniendo 10% Pd/C (25 mg, cat.) se agitó a temperatura ambiente bajo una atmósfera de hidrógeno introducido por medio de un globo. Después de 2 h la reacción se filtró a través de Celite y la torta filtro se lavó con EtOAc. El filtrado transparente, incoloro, se concentró in vacuo para producir 501 mg (1.38 mmol, 100%) de compuesto 472 como un sólido blanco. No se requirió de purificación adicional. CLAR: 99% a 3.04 min. (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, 10-90% metanol acuoso durante 4 min. conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ESI): m/z 382.2 $[M+NH_4]^+$.

Ejemplo 473

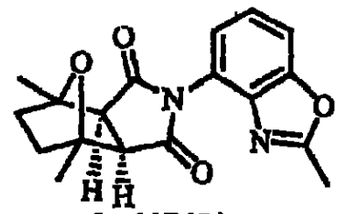
(3aα,4β,5β,7β,7aα)-4-[5-(Acetiloxi)octahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2-(trifluorometil)benzonitrilo (473)



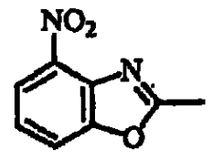
A una solución de compuesto 471C (1.50 g, 3.95 mmol) en 10 mL de piridina, que se enfrió hasta 0°C bajo argón, se agregó anhidrido acético (0.42 mL, 4.4 mmol) gota a gota, seguido por DMAP (5 mg, 0.04 mmol). La agitación se continuó a temperatura ambiente por 4 h. La solución se concentró in vacuo y el residuo resultante se diluyó con acetato de etilo, y se lavó consecutivamente con HCl 1N (2x), salmuera (2x), $NaHCO_3$ saturado, y salmuera (2x). La capa orgánica se secó sobre $MgSO_4$ y se concentró in vacuo. El sólido resultante se secó a 60°C (20 h, 0.5 Torr) para dar 1.55 g (3.67 mmol, 93%) de compuesto 473 como un sólido cristalino blanco. CLAR: 99% a 2.10 min. (tiempo de retención) (Columna Phenomenex Luna C18, 2 x 30 mm, 0-100% acetonitrilo acuoso durante 3 min. conteniendo 10 mM NH_4OAc a 1 mL/min., observando a 220 nm). EM (ESI): m/z 421.4 $[M-H]^-$.

Ejemplo 474

(3aα,4β,7β,7aα)-Hexahidro-4,7-dimetil-2-(2-metil-4-benzoxazolil)-4,7-epoxi-1H-isoindol-1,3(2H)-diona (474F)

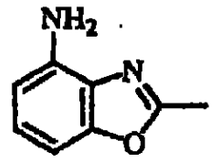


A. 2-Metil-4-nitrobenzoxazol (474A)



Se agregó al 2-amino-3-nitrofenol (6.17 g, 40.0 mmol) trietilortoacetato (25.96 g, 160.0 mmol) y la mezcla se calentó a 100°C por 12 h para dar una solución rojo oscuro. El enfriamiento hasta temperatura ambiente produjo una masa cristalina que se filtró y lavó con hexano para dar el compuesto 474A (6.78 g, 95%) como agujas color marrón claro. CLAR: 98.1% a 1.86 min. (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso durante 4 min. conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 179.08 $[M+H]^+$.

B.4-Amino-2-metilbenzoxazol (474B)



El compuesto 474A (6.78 g, 38.1 mmol) se disolvió en una mezcla 1:1 de 10% ácido acético/acetato de etilo (100 mL volumen total) y se calentó hasta 65°C. Se agregó en

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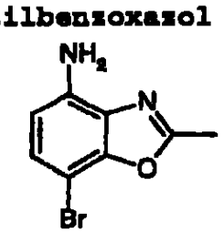
porciones polvo de hierro (10.63 g, 190.2 mmol). Después de agitar por 3 h, la CCD indicó el consumo completo del material de partida. La mezcla de reacción enfriada se filtró a través de una almohadilla de Celite y la almohadilla se lavó con 50 mL de acetato de etilo. La capa orgánica se separó, se lavó con agua (2 x 25 mL), salmuera (1 x 25 mL), se secó sobre $MgSO_4$, se filtró y se concentró in vacuo. El material crudo fue purificado por cromatografía instantánea sobre gel de sílice eluyendo con 25% éter/CH_2Cl_2 para dar 3.90 g (69%) de compuesto 474B como un sólido café claro. CLAR: 95.8% a 2.43 min. (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso durante 4 min. conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 149.11 $[M+H]^+$.

C. 4-Amino-7-bromo-2-metilbenzoxazol (474C)



El compuesto 474B (3.90 g, 26.3 mmol) se disolvió en DMF (45 mL) y se enfrió hasta 5°C y se agregó N-bromosuccinimida (4.68 g, 26.3 mmol) en porciones pequeñas y la reacción se agitó por 5 h. La mezcla se vació en 150 mL de agua hielo para dar un sólido coloreado crema que se filtró, se lavó con agua, se disolvió en CH_2Cl_2, se secó sobre $MgSO_4$, se filtró y

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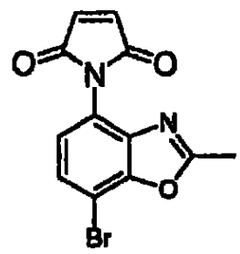
concentró in vacuo. La purificación del material crudo por cromatografía instantánea sobre gel de sílice eluyendo con 20% éter/CH_2Cl_2 dio el compuesto 474C (3.36 g, 56%) como un sólido beige. CLAR: 95.4% a 2.583 min. (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso durante 4 min. conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 228.03 $[M+H]^+$.

D. 1-(7-Bromo-2-metil-benzoxazol-4-il)-pirrol-2,5-diona (474D)



El compuesto 474C (1.40 g, 6.17 mmol) se disolvió en 20 mL de ácido acético, se agregó anhidrido maleico (0.635 g, 6.47 mmol) y la reacción se calentó a reflujo bajo nitrógeno por 5 h. El solvente se separó in vacuo y el producto crudo fue purificado por cromatografía instantánea sobre gel de sílice eluyendo con 10% éter/CH_2Cl_2 para dar el compuesto 474D (1.73 g, 91%). como un sólido amarillo pálido. CLAR: 93.6% a 1.36 min. (Columna Phenomenex, 30 x 4.6 mm, 10-90% metanol acuoso durante 2 min. conteniendo 0.1% TFA, 5 mL/min., observando a 220 nm. EM (ES): m/z 308.02 $[M+H]^+$.

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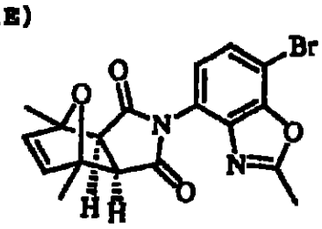
E. (3aα,4β,7β,7aα)-2-(7-Bromo-2-metil-4-benzoxazolil)-3a,4,7,7a-tetrahidro-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3(2H)-diona (474E)



El compuesto 474D (0.307 g, 1.00 mmol) se disolvió en benceno (2 mL) y se agregó 2,5-dimetilfurano (0.154 g, 1.60 mmol) por medio de una jeringa. La mezcla de reacción se calentó a 60°C por 12 h. La mezcla de reacción enfriada se concentró in vacuo a 40°C para dar el compuesto 474E como una espuma blanca descolorida que se usó directamente en la siguiente reacción sin purificación.

F. (3aα,4β,7β,7aα)-Hexahidro-4,7-dimetil-2-(2-metil-4-benzoxazolil)-4,7-epoxi-1H-isoindol-1,3(2H)-diona (474F)

El compuesto 474E (0.403 g, 1.00 mmol) se disolvió en EtOH/EtOAc (4 mL/4 mL) y se agregó 10% Pd/C (100 mg). La mezcla de reacción se agitó a temperatura ambiente por 6 h bajo una atmósfera de H_2 suministrada por un globo y después se filtró a través de Celite. La concentración del filtrado in vacuo dio un sólido café. La purificación por cromatografía instantánea sobre gel de sílice eluyendo con 10% acetona/$CHCl_3$ (250 mL), 15% acetona/$CHCl_3$ (250 mL), y 20%

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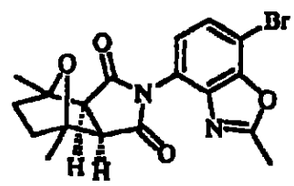
acetona/$CHCl_3$ (250 mL) dio el compuesto 474F (0.089 g, 27%) como una espuma blanca. CLAR: 91% a 2.28 min. (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso durante 4 min. conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 328.34 $[M+H]^+$.

Ejemplo 475

(3aα,4β,7β,7aα)-2-(7-Bromo-2-metil-4-benzoxazolil)hexahidro-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3(2H)-diona(475)



El compuesto 474E (0.202 g, 0.501 mmol) se disolvió en 1/1 EtOAc/EtOH (10 mL) y se agregó 10% Pt/C (100 mg). La mezcla de reacción se agitó a temperatura ambiente bajo un globo de H_2 por 6 h. La reacción se filtró a través de Celite y se concentró in vacuo. La purificación por cromatografía instantánea sobre gel de sílice eluyendo con 10% éter/CH_2Cl_2 dio 0.063 g (31%) del compuesto 475 como un aceite incoloro que se solidificó con reposo para dar un sólido blanco. CLAR: 92.5% a 2.83 min. (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso durante 4 min. conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 406.21 $[M+H]^+$.

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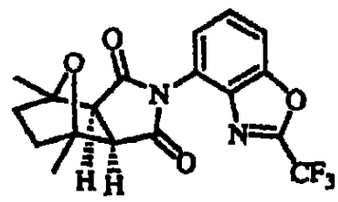
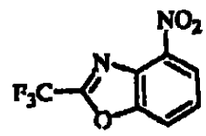
Ejemplo 476

(3aα,4β,7β,7aα)-Hexahidro-4,7-dimetil-2-[2-(trifluorometil-4-benzoxazolil]-4,7-epoxi-1H-isoindol-1,3(2H)-diona(476D)



A. 4-Nitro-2-trifluorometilbenzoxazol (476A)



Se agregó 2-Amino-3-nitrofenol (10.00 g, 64.88 mmol) a 100 mL de anhidrido trifluoroacético vigorosamente agitado y la mezcla resultante se agitó a temperatura ambiente por 12 h. El solvente se separó in vacuo para dar un sólido azul obscuro que se disolvió en 200 mL de CH_2Cl_2 y se lavó secuencialmente con 10% NaOH (2 x 100 mL), agua (100 mL), salmuera (100 mL), y se secó sobre $MgSO_4$. La filtración y la concentración in vacuo dio el compuesto 476A (10.78 g, 72%) como un sólido café. No se requirió purificación adicional. CLAR: 92.9% a 2.43 min. (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso durante 4 min. conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm).

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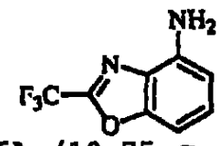
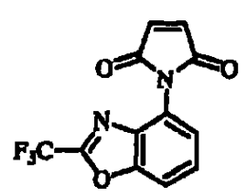
B. 4-Amino-2-trifluorometilbenzoxazol (476B)



El compuesto 476A (10.75 g, 46.30 mmol) se disolvió en 1:1 EtOAc/10% HOAc (250 mL) y se calentó hasta 65°C. Se agregó polvo de hierro (12.93 g, 231.5 mmol) en porciones y la reacción se agitó por 6 h a 65°C. Después de enfriar, la mezcla se filtró a través de Celite enjuagando con EtOAc. La capa orgánica se separó, se lavó con H_2O (3 x 100 mL), salmuera (100 mL), se secó sobre $MgSO_4$, y se concentró in vacuo para dar un aceite café. El material crudo fue purificado por cromatografía instantánea sobre gel de sílice eluyendo con 70/30 CH_2Cl_2/hexanos para dar el compuesto 476B (7.02 g, 75%) como un sólido amarillo cristalino. CLAR: 96.7% a 2.68 min. (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso durante 4 min. conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm).

C. 1-(2-Trifluorometil-benzoxazol-4-il)-pirrol-2,5-diona (476C)



El compuesto 476B (0.500 g, 2.48 mmol) se disolvió en ácido acético (10 mL) y se agregó anhidrido maleico (0.267 g, 2.72 mmol). La mezcla se calentó a reflujo por 3 h, se enfrió y el solvente se separó in vacuo para dar un sólido café claro. El producto crudo fue purificado por cromatografía instantánea sobre gel de sílice eluyendo con 2% $MeOH/CH_2Cl_2$ para dar el compuesto 476C (0.40 g, 57%) como un sólido blanco descolorido. CLAR: 89.7% a 2.38 min. (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso durante 4 min. conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 283.21 $[M+H]^+$.

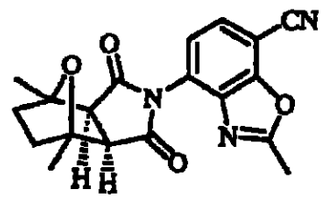
D. (3aα,4β,7β,7aα)-Hexahidro-4,7-dimetil-2-[2-(trifluorometil)-4-benzoxazolil]-4,7-epoxi-1H-isoindol-1,3(2H)-diona (476D).

El compuesto 476C (0.24 g, 0.85 mmol) y 2,5-dimetilfurano (0.132 g, 1.37 mmol) se combinaron en 3 mL de benceno en un tubo sellado y se calentaron a 60°C por 12 h. La mezcla se enfrió y se concentró in vacuo para dar un aceite amarillo que se disolvió en 1/1 EtOAc/EtOH (6 mL). Se agregó 10% Pd/C (100 mg) y la mezcla se agitó bajo un globo de H_2 por 3.5 h. La reacción se filtró a través de Celite y el solvente se separó in vacuo para dar el producto crudo como un aceite amarillo pálido. La purificación por

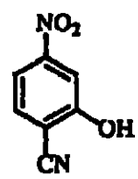
cromatografía instantánea sobre gel de sílice eluyendo con 2% Et_2O/CH_2Cl_2 dio 0.107 g (33%) del compuesto 476D como una espuma blanca. CLAR: 96.5% a 2.80 min. (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso durante 4 min. conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 381.17 $[M+H]^+$.

Ejemplo 477

(3aα,4β,7β,7aα)-2-Metil-4-(octahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-7-benzoxazoCLarbonitrilo(477E)



A. 2-Ciano-5-nitrofenol (477A)



El 3,4-Metilendioxinitrobenceno (1.67 g, 10.0 mmol) se disolvió en 20 mL de HMPA y se agregó cianuro de sodio (0.49 g, 10.0 mmol). La reacción se calentó a 150°C bajo nitrógeno y se agregaron tres porciones de cianuro de sodio (0.245 g, 5.00 mmol, total) durante 15 min. La reacción se mantuvo a 150°C por 45 min., se enfrió, y se vació en 50 mL de H_2O seguido por la adición de 50 mL de 5% NaOH. La capa acuosa se extrajo con éter (2 x 25 mL) y la capa orgánica se descartó.

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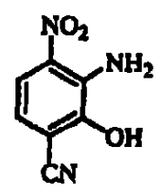
La capa acuosa básica se acidificó cuidadosamente hasta un pH de 4 por la adición de 10% HCl y se extrajo con éter (3 x 25 mL). Las capas orgánicas combinadas se lavaron con salmuera (25 mL), se secaron sobre sulfato de sodio y se concentró in vacuo. La purificación por cromatografía instantánea sobre gel de sílice eluyendo con 5% $MeOH/CH_2Cl_2$ dio 1.05 g (64%) del compuesto 477A como un sólido amarillo-café. CLAR: 91.6% a 1.03 min. (tiempo de retención) (Columna Phenomenex, 30 x 4.6 mm, 10-90% metanol acuoso durante 2 min. conteniendo 0.1% TFA, 5 mL/min., observando a 220 nm. EM (ES): m/z 165.23 $[M+H]^+$.

B. 2-Amino-4-ciano-3-hidroxinitrobenceno (477B)



El compuesto 477A (0.438 g, 2.67 mmol) se disolvió en 25 mL de DEMO y se agregó yoduro de trimetilhidrazinio (0.534 g, 2.67 mmol). Se agregó pentóxido de sodio (0.880 g, 8.01 mmol) bajo N_2 para dar una solución rojo intenso y se continuó la agitación durante la noche a temperatura ambiente. La mezcla de reacción se vació dentro de 50 mL de 10% HCl y se extrajo con EtOAc (2 x 25 mL). Las capas orgánicas combinadas se lavaron con agua (25 mL), salmuera (25 mL), se secaron sobre sulfato de sodio y se concentraron in vacuo para dar el

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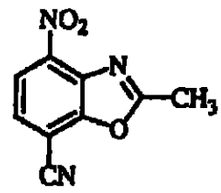
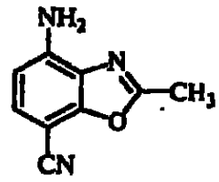
compuesto 477B como un sólido rojo aceitoso que se usó directamente en la siguiente reacción sin purificación adicional.

C. 7-Ciano-2-metil-4-nitrobenzoxazol (477C)



El compuesto 477B (0.360 g, 2.01 mmol) y trietil ortoacetato (1.30 g, 8.04 mmol) se combinaron y calentaron a reflujo bajo nitrógeno por 1 h. El solvente se separó in vacuo y el residuo resultante purificado por cromatografía instantánea eluyendo con 5% éter/CH_2Cl_2 para dar 0.255 g (63%) de compuesto 477C como un sólido café. CLAR: 98.4% a 1.80 min. (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso durante 4 min. conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 204.28 $[M+H]^+$.

D. 4-Amino-7-ciano-2-metilbenzoxazol (477D)



El compuesto 477C (0.156 g, 0.77 mmol) se disolvió en una mezcla 1:1 de EtOAc/10% HOAc (20 mL) y se calentó hasta 65°C. Se agregó polvo de hierro (malla 325, 0.214 g, 3.83 mmol) y la reacción se agitó por 4 h. La mezcla enfriada se filtró a través de Celite y el filtrado resultante se lavó con agua (25 mL), salmuera (25 mL), se secó sobre $MgSO_4$, y se concentró para dar el compuesto 477D (0.118 g, 89%) como un sólido color naranja. CLAR: 87% a 2.03 min. (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso durante 4 min. conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 174.05 $[M+H]^+$.

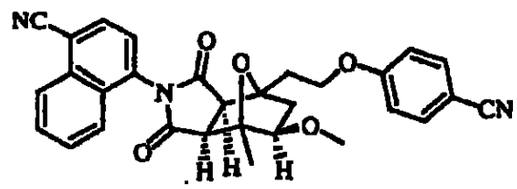
E. (3aα,4β,7β,7aα)-2-Metil-4-(octahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-7-benzoxazoCLarbonitrilo (477E)

El compuesto 477D (0.060 g, 0.35 mmol) y el compuesto 20A (0.071 g, 0.37 mmol) se combinaron en un tubo sellado con tolueno (2 mL), trietilamina (0.24 mL, 1.7 mmol), y $MgSO_4$ (0.104 g, 0.866 mmol). El tubo sellado se calentó a 135°C por dos días. La mezcla enfriada de reacción se diluyó con EtOAc, se filtró, y se concentró in vacuo para dar el producto crudo como un aceite café. La purificación por cromatografía instantánea sobre gel de sílice eluyendo con 1/1 EtOAc/hexanos dio 0.014 g (12%) de compuesto 477E como un

sólido blanco descolorido. CLAR: 96.5% a 2.27 min. (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso durante 4 min. conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 352.23 $[M+H]^+$.

Ejemplo 478

(3aα,4β,5β,7β,7aα)-4-[7-[2-(4-Cianofenoxi)etil]octahidro-5-metoxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo, enantiómero de elución lenta (478)



Se agregó n-BuLi (0.050 mL, 1.6 M, 0.075 mmol) a una solución de compuesto 244ii (33.7 mg, 0.0683 mmol) en THF (1.0 mL) a -78°C bajo argón. La mezcla de reacción se calentó hasta temperatura ambiente y se agregó metil fluorosulfonato (0.010 mL, 0.12 mmol) gota a gota. Una vez que se consumió el material de partida, como fue evidente por CLAR, la reacción se apagó con H_2O y la mezcla acuosa resultante se extrajo con CH_2Cl_2 (3 x 5 mL). Las capas orgánicas combinadas se secaron sobre $MgSO_4$ y se concentraron bajo presión reducida. La purificación por CLAR preparativa de fase inversa [22.09 min. (Columna YMC S5 ODS, 20 x 100 mm, 0-100% metanol acuoso durante 25 min. conteniendo 0.1% TFA, 20 mL/min., observando

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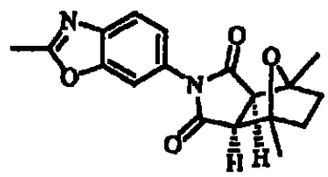
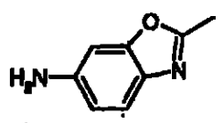
a 220 nm)] dio 13.0 mg (38%) de compuesto 478 como un sólido blanco. CLAR: 93% a 3.35 min. (Columna YMC S5 ODS, 4.6 x 50 mm, 10-90% metanol acuoso durante 4 min. conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 508.17 $[M+H]^+$.

Ejemplo 479

(3aα,4β,7β,7aα)-Hexahidro-4,7-dimetil-2-(2-metil-6-benzoxazolil)-4,7-epoxi-1H-isoindol-1,3(2H)-diona (479B)



A. 2-Metil-6-aminobenzoxazol (479A)



A una solución de 2-metil-6-nitrobenzoxazol (100 mg, 0.560 mmol) en AcOH (2 mL) se agregó polvo de hierro (malla 325, 63.0 mg, 1.12 mmol) a 70°C en una porción sencilla. Después de 15 min. a 70°C se agregó polvo de hierro adicional (malla 325, 63.0 mg, 1.12 mmol) y la agitación continuó por 15 min. La mezcla se enfrió y concentró bajo presión reducida. El residuo resultante se tomó en EtOAc y se lavó con Na_2CO_3 saturado seguido por H_2O. La capa orgánica se secó sobre $MgSO_4$, concentró bajo presión reducida y fue purificada por cromatografía instantánea sobre gel de sílice eluyendo

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con un gradiente de 0 hasta 25% EtOAc en CH_2Cl_2 para resultar 69 mg (83%) de compuesto 479A como un sólido. CLAR: 97% a 0.24 min. (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm Ballistic, 10-90% metanol acuoso durante 4 min. conteniendo 0.2% H_3PO_4, 4 mL/min., observando a 220 nm). EM (ES): m/z 149.2 $[M+H]^+$.

B. (3aα,4β,7β,7aα)-Hexahidro-4,7-dimetil-2-(2-metil-6-benzoxazolil)-4,7-epoxi-1H-isoindol-1,3(2H)-diona (479B)

El compuesto 479A (30 mg, 0.20 mmol), $MgSO_4$ (60 mg, 0.50 mmol), trietilamina (140 µL, 1.00 mmol) y el compuesto 20A (45 mg, 0.23 mmol) se tomaron en 0.25 mL de tolueno y se colocaron en un tubo sellado. El tubo sellado se calentó a 135°C por 14 h y la reacción se dejó enfriar a temperatura ambiente. La mezcla se filtró a través de una almohadilla corta de Celite, eluyendo con MeOH y el solvente se separó in vacuo. El residuo fue purificado por cromatografía instantánea sobre gel de sílice eluyendo con un gradiente de 0 hasta 50% EtOAc en CH_2Cl_2 para dar 49 mg (65%) de compuesto 479B como un sólido café claro. CLAR: 98% a 2.30 min. (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso durante 4 min. conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 326.9 $[M+H]^+$.

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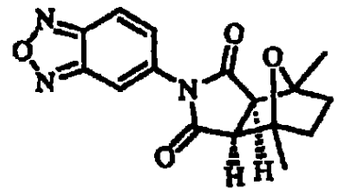
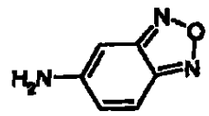
Ejemplo 480

(3aα,4β,7β,7aα)-2-(2,1,3-Benzoxadiazol-5-il)hexahidro-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3(2H)-diona (480B)



A. 5-Amino-2,1,3-benzoxadiazol (480A)



A una solución de ácido 2,1,3-benzoxadiazol-5-carboxílico (102 mg, 0.621 mmol) en THF (3 mL), se agregó trietilamina (103 µL, 0.739 mmol) seguido por DPPA (160 µL, 0.739 mmol) a temperatura ambiente. La mezcla se agitó por 4 h, se diluyó con CH_2Cl_2 y se lavó con agua. La capa orgánica se secó sobre $MgSO_4$, se concentró y fue purificada por cromatografía instantánea sobre gel de sílice con 0 hasta 50% EtOAc en CH_2Cl_2. El material resultante se disolvió en AcOH (2 mL), y se agregó agua (0.7 mL) gota a gota produciendo una solución ligeramente turbia que se calentó a 105°C por 30 min. La mezcla se enfrió, se hizo básica con solución saturada de Na_2CO_3 y se extrajo varias veces con THF. Las capas orgánicas combinadas se secaron sobre $MgSO_4$, se concentraron y fueron purificadas por cromatografía

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instantánea sobre gel de sílice eluyendo con 0 hasta 15% MeOH en CH_2Cl_2 para dar 34 mg (41%) de compuesto 480A como un sólido amarillo. CLAR: 100% a 1.27 min. (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm Ballistic, 10-90% metanol acuoso durante 4 min. conteniendo 0.2% H_3PO_4, 4 mL/min., observando a 220 nm). EM (ES): m/z 136.0 $[M+H]^+$.

B. (3aα,4β,7β,7aα)-2-(2,1,3-Benzoxadiazol-5-il)hexahidro-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3(2H)-diona (480B)

El compuesto 480A (34 mg, 0.25 mmol), $MgSO_4$ (76 mg, 0.63 mmol), trietilamina (180 µL, 1.26 mmol) y compuesto 20A (74 mg, 0.38 mmol) se disolvieron en 0.25 mL de tolueno y se colocaron en un tubo sellado. El tubo sellado se calentó a 135°C por 14 h. La mezcla de reacción enfriada se filtró a través de una almohadilla corta de Celite, eluyendo con acetona y el solvente se eliminó in vacuo. El residuo fue purificado por CLAR preparativa de fase inversa (YMC S5 ODS 20 x 100 mm, eluyendo con 30-100% metanol acuoso durante 10 min. conteniendo 0.1% TFA, 20 mL/min.). La concentración de las fracciones deseadas resultó en un residuo que se dividió entre CH_2Cl_2 y una solución saturada de $NaHCO_3$. La capa acuosa se extrajo una vez con CH_2Cl_2 y las fases orgánicas combinadas se secaron sobre Na_2SO_4. La concentración bajo presión reducida dio 42 mg (53%) del compuesto 480B como un sólido

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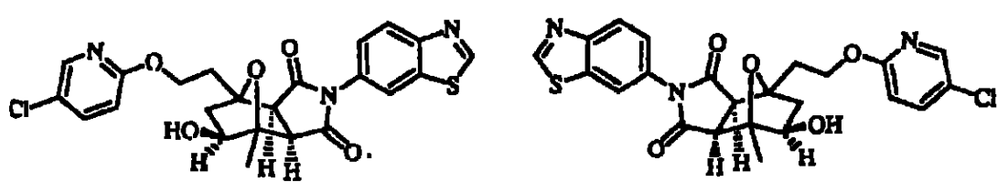
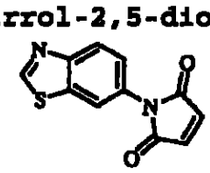
amarillo. CLAR: 100% a 2.62 min. (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso durante 4 min. conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). ^{1}H RMN (400 MHz, $CDCl_3$) δ = 7.91 (d, 1H), 7.90 (dd, 1H), 7.37 (dd, 1H), 3.09 (s, 2H), 1.85 (s, 4H), 1.67 (s, 6H).

Ejemplo 481

[3aR-[3aα,4β,5β,7β,7aα)]-2-[6-Benzotiazolil)-7-[2-[(5-cloro-2-piridinil)oxi]etil]hexahidro-5-hidroxi-4-metil-4,7-epoxi-1H-isoindol-1,3(2H)-diona (481D) y [3aS-(3aα,4β,5β,7β,7aα)]-2-[6-Benzotiazolil)-7-[2-[(5-cloro-2-piridinil)oxi]etil]hexahidro-5-hidroxi-4-metil-4,7-epoxi-1H-isoindol-1,3(2H)-diona (481E)



A. 1-Benzotiazol-6-il-pirrol-2,5-diona (481A)



Una mezcla de 5-aminobenzotiazol (2.00 g, 13.3 mmol) y anhidrido maleico (1.96 g, 20.0 mmol) en AcOH (27 mL) se calentó a 115°C por 20 h. La mezcla se enfrió y se concentró

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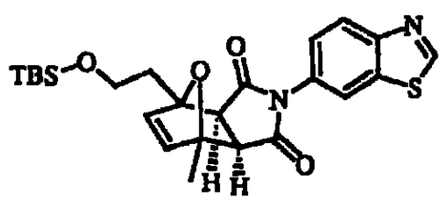
bajo presión reducida. El residuo se tomó en THF y se lavó con Na_2CO_3 saturado. La capa acuosa se extrajo varias veces con THF y las capas orgánicas combinadas se secaron sobre $MgSO_4$. La purificación por cromatografía instantánea sobre gel de sílice eluyendo con 0 hasta 50% EtOAc en CH_2Cl_2 dio 1.37 g (45%) de compuesto 481A como un sólido amarillo pálido. CLAR: 100% a 2.62 min. (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso durante 4 min. conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 231.0 $[M+H]^+$.

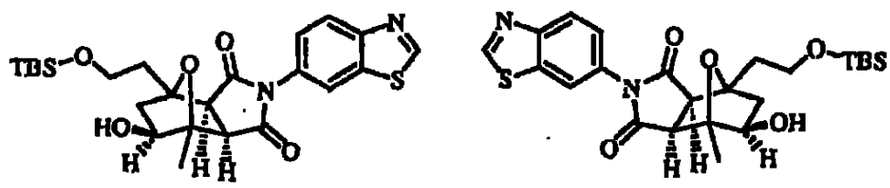
B. (3aα,4β,7β,7aα)-2-(6-Benzotiazolil)-4-[2-[[(1,1-dimetiletil)dimetilsilil]oxi]etil]-3a,4,7,7a-tetrahidro-7-metil-4,7-epoxi-1H-isoindol-1,3(2H)-diona (481B)



Una suspensión del compuesto 481A (445 mg, 1.93 mmol) y del compuesto 204A (929 mg, 3.87 mmol) en benceno (2 mL) se calentó a 60°C y se agregó acetona hasta que se obtuvo una solución transparente. La mezcla resultante se agitó a 60°C por 24 h y después se concentró lentamente in vacuo. El residuo resultante se disolvió en acetona y se concentró lentamente in vacuo. Este proceso se repitió un total de tres veces. La purificación por cromatografía instantánea sobre

gel de sílice eluyendo con 0 hasta 30% de acetona en hexanos dio 820 mg (90%) de compuesto 481B como un sólido blanco. CLAR: 100% a 2.62 min. (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso durante 4 min. conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 471.3 $[M+H]^+$.

C. [3aR-(3aα,4β,5β,7β,7aα)]-2-(6-Benzotiazolil)-7-[2-[[(1,1-dimetiletil)dimetilsilil]oxi]etil]hexahidro-5-Hidroxi-4-metil-4,7-epoxi-1H-isoindol-1,3(2H)-diona (481Ci) y [3aS-(3aα,4β,5β,7β,7aα)]-2-(6-Benzotiazolil)-7-[2-[[(1,1-dimetiletil)dimetilsilil]oxi]etil]hexahidro-5-hidroxi-4-metil-4,7-epoxi-1H-isoindol-1,3(2H)-diona (481Cii)



A una solución de compuesto 481B (75 mg, 0.16 mmol) en THF (1 mL) se agregó catalizador de Wilkinson (32 mg, 0.030 mmol) y catecolborano (1.0 M en THF, 1.6 mL, 1.6 mmol) a temperatura ambiente bajo nitrógeno. La mezcla resultante se agitó por 2.5 h antes de que se enfriara hasta 0°C. Se agregaron EtOH (5 mL), NaOH 3N (2 mL) y H_2O_2 (30%, 1 mL) secuencialmente, y la mezcla se agitó por 2 h a 0°C. La reacción se apagó por la adición de una solución fría al 10%

de Na_2SO_3 (en exceso) seguida por agua. La capa acuosa se extrajo varias veces con CH_2Cl_2 y las capas orgánicas combinadas se secaron sobre Na_2SO_4. La concentración bajo presión reducida seguida por la purificación por cromatografía instantánea sobre gel de sílice eluyendo con 0 hasta 100% de EtOAc en hexanos dio 13 mg (17%) de una mezcla racémica de los compuestos 481Ci y 481Cii como un sólido café claro. CLAR: 96% a 3.58 min. (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm Ballistic, 10-90% metanol acuoso durante 4 min. conteniendo 0.2% H_3PO_4, 4 mL/min., observando a 220 nm). EM (ES): m/z 489.3 $[M+H]^+$. La mezcla racémica se separó en sus enantiómeros individuales por CLAR quiral preparativa en fase normal (columna CHIRALPAK AD 5 x 50 cm; eluyendo con 20% MeOH/EtOH (1:1) en heptano (isocrático) a 50 mL/min.) para dar el enantiómero de elución más rápida, compuesto 481Ci: (CLAR quiral: 9.40 min.; columna CHIRALPAK AD 4.6 x 250 mm; eluyendo con 20% MeOH/EtOH (1:1) en heptano a 1 mL/min.) y el enantiómero de elución más lenta, compuesto 481Cii: (CLAR quiral: 10.47 min.; columna CHIRALPAK AD 4.6 x 250 mm; eluyendo con 20% MeOH/EtOH (1:1) en heptano a 1 mL/min.). La conformación absoluta de los compuestos 481Ci y 481Cii no se determinó. Por simplicidad en la nomenclatura, el compuesto 481Ci se designa en la presente como que tiene una configuración "R" y el compuesto 481Cii como que tiene una configuración "S". Los productos enantioméricamente puros

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derivados de los compuestos 481Ci se designan en la presente por tener una configuración "R" y los productos enantioméricamente puros derivados del compuesto 481Cii se designan en la presente por tener una configuración "S".

D. [3aR-(3aα,4β,5β,7β,7aα)]-2-(6-Benzotiazolil)-7-[2-[(5-cloro-2-piridinil)oxi]etil]hexahidro-5-hidroxi-4-metil-4,7-epoxi-1H-isoindol-1,3(2H)-diona (481D)

El compuesto 481Ci (84 mg, 0.17 mmol) se suspendió en EtOH (2 mL) y se agregó HCl concentrado (40 µL) a temperatura ambiente. La mezcla se agitó por 15 min. antes de que se agregaran varias gotas de una solución saturada de $NaHCO_3$. La concentración bajo presión reducida produjo un residuo que se dividió entre CH_2Cl_2 y solución saturada de $NaHCO_3$. La capa acuosa se extrajo varias veces con CH_2Cl_2 y finalmente con EtOAc. Las fases orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y purificaron por CCD preparativa eluyendo con 50% acetona en $CHCl_3$. Este procedimiento sirvió para eliminar el grupo TBS del compuesto 481Ci, produciendo el alcohol primario libre. Una porción de 12 mg (0.03 mmol) del alcohol libre del compuesto 481Ci reaccionó con 5-cloro-2-piridinol (8 mg, 0.06 mmol), PPh_3 (17 mg, 0.060 mmol) y di-tert-butilazodicarboxilato (15 mg, 0.060 mmol) en THF (0.5 mL) según el procedimiento general descrito en el Ejemplo

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244. La mezcla se agitó por 24 h a temperatura ambiente, se diluyó con NaOH 1N y la capa acuosa se extrajo varias veces con CH_2Cl_2. Las capas orgánicas combinadas se secaron sobre Na_2SO_4, se concentraron y purificaron por CCD preparativa, eluyendo con 25% acetona en $CHCl_3$ para dar 9 mg (58%) del compuesto 481D como un sólido blanco. CLAR: 98% a 2.94 min. (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm Ballistic, 10-90% metanol acuoso durante 4 min. conteniendo 0.2% H_3PO_4, 4 mL/min., observando a 220 nm). EM (ES): m/z 486.2 $[M+H]^+$.

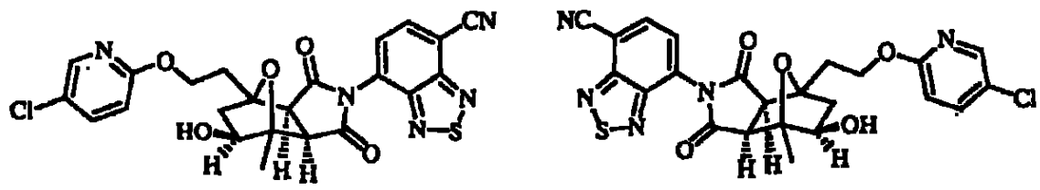
E. [3aS-(3aα,4β,5β,7β,7aα)]-2-(6-Benzotiazolil)-7-[2-[(5-cloro-2-piridinil)oxi]etil]hexahidro-5-hidroxi-4-metil-4,7-epoxi-1H-isoindol-1,3(2H)-diona (481E)

Como se describe en el Ejemplo 481D, el compuesto 481Cii (58 mg, 0.12 mmol) se trató con EtOH (2 mL) conteniendo HCl 12N (40 µL) para producir el producto de aCLohol primario libre del compuesto 481Cii. 15 mg (0.040 mmol) del aCLohol libre del compuesto 481Cii reaccionaron con 5-cloro-2-piridinol (10 mg, 0.080 mmol), PPh_3 (21 mg, 0.080 mmol) y di-tert-butilazodicarboxilato (18 mg, 0.080 mmol) en THF (0.5 mL) en la forma antes descrita, y el producto resultante se purificó como se describe arriba para producir 8 mg (41%) de compuesto 481E como un sólido blanco. CLAR: 99% a 2.93 min.

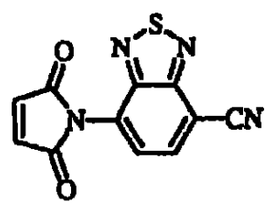
(tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm Ballistic, 10-90% metanol acuoso durante 4 min. conteniendo 0.2% H_3PO_4, 4 mL/min., observando a 220 nm). EM (ES): m/z 486.2 $[M+H]^+$.

Ejemplo 482

[3aR-(3aα,4β,5β,7β,7aα)]-7-[7-[2-[(5-Cloro-2-piridinil)oxi]etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2,1,3-benzotiadiazol-4-carbonitrilo (482F) y [3aS-(3aα,4β,5β,7β,7aα)]-7-[7-[2-[(5-Cloro-2-piridinil)oxi]etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2,1,3-benzotiadiazol-4-carbonitrilo (482G)



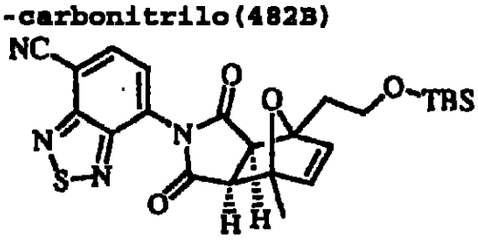
A. 7-(2,5-Dioxo-2,5-dihidro-pirrol-1-il)-benzo[1,2,5]tiadiazol-4-carbonitrilo (482A)



Se agregó anhidrido maleico (667 mg, 6.80 mmol) a una solución de compuesto 424A (600 mg, 3.41 mmol) en THF (9 mL). La mezcla se calentó a 110°C por 10 h. La reacción se

concentró bajo presión reducida y se agregó anhidrido acético (1 mL) al residuo. La mezcla de reacción se calentó a 75°C por 30 min. y después se enfrió hasta temperatura ambiente. La purificación por cromatografía instantánea sobre gel de sílice eluyendo con 3% acetona/$CHCl_3$ dio 758 mg (2.96 mmol, 67%) del compuesto 482A. CLAR: 97% a 1.98 min. (tiempo de retención) (YMC S5 ODS 4.6 x 50 mm, 10%-90% metanol acuoso durante 4 min. gradiente con 0.2% H_3PO_4, observando a 220 nm). EM (ES): m/z 257.01 $[M+H]^+$.

B. (3aα,4β,7β,7aα)-7-[4-[2-[[(1,1-Dimetiletil)dimetilsilil]oxi]etil]-1,3,3a,4,7,7a-hexahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2,1,3-benzotiadiazol-4-carbonitrilo(482B)



Una solución del compuesto 482A (758 mg, 2.96 mmol) y del compuesto 204A (711 mg, 2.96 mmol) en benceno (2 mL) y acetona (2 mL) se calentó a 60°C por 6 h. La mezcla de reacción se concentró in vacuo a 42°C por 40 min. para dar 1.5 g del compuesto crudo 482B, que se usó directamente en la siguiente etapa sin purificación adicional.

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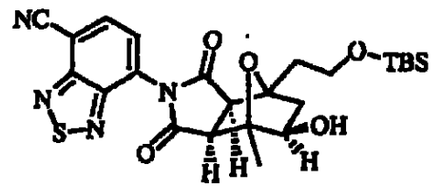
c. (3aα,4β,5β,7β,7aα)-7-[7-[2-[[(1,1-Dimetiletil)dimetilsilil]oxi]etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2,1,3-benzotiadiazol-4-carbonitrilo (482C)



Se agregó complejo de borano-dimetilsulfuro (0.66 mL, 6.96 mmol) a una solución de compuesto 482B (1.15 g, 2.32 mmol) en THF (6 mL) a 0°C. Después de agitar a 0°C por 2 h, la mezcla de reacción se apagó con solución amortiguadora de fosfato (60 mL, pH 7.2) y después se agregó EtOH (35 mL), H_2O_2 (8 mL, 30% acuoso) y THF (4 mL). La mezcla de reacción se agitó a 0°C por 1 h y se extrajo después con CH_2Cl_2 (4 x 100 mL). Las capas orgánicas combinadas se lavaron con 10% Na_2SO_3 acuoso(1 x 160 mL) seguido por salmuera (1 x 160 mL) y se secaron sobre Na_2SO_4. La purificación por cromatografía instantánea sobre gel de sílice eluyendo con 10% acetona/$CHCl_3$ dio 250 mg (0.486 mmol, 21%) de compuesto 482C como un sólido color naranja. CLAR: 85% a 3.70 min. (tiempo de retención) (YMC S5 ODS 4.6 x 50 mm, 10%-90% metanol acuoso durante 4 min. de gradiente con 0.2% H_3PO_4, observando a 220 nm). EM (ES): m/z 515.27 $[M+H]^+$.

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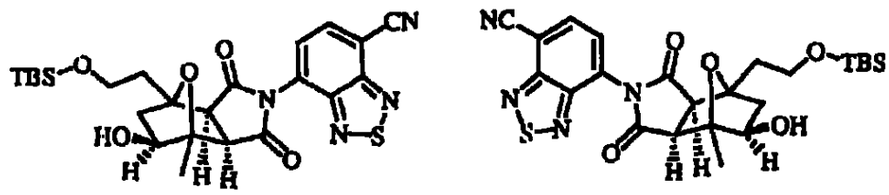
D. [3aR-(3aα,4β,5β,7β,7aα)]-7-[7-[2-[[(1,1-Dimetiletil)dimetilsilil]oxi]etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2,1,3-benzotiadiazol-4-carbonitrilo y [3aS-(3aα,4β,5β,7β,7aα)]-7-[7-[2-[[(1,1-dimetiletil)dimetilsilil]oxi]etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2,1,3-benzotiadiazol-4-carbonitrilo (482Di y 482Dii)



Los compuestos racémicos 482C se separaron por CLAR quiral preparativa en fase normal usando una columna Chiracel (5 cm x 50 cm), eluyendo con 10% EtOH en hexano a 50 mL/min. para dar el compuesto de elución más rápida 482Di (CLAR quiral: 11.89 min.; columna CHIRACLEL OD 4.6 x 250 mm; elución isocrática con 12% EtOH en hexano a 2 mL/min.) y el compuesto de elución más lenta 482Dii (CLAR quiral: 16.10 min.; columna CHIRACLEL OD 4.6 x 250 mm; elución isocrática con 12% EtOH en hexano a 2 mL/min.). La conformación absoluta de los compuestos 482Di y 482Dii no se determinó. Por simplicidad en la nomenclatura, el compuesto 482Di se designa en la presente como que tiene una configuración "R" y el compuesto 482Dii como que tiene una configuración "S". Los productos enantioméricamente puros derivados de los

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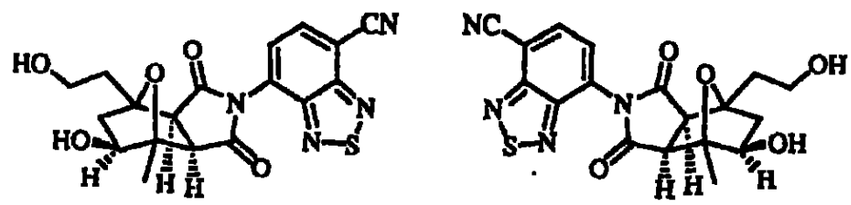
compuestos 482Di se designan en la presente por tener una configuración "R" y los productos enantioméricamente puros derivados del compuesto 482Dii se designan en la presente por tener una configuración "S".

E. [3aR-(3aα,4β,5β,7β,7aα)]-7-[Octahidro-5-hidroxi-7-(2-hidroxietil)-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2,1,3-benzotiadiazol-4-carbonitrilo (482Ei) y [3aR-(3aα,4β,5β,7β,7aα)]-7-[Octahidro-5-hidroxi-7-(2-hidroxietil)-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2,1,3-benzotiadiazol-4-carbonitrilo (482Eii)



El compuesto 482Di (91 mg, 0.18 mmol) se disolvió en 2% de HCl 12N/EtOH (3.0 mL) y la mezcla se agitó a temperatura ambiente por 20 min. Se agregó $NaHCO_3$ saturado frío a la mezcla hasta que se hizo básica (pH 8). La reacción se extrajo con EtOAc. Las capas orgánicas se lavaron después con salmuera y se secaron sobre sulfato de sodio anhidro. La concentración in vacuo dio 73 mg (0.18 mmol, 100%) del compuesto 482Ei como un sólido amarillo que no se purificó adicionalmente. CLAR: 95% a 1.73 min. (tiempo de retención) (YMC S5 ODS 4.6 x 50 mm, 10%-90% metanol acuoso durante 4

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min. de gradiente con 0.2% H_3PO_4, observando a 220 nm). EM (ES): m/z 401.13 $[M+H]^+$.

El compuesto 482Dii (90 mg, 0.17 mmol) se disolvió en 2% de HCl 12N/EtOH (3.0 mL) y la mezcla se agitó a temperatura ambiente por 20 min. Se agregó $NaHCO_3$ saturado frío a la mezcla hasta que se hizo básica (pH 8). La reacción se extrajo con EtOAc. Las capas orgánicas después se lavaron con salmuera y se secaron sobre sulfato de sodio anhidro. La concentración in vacuo dio 70 mg (0.17 mmol, 100%) del compuesto 482Eii como un sólido color naranja que no se purificó adicionalmente. CLAR: 90% a 1.74 min. (tiempo de retención) (YMC S5 ODS 4.6 x 50 mm, 10%-90% metanol acuoso durante 4 min. de gradiente con 0.2% H_3PO_4, observando a 220 nm). EM (ES): m/z 401.14 $[M+H]^+$.

F. [3aR-(3aα,4β,5β,7β,7aα)]-7-[7-[2-[(5-Cloro-2-piridinil)oxi]etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2,1,3-benzotiadiazol-4-carbonitrilo (482F)

Se agregó DBAD (21 mg, 0.090 mmol) a una solución de PPh_3 (24 mg, 0.090 mmol) en THF (0.4 mL). Después de agitar por 10 min., se agregó 5-cloro-2-piridinol (12 mg, 0.090 mmol) y la mezcla de reacción se agitó por 5 min. adicionales. El compuesto 482Ei (18 mg, 0.045 mmol) se agregó y la mezcla se agitó a temperatura ambiente por 1 h. La

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reacción después se concentró bajo presión reducida. La purificación por CCD preparativa eluyendo con 20% acetona/$CHCl_2$ dio 12 mg (0.023 mmol, 52%) de compuesto 482F. CLAR: 98% a 3.15 min. (tiempo de retención) (YMC S5 ODS 4.6 x 50 mm, 10%-90% metanol acuoso durante 4 min. de gradiente con 0.2% H_3PO_4, observando a 220 nm). EM (ES): m/z 512.11 $[M+H]^+$.

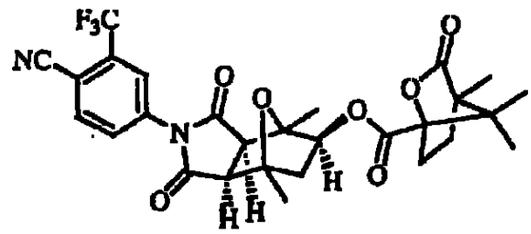
G. [3aS-(3aα,4β,5β,7β,7aα)]-7-[7-[2-[(5-Cloro-2-piridinil)oxi]etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2,1,3-benzotiadiazol-4-carbonitrilo (482G)

Se agregó DBAD (21 mg, 0.090 mmol) a una solución de PPh_3 (24 mg, 0.090 mmol) en THF (0.4 mL). Después de agitar por 10 min., se agregó 5-cloro-2-piridinol (12 mg, 0.090 mmol) y la mezcla de reacción se agitó por 5 min. adicionales. Se agregó el compuesto 482Eii (18 mg, 0.045 mmol) y la mezcla se agitó a temperatura ambiente por 1 h. La reacción después se concentró bajo presión reducida. La purificación por CCD preparativa eluyendo con 20% acetona/$CHCl_3$ dio 11 mg (0.021 mmol, 47.0%) del compuesto 482G. CLAR: 98% a 3.15 min. (tiempo de retención) (YMC S5 ODS 4.6 x 50 mm, 10%-90% metanol acuoso durante 4 min. de gradiente con 0.2% H_3PO_4, observando a 220 nm). EM (ES): m/z 512.15 $[M+H]^+$.

94.2

Ejemplo 483

Éster de [3aS-(3aα,4β,5β,7β,7aα)]-2-[4-ciano-3-(trifluorometil)fenil]octahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-1H-isoindol-5-ilo del ácido (1S,4R)-4,7,7-Trimetil-3-oxo-2-oxabiciclo[2,2,1]heptano-1-carboxílico, (483)

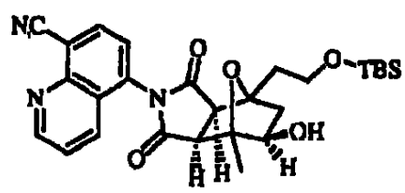


A una solución del compuesto 471Di (25 mg, 0.066 mmol) en 0.25 mL de CH_2Cl_2 a temperatura ambiente y bajo argón, se agregó una solución de ácido (1S)-(-)-canfánico (20 mg, 0.10 mmol) en 0.2 mL de CH_2Cl_2. Una solución de DCC (20 mg, 0.10 mmol) en 0.25 mL de CH_2Cl_2 se agregó después seguida por DMAP (4.0 mg, 0.034 mmol). Se obtuvo inmediatamente un precipitado blanco, y se continuó la agitación durante la noche. El precipitado se separó por filtración y el filtrado se diluyó con EtOAc. La solución resultante se lavó con HCl 1N, salmuera, $NaHCO_3$ saturado y salmuera, después se secó sobre $MgSO_4$. La concentración in vacuo resultó en un residuo aceitoso viscoso. El material crudo se sometió a cromatografía instantánea sobre una columna de 20 cm^3 de gel de sílice eluyendo con 50% EtOAc en hexanos hasta 32 mg de un sólido blanco. La recristalización de CH_2Cl_2/hexano produjo 20 mg (86%) del compuesto 483 como cristales grandes. Este

material se sometió a estudios de difracción de cristal en rayos X, para obtener la estereoquímica exacta del compuesto 471Di como se hace referencia a la estereoquímica fija conocida del apéndice del ácido (1S)-(-)-canfánico. CLEM: 100% a 1.9 min. (tiempo de retención) (Columna Phenomenex Luna C18, 2 x 30 mm, 0-100% acetonitrilo acuoso durante 3 min. conteniendo 10 mM NH_4OAc a 1 mL/min., observando a 220 nm). EM (ESI): m/z 559.3 $[M-H]^-$.

Ejemplo 484

(3aα,4β,5β,7β,7aα)-5-[7-[2-[[(1,1-Dimetiletil)dimetilsilil]oxi]etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-8-quinolincarbonitrilo (484)



A un fondo redondo de 25 mL, seco de tres cuellos, se agregó $TiCl_2Cp_2$ (0.500 g, 2.01 mmol) y THF (4 mL) para dar una solución rojo profundo. Se agregó polvo de zinc activado (0.392 g, 6 mmol, preparado como se describe en Fieser y Fieser, Volumen 1, p. 1276) y la suspensión se agitó por 30 min., tiempo durante el cual cambió el color de rojo ladrillo a verde esmeralda. El polvo de zinc sin reaccionar se dejo asentar. En un matraz de fondo redondo de 25 mL de tres

cuellos, separado, se agregó el compuesto 464F (0.202 g, 0.399 mmol), THF (1 mL) y 1,4-ciclohexadieno (0.380 mL, 4.02 mmol). Se agregó el reactivo Ti(III) (0.90 mL, 0.45 mmol) por medio de un embudo de adición a un tapón de algodón al fondo enjuagando con THF (1 mL). Después de 1 h, la CLAR mostró una conversión del ~50% y se agregaron 0.9 mL adicionales (0.45 mmol) del reactivo de titanio. Después de 1 h, la CLAR mostró un consumo completo del material de partida. Se agregó cloruro de amonio saturado (5 mL), seguido por 10 mL de EtOAc. La capa orgánica se separó, se lavó con salmuera (5 mL), se secó sobre Na_2SO_4, y se concentró in vacuo para dar el producto crudo como un semi-sólido color naranja. El material crudo se purificó por cromatografía instantánea sobre gel de sílice eluyendo con 50% CH_2Cl_2/48% EtOAc/2% MeOH para dar 0.10 g (59%) de compuesto 484 como una espuma amarillo claro. CLAR: 91% a 3.65 min. (tiempo de retención) (Columna YMC S5 ODS, 4.6x 50 mm, eluyendo con 10-90% metanol acuoso durante 4 min. conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 508.27 $[M+H]^+$.

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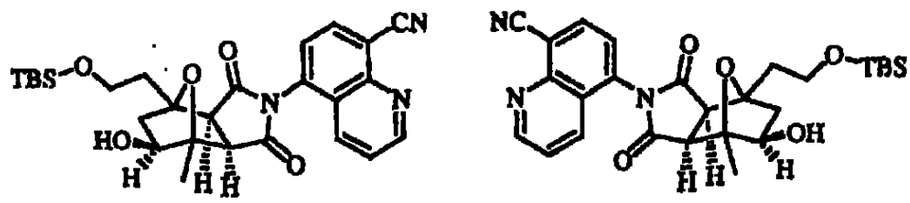
Ejemplo 485

[3aR-(3aα,4β,5β,7β,7aα)]-5-[7-[2-[[(1,1-Dimetiletil)dimetilsilil]oxi]etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-8-quinolincarbonitrilo (485i) y [3aS-(3aα,4β,5β,7β,7aα)]-5-[7-[2-[[(1,1-Dimetiletil]dimetilsilil]oxi]etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-8-quinolincarbonitrilo (485ii)



El compuesto racémico 484, se separó en sus antípodos individuales por CLAR quiral preparativa en fase normal. Una columna de ChiraCLel OD (50 x 500 mm) se usó con una relación de flujo de 50 mL/min. (20% EtOH/hexanos) observando a 220 nm. El antípodo de elución más rápida, el compuesto 485i tuvo un tiempo de retención de 35.8 min. y el antípodo más lento, el compuesto 485ii tuvo un tiempo de retención de 49.7 min. Los antípodqs se aislaron como sólidos blancos después de la separación. Compuesto 485i: CLAR: 100% a 4.980 min. (tiempo de retención) (columna Chiracel OD (5 x 50 mm), 2.0 mL/min., 20% EtOH/hexanos. observando a 220 nm), >99% ee. EM (ES): m/z 508.23 $[M+H]^+$. Compuesto 485ii: CLAR: 98.6% a 7.357 min. (tiempo de retención) (columna Chiracel OD (5 x 50 mm), 2.0

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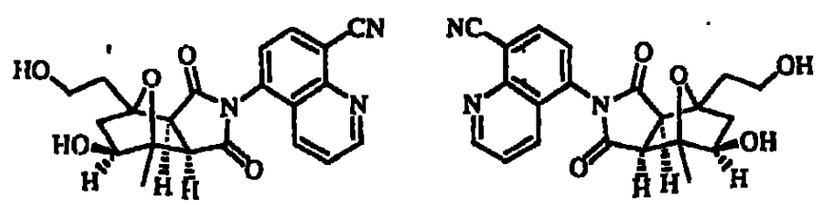
mL/min., 20% EtOH/hexanos, observando a 220 nm), 97.2% ee. EM (ES): m/z 508.21 $[M+H]^+$. La conformación absoluta de los compuestos 485i y 485ii no se determinó. Por simplicidad en la nomenclatura, el compuesto 485i se designa en la presente como que tiene una configuración "R" y el compuesto 485ii como que tiene una configuración "S". Los productos enantioméricamente puros derivados de los compuestos 485i se designan en la presente por tener una configuración "R" y los productos enantioméricamente puros derivados del compuesto 485ii se designan en la presente por tener una configuración "S".

Ejemplo 486

[3aR-(3aα,4β,5β,7β,7aα)]-5-[Octahidro-5-hidroxi-7-(2-hidroxietil)-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-8-quinolincarbonitrilo (486i) y [3aS-(3aα,4β,5β,7β,7aα)]-5-[Octahidro-5-hidroxi-7-(2-hidroxietil)-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-8-quinolincarbonitrilo (486ii)



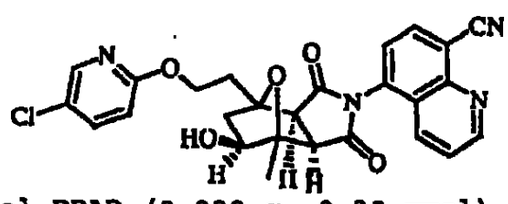
Los compuestos 485i y 485ii se convirtieron a los productos de alcohol primario libre, como se describen en el Ejemplo 466 para dar los compuestos 486i y 486ii como sólidos blancos.

Compuesto 486i: CLAR: 98% a 1.650 min. (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso durante 4 min. conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 394.21 $[M+H]^+$.

Compuesto 486ii: CLAR: 98% a 1.663 min. (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso durante 4 min. conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 394.20 $[M+H]^+$.

Ejemplo 487

[3aR-(3aα,4β,7β,7aα)]-5-[7-[2-[(5-Cloro-2-piridinil)oxi]etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-8-quinolincarbonitrilo (487)

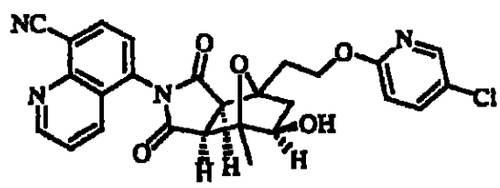


Se agregó el DBAD (0.088 g, 0.38 mmol) a una solución de trifenilfosfina (0.100 g, 0.382 mmol) en THF (1.0 mL) a 22°C y se agitó por 10 min. Se agregó 5-cloro-2-piridinol (0.049 g, 0.38 mmol) como un sólido y la agitación continuó por 10 min. La mezcla de reacción se agregó al compuesto 486i (0.100 g, 0.250 mmol) en THF (1.0 mL). Después de agitar por 3 h, la reacción se concentró in vacuo y fue purificada por

cromatografía instantánea sobre gel de sílice eluyendo con 20-50% acetona/cloroformo para dar 0.080 g (63%) de compuesto 487 como un sólido blanco. CLAR: 100% a 3.023 min. (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso durante 4 min. conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 505.16 $[M+H]^+$.

Ejemplo 488

[3aS-(3aα,4β,7β,7aα)]-5-[7-[2-[(5-Cloro-2-piridinil)oxi]etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-8-quinolincarbonitrilo (488)



Se agregó DBAD (0.088 g, 0.38 mmol) a una solución de trifenilfosfina (0.100 g, 0.382 mol) en THF (1.0 mL) a 22°C y se agitó por 10 min. Se agregó 5-Cloro-2-piridinol (0.049 g, 0.38 mmol) como un sólido y se continuó la agitación por 10 min. La mezcla de reacción se agregó al compuesto 486ii (0.100 g, 0.250 mmol) en THF (1.0 mL). Después de agitar por 3 h, la reacción se concentró in vacuo y fue purificada por cromatografía instantánea sobre gel de sílice eluyendo con 10-50% acetona/cloroformo para dar 0.080 g (63%) del compuesto 488 como un sólido blanco. CLAR: 95% a 3.030 min.

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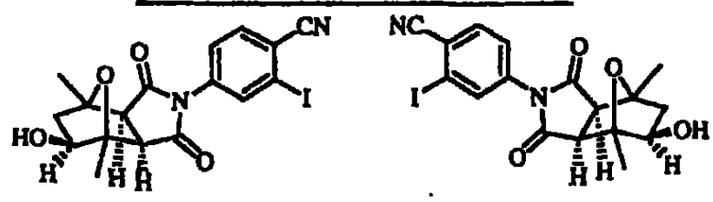
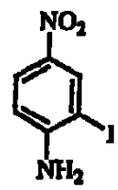
(tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso durante 4 min. conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 505.12 $[M+H]^+$.

Ejemplo 489

[3aR-(3aα,4β,5β,7β,7aα)]-4-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-yodobenzonitrilo (489Gi) y [3aS-(3aα,4β,5β,7β,7aα)]-4-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-yodobenzonitrilo (489Gii)



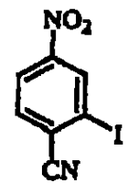
A. 2-yodo-4-nitro-fenilamina (489A)



A una mezcla de yodo (46.0 g, 0.180 mol) y sulfato de plata (56.3 g, 0.180 mol) en etanol anhidro (500 mL) se agregó 4-nitroanilina (25.0 g, 0.180 mol) y la mezcla de reacción se agitó por 5 h a temperatura ambiente. La solución amarilla resultante se filtró y se concentró in vacuo. El residuo resultante se disolvió en 400 mL de acetato de etilo,

se lavó con una solución 1N de hidróxido de sodio (2 x 250 mL), se secó sobre sulfato de sodio, se filtró, y se concentró in vacuo para resultar en 45.5 (95%) del compuesto 489A, como un sólido amarillo. CLAR: 98% a 2.837 min. (tiempo de retención) (columna Shimadzu VP-ODS, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso durante 4 min. conteniendo 0.1% de ácido trifluoroacético, 4 mL/min., observando a 220 nm). EM (ES): m/z 265.08 $[M+H]^+$.

B. 2-yodo-4-nitro-benzonitrilo (489B)



El compuesto 489A (10.0 g, 37.9 mmol) se disolvió en una mezcla de 20 mL de HCl 12N/40 mL agua y después se enfrió hasta 0°C. A esta mezcla se le agregó lentamente una solución de nitrito de sodio (5.23 g, 75.8 mmol) en 10 mL de agua mientras se mantenía la temperatura de reacción a 0°C. La reacción se agitó por 1 h a 0°C y después se agregó lentamente a una solución mecánicamente agitada de cianuro cuproso recientemente preparado (3.0 g, 33 mmol, preparado como se describe en Vogel's Textbook of Practical Organic Chemistry, 5ª edición, pág. 429) y cianuro de potasio (6.30 g, 96.7 mmol) en agua (50 mL) a 50°C. La reacción se agitó por 1 h a 50°C, se enfrió hasta 25°C y se extrajo con cloruro

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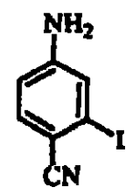
de metileno (2 x 200 mL). La porción orgánica se secó sobre sulfato de sodio, se filtró y se concentró in vacuo. El residuo resultante fue purificado por cromatografía sobre gel de sílice eluyendo con 4:1 hexano:acetato de etilo para resultar 4.6 g (44%) de compuesto 489B como un sólido color naranja. CLAR: 98% a 2.647 min. (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso durante 4 min. conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm).

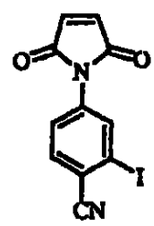
C. 4-Amino-2-yodo-benzonitrilo (489C)



Una mezcla del compuesto 489B (4.60 g, 16.8 mmol), tetrahidrofurano (75 mL), etanol (100 mL), solución de cloruro de amonio (1.51 g, 28.3 mmol, disuelta en 100 mL de agua), y fierro (malla 325, 4.21 g, 75.4 mmol) se agitó mecánicamente. La mezcla de reacción se calentó a reflujo por 3 h o hasta que se había consumido todo el material de partida. La mezcla de reacción se enfrió, se filtró a través de Celite y se concentró in vacuo. El residuo resultante se disolvió en acetato de etilo (200 mL) y se lavó con hidróxido de sodio 1N (2 x 150 mL), se secó sobre sulfato de sodio, se filtró y se concentró in vacuo para producir 3.97 g (97%) de compuesto 489C como un sólido

oscuro. CLAR: 95% a 1.877 min. (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso durante 4 min. conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 245.13 $[M+H]^+$.

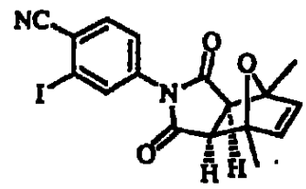
D. 4-(2,5-Dioxo-2,5-dihidro-pirrol-1-il)-2-yodo-benzonitrilo (489D)



El compuesto 489C (3.97 g, 16.3 mmol) y anhidrido maleico (2.41 g, 24.4 mmol) se pusieron a reflujo en ácido acético glacial (15 mL) por 5 h. La reacción se enfrió hasta 25°C y después se vació sobre hielo (100 mL). El precipitado resultante se aisló por filtración y se lavó con agua (2 x 25 mL) y se secó bajo vacío para resultar 4.78 g (90%) de compuesto 489D como un sólido café claro. CLAR: 82% a 2.68 min. (tiempo de retención) columna C Shimadzu VP-ODS, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso durante 4 min. conteniendo 0.1% de ácido trifluoroacético, 4 mL/min., observando a 220 nm). EM (ES): m/z 325.04 $[M+H]^+$.

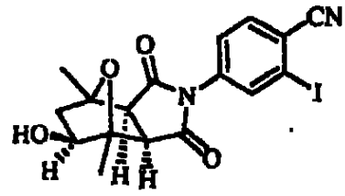
E. (3aα,4β,7β,7aα)-4-(1,3,3a,4,7,7a-Hexahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-yodobenzonitrilo (489E)

953



Una solución de compuesto 489D (0.40 g, 1.2 mmol) en 2,5-dimetilfurano (2.0 g) se agitó a 75°C por 2 h. La reacción se decantó de cualesquiera materiales insolubles y los materiales en forma de partículas se lavaron con éter de dietilo. El decantado combinado y los lavados con éter se combinaron y se concentraron in vacuo mientras se mantenía una temperatura de <50°C. El residuo resultante se trituró con hexanos para producir 0.56 g (94% con base en la pureza) del compuesto 489E como un sólido café claro. Debido a la propensión del producto para someterse a una reacción retro-Diels-Alder, no se intentó purificación adicional. CLAR: 85% a 3.01 min. (tiempo de retención) (columna Shimadzu VP-ODS, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso durante 4 min. conteniendo 0.1% de ácido trifluoroacético, 4 mL/min., observando a 254 nm). EM (ES): m/z 421.05 $[M+H]^+$.

F. (3aα,4β,5β,7β,7aα)-4-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-yodobenzonitrilo (489F)



954

A una solución del compuesto 489E (0.40 g, 0.95 mmol) en THF seco (5 mL) se enfrió hasta 0°C, se agregó complejo de borano-dimetilsulfuro (0.2 mL, 1.9 mmol, 10 M) y la solución de reacción se dejó calentar hasta 25°C. Después de agitar por 30 min., la reacción se enfrió hasta 0°C y se agregó lentamente una solución amortiguadora de fosfato de un pH de 7 (6.6 mL), seguida por la adición de peróxido de hidrógeno al 30% (0.7 mL). La reacción se agitó a 25°C por 1 h y después se dividió entre acetato de etilo (100 mL) y agua (100 mL). Se aisló la porción orgánica, se secó sobre sulfato de sodio, se filtró y se concentró in vacuo. El residuo resultante se purificó por gel de sílice eluyendo con 3:1 cloruro de metileno:acetato de etilo para resultar 0.11 g (25%) de compuesto 489F como un sólido blanco. CLAR: 99% a 2.527 min. (tiempo de retención) (columna Shimadzu VP-ODS, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso durante 4 min. conteniendo 0.1% de ácido trifluoroacético, 4 mL/min., observando a 220 nm). EM (ES): m/z 439.09 $[M+H]^+$.

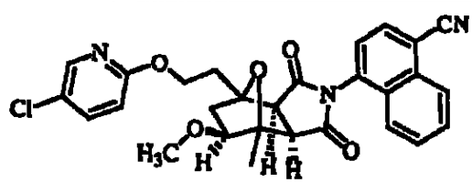
G. [3aR-(3aα,4β,5β,7β,7aα)]-4-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-yodobenzonitrilo (489Gi) y [3aS-(3aα,4β,5β,7β,7aα)]-4-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-yodobenzonitrilo (489Gii)

955

Los compuestos racémicos 489F, se separaron en sus antípodos individuales por CLAR quiral preparativa en fase normal. Se usó una columna ChiraCLel AD (50 x 500 mm) con una relación de flujo de 50 mL/min. (70% Isopropanol/hexanos) observando a 220 nm. El antípodo de elución más rápida, compuesto 489Gi tuvo un tiempo de retención de 4.587 min. y el antípodo de elución más lenta, compuesto 489Gii tuvo un tiempo de retención de 6.496 min. Ambos antípodos se aislaron como sólidos blancos después de la separación. La conformación absoluta de los compuestos 489Gi y 489Gii no se determinó. Por simplicidad en la nomenclatura, el compuesto 489Gi se designa en la presente como que tiene una configuración "R" y el compuesto 489Gii como que tiene una configuración "S".

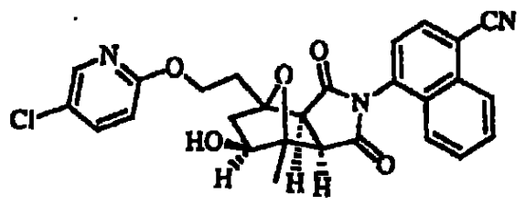
Ejemplo 490

(3aα,4β,5β,7β,7aα)-4-[7-[2-[(5-Cloro-2-piridinil)oxi]etil]octahidro-5-metoxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo (490B)



A. **(3aα,4β,7β,7aα)-4-[7-[2-[(5-Cloro-2-piridinil)oxi]etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo (490A)**

956



Una mezcla de trifenilfosfina (166 mg, 0.633 mmol) y DBAD (146 mg, 0.633 mmol) se disolvió en THF (4 mL) bajo nitrógeno y la solución amarilla se agitó por 10 min. Se agregó 5-cloro-piridin-2-ol (82 mg, 0.63 mmol) y la mezcla se agitó por 5 min. después de lo cual se agregó el compuesto 242B (165 mg, 0.327 mmol). La mezcla se agitó por 12 h y el solvente se separó bajo una corriente de nitrógeno. El aceite resultante se adsorbió sobre gel de sílice (1 g) y fue purificado por cromatografía instantánea sobre un cartucho de sílice para cromatografía Jones (5 g/25 mL) eluyendo con un gradiente de 0-50% acetona en cloroformo para dar 79.4 mg (47%) de compuesto 490A como una espuma blanca. CLAR: 99% a 3.48 min. (tiempo de retención) (columna Phenomenex ODS, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso durante 4 min. conteniendo 0.1% TFA, 4 mL/min., observando a 220 nm). EM (ES): m/z 504.17 $[M+H]^+$.

B. (3aα,4β,5β,7β,7aα)-4-[7-[2-[(5-Cloro-2-piridinil)oxi]etil]octahidro-5-metoxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo (490B)

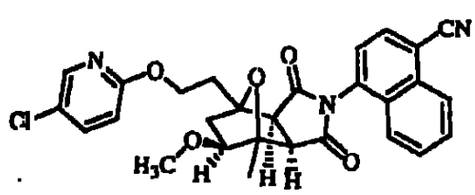
957

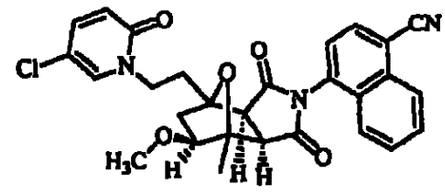
El compuesto 490A (24 mg, 0.048 mmol) se secó en un vial de 1 dracma con una barra de agitación magnética. Se agregaron óxido de plata (57 mg, 0.24 mmol), CH_3CN (500 µL) y yodometano (20 µL, 0.32 mmol) bajo nitrógeno y la mezcla se colocó en un bloque calentado (82°C) y se agitó por 14 h. La mezcla se hizo café después de 20 min., después verde. La mezcla se filtró a través de Celite y Florisil y fue purificada por CLAR preparativa de fase inversa (columna Shimadzu Shimpac VP ODS, 20 x 50 mm, 0-100% metanol acuoso durante 6 min. conteniendo 0.1% TFA, observando a 220 nm) para dar 6.9 mg (28%) de compuesto 490B como una espuma blanca. CLAR: 99% a 3.64 min., 3.76 min. (atropisómeros, tiempo de retención) (columna Phenomenex ODS, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso durante 4 min. conteniendo 0.1% TFA, 4 mL/min., observando a 220 nm). EM (ES): m/z 518.19 $[M+H]^+$.

Ejemplo 491

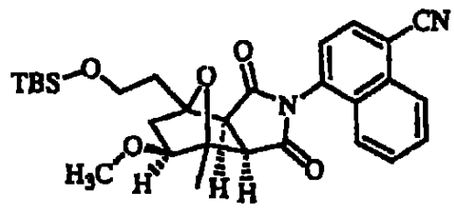
[3aR-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[(5-Cloro-2-piridinil)oxi]etil]octahidro-5-metoxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo, (491Ci) y [3aR-(3aα,4β,5β,7β,7aα)]-4-[7-[2-(5-Cloro-2-oxo-1(2H)-piridinil)etil]octahidro-5-metoxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo (491Cii)

958





A. (3aα,4β,5β,7β,7aα)-4-[7-[2-[[(1,1-Dimetiletil)dimetilsilil]oxi]etil]octahidro-5-metoxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo (491A)



El compuesto 243Cii (142 mg, 0.280 mmol) se secó en un vial de 1 dracma equipado con una barra de agitación magnética y una tapa forrada con Teflón. Se agregó óxido de plata (324 mg, 1.40 mmol), CH_3CN (3 mL) y yodometano (90 µL, 1.4 mmol) bajo nitrógeno y la mezcla se colocó en un bloque caliente (82°C). La reacción se agitó durante la noche, después se filtró a través de Celite y se concentró in vacuo. El residuo resultante fue purificado por cromatografía instantánea sobre gel de sílice eluyendo con un gradiente de 0-50% acetona en cloroformo para dar 62.2 mg (43%) de compuesto 491A. CLAR: 99% a 3.87 y 3.95 min. (atropisómeros, tiempo de retención) (columna Phenomenex ODS, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso durante 4 min. conteniendo 0.1% TFA, 4 mL/min., observando a 220 nm). EM (ES): m/z 521.37 $[M+H]^+$.

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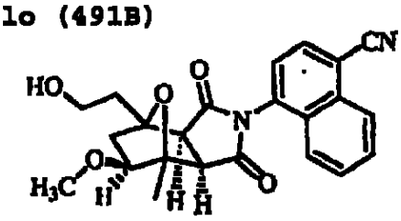
B. 3aα,4β,5β,7β,7aα)-4-[Octahidro-7-(2-hidroxietil)-5-metoxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo (491B)



El compuesto 491A (62.2 mg, 0.119 mmol) se disolvió en etanol (2 mL) y se agregó ácido clorhídrico 12 N (50 µL) y la mezcla se agitó por 10 min. El solvente se eliminó in vacuo y el producto fue purificado por cromatografía instantánea sobre gel de sílice eluyendo con un gradiente de 0-20% acetona en cloroformo para dar 40.3 mg (83%) de compuesto 491B como un sólido blanco. CLAR: 96% a 2.30 y 2.45 min. (atropisómeros, tiempo de retención) (columna Phenomenex ODS, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso durante 4 min. conteniendo 0.1% TFA, 4 mL/min., observando a 220 nm). EM (ES): m/z 407.22 $[M+H]^+$.

C. [3aR-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[(5-Cloro-2-piridinil)oxi]etil]octahidro-5-metoxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo, enantiómero de elución lenta (491Ci) y [3aR-(3aα,4β,5β,7β,7aα)]-4-[7-[2-(5-Cloro-2-oxo-1(2H)-piridinil)etil]octahidro-5-metoxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo (491Cii)

960

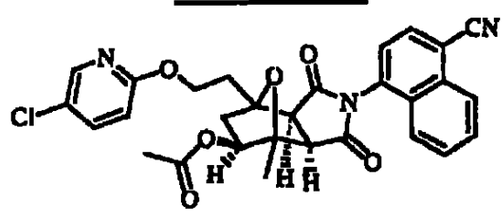
Se disolvieron trifenilfosfina (40 mg, 0.15 mmol) y DBAD (35 mg, 0.15 mmol) en THF bajo nitrógeno y se agitó 10 min. Se agregó 5-Cloropiridin-2-ol (20 mg, 0.15 mmol) y la mezcla se agitó por 5 min. Se agregó el compuesto 491B (40.3 mg, 0.0991 mmol) y la mezcla resultante se agitó por 2.5 h. El solvente se concentró in vacuo y el residuo resultante se purificó por cromatografía sobre Florisil (1.3 g) eluyendo con un gradiente de 0-40% acetona en cloroformo para dar 140 mg de una mezcla de 491Ci, 491Cii y DBAD. El aceite se suspendió en diclorometano (3 mL) y se agregó ácido trifluoroacético (2 mL). Después de 45 min., el solvente se separó in vacuo y el aceite resultante se dividió entre bicarbonato de sodio saturado (20 mL) y EtOAc (20 mL). La capa acuosa se extrajo con EtOAc (2 x 20 mL) y las capas orgánicas combinadas se secaron sobre sulfato de magnesio. La purificación por CLAR preparativa de fase inversa (columna Shimadzu Shimpac VP ODS, 20 x 50 mm, 0-100% metanol acuoso durante 6 min. conteniendo 0.1% TFA, observando a 220 nm) dio 22 mg (44%) de compuesto 491Ci y 4.6 mg (9% rendimiento) de compuesto 491Cii. Compuesto 491Ci: CLAR: 95% a 3.50 min. (tiempo de retención) (columna Phenomenex ODS, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso durante 4 min. conteniendo 0.1% TFA, 4 mL/min., observando a 220 nm). EM (ES): m/z 518.28 $[M+H]^+$. Compuesto 491Cii: CLAR: 85% a 2.94 y 3.07 min. (atropisómeros, tiempo de retención) (columna Phenomenex ODS,

961

4.6 x 50 mm, eluyendo con 10-90% metanol acuoso durante 4 min. conteniendo 0.1% TFA, 4 mL/min., observando a 220 nm). EM (ES): m/z 518.27 $[M+H]^+$.

Ejemplo 492

[3aR-(3aα,4β,5β,7β,7aα)]-4-[5-(Acetiloxi)-7-[2-[(5-cloro-2-Piridinil)oxi]etil]octahidro-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo, enantiómero de elución lenta (492)



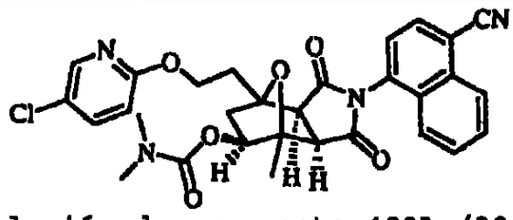
Se agregó cloruro de acetilo (25 µL, 0.35 mmol) a una solución de compuesto 490A (30 mg, 0.060 mmol) en piridina (600 µL). La mezcla se agitó durante la noche, diluida con ácido clorhídrico (0.5 N, 10 mL), se extrajo con cloroformo (3 x 7 mL). Las capas orgánicas se combinaron, se lavaron con agua (3 x 4 mL) y salmuera (4 mL), se secaron sobre sulfato de magnesio y se concentraron in vacuo. La purificación por cromatografía instantánea sobre gel de sílice eluyendo con un gradiente de 0-50% acetona en cloroformo dio 17 mg (53%) de compuesto 492. CLAR: 99% a 3.48 y 3.63 min. (atropisómeros, tiempo de retención) (columna Phenomenex ODS, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso durante 4 min. conteniendo

962

0.1% TFA, 4 mL/min., observando a 220 nm). EM (ES): m/z 546.15 $[M+H]^+$.

Ejemplo 493

Éster de [3aR-(3aα,4β,5β,7β,7aα)]-7-[2-[(5-cloro-2-piridinil)oxi]etil]-2-(4-ciano-1-naftalenil)octahidro-4-metil-1,3-dioxo-4,7-epoxi-1H-isoindol-5-ilo del ácido dimetiCLarbámico, enantiómero de elución lenta (493)



A una solución de compuesto 490A (30 mg, 0.060 mmol) en piridina (300 µl) se agregó cloruro de dimetiCLarbamilo (28 µl, 0.30 mmol) y la mezcla se agitó a 25°C por 12 h. Se agregó una porción adicional de cloruro de dimetiCLarbamoilo (28 µL, 0.30 mmol) y la reacción se calentó a 70°C por 12 h. Se agregaron una tercera porción de cloruro de dimetiCLarbamoilo (28 µl, 0.30 mmol) así como piridina (300 µl) y la mezcla se agitó a 100°C por 24 h. La solución se diluyó con HCl 0.5 N (10 mL) y se extrajo con cloroformo (3 x 7 mL). Las capas orgánicas se combinaron y se lavaron con agua (3 x 4 mL) y salmuera (4 mL), se secaron sobre sulfato de magnesio y se concentró in vacuo. La purificación por CLAR preparativa de fase inversa (columna Shimadzu Shimpac VP ODS,

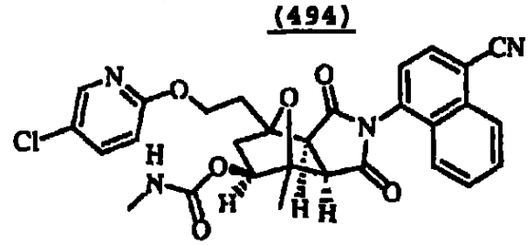
963

20 x 50 mm, 0-100% metanol acuoso durante 6 min. conteniendo 0.1% TFA, observando a 220 nm) dio 15.7 mg (46%) de compuesto 493 como un sólido blanco. CLAR: 99% a 3.52 min. y 3.69 min. (atropisómeros, tiempo de retención) (columna Phenomenex ODS, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso durante 4 min. conteniendo 0.1% TFA, 4 mL/min., observando a 220 nm). EM (ES): m/z 575.10 $[M+H]^+$.

Ejemplo 494

[3aR-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[(5-Cloro-2-piridinil)oxi]etil]octahidro-4-metil-5-[[(metilamino)carbonil]oxi]-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo, enantiómero de elución lenta

(494)



Se agregó isocianato de metilo (36 µL, 0.60 mmol) a una solución de compuesto 490A (30 mg, 0.060 mmol) en dioxano (600 µL) y se calentó a 80°C durante la noche. Se agregó una porción adicional de isocianato de metilo (36 µL, 0.60 mmol) y la mezcla se calentó a 100°C por 24 h. Se agregó una tercera porción de isocianato de metilo (36 µL, 0.60 mmol) y la mezcla se agitó a 100°C por 24 h. El solvente se separó in

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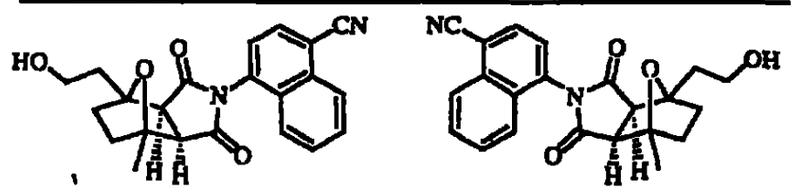
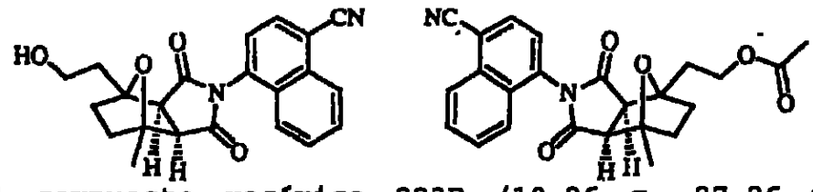
vacuo y el aceite fue purificado por CLAR preparativa de fase inversa (columna Shimadzu Shimpac VP ODS, 20 x 50 mm, 0-100% metanol acuoso durante 6 min. conteniendo 0.1% TFA, observando a 220 nm) para dar 20 mg (59%) de compuesto 494 como un vidrio transparente. CLAR: 99% a 3.33 min. y 3.42 min. (atropisómeros, tiempo de retención) (columna Phenomenex ODS, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso durante 4 min. conteniendo 0.1% TFA, 4 mL/min., observando a 220 nm). EM (ES): m/z 561.08 $[M+H]^+$.

Ejemplo 495

[3aR(3aα,4β,5β,7β,7aα)]-4-[Octahidro-4-(2-hidroxietil)-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo (495Ai) y [3aS(3aα,4β,5β,7β,7aα)]-4-[Octahidro-4-(2-hidroxietil)-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo (495B)



A. [3aS-(3aα,4β,5β,7β,7aα)]-4-[Octahidro-4-(2-hidroxietil)-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo (495Ai) y (3aα,4β,5β,7β,7aα)-4-[2-(Acetiloxi)etil]-2-(4-ciano-1-naftalenil)hexahidro-7-metil-4,7-epoxi-1H-isoindol-1,3(2H)-diona (495Aii)



El compuesto racémico 223B (10.26 g, 27.26 mmol) se disolvió en THF anhidro (500 mL) en una botella de 10 L. Se agregó éter de metil tert-butilo (4.86 L), acetato de vinilo (216 mL) y se agregó Lipasa (108 g, [Sigma, Lipasa tipo II, cruda de páncreas porcino, producto No. L3126, Lote No. 021K1445]). La mezcla de reacción se agitó por 24 h a temperatura ambiente y la reacción se observó por CLAR usando las siguientes condiciones: Una muestra de 200 µL de la mezcla de reacción se filtró, se secó bajo una corriente de nitrógeno y se sometió a un análisis CLAR (columna YMC ODS, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso durante 4 min. conteniendo 0.1% TFA, 4 mL/min., observando a 220 nm). La reacción se detuvo después de que el 60% del material de partida se había consumido. La enzima se separó por filtración y el filtrado se concentró in vacuo. El residuo resultante se disolvió en $CHCl_3$ y se absorbió sobre gel de sílice. La purificación por cromatografía instantánea sobre gel de sílice eluyendo con un gradiente de 1-5% MeOH en $CHCl_3$ dio 3.78 g (37%) de compuesto 495Ai y 6.84 g (60%) de compuesto 495Aii, ambos como sólidos blancos. Compuesto 495Ai: CLAR: 99% a 3.47 min. (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso

durante 4 min. conteniendo 0.1% TFA, 4 mL/min., observando a 220 nm). EM (ES): m/z 377.09 $[M+H]^+$. CLAR quiral preparativa en fase normal: 37.8 min. (tiempo de retención) (columna chiralpak AD, 4.6 x 250 mm, 10 micras, 40°C, elución isocrática con 8% EtOH/MeOH (1:1) en heptano, observando a 220 nm), 99% ee. Compuesto 495Aii: CLAR: 99% a 2.92 min. (tiempo de retención) (Columna YMC S5 ODS. 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso durante 4 min. conteniendo 0.1% TFA, 4 mL/min., observando a 220 nm).

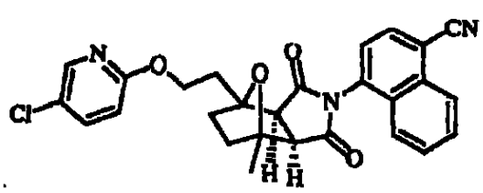
B. [3aR-(3aα,4β,5β,7β,7aα)]-4-[Octahidro-4-(2-hidroxietil)-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo (495B)

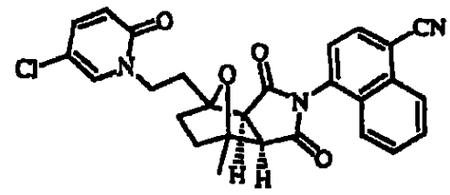
Se agregó lipasa (134 g, [Sigma, Lipasa tipo II, cruda de páncreas de porcino, producto No. L3126, Lote No. 021K1445]) a 3.5 L de agua desionizada. La mezcla se centrifugó para eliminar la mayoría del material suspendido. El pH del sobrenadante se ajustó a 7.06 con hidróxido de sodio 1N y se agregó una solución de compuesto 495Aii (8.04 g, 19.2 mmol) en TBME (1.5 L). El pH se incrementó hasta 7.16 por adición de hidróxido de sodio 1N. La mezcla de reacción se agitó a temperatura ambiente y se observó por CLAR analítica como se describe en el Ejemplo 495A. Después de 30 min., La reacción se filtró a través de Celite y el filtrado se extrajo con acetato de etilo (4 x 1 L) hasta que la CLAR

mostró que se había eliminado todo el aCLohol. Las fracciones orgánicas se combinaron, se secaron sobre sulfato de magnesio, se filtraron y se concentraron in vacuo. La purificación por cromatografía instantánea sobre gel de sílice (columna Jones, 50 g) usando un gradiente de 0-70% acetona en cloroformo seguida por 5% MeOH en cloroformo dio 2.44 g (33%) del compuesto 495B como un sólido blanco. CLAR: 99% a 2.89 min. (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso durante 4 min. conteniendo 0.1% TFA, 4 mL/min., observando a 220 nm). EM (ES): m/z 377.09 $[M+H]^+$. CLAR quiral preparativa en fase normal: 11.1 min. (tiempo de retención) (columna chiralpak AD, 4.6 x 250 mm, 10 micras, 40°C, elución isocrática con 8% EtOH/MeOH (1:1) en heptano, observando a 220 nm), 95% ee.

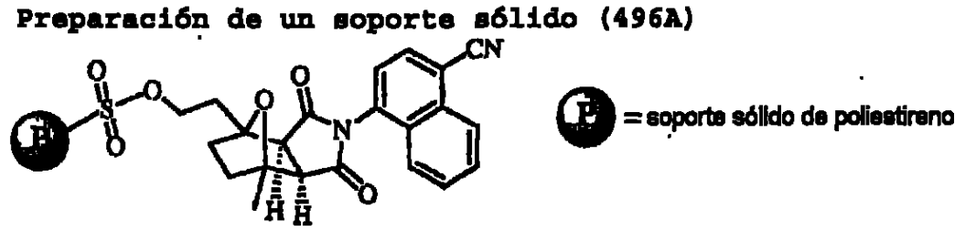
Ejemplo 496

[3aR-(3aα,4β,7β,7aα)]-4-[4-[2-[(5-Cloro-2-piridinil)oxi]etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo (496Bi) y [3aR-(3aα,4β,7β,7aα)]-4-[4-[2-(5-Cloro-2-oxo-1(2H)-piridinil)etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo (496Bii)





A. Preparación de un soporte sólido (496A)



Una mezcla de CH_2Cl_2 anhidro (10 mL) y piridina (10 mL) se agregó bajo nitrógeno al clorosulfonil poliestireno (Argonaut, 1.70 mmol/g, 3.0 g, 5.1 mmol) y el compuesto 495Ai (3.78 g, 10.0 mmol) en un tubo de síntesis de polímeros. La mezcla cambió hacia un gel de color amarillo y se agitó vigorosamente (agitador de acción con la muñeca por 4 h.). Todos los solventes se absorbieron por la resina y se observó seca. La resina se lavó en porciones con CH_2Cl_2 (200 mL) y los lavados se combinaron y se extrajeron con 200 mL de HCl 1N. La fracción de HCl es volvió a extraer con acetato de etilo (200 mL). Las fracciones orgánicas se combinaron y extrajeron con agua (50 mL), salmuera (50 mL) y las fracciones orgánicas se secaron sobre sulfato de sodio, se filtraron y concentraron para dar 2.1 g de compuesto enlazado a la resina 496A (89% cargado con base en la recuperación del compuesto no enlazado 495Ai). La resina se lavó consecutivamente con DMF (5X), DMF: agua (3:1, 5X), THF (3X) y CH_2Cl_2 (3X) (~30 mL cada lavado). La resina se secó in vacuo por 1 h para dar 5.35 g de resina. La resina estaba todavía húmeda y se volvió a tratar

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con el aCLohol. El proceso de carga antes descrito se repitió usando el compuesto recuperado sin reaccionar 495Ai del procedimiento anterior. El compuesto recuperado 495Ai (2.1 g, 5.6 mmol) y diclorometano anhidro (15 mL) y piridina (15 mL) y la resina se combinaron y sometieron a las condiciones de reacción antes descritas. La resina resultante se lavó como se describe previamente y se secó in vacuo durante la noche para dar 4.49 g de resina (87% cargada, con base en el compuesto no enlazado recuperado 495Ai). El aCLohol de partida se recuperó de la mezcla de diclorometano:piridina como se describe previamente (2.04 g de sólido blanco, lo que sugeriría una carga del 92% con base en el aCLohol recuperado). El incremento en peso de la resina es usualmente más preciso para evaluación de la carga. La carga de resina se caCLuló que era 0.87 (determinada por el incremento en peso de la resina) X 1.08 mmol/g (caCLulado como carga al 100%) = 0.94 mmol/g. La resina se usó como estaba para la siguiente etapa.

B. [3aR-(3aα,4β,7β,7aα)]-4-[4-[2-[(5-Cloro-2-piridinil)oxi]etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo (496Bi) y [3aR-(3aα,4β,7β,7aα)]-4-[4-[2-(5-Cloro-2-oxo-1(2H)-piridinil)etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo (496Bii)

El siguiente procedimiento describe un proceso general para el cual las configuraciones de los compuestos de Fórmula I se pueden elaborar usando métodos automatizados. La información adicional sobre tales métodos automatizados sintéticos, se puede encontrar en el Ejemplo 8. Los compuestos 496Bi y 496Bii son un ejemplo de compuestos elaborados por tal procedimiento. Para los compuestos 496Bi y 496Bii, el 4-cloropiridinol representa el reactivo nucleófilo. Una definición más amplia del término nucleófilo, está contenida en el cuerpo de este documento, y es bien entendida por alguien experto en la técnica. Se usó un MiniReactor Bohdan equipado con un bloque de calentamiento/enfriamiento con viales de 0.5 dracmas apilados uno sobre el otro para aCLanzar el mismo nivel que los tubos del reactor. Se midió la resina (compuesto 496A) en los viales individuales al usar una vez cada placa del módulo de transferencia de resina Bohdan "10 mg" y "20 mg". Los pesos de resina suministrados estaban en el intervalo desde 17-23 mg (0.016-0.022 mmol). Se agregó carbonato de cesio usando la placa Bohdan de "20 mg" que suministraba ~57-60 mg (0.17-0.18 mmol). Los nucleófilos se pesaron sobre viales de 1 Dracma y se diluyeron en THF hasta 0.06 M usando un manipulador de líquidos de ocho canales Tecan. Las soluciones resultantes (250 µL, 0.015 mmol) se agregaron manualmente por medio de

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una micro-pipeta a cada uno de los viales de reacción conteniendo resina, y la configuración resultante de los viales de reacción se colocó en el reactor Bohdan. Cuando los nucleófilos son aminas, se agregan ~13 µL de diisopropiletilamina a la solución de THF de la amina. Los viales se taparon (cubiertos con teflón) y las reacciones se calentaron con agitación orbital (carrera corta 500 rpm) a 70°C por 24 h. Las reacciones se enfriaron hasta 25°C y se agregó 1 mL de una mezcla de heptano y acetato de etilo (1:1) seguida por 0.5 mL de agua. La capa orgánica se extrajo manualmente y se transfirió individualmente a un tubo de bloque de síntesis conteniendo sulfato de magnesio (~150 mg). La configuración de los tubos del bloque de síntesis se filtró simultáneamente y los filtrados se recolectaron individualmente en microtubos (bloque de 96 pozos). La capa acuosa se volvió a extraer con 1 mL de una mezcla de heptano y acetato de etilo (1:1), la capa orgánica se filtró como se describe arriba y el filtrado se recolectó individualmente como se describe arriba en los microtubos existentes.

El análisis de la configuración de los compuestos preparados por el procedimiento anterior, se llevó a cabo usando el siguiente método automatizado. Una porción de 120 µl de cada una de las reacciones anteriores (filtrados) formó alícuotas en dos bloques de 96 pozos profundos para el

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análisis. El solvente se concentró in vacuo y las placas se volvieron a diluir con metanol (500 µL). Se analizó una placa por CLEM (columna Phenomenex ODS, 4.6 x 50 mm, 4 mL/min., gradiente 0% A hasta 100% B (A: 90% agua, 10% MeOH, 0.1% TFA; B: A: 90% MeOH, 10% agua. 0.1% TFA) y la otra por RMN de flujo (Varian Inova-500 MHz, MeOH, secuencia de supresión de pulsos de solvente WET, 128 barridos, sonda de celda de flujo de 60 µl). Los criterios para la entrega fueron: ión molecular correcto presente y pureza por CLAR/RMN >70%. Los compuestos que no reunieron los criterios deseados se purificaron por CLAR preparativa de fase inversa (columna Shimadzu UP-ODS, 20 x 50 mm, 20 mL/min., gradiente 40% B hasta 100% B en 6 min. con retención de 2 min. (A: 90% agua, 10% MeOH, 0.1% TFA; B: A: 90% MeOH, 10% agua, 0.1% TFA). La purificación por CLAR produjo 3.4 mg (21%) de compuesto 496Bi como un sólido vidrioso y 6.8 mg (41%) de compuesto 496Bii como un sólido vidrioso. Compuesto 496Bi: CLAR: 96% a 3.47 min. y 3.62 min. (atropisómeros, tiempo de retención) (columna Phenominex ODS, 4.6 x 50 mm, 4 mL/min., gradiente 0% A hasta 100% B (A: 90% agua, 10% MeOH, 0.1% TFA; B: A: 90% MeOH, 10% agua, 0.1% TFA), observando a 220 nm). EM (ES): m/z 487.94 $[M+H]^+$. Compuesto 496Bii: CLAR: 96% a 3.00 min. y 3.12 min. (atropisómeros, tiempo de retención) (columna Phenominex ODS, 4.6 x 50 mm, 4 mL/min., gradiente 0% A hasta 100% B (A:

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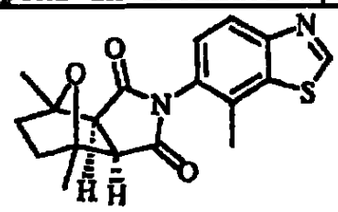
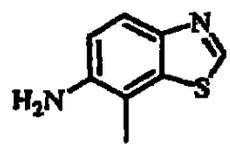
90% agua, 10% MeOH, 0.1% TFA; B: A: 90% MeOH, 10% agua, 0.1% TFA), observando a 220 nm). EM (ES): m/z 488.12 [M+H]⁺. Compuestos adicionales hechos por este procedimiento se establecen en la Tabla 17.

Ejemplo 497

(3aα,4β,5β,7β,7aα)-Hexahidro-4,7-dimetil-2-(7-metil-6-benzotiazolil)-4,7-epoxi-1H-isoindol-1,3(2H)-diona (497B)



A. 6-Amino-7-metilbenzotiazol (497A)



Se preparó el 7-Metil-6-nitrosobenzotiazol a partir de 6-nitrobenzotiazol según el procedimiento general descrito por Bartoli et al. Synlett 270 (1976). A una solución de 7-metil-6-nitrosobenzotiazol (889 mg, 5.00 mmol) en AcOH (40 mL) a 70°C se agregó polvo de hierro (malla 325, 559 mg, 10.0 mmol) en una porción sencilla. La mezcla de reacción obscura resultante se agitó por 15 min. antes de que se enfriara y se concentró in vacuo para dejar un residuo que se dividió entre HCl 1N (50 mL) y CH_2Cl_2 (50 mL). Las capas se separaron y la capa orgánica se lavó una vez con HCl 1N (25 mL). Las capas

acuosas combinadas se hicieron básicas por la adición de $NaHCO_3$ sólido y se extrajeron dos veces con EtOAc. Se combinaron las fases orgánicas, se secaron sobre $MgSO_4$ y se concentró in vacuo para dar 534 mg (65%) de compuesto 497A como un sólido café claro. CLAR: 96% a 0.55 min. (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm Ballistic, 10-90% metanol acuoso durante 4 min. conteniendo 0.2% H_3PO_4, 4 mL/min. observando a 220 nm). EM (ES): m/z 165.0 $[M+H]^+$.

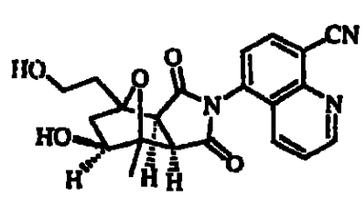
B. (3aα,4β,5β,7β,7aα)-Hexahidro-4,7-dimetil-2-(7-metil-6-benzotiazolil)-4,7-epoxi-1H-isoindol-1,3(2H)-diona (497B)

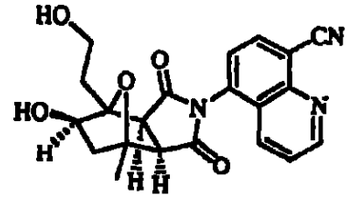
Se tomaron 6-Amino-7-metilbenzotiazol (29 mg, 0.18 mmol), $MgSO_4$ (54 mg, 0.45 mmol), trietilamina (125 µL, 0.897 mmol) y compuesto 20A (52 mg, 0.26 mmol) en 0.18 mL de DME y se colocaron en un tubo sellado. El tubo sellado se calentó a 135°C por 14 h. La mezcla de reacción enfriada se filtró a través de a una almohadilla corta de Celite eluyendo con EtOAc y el solvente se separó in vacuo. El residuo fue purificado por CLAR preparativa de fase inversa (Columna YMC S5 ODS, 20 x 100 mm, eluyendo con 30-100% metanol acuoso durante 10 min. conteniendo 0.1% TFA, 20 mL/min., observando a 220 nm). La concentración de las fracciones deseadas resultó en un residuo que se dividió entre CH_2Cl_2 (10 mL) y $NaHCO_3$ saturado, solución (10 mL). La capa acuosa se extrajo

una vez con CH_2Cl_2 y las fases orgánicas combinadas se secaron sobre Na_2SO_4 y se concentraron in vacuo para dar 42 mg (68%) de compuesto 497B como un sólido café claro. CLAR: 2.36 min. y 2.55 min. (atropisómeros, tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso durante 4 min. conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 343.3 $[M+H]^+$.

Ejemplo 498

(3aα,4β,5β,7β,7aα)-5-[Octahidro-5-hidroxi-7-(2-hidroxietil)-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-8-quinolincarbonitrilo (498i) y (3aα,4β,5β,7β,7aα)-5-[Octahidro-5-hidroxi-4-(2-hidroxietil)-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-8-quinolincarbonitrilo (498ii)





El compuesto 464E (0.500 g, 1.02 mmol) se disolvió en THF (5.00 mL) y se enfrió hasta 0°C. BH_3•DEM (0.193 mL, 2.04 mmol) se agregó después lentamente, seguido por calentamiento a 25°C. Después de 1 h, la reacción se enfrió hasta 0°C y se agregó una solución amortiguadora de fosfato de pH 7 (15.0 mL) resultando en la evolución del gas. Se agregaron después EtOH (7.0 mL) y peróxido de hidrógeno (30%, 1.5 mL) y la

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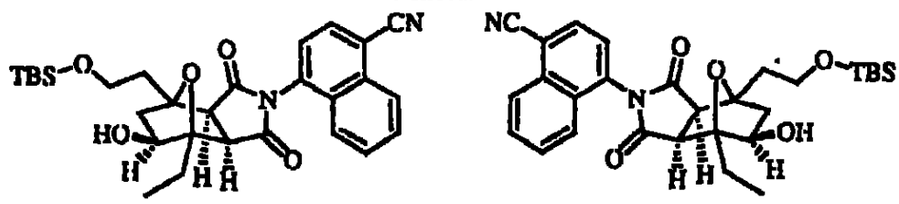
reacción se calentó hasta 25°C durante 2 h. Después de 3 h, la mezcla se extrajo con cloruro de metileno (3 x 50 mL). Las capas orgánicas combinadas se lavaron una vez con salmuera y se secaron sobre sulfato de sodio anhidro. El producto formó después un complejo con boro después de la preparación. Todos los intentos para romper este complejo fracasaron para dar el producto libre. El material crudo se llevó a la siguiente etapa sin purificación adicional.

La mezcla cruda de reacción se disolvió en 2% HCl conc./MeOH (5.0 mL) a temperatura ambiente. Después de 1 h, los volátiles se separaron in vacuo y el residuo resultante se disolvió en cloruro de metileno y se lavó una vez con bicarbonato de sodio acuoso saturado y se secaron sobre sulfato de sodio anhidro. La eliminación del solvente in vacuo dio la mezcla cruda de compuestos 498i y 498ii como un sólido amarillo. La mezcla de compuestos se separó por CLAR preparativa de fase inversa: Compuesto 498i: 17.994 min. (tiempo de retención) y compuesto 498ii: 19.767 min. (tiempo de retención) (Columna YMC S5 ODS, 30 x 250 mm, 25 mL/min., 10-90% metanol acuoso durante 35 min. conteniendo 0.1% TFA, observando a 220 nm). La eliminación del solvente in vacuo dio 0.012 g (3%) de compuesto 498i como un sólido blanco y 0.009 g (2%) de compuesto 498ii como un sólido blanco. Compuesto 498i: CLAR: 85% a 1.843 min. (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, eluyendo con 10-90% metanol

acuoso durante 4 min. conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 394.21 $[M+H]^+$. Compuesto 498ii: CLAR: 98% a 1.650 min. (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm. eluyendo con 10-90% metanol acuoso durante 4 min. conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 394.21 $[M+H]^+$.

Ejemplo 499

[3aR-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[[(1,1-Dimetiletil)dimetilsilil]oxi]etil]-4-etiloctahidro-5-hidroxi-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo (499i) y [3aS-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[[(1,1-Dimetiletil)dimetilsilil]oxi]etil]-4-etiloctahidro-5-hidroxi-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo (499ii)



El compuesto racémico 434C se separó en sus antípodos individuales por CLAR quiral preparativa en fase normal usando una columna Chiracel AD (5 cm x 50 cm), eluyendo con 8% EtOH en hexano a 50 mL/min. para dar el compuesto de elución más rápida 499i (CLAR quiral: 6.74 min.; columna CHIRACLEL AD 4.6 x 250 mm; elución isocrática con 10% EtOH en

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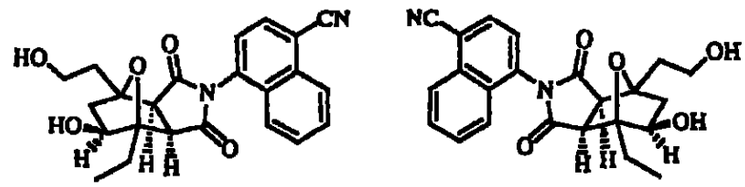
hexano a 2 mL/min.) y el compuesto de elución más lenta 499ii (CLAR quiral: 9.99 min.; columna CHIRACLEL AD 4.6 x 250 mm, elución isocrática con 10% EtOH en hexano a 2 mL/min.). Para cada compuesto 499i ó 499ii: CLAR: 100% a 3.96 min. (tiempo de retención) (columna YMC CombiSreen ODS, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso conteniendo 0.2% ácido fosfórico durante 4 min., 4 mL/min., observando a 220 nm). EM (ES): m/z 521.25 $[M+H]^+$. La estereoquímica absoluta para los compuestos 499i y 499ii no se estableció. Por simplicidad en la nomenclatura, el compuesto 499i se designa aquí como que tiene la configuración "R" y el compuesto 499ii como que tiene la configuración "S". Los productos enantioméricamente puros derivados del compuesto 499i se designan en la presente como que tienen una configuración "R" y los productos enantioméricamente puros derivados del compuesto 499ii se designan en la presente como que tienen una configuración "S".

Ejemplo 500

[3aR-(3aα,4β,5β,7β,7aα)]-4-[4-Etiloctahidro-5-hidroxi-7-(2-hidroxietil)-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo (500i) y [3aS-(3aα,4β,5β,7β,7aα)]-4-[4-Etiloctahidro-5-hidroxi-7-(2-hidroxietil)-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo (500ii)



El compuesto 499i (24.0 mg, 0.0461 mmol) se disolvió en 2% de HCl conc./EtOH (0.8 mL) y la mezcla se agitó a temperatura ambiente por 20 min. El $NaHCO_3$ frío saturado se agregó a la mezcla hasta que la solución aCLanzó un pH de 8, después se extrajo con EtOAc. Las capas orgánicas se combinaron, se lavaron con salmuera y se secaron sobre sulfato de sodio anhidro. La concentración in vacuo dio 14.7 mg (78%) del compuesto 500i como un sólido blanco que no requirió de purificación adicional. CLAR: 95% a 2.40 min. (tiempo de retención) (YMC S5 ODS 4.6 x 50 mm, 10%-90% metanol acuoso durante 4 min. gradiente con 0.2% H_3PO_4, observando a 220 nm).

El compuesto 499ii (18.0 mg, 0.0346 mmol) se disolvió en 2% HCl conc./EtOH (0.6 mL) y la mezcla se agitó a temperatura ambiente por 20 min. Se agregó $NaHCO_3$ saturado frío a la mezcla hasta que la solución aCLanzó un pH de 8, después se extrajo con EtOAc. Las capas orgánicas se combinaron, se lavaron con salmuera y se secaron sobre sulfato de sodio anhidro. La concentración in vacuo dio 14.1 mg (99%) de compuesto 500ii como un sólido blanco que no requirió de purificación adicional. CLAR: 95% a 2.40 min. (tiempo de retención) (YMC S5 ODS 4.6 x 50 mm, 10%-90% metanol acuoso durante 4 min. gradiente con 0.2% H_3PO_4, observando a 220 nm).

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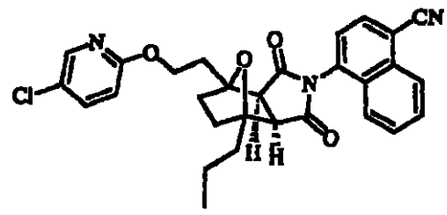
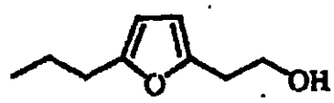
Ejemplo 501

[3aR-(3aα,4β,7β,7aα)]-4-[4-[2-[(5-Cloro-2-piridinil)oxi]etil]octahidro-1,3-dioxo-7-propil-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo (501D)

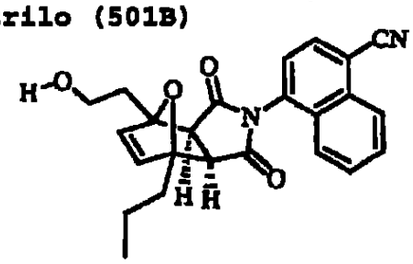


A. 2-(5-Propil-furan-2-il)-etanol (501A)



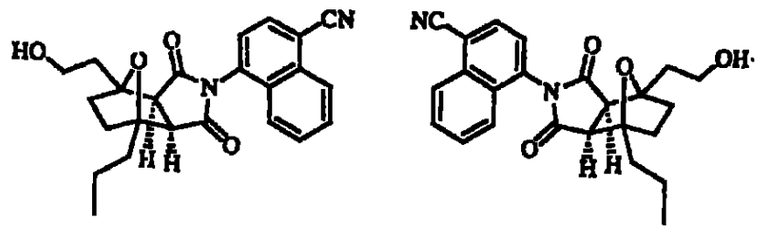
A una solución de 2-propilfurano (3.00 g, 31.2 mmol) en THF (31 mL) a -78°C, se agregó n-BuLi (15.0 mL, 2.5 M, 37.4 mmol) gota a gota durante 10 min. La reacción se calentó a temperatura ambiente y se agitó por 3.5 h. Después de enfriar a 0°C, se agregó óxido de etileno (2.33 mL, 46.8 mmol), la reacción se calentó hasta temperatura ambiente y continuó la agitación por 19 h. La reacción después se enfrió hasta 0°C y se apagó con NH_4Cl sat. (20 mL), seguido por la extracción con Et_2O (2 x 50 mL). Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre Na_2SO_4, se filtraron, y se concentraron para dar 4.38 g (91%) de compuesto 501A como un aceite color naranja brillante. Este material se usó sin purificación adicional. CLAR: 94% a 2.91 min. (tiempo de retención) (columna YMC Combiscreen ODS-A, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso conteniendo 0.2% ácido fosfórico durante 4 min., 4 mL/min., observando a 220 nm). EM (ES): m/z 137.13 $[M-H_2O+H]^+$.

B. (3aα,4β,7β,7aα)-4-[1,3,3a,4,7,7a-Hexahidro-4-(2-hidroxietil)-1,3-dioxo-7-propil-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo (501B)



Una suspensión de 2-(5-propil-furan-2-il)-etanol (2.50 g, 16.2 mmol) y 4-(2,5-dihidro-2,5-dioxo-1H-1-il)-1-naftalencarbonitrilo (4.02 g, 16.2 mmol) en benceno (16 mL) se calentó hasta 60°C. Después de 3 h, la reacción se concentró in vacuo para dar una espuma café. Se agregó metanol (17 mL) y la mezcla se sonicó para dar un sólido beige fino con un sobrenadante café. La filtración dio 1.75 g (27%) de compuesto 501B como un sólido blanco descolorido. Este material se usó sin purificación adicional. CLAR: 85% a 3.02 min. y 3.14 min. (atropisómeros, tiempo de retención) (columna YMC Combiscreen ODS-A, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso conteniendo 0.2% ácido fosfórico durante 4 min., 4 mL/min., observando a 220 nm). EM (ES): m/z 403.31 $[M+H]^+$.

C. [3aR-(3aα,4β,7β,7aα)]-4-[Octahidro-4-(2-hidroxietil)-1,3-dioxo-7-propil-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo (501Ci) y [3aS-(3aα,4β,7β,7aα)]-4-[Octahidro-4-(2-hidroxietil)-1,3-dioxo-7-propil-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo (501Cii)



A una suspensión del compuesto 501B (1.60 g, 3.97 mmol) en acetato de etilo (79.5 mL) se agregó 10% Pd/C (0.422 g, 0.397 mmol). Se burbujeó gas hidrógeno a través de la reacción por varios minutos y la reacción se dejó agitar bajo una atmósfera de hidrógeno por 3 h. La reacción se filtró a través de Celite y el filtrado se concentró in vacuo para dar un sólido blanco (1.74 g). El material crudo se disolvió en una cantidad mínima de cloruro de metileno y se cargó sobre 120 g de un cartucho ISCO de gel de sílice. La elución con un gradiente por etapas de 0 hasta 100% acetato de etilo/hexano dio 1.06 g (66%) de la mezcla racémica de compuestos 501Ci y 501Cii como una espuma blanca. Una porción de 500 mg de la mezcla racémica se separó por CLAR quiral preparativa en fase normal (columna Chiralpak AD; 5 x 50 cm; elución isocrática con 13% MeOH/EtOH (1:1) en heptano a 50 mL/min., observando a

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220 nm) para dar 245 mg del enantiómero de elución más rápida, compuesto 501Ci y 245 mg del enantiómero de elución más lenta, compuesto 501Cii, ambos como espumas blancas. Compuesto 501Ci: CLAR quiral preparativa en fase normal: 28.0 min. (tiempo de retención), >95% ee (columna Chiralpak AD 4.6 x 250 mm, eluyendo con 12% MeOH/EtOH (1:1) en heptano a 1.0 mL/min.). CLAR: 99% a 3.04 y 3.17 min. (atropisómeros, tiempo de retención) (columna YMC Combiscreen ODS-A, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso durante 4 min. conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). HREM m/z CaCLulado para $C_{24}H_{23}N_2O_4$ $[M-H]^-$: 403.1658. Encontrado 403.1644. Compuesto 501Cii: CLAR quiral: 65.7 min. (tiempo de retención), >95% ee (CLAR quiral: 65.7 min.; >95% ee; columna Chiralpak AD 4.6 x 250 mm; eluyendo con 12% MeOH/EtOH (1:1) en heptano a 1.0 mL/min.). CLAR: 98% a 3.02 y 3.15 min. (atropisómeros, tiempo de retención) (columna YMC Combiscreen ODS-A, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso durante 4 min. conteniendo 0.2% ácido fosfórico, 4mL/min., observando a 220 nm). La estereoquímica absoluta de los compuestos 501Ci y 501Cii no se determinó. Por simplicidad en la nomenclatura, el compuesto 501Ci se designa en la presente como que tiene una configuración "R" y el compuesto 501Cii como que tiene una configuración "S". Los productos enantioméricamente puros derivados de los compuestos 501Ci se designan en la presente por tener una configuración "R" y los

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productos enantioméricamente puros derivados del compuesto 501Cii se designan en la presente por tener una configuración "S".

D. [3aR-(3aα,4β,7β,7aα)]-4-[4-[2-[(5-Cloro-2-piridinil)oxi]etil]octahidro-1,3-dioxo-7-propil-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo (501D)

A una solución de DBAD (17.1 mg, 0.0741 mmol) en THF (0.5 mL) se agregó PPh_3 (19.4 mg, 0.0741 mmol). Después de 10 min., se agregó 5-cloro-2-piridinol (9.6 mg, 0.074 mmol). Después de 5 min., se agregó el compuesto 501Ci (20.0 mg, 0.0494 mmol). Después de 1 h, se agregaron DBAD (17.1 mg, 0.0741 mmol), PPh_3 (19.4 mg, 0.0741 mmol), y 5-cloro-2-piridinol (9.6 mg, 0.074 mmol). Después de 3 h, el solvente se separó in vacuo para dar un residuo amarillo. La CLAR en fase preparativa inversa (columna YMC ODS, 20 x 100 mm, eluyendo con 40-100% metanol acuoso conteniendo 0.1% TFA durante 30 min., 25 mL/min., observando 220 nm) dio 9.5 mg (37%) de la sal del ácido trifluoroacético del compuesto 501D como un residuo incoloro, transparente. CLAR: 99% a 7.88 min. y 8.11 min. (atropisómeros, tiempo de retención) (Zorbax SB C18 4.6 x 75 mm, eluyendo con 10-90% metanol acuoso durante conteniendo 0.2% ácido fosfórico durante 8 min., 2.5 mL/min., observando a 220 nm). HREM m/z CaCLulado por $C_{29}H_{27}N_3O_4Cl$ $[M+H]^+$: 516.1690. Encontrado 516.1676.

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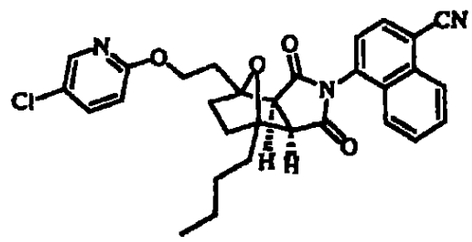
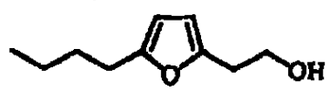
Ejemplo 502

[3aR-(3aα,4β,7β,7aα)]-4-[4-Butil-7-[2-[(5-cloro-2-piridinil)oxi]etil]octahidro-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo (502D)



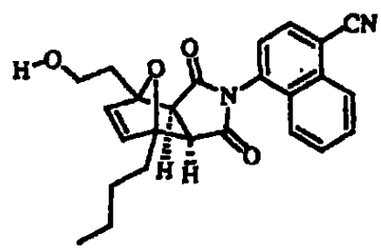
A. 2-(5-Butil-furan-2-il)-etanol (502A)



A una solución de 2-butilfurano (3.00 g, 24.2 mmol) en THF (24 mL) a -78°C, se agregó n-BuLi (11.6 mL, 2.5 M, 29.0 mmol) gota a gota durante 10 min. La reacción se calentó a temperatura ambiente y se agitó por 3.5 h. Después de enfriar a 0°C, se agregó óxido de etileno (1.81 mL, 36.2 mmol), la reacción se calentó a temperatura ambiente y se continuó la agitación por 19 h. La reacción después se enfrió hasta 0°C y se apagó con NH_4Cl sat. (20 mL), seguida por la extracción con éter de dietilo (2 x 50 mL). Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre Na_2SO_4, se filtraron, y se concentró in vacuo para dar 4.07 g (100%) del compuesto 502A como un aceite color naranja brillante. Este material se usó sin purificación adicional. CLAR: 96% a 3.23 min. (tiempo de retención) (columna YMC Combiscreen ODS-

A, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso conteniendo 0.2% ácido fosfórico durante 4 min., 4 mL/min., observando a 220 nm). EM (ES): m/z 169.22 $[M+H]^+$.

B. (3aα,4β,7β,7aα)-4-[4-Butil-1,3,3a,4,7,7a-hexahidro-7-(2-hidroxietil)-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo (502B)



Una suspensión del compuesto 502A (2.50 g, 14.9 mmol) y 4-(2,5-dihidro-2,5-dioxo-1H-1-il)-1-naftalencarbonitrilo (3.70 g, 14.9 mmol) en benceno (15 mL) se calentó hasta 60°C. Después de 3 h, la reacción se concentró in vacuo para dar una espuma café. Se agregó metanol (17 mL) y la mezcla se sonicó para dar un sólido beige fino con un sobrenadante café-naranja. La filtración del precipitado dio 2.64 g (44%) de compuesto 502B como un sólido blanco descolorido. Este material se usó sin purificación adicional. CLAR: 95% a 3.25 min. y 3.35 min. (atropisómeros, tiempo de retención) (columna YMC Combiscreen ODS-A, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso conteniendo 0.2% ácido fosfórico durante 4 min., 4 mL/min., observando a 220 nm). EM (ES): m/z 417.29 $[M+H]^+$.

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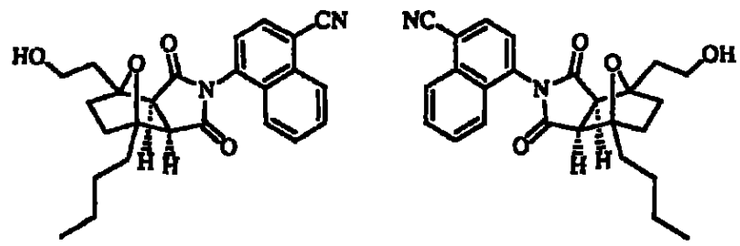
C. [3aR-(3aα,4β,7β,7aα)]-4-[4-Butiloctahidro-7-(2-hidroxietil)-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo (502Ci) y [3aS-(3aα,4β,7β,7aα)]-4-[4-Butiloctahidro-7-(2-hidroxietil)-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo (502Cii)



A una suspensión de compuesto 502C (1.47 g, 3.52 mmol) en acetato de etilo (70 mL) se agregó 10% Pd/C (0.375 g, 0.352 mmol). Se burbujeó hidrógeno a través de la reacción por varios minutos y la reacción se dejó agitar bajo una atmósfera de hidrógeno por 3 h. La reacción se filtró a través de Celite®, se enjuagó con acetato de etilo (2 x 70 mL). El filtrado se concentró in vacuo para dar una espuma blanca (1.50 g). El material crudo se disolvió en una cantidad mínima de cloruro de metileno y se cargó sobre un cartucho ISCO con 120 g gel de sílice. La elución con un gradiente por etapas de 0 hasta 100% acetato de etilo/hexano dio 1.05 g (74%) de una mezcla racémica de compuestos 502Ci y 502Cii como una espuma blanca. Una porción de 438 mg de la mezcla racémica de compuestos 502Ci y 502ii se separó por CLAR quiral preparativa en fase normal (columna Chirapak AD,

5 x 50 cm, elución isocrática con 12% MeOH/EtOH (1:1) en heptano a 50 mL/min., observando a 220 nm) para resultar 178 mg del enantiómero de elución más rápida, compuesto 502Ci como una espuma blanca y 132 mg del enantiómero de elución más lenta, compuesto 502Cii, como un aceite viscoso, transparente. Compuesto 502Ci: CLAR quiral: 25.5 min. (tiempo de retención), >95% ee (CLAR quiral: columna Chiralpak AD 4.6 x 250 mm, eluyendo con 12% MeOH/EtOH (1:1) en heptano a 1.0 mL/min.) y CLAR: 99% a 6.50 min. y 6.71 min. (atropisómeros, tiempo de retención) (columna YMC Combiscreen ODS-A, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso conteniendo 0.2% ácido fosfórico durante 4 min., 4 mL/min., observando a 220 nm) HREM m/z CaCLulado para $C_{25}H_{25}N_2O_4$ $[M-H]^-$: 417.1814. Encontrado 417.1800. Compuesto 502Cii: CLAR: 55.6 min. (tiempo de retención), >95% ee (CLAR quiral: columna Chiralpak AD 4.6 x 250 mm; eluyendo con 12% MeOH/EtOH (1:1) en heptano a 1.0 mL/min.). CLAR: 99% a 3.26 min. y 3.38 min. (atropisómeros, tiempo de retención) (columna YMC Combiscreen ODS-A, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso conteniendo 0.2% ácido fosfórico durante 4 min. 4 mL/min., observando a 220 nm). La estereoquímica absoluta de los compuestos 502Ci y 502Cii no se determinó. Por simplicidad en la nomenclatura, el compuesto 502Ci se designa en la presente como que tiene una configuración "R" y el compuesto 502Cii como que tiene una configuración "S". Los productos enantioméricamente puros

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derivados de los compuestos 502Ci se designan en la presente por tener una configuración "R" y los productos enantioméricamente puros derivados del compuesto 502Cii se designan en la presente por tener una configuración "S".

D. [3aR-(3aα,4β,7β,7aα)]-4-[4-Butil-7-2-[(5-cloro-2-piridinil)oxi]etil]octahidro-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo (502D)

A una solución de compuesto 502Ci (20.0 mg, 0.0478 mmol), PPh_3 (37.6 mg, 0.143 mmol) y 5-cloro-2-piridinol (18.6 mg, 0.143 mmol) en THF (0.5 mL) se agregó DBAD (33.0 mg, 0.143 mmol). La solución resultante se agitó a temperatura ambiente por 15.5 h. El solvente se separó in vacuo para dar un residuo amarillo. CLAR preparativa (columna Shimadzu VP ODS, 20 x 250 mm, eluyendo con 40-100% metanol acuoso conteniendo 0.1% TFA durante 30 min. y 100% por 25 min., 25 mL/min., observando a 220 nm) dio 9.4 mg (37%) de la sal del ácido trifluoroacético del compuesto 502D como un residuo transparente, incoloro. CLAR: 99% a 8.14 min. y 8.36 min. (atropisómeros, tiempo de retención) (columna Zorbax SB C18, 4.6 x 75 mm, eluyendo con 10-90% metanol acuoso conteniendo 0.2% ácido fosfórico durante 8 min., 2.5 mL/min., observando a 220 nm). HREM m/z CaCLulado para $C_{30}H_{29}N_3O_4Cl$ $[M+H]^+$: 530.1847. Encontrado 530.1855.

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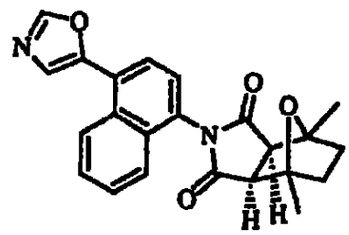
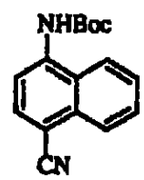
Ejemplo 503

(3aα,4β,7β,7aα)-Hexahidro-4,7-dimetil-2-[4-(5-oxazolil)-1-naftalenil]-4,7-epoxi-1H-isoindol-1,3(2H)-diona (503E)



A. Ester de tert-butilo del ácido (4-Ciano-naftalen-1-il)-carbámico (503A)



A una solución de 4-amino-1-naftalencarbonitrilo (9.67 g, 57.5 mmol) en THF (100 mL) a temperatura ambiente se agregó, durante 10 min., hexametildisilazano de sodio (1.0 M en THF, 133 mL, 133 mmol). Después de agitar por 15 min., se agregó una solución de di-t-butildicarbonato (15.1 g, 69.0 mmol) en THF (20 mL). Después de agitar por 18 h a temperatura ambiente, la mezcla de reacción se dividió entre Et_2O (400 mL) y solución saturada de bisulfato de potasio (200 mL). La capa orgánica se lavó con solución saturada de bisulfato de potasio (200 mL), solución saturada de bicarbonato de sodio (200 mL) y salmuera (100 mL). El secado sobre sulfato de magnesio anhidro, el tratamiento con carbón decolorante y la concentración in vacuo, resultó en un residuo que fue parcialmente purificado por cromatografía

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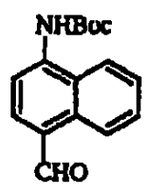
instantánea sobre gel de sílice eluyendo con 20% acetato de etilo en hexano. El material parcialmente purificado se cristalizó de acetato de etilo/hexano para dar 5.26 g de compuesto 503A como cristales incoloros. El licor madre se concentró y se cristalizó de acetato de etilo/hexano para dar 2.8 g adicionales de compuesto 503A para dar un total de 8.06 g (52%) de compuesto 503A. ^{1}H RMN (400 MHz, DEMO-d^6): δ 9.81 (s, 1H), 8.36 (d, 1H, J = 8.5 Hz), 8.11(m, 2H), 7.92 (d, 1H, J = 8 Hz), 7.78 (m, 1H), 7.67 (m, 1H), 1.53 (s, 9H).

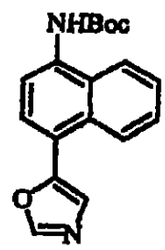
B. Éster de tert-butilo del ácido (4-Formil-naftalen-1-il)-carbámico (503B)



Una mezcla de compuesto 503A (4.02 g, 15.0 mmol), níquel Raney (1.5 g), hipofosfito de sodio (9.00 g, 86.5 mmol), piridina (50 mL), agua (25 mL) y ácido acético (25 mL) se agitó a 45°C por 5 h. La mezcla se filtró a través de Celite y la torta filtro se enjuagó con etanol caliente (100 mL). Después de agregar agua (600 mL) al filtrado y dejarlo reposar por 1 h, el precipitado resultante se filtró y se enjuagó con agua. El secado in vacuo resultó en 3.38 g de un sólido blanco que fue una mezcla 3:1 de compuestos 503B y 503A. El material se usó en la siguiente etapa sin

purificación adicional. ^{1}H RMN (400 MHz, DEMO-d^6): δ 10.28 (s, 1H), 9.77 (s, 1H), 9.27 (d, 1H, J = 8.5 Hz), 8.31 (m, 1H), 8.13 (m, 1H), 8.00 (d, 1H, J = 8 Hz), 7.80 (m, 1H), 7.70 (m, 1H), 1.54 (s, 9H).

C. Éster de tert-butilo del ácido (4-Oxazol-5-il-naftalen-1-il)-carbámico (503C)



La mezcla anterior de compuestos 503A y 503B (3.37 g, 10.0 mmol; corregida por la presencia del compuesto 503A), isocianato de toluen-sulfonilo (2.15 g, 11.0 mmol) y carbonato de potasio (1.66 g, 12.0 mmol) en 50 mL de metanol se puso a reflujo por 4 h. La mezcla de reacción se dividió entre agua (200 mL) y cloroformo (200 mL). Después de extraer la capa acuosa con cloroformo (100 mL), las capas orgánicas combinadas se secaron sobre sulfato de magnesio y se concentraron in vacuo. El residuo crudo fue purificado por cromatografía instantánea sobre gel de sílice eluyendo con un gradiente de 10-40% acetato de etilo en hexano para dar 1.35 g (44%) de compuesto 503C como un sólido blanco. ^{1}H RMN (400 MHz, DEMO-d^6): δ 9.45 (s, 1H), 8.57 (s, 1H), 8.20 (m, 2H), 7.76 (m, 2H), 7.64 (s, 1H), 7.62 (m, 2H), 1.51 (s, 9H).

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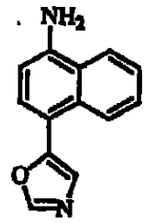
D. 4-Oxazol-5-il-naptalen-1-ilamina (503D)



El compuesto 503C (1.34 g, 4.3 mmol) se disolvió en ácido trifluoroacético (10 mL) y la mezcla resultante se dejó reposar por 1 h a temperatura ambiente. Después de eliminar los volátiles in vacuo, el residuo se co-evaporó del acetato de etilo/heptano (2 x 50 mL) para eliminar trazas de ácido trifluoroacético. Después de dividir el residuo entre acetato de etilo (100 mL) y NaOH 1N (75 mL), la capa orgánica se lavó con salmuera (50 mL), se secó sobre sulfato de magnesio y se concentró in vacuo para resultar 900 mg (99%) de compuesto 503D como un sólido amarillo cristalino. Condiciones CLAR: 95% a 0.92 min. (tiempo de retención) (columna Phenomenex de 5 micras ODS, 4.6 x 30 mm, 10%-90% metanol acuoso durante 2 min. gradiente con 0.1% TFA, observando a 254 nm.). EM (ES):m/z 211.22 $[M+H]^+$.

E. (3aα,4β,7β,7aα)-Hexahidro-4,7-dimetil-2-[4-(5-oxazolil)-1-naftalenil]-4,7-epoxi-1H-isoindol-1,3(2H)-diona (503E)

Una mezcla de compuesto 503D (42 mg, 0.020 mmol) y 20A (78 mg, 0.40 mmol) en ácido acético (1.0 mL) se puso a reflujo por 18 h. La mezcla de reacción se enfrió hasta

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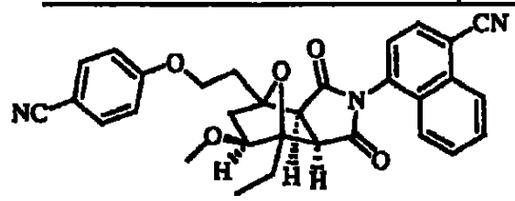
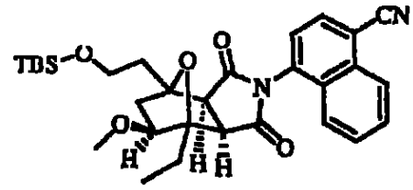
temperatura ambiente, se concentró in vacuo y el residuo se dividió entre acetato de etilo (30 mL) y solución saturada de bicarbonato de sodio (30 mL). La capa orgánica se aisló, se secó sobre sulfato de magnesio y se concentró in vacuo. La purificación por cromatografía instantánea sobre una columna de 2.5 x 15 cm de gel de sílice, usando un gradiente de 40-60% de acetato de etilo en hexano dio 28 mg (37%) de compuesto 503E, como un polvo blanco. CLAR: 99% a 1.46 min. y 1.36 min. (atropisómeros, tiempo de retención) (Phenomenex 5 micras ODS 4.6 x 30 mm, 10%-90% metanol acuoso durante 2 min. gradiente con 0.1% TFA, observando a 254 nm.). EM (ES):m/z 389.10 $[M+H]^+$.

Ejemplo 504

[3aS-[3aα,4β,5β,7β,7aα)]-4-[7-[2-(4-Cianofenoxi)etil]-4-etiloctahidro-5-metoxi-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo (504C)

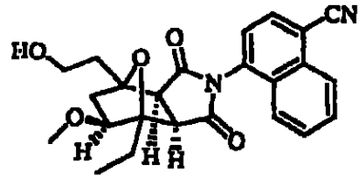


A. [3aS-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[[(1,1-Dimetiletil)dimetilsilil]oxi]etil]-4-etiloctahidro-5-metoxi-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo (504A)



A una solución de compuesto 499ii (0.235 g, 0.451 mmol) en CH_2CN (6 mL), se agregó óxido de plata (0.523 g, 2.26 mmol) y yodometano (0.56 mL, 9.0 mmol, se agitó sobre K_2CO_3 antes de la adición). La suspensión resultante se colocó en un baño de aceite precalentado (80°C). Después de 24 h, la reacción se enfrió hasta temperatura ambiente, se diluyó con CH_3CN (20 mL), se filtró a través de un tapón de Celite, y se concentró in vacuo para dar una goma café. La purificación por cromatografía instantánea sobre gel de sílice eluyend con 30% acetato de etilo/hexanos dio 0.156 g (65%) de compuesto 504A como un sólido blanco. CLAR: 95% a 4.17 min. y 4.25 min. (atropisómeros, tiempo de retención) (columna YMC CombiSreen ODS, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso conteniendo 0.2% ácido fosfórico durante 4 min., 4 mL/min., observando a 220 nm). EM (ES): m/z 521.25 $[M+H]^+$.

B. (3aα,4β,5β,7β,7aα)-4-[4-Etiloctahidro-7-(2-hidroxietil)-5-metoxi-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo (504B)



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A una solución de compuesto 504A (0.156 g, 0.292 mmol) en etanol (6 mL) se agregó HCl 1N (0.44 mL, 0.44 mmol). Después de 20 min., la reacción se enfrió hasta 0°C y se apagó con $NaHCO_3$ acuoso saturado (2 mL) para dar a una suspensión blanca. Se agregó H_2O hasta que se disolvió el sólido. La mezcla se extrajo con acetato de etilo (3 x 30 mL). Las capas orgánicas combinadas se lavaron con salmuera (20 mL), se secaron sobre Na_2SO_4, se filtraron, y se concentraron in vacuo para dar un sólido blanco. La purificación por cromatografía instantánea sobre gel de sílice eluyendo con 5% $MeOH/CH_2Cl_2$ dio 120 mg (99%) del compuesto 504A como un sólido blanco. CLAR: 98% a 5.17 y 5.44 min. (atropisómeros, tiempo de retención) (columna YMC CombiSreen ODS, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso conteniendo 0.2% ácido fosfórico durante 8 min., 2.5 mL/min., observando a 220 nm). HREM m/z CaCLulado para $C_{24}H_{24}N_2O_5$ $[M-H]^+$: 419.1607. Encontrado 419.1611.

C. [3aS-(3aα,4β,5β,7β,7aα)]-4-[7-[2-(4-Cianofenoxi)etil]-4-etiloctahidro-5-metoxi-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo (504C)

A una solución de compuesto 504B (20 mg, 0.048 mmol) en THF anhidro (0.5 mL) se agregó PPh_3 (37.0 mg, 0.143 mmol), para-cianofenol (17.0 mg, 0.143 mmol) y DBAD (32.0 mg, 0.143 mmol). Después de 30 min., la solución se concentró para dar

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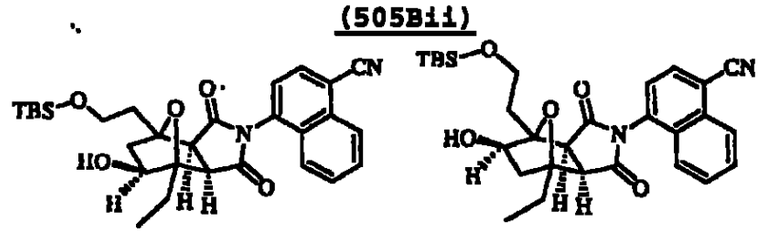
una goma café. La purificación por CLAR preparativa de fase inversa (Columna YMC S5 ODS, 20 x 250 mm, eluyendo con 10-90% metanol acuoso conteniendo 0.2% ácido fosfórico durante 35 min., 20 mL/min., observando a 220 nm) dio 16 mg (64%) de compuesto 504C como un aceite transparente, incoloro. CLAR 98% a 6.84 y 7.10 min. (atropisómeros, tiempo de retención) (columna Zorbax SB C18, 4.6 x 75 mm, eluyendo con 10-90% metanol acuoso conteniendo 0.2% ácido fosfórico durante 8 min., 2.5 mL/min., observando a 220 nm). HREM m/z CaCLulado para $C_{31}H_{27}N_3O_5$, $[M + NH_4]^+$: 539.2295. Encontrado 539.2302.

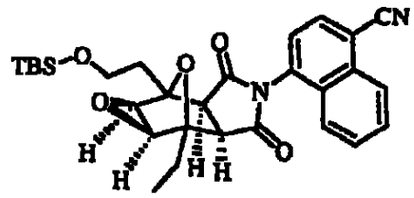
Ejemplo 505

(3aα,4β,5β,7β,7aα)-4-[7-[2-[[(1,1-Dimetiletil)dimetilsilil]oxi]etil]-4-etiloctahidro-5-hidroxi-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo (505Bi) y (3aα,4β,5β,7β,7aα)-4-[4-[2-[[(1,1-Dimetiletil)dimetilsilil]oxi]etil]-7-etiloctahidro-5-hidroxi-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo (505Bii)



998

A. (1aα,2β,2aα,5aα,6β,7aα)-4-[2-[2-[[(1,1-Dimetiletil)dimetilsilil]oxi]etil]-6-etiloctahidro-3,5-dioxo-2,6-epoxi-4H-oxireno[f]isoindol-4-il]-1-naftalencarbonitrilo (505A)



A una solución de compuesto 434B (1.01 g, 2.01 mmol) en cloruro de metileno (20 mL) se agregó 60% de m-CPBA (0.863 g, 3.00 mmol). Después de 48 h, la reacción se diluyó con cloruro de metileno (50 mL) y se lavó con Na_2SO_3 sat. (20 mL) y $NaHCO_3$ sat. (20 mL). Las capas acuosas combinadas se extrajeron con CH_2Cl_2 (20 mL). Las capas orgánicas combinadas se lavaron con salmuera (30 mL), se secaron sobre Na_2SO_4, se filtraron, y se concentraron in vacuo para dar 1.01 g (97%) de compuesto 505A como un sólido amarillo. Este material usado sin purificación adicional. CLAR: 95% a 4.22 min. (tiempo de retención) (columna Phenominex Luna C18, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso conteniendo 0.2% ácido fosfórico durante 4 min., 4 mL/min., observando a 220 nm). HREM m/z CaCLulado para $C_{29}H_{34}N_2O_5Si$ $[M-H]^+$: 517.2159. Encontrado 517.2163.

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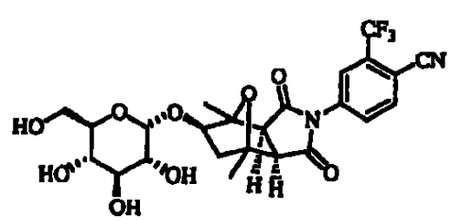
B. (3aα,4β,5β,7β,7aα)-4-[7-[2-[[(1,1-Dimetiletil)dimetilsilil]oxi]etil]-4-etiloctahidro-5-hidroxi-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo (505Bi) y (3aα,4β,5β,7β,7aα)-4-[4-[2-[[(1,1-Dimetiletil)dimetilsilil]oxi]etil]-7-etiloctahidro-5-hidroxi-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo (505Bii)

A una solución roja de bicloruro de titanoceno (0.500 g, 2.00 mmol) en THF anhidro (4.0 mL) se agregó polvo de zinc (0.392 g, 6.00 mmol). La suspensión resultante se agitó vigorosamente por 1 h bajo una atmósfera de argón para dar una suspensión verde. El zinc en exceso se eliminó por filtración a través de un microfiltro de 0.45 μm para dar una solución verde de cloruro de diciclopentadienil titanio (III). A una solución de compuesto 505A (0.207 g, 0.399 mmol) y 1,4-ciclohexadieno (0.380 mL, 4.02 mmol) en THF anhidro (1 mL) se agregó gota a gota una solución 0.5 M del cloruro de diciclopentadienil titanio (III) antes descrito (0.9 mL, 0.45 mmol). Después de 1 h, se agregó una alícuota adicional de la solución 0.5 M de cloruro de diciclopentadienil titanio (III) (0.9 mL, 0.45 mmol), y la agitación continuó por 1 h. La reacción después se apagó con agua (2 mL) y se diluyó con acetato de etilo (10 mL). Las capas se separaron y la capa orgánica se lavó con salmuera (5 mL), se secó sobre Na_2SO_4, se

filtró, y se concentró in vacuo para dar una goma amarilla. El material crudo se disolvió en una cantidad mínima de cloruro de metileno y se cargó sobre una columna ISCO de 35 g de gel de sílice. La elución con gradiente con 0-80% acetato de etilo en hexano dio 0.043 g (21%) del compuesto 505Bi como un sólido blanco y 0.023 g (11%) del compuesto 505Bii como un sólido blanco. Compuesto 505Bi: CLAR: 3.92 min. (tiempo de retención) (columna YMC CombiSreen ODS-A, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso conteniendo 0.2% ácido fosfórico durante 4 min., 4 mL/min., observando a 220 nm). EM (ES): m/z 521.36 $[M+H]^+$. Compuesto 505Bii: CLAR: 91% a 3.97 min. (tiempo de retención) (columna YMC CombiScreen ODS-A, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso conteniendo 0.2% ácido fosfórico durante 4 min., 4 mL/min., observando a 220 nm). EM (ES): m/z 521.34 $[M+H]^+$.

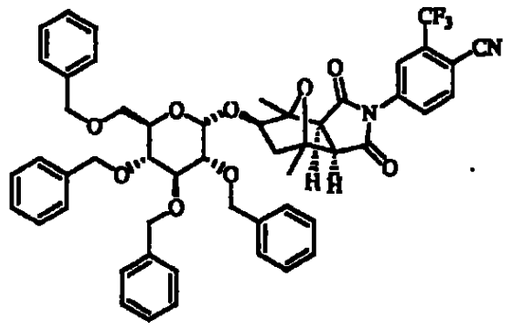
Ejemplo 506

4-[[3aS-(3aα,4β,5β,7β,7aα)]-5-(α-D-Glucopiranosiloxi)octahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2-(trifluorometil)benzonitrilo (506B)



1001

A. [3aS-(3aα,4β,5β,7β,7aα)]-4-[Octahidro-4,7-dimetil-1,3-dioxo-5-[[2,3,4,6-tetraquis-O-(fenilmetil)-α-D-glucopiranosil]oxi]-4,7-epoxi-2H-isoindol-2-il]-2-(trifluorometil)benzonitrilo (506A)



Se preparó el bromuro de 2,3,4,6-Tetra-O-bencil-α-D-glucopiranosilo, según el procedimiento de Spohr et al. Can. J. Chem. 71, 1928-42 (1993). Se agregó bromuro de oxalilo (0.48 mL, 0.95 mmol, 2 M en CH_2Cl_2) gota a gota a una solución de 2,3,4,6-tetra-O-bencil-D-glucopiranosa (412 mg, 0.763 mmol) en CH_2Cl_2 (5 mL) y DMF (0.28 mL) a temperatura ambiente bajo Ar. La mezcla de reacción se agitó por 20 min., se vació sobre una mezcla de hielo y H_2O (1:1, 30 mL) y se diluyó con CH_2Cl_2 (30 mL). Las capas se separaron y la capa orgánica se lavó con H_2O fría (2 x 30 mL) y salmuera (1 x 30 mL) y se secaron sobre $MgSO_4$. La concentración in vacuo dio el bromuro deseado como un aceite café. Este aceite se tomó en CH_2Cl_2 (2 mL) y DMF (1 mL). Se agregaron el compuesto 471Dii (100 mg, 0.763 mmol), bromuro de tetrabutilamonio (111 mg, 0.526 mmol) y mallas de 4 A (600 mg) a esta solución y la reacción se

agitó bajo Ar por 4 d. La reacción se apagó con MeOH (2 mL), se agitó por 0.5 h, se diluyó con CH_2Cl_2 (10 mL) y después se filtró a través de un embudo aglomerado de vidrio de porosidad media, enjuagando con CH_2Cl_2 (5 mL). El solvente se separó in vacuo y el residuo resultante se disolvió en CH_2Cl_2 (25 mL). La solución orgánica se lavó con $NaHCO_3$ sat. acuoso (1 x 20 mL) y H_2O (1 x 20 mL) y se secó sobre $MgSO_4$. La purificación por cromatografía instantánea sobre SiO_2 eluyendo con 50% EtOAc/hexanos dio 79 mg (33%) de 506A como un sólido blanco. CLAR: 99% a 4.56 min. (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso durante 4 min. conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 902 $[M+H]^+$.

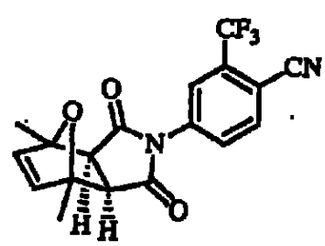
B. 4-[[3aS-(3aα,4β,5β,7β,7aα)]-5-(α-D-Glucopiranosiloxi)octahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2-(trifluorometil)benzonitrilo (506B)

Se agregó hidróxido de paladio (62 mg, 20 % peso de Pd (base seca) sobre carbón, húmedo) a una solución de 506A (65 mg, 0.07 mmol) en EtOAc (2 mL) y la mezcla se agitó bajo una atmósfera de hidrógeno, introducida por medio de un globo. Después de 5 h, la reacción estuvo completa como fue evidente por CLAR, de manera que la mezcla se filtró a través de un embudo aglomerado de vidrio de porosidad media, enjuagando con MeOH (2 mL) y se concentró in vacuo. El residuo

resultante se disolvió en MeOH (2 mL) y se filtró a través de un filtro jeringa Gelman Acrodisc CR de 13 mm con una membrana de 0.45 μM de PTFE. La concentración produjo 38 mg de 506B como un sólido blanco. CLAR: 90% a 2.16 min. (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso durante 4 mín. conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 543.20 $[M+H]^+$. Se recristalizó una porción de 10 mg de MeOH:H_2O para dar cristales apropiados para estudios de difracción de cristal por rayos X, para obtener la estereoquímica exacta del compuesto 506B como se hace referencia a la estereoquímica fija conocida del apéndice de D-glucósido.

Ejemplo 507

(3aα,4β,7β,7aα)-4-(1,3,3a,4,7,7a-Hexahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo (507)

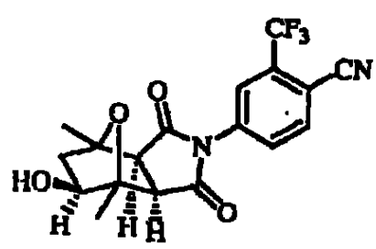


A 25 g (94.2 mmol) del compuesto 471A se agregó 2,5-dimetilfurano puro (30 mL, 280 mmol), y la suspensión espesa

resultante se calentó a 60°C por 1 hasta 3 h con agitación mecánica. La suspensión resultante se enfrió hasta 0-5 °C, y se diluyó con tolueno frío (25 mL, 0-10 °C). La suspensión fría se filtró bajo vacío. El matraz y la torta filtro se lavaron con tolueno frío (2 x 25 mL), y la torta se desprendió del licor con vacío interior. El precipitado se secó in vacuo para dar 31.3 g (91.6%) de un compuesto 507 como un sólido café claro. CLAR: 99.6%, 19.43 min. (tiempo de retención) (Columna: Zorbax™ SB-C18, 4.6 x 15 cm; Fase Móvil: 40% CH_3CN/60% H_2O w/ 0.1% v/v TFA, isocrático; Relación de flujo: 1 mL/min.; Detección: λ_{max} 210 nm; Temperatura: 30 °C; Volumen de Inyección: 5 µL).

Ejemplo 508

(3aα,4β,5β,7β,7aα)-4-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo (508)



Al THF (275 mL) que se había enfriado hasta -3 °C se agregó el compuesto 507 (55.0 g, 152 mmol), que resultó en una suspensión. Se agregó a la suspensión el metilsulfuro de

1005

borano (14.4 mL, 152 mmol), a una velocidad tal que la temperatura no superó los 0 °C. La mezcla de reacción se calentó lentamente hasta 20°C durante 2.5 h. La temperatura de la mezcla de reacción se regresó después hasta 0 °C, en donde con la solución amortiguadora de fosfato (1056 mL, pH 7) se agregó cuidadosamente a una velocidad para controlar la evolución del gas hidrógeno y mantener una temperatura de ≤20 °C. La suspensión resultante se disolvió al agregar etanol (528 mL, 190 grados). A 15°C, se agregó peróxido de hidrógeno (55 mL, 30 % peso) a una velocidad para mantener la temperatura a ≤20 °C. La solución homogénea se dejó agitando por 12 h a 20°C y un pH de 7.8, con lo que sucedió la cristalización. La suspensión espesa resultante, se recolectó por filtración y se lavó con agua (4 X 100 mL) y éter de metil-tert-butilo (2 X 100 mL). El secado in vacuo resultó en 37.3 g (64.6%) de compuesto 508. El licor madre acuoso se extrajo con acetato de etilo (3 X 500 mL). Los orgánicos ricos combinados se lavaron con sulfito de sodio acuoso al 10% en peso (1 X 100 mL), y cloruro de sodio acuoso al 25 % en peso (1 X 100 mL). Los orgánicos se secaron sobre sulfato de sodio, se filtraron, y se concentraron para recuperar 8.9 g (15.4%) de compuesto 508, y se recuperó una tercera fracción de 11.5 g (20%) del compuesto 508 del lavado de la torta de éter metil-tert-butilo. Las tres muestras sólidas anteriores de material crudo se volvieron a cristalizar por

separado a partir de etanol de 190 grados (1 g / 10 mL) para resultar un total de 35.6 g (61.7%) del compuesto 508, que tiene un nivel de pureza de 98.7% como se determina por el análisis CLAR (condiciones a continuación). Una segunda recolección del compuesto 508 se aisló del licor madre para resultar 9.3 g (16.1%) de sólido que tiene un nivel de pureza de 98.4% como se determina por análisis CLAR. El licor madre restante fue purificado por cromatografía en gel de sílice usando 200 g de SiO_2 y eluyendo con 4 L de 50 %V de acetato de etilo y 50 %V de heptano para dar 5.6 g (9.7%) del compuesto 508, que tiene un nivel de pureza de 94.0% como se determinó por análisis CLAR. Condiciones CLAR: 9.74 minutos de tiempo de retención sobre una columna YMC S5 ODS-AQ (4.6 x 150 mm) usando una elución de gradiente desde el 100% del solvente A hasta el 100% del solvente B durante 15 minutos a 1.0 mL/min. Solvente A = 95 %V agua (0.01 M NH_4OAc); 5 %V acetonitrilo. Solvente B = 5 %V agua (0.01 M NH_4OAc); 95 %V acetonitrilo. Detector de longitud de onda dual fijado a 210 y 245 nm. EM (ES): m/z 381.11 $[M+H]^+$.

Ejemplo 509

(3aα,4β,5β,7β,7aα)-4-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo (509)

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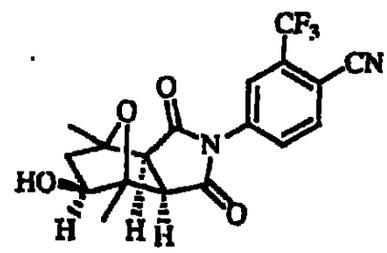
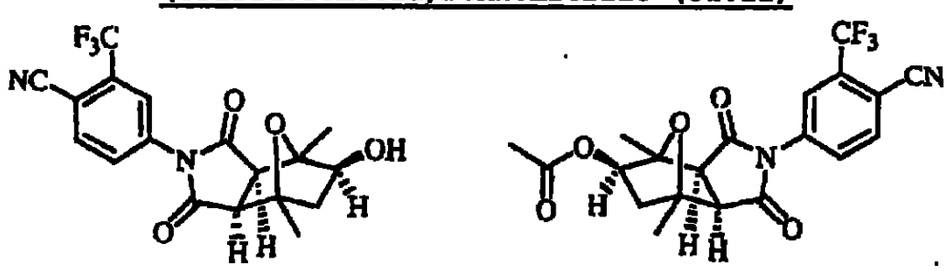


El compuesto 471A (0.37 g, 1.4 mmol) y 2,5-dimetilfurano (0.73 mL, 6.9 mmol) se combinaron para formar una suspensión que se calentó a 60°C por 1 h. La mezcla de reacción se enfrió hasta -10°C y THF (1.0 mL) se agregó seguido de la adición de borano tetrahidrofurano (2.1 mL, 1 M). La mezcla de reacción se agitó por 30 minutos a 0°C y 30 minutos a +10°C. A la mezcla de reacción se agregó acetona (3.0 mL), y la mezcla resultante se calentó hasta 20°C y se mantuvo a 20°C por 1 h. A esta solución se agregó bicarbonato de sodio (1.5 mL, pH 9, 8% peso) y la mezcla después se enfrió hasta 5°C antes de agregar peróxido de hidrógeno (0.3 mL, 30 %peso). La adición de peróxido de hidrógeno fue exotérmica llevando la temperatura hasta 20°C. Una solución de sulfito de sodio (4.0 mL, 10 %peso) se agregó a 20°C resultando en una exotermia hasta 30°C. La fase bifásica se dejó reposar a 25°C por 12 h. Después de que se separaron las fases, los desechos acuosos se extrajeron nuevamente dos veces con acetato de etilo (5 mL) y las capas orgánicas combinadas se lavaron con agua (2 mL) seguida por cloruro de sodio (2 mL, 25 %peso). Las capas orgánicas se concentraron in vacuo para dar un aceite amarillo que se cristalizó rápidamente. Al producto crudo se agregó etanol de 190 grados (5.0 mL) y la mezcla se calentó a 60°C para resultar la

disolución completa. El enfriamiento a 20°C por 17 h resultó en la cristalización. La suspensión de cristales se recolectó por filtración, se lavó con heptano (5 mL), y se secó a 60°C bajo vacío (30 pulgadas (762 mm)/Hg) para resultar 0.23 g (44 %) de compuesto 509 que tiene un 93.1 de % de área CLAR. Condiciones CLAR: 9.74 minutos de tiempo de retención en una columna YMC S5 ODS-AQ (4.6 x 150 mm) usando una elución de gradiente desde el 100% del solvente A hasta el 100% del solvente B durante 15 minutos a 1.0 mL/min. Solvente A = 95 %V agua (0.01 M NH_4OAc); 5 %V acetonitrilo. Solvente B = 5 %V agua (0.01 M NH_4OAc); 95 %V acetonitrilo. Detector fijado a 245 nm. EM (ES): m/z 381.11 $[M+H]^+$.

Ejemplo 510

[3aR-(3aα,4β,5β,7β,7aα)]-4-Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo (510i) y [3aS-(3aα,4β,5β,7β,7aα)-4-[5-(Acetiloxi)octahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2-(trifluorometil)benzonitrilo (510ii)



1009

El compuesto 509 (4 mg), acetato de vinilo (0.1 mL) y tolueno (2 mL) se combinaron y se agregaron 20 mg de cada una de las enzimas mostradas en la Tabla 12. La mezcla se agitó con una barra de agitación magnética a temperatura ambiente en un tubo cerrado de 16 x 100 mm por el periodo de tiempo enlistado en la Tabla 12. La acetilación enantioselectiva de la mezcla racémica resultó en la formación del compuesto 510i y el compuestò acetilado 510ii. La pureza enantiomérica del compuesto 510i se determinó por CLAR quiral (método a continuación) y los resultados para cada enzima son como se muestran en la Tabla 12. La información resultante se usó para preparar un lote a gran escala de los compuestos 510i y 510ii como se describe a continuación.

Tabla 12

Enzima	Proveedor	Fuente	Tiempo	Comp. 510i	Comp. 510i	Comp. 510i	Comp. 510ii
			H	Mg/mL	% rendimiento	% ee	Mg/mL
AK-20	Amano	*Pseudomonas fluorescens*	15	0.74	39	100	1.02
AP-12	Amano	*Aspergillus niger*	144	1.10	58	55.4	0.74
PS-30	Amano	*Pseudomonas cepacia*	15	0.46	24	100	1.24
Acilasa 30000	Amano	*Aspergillus*	15	0.51	27	12.2	1.26
Quirazima L3	Boehringer	*Candida rugosa*	144	0.81	42	87.2	1.04
Lipasa tipo VII	Sigma	*Candida rugosa*	144	0.74	39	100	1.06

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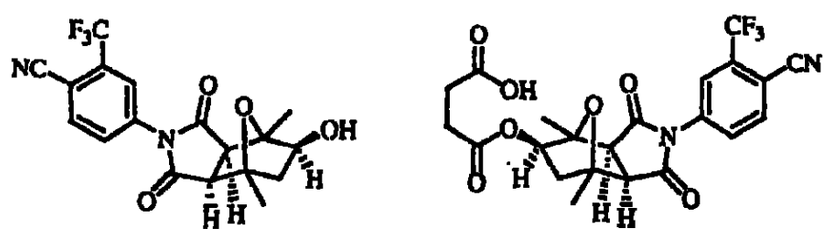
Se agregaron a un matraz enchaquetado de 500 mL la lipasa de Amano AK20 de *Pseudomonas fluorescens* (25 g), compuesto 509 (25 g), metil-isobutil-cetona (475 mL) y acetato de vinilo (25 mL). El matraz se mantuvo a 25°C con un baño de agua en circulación y se agitó con una barra de agitación magnética. La incubación se continuó por 42 h, punto en el cual el exceso enantiomérico del compuesto 510i aCLanzó 100%. La solución se filtró a través de papel filtro Whatman 4 para eliminar la enzima, y se lavó la torta filtro con 50 mL de metil isobutil cetona. El filtrado se concentró in vacuo y el residuo resultante se disolvió en EtOAc (50 mL) seguido por la adición de heptano (50 mL). Esta solución se cargó sobre una columna de cartucho Phenomenex (sílice 800 g) en un sistema Biotage 75L y se eluyó la columna con 75% EtOAc/heptano a una relación de flujo de 110 mL/min. Las fracciones se recolectaron (500 mL) que contenían al compuesto 510ii y después se cambió el solvente de elución a 100% de EtOAc para eluir completamente el compuesto 510i. Las fracciones deseadas se acumularon y se eliminó el solvente in vacuo para producir 11.0 g del compuesto 510i, (44%, 100%ee) y 12.10 g de compuesto 510ii (44%). El compuesto 510i se volvió a cristalizar a partir de 95% EtOH (5 mL/g) en dos recolecciones para resultar 9.61 g (38%) de compuesto 510i como un sólido cristalino blanco. Los compuestos 510i: CLAR quiral: 10.02 min. (tiempo de retención) (columna CHIRALPAK

AD 4.6 x 250 mm; elución isocrática con 20% MeOH/EtOH (1:1) en heptano a 1 mL/min.). CLAR: 99% a 2.45 min. (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso durante 4 min. conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 381.11 $[M+H]^+$.

Ejemplo 511

[3aR-(3aα,4β,5β,7β,7aα)]-4-[Octahidro-5-hidroxi-4,7-dimetil-1,3,dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo (511i) y mono[3aS-(3aα,4β,5β,7β,7aα)]-[2-[4-ciano-3-(trifluorometilfeniloctahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-1H-isoindol-5-il]éster del ácido butanodioico - (511ii)



Una mezcla del compuesto racémico 509 (10 mg), anhidrido succínico (100 mg) y lipasa AK-20 de Amano (50 mg) en tolueno o MTBE (5 mL), se agitó a temperatura ambiente por 20 horas. Después de 16 y 20 h, se tomaron muestras (0.1 mL) de cada mezcla de reacción, se evaporaron, se redisolvieron en acetonitrilo (1 mL) y se analizaron por CLAR de fase inversa

(YMC Pro-pack ODS-A, 3(, 15 X 0.6 cm, acetonitrilo:agua 20:80 hasta 90:10 en 12 min.) para determinar la relación de área de los productos del compuesto 511i (RT = 8.8 min.) y compuesto 511ii (RT = 9.9 min.). Se separó una segunda muestra (0.1 mL) de cada mezcla de reacción, se evaporó y se redisolvió en 1 mL de aCLohol isopropílico-heptano (1:1) y se analizó por CLAR quiral (Chiralpak AD, 25 X 0.46 cm, 20 °C, heptano:etanol 85:15, 0.5 mL/min., UV 210 nm) para determinar el % ee del compuesto 511i (TR = 32.2 min) y compuesto 471Dii (TR = 34.8 min.). Después de 20 h, las mezclas de reacción se filtraron completamente para separar los componentes insolubles (enzima, etc.). Los filtrados se lavaron con $NaHCO_3$ acuoso al 5% (3 X 1 volumen) y agua (3 X 1 volumen), se evaporaron in vacuo y se analizaron por CLAR como se describió arriba. Los resultados mostraron un rendimiento promedio de 48% (el rendimiento máximo teórico es del 50%) y 100% ee para el compuesto 511i. La separación completa del compuesto 511ii se logra por medio de la extracción con $NaHCO_3$ antes descrita. La Tabla 13 proporciona los detalles de cada reacción como se determina por los métodos antes descritos Compuesto 511i: CLAR quiral: 10.02 min.; columna CHIRALPAK AD 4.6 x 250 mm; elución isocrática con 20% MeOH/EtOH (1:1) en heptano a 1 mL/min., 100% ee. CLAR: 99% a 2.45 min. (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso durante 4 min.

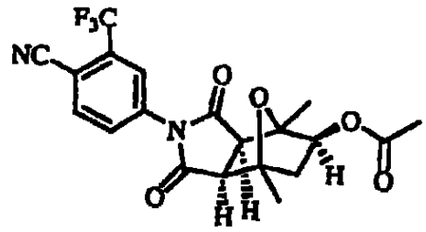
conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 381.11 $[M+H]^+$.

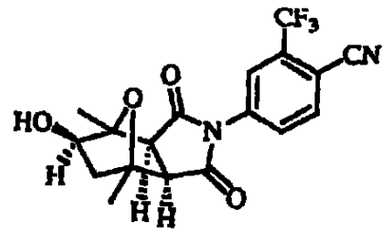
Tabla 13.

Solvente	Solvente	Comp. 509	Lipasa AK-20	Anhidrido succínico	Tiempo	Comp. 511i	Comp. 511ii	Comp. 511i	Comp. 471ii	Comp. 511i
	Vol., ml	mg	mg	mg	Hr	8.8 min	9.9 min	32.2 min	34.8 min	cc%
						Relación de Area	Relación de Area	%	%	
Tolueno	5	10	50	100	16	53%	47%	93.1%	6.9%	86.2%
					20	54%	46%	96.0%	4.0%	92.0%
Tolueno lavado con NaHCO3						100%	0%	96.1%	3.9%	92.2%
MTBE	5	10	50	100	16	49%	51%	100.0%	0.0%	100.0%
					20	50%	50%	100.0%	0.0%	100.0%
MTBE lavado con NaHCO3						100%	0%	100.0%	0.0%	100.0%

Ejemplo 512

[3aR-(3aα,4β,5β,7β,7aα)-4-[5-(Acetiloxi)octahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2-(trifluorometil)benzonitrilo (512i) y [3aS-(3aα,4β,5β,7β,7aα)]-4-[Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo (512ii)





Se configuraron una serie de matraces de 50 mL y se pesaron las enzimas (ver Tabla 14 por tipo de enzima y cantidades) dentro de cada uno seguido por la adición de solución amortiguadora de fosfato (BF45, 5 mL, 100 mM, pH 7). Una solución de compuesto 473 (5 mg) en DEMO (50 µL) se agregó a cada matraz. Los matraces se agitaron a 200 rpm a 28 °C por 24 horas. Después de 24 horas, las mezclas de reacción se extrajeron con EtOAc (10 mL). Se evaporó una porción del extracto de EtOAc (1 mL), se volvió a disolver en acetonitrilo (1 mL) y se analizó por CLAR de fase inversa (C-18, acetonitrilo:agua 20:80 hasta 90:10 en 12 min.) para determinar la relación de área del compuesto 512i (TR = 11.0 min) y compuesto 512ii, (TR = 8.9 min.). Se evaporó otra porción del extracto de EtOAc (4 mL) se volvió a disolver en 1 mL de aCLohol isopropílico-heptano (1:1) y se analizó por CLAR quiral (Chiralpak AD, heptano:etanol 85:15, 0.5 mL/min) para determinar el % ee del compuesto 512ii (RT = 34.8 min.) y compuesto 471Di (TR = 32.2 min.) en este sistema. La Tabla 14 proporciona detalles para una configuración de enzimas diferentes examinadas y los rendimientos resultantes y el % ee de los productos deseados.

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Tabla 14.

Enzima	Proveedor	Fuente	Cant de Enz	Relación del área por CLAR		Exo-ACLohol	Exo-ACLohol	% ee de
			mg	Comp. 512ii	Comp. 512i	Comp. 471Di	Comp. 511ii	Comp. 512i
Lipasa AP-12	Amano	Aspergillus niger	5	18%	82%	18.8%	81.2%	62.5%
Lipasa AP-12	Amano	Aspergillus niger	25	50%	50%	41.0%	59.0%	17.9%
Lipasa PS	Amano	Pseudomonas cepacia	5	20%	80%	31.3%	68.7%	37.4%
Lipasa PS	Amano	Pseudomonas cepacia	25	46%	54%	40.2%	59.8%	19.6%
Acilasa 150000	Amano	Especie Aspergillus	5	30%	70%	52.0%	48.0%	-3.9%
Acilasa 150001	Amano	Especie Aspergillus	25	71%	29%	50.4%	49.6%	-0.8%
Newlasa F	Amano	Rhizopus niveus	50	3%	97%	31.3%	68.7%	37.5%
Newlasa F	Amano	Rhizopus niveus	100	3%	97%	25.7%	74.3%	48.5%
Acilasa I	Sigma	Aspergillus melleus	5	10%	90%	9.7%	90.3%	80.6%
Acilasa I	Sigma	Aspergillus melleus	25	38%	62%	10.9%	89.1%	78.3%
Esterasa	Sigma	Hígado de porcino	5	76%	24%	36.0%	64.0%	27.9%

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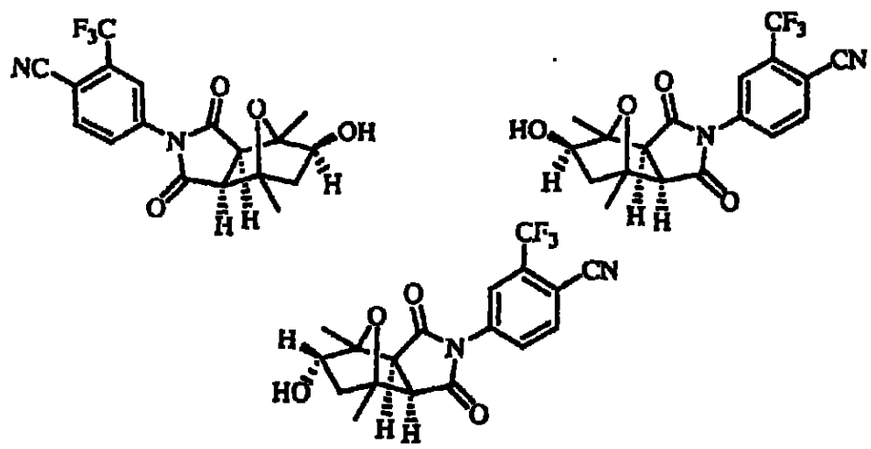
Ejemplo 513

[3aR-(3aα,4β,5β,7β,7aα)]-4-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo (513i) y [3aS-(3aα,4β,5β,7β,7aα)]-4-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-trifluorometil)benzonitrilo y (513ii) y (3aα,4β,5α,7β,7aα)-4-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo (513iii)



Se establecieron una serie de reacciones de biotransformación microbiana para generar los compuestos 513i, 513ii y 513iii. Los detalles de las reacciones para los diversos microorganismos se muestran en la Tabla 15, y se describe un procedimiento general a continuación. Se inoculó un vial deshielado del microbio (1 mL de cultivo) en un medio estéril de soya-glucosa (10 mL) en un matraz de 50 mL. Los

microbios se hicieron crecer por agitación a 200 rpm a 28°C por 40 h. Se agregó una solución de compuesto 472 (10 mg en 100 µL de DEMO) a cada matraz y los matraces se agitaron a 200 rpm a 28°C. A las 24 y 48 h, se extrajeron 5 mL de las mezclas de reacción por EtOAc (10 mL). Se evaporó una porción de extracto de EtOAc (1 mL), se volvió a disolver en acetonitrilo (1 mL) y se analizó por CLAR de fase inversa (C-18, acetonitrilo: agua 20:80 hasta 90:10 en 12 min.) para determinar la relación de área del compuesto 472 (RT = 11.2 min.) y los compuestos producto 513i (RT = 8.9 min.), 513ii (RT = 8.9 min.) y 513iii (RT = 9.6 min.). Se evaporó una segunda porción del extracto de EtOAc (4 mL), se volvió a disolver en aCLohol de isopropilo-heptano (1:1, 1 mL) y se analizó por CLAR quiral (Chiralpak AD, Heptano:Etanol 85:15, 0.5 mL/min.) para determinar el % ee de los compuestos 513i (RT = 32.2 min.) compuesto 513ii (RT = 34.8 min.) en este sistema.

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Tabla 15.

Microorganismo	ID	Tiempo	Análisis por fase inversa CLAR (relación de área)			Análisis de % ee por CLAR		% ee de
		Hrs	Comp. 513i	Comp.513ii	Comp. 472	Comp.513i	Comp. 513ii	Comp. 513i
Especie Streptomyces	SC1754	24	7%	0%	93%	96.9%	3.1%	93.9%
		48	12%	0%	88%	96.7%	3.3%	93.3%
Especie Streptomyces	SC3740	24	1%	0%	99%	88.0%	12.0%	76.0%
		48	2%	0%	98%	85.8%	14.2%	71.7%
Nocardia interforma	ATCC 21072	24	5%	0%	95%	93.2%	6.8%	86.3%
		48	8%	0%	92%	92.6%	7.4%	85.1%
Streptomyces antibioticus	ATCC 14890	24	11%	1%	88%	95.7%	4.3%	91.4%
		48	48%	13%	39%	94.1%	5.9%	88.2%
Streptomyces mediocidicus	ATCC 13278	24	1%	0%	99%	82.0%	18.0%	64.1%
		48	7%	0%	93%	79.4%	20.6%	58.8%
Streptomyces griseus	NRRL B8090	24	23%	0%	77%	85.0%	15.0%	70.0%
		48	28%	0%	72%	85.9%	14.1%	71.8%
Amycolatopsis orientalis	ATCC 43490	24	12%	1%	86%	81.3%	18.7%	62.5%
		48	25%	4%	71%	77.4%	22.6%	54.9%

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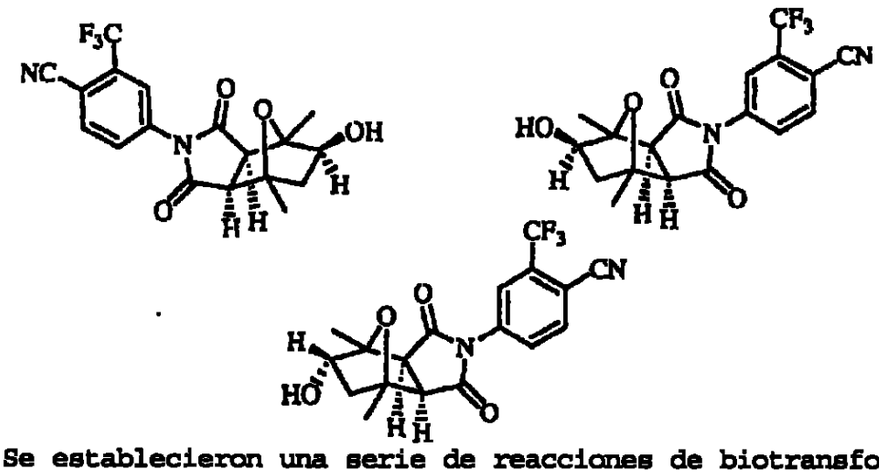
Ejemplo 514

[3aR-(3aα,4β,5β,7β,7aα)]-4-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo (514i) y [3aS-(3aα,4β,5β,7β,7aα)]-4-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo y (514ii) y (3aα,4β,5α,7β,7aα)-4-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo (514iii)



Se establecieron una serie de reacciones de biotransformación microbiana, para generar los compuestos 514i, 514ii y 514iii. Los detalles de las reacciones para los diversos microorganismos se muestran en la Tabla 16 y se describe a continuación un procedimiento general. Se usó un cultivo de 1 mL de *Streptomyces griseus* SC13971 de un vial congelado, para inocular 100 mL de medio (0.5% de nutrisoya tostada, 2% glucosa, 0.5% extracto de levadura, 0.5% K_2HPO_4, 0.5% NaCl, ajustado a un pH de 7 con HCl 1N

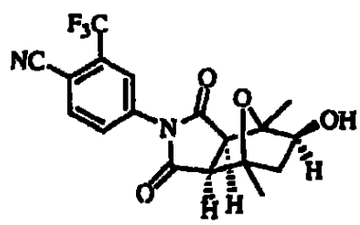
(R. V. Smith y J. P. Rosazza, Arch. Biochem. Biophys., 161, 551-558 (1974)) en un matraz de 500 mL Erlenmeyer, y el matraz se incubó a 28°C a 200 rpm por 3 días. Se usaron 10 mL de este cultivo, para inocular 100 mL de medio (como arriba) en un matraz de 500 mL Erlenmeyer, y el matraz se incubó a 28°C a 200 rpm por 1 día. Para los hongos filamentosos *Mucor rouxii* y *Cunninghamella echinulata*, se usó 1 mL de suspensión de esporas, preparada al lavar una superficie de agar en plano inclinado con 10 mL agua, para inocular 100 mL de medio (como arriba) en un matraz de 500 mL Erlenmeyer, y el matraz se incubó a 28°C a 200 rpm por 1 día. Se agregó el compuesto 472 (30 mg en 1 mL de metanol) a cada cultivo y las incubaciones continuaron por 6 hasta 10 días. Se separaron muestras de 10 mL del caldo de cultivo en cada matraz, y se extrajeron con acetato de etilo (20 mL). Muestras de 10 mL de la capa orgánica, se evaporaron individualmente hasta sequedad a 40 °C bajo una corriente de nitrógeno. Los residuos se disolvieron en 1.2 mL de isopropanol y se analizaron por CLAR de fase inversa (YMC Pak ODS 150 x 6 mm, 3 μ C-18, acetonitrilo: agua 20:80 hasta 90:10 en 12 min., 1 mL/min., 40 °C) para determinar la concentración de compuesto 472 (RT = 11.2 min.) y los compuestos producto 514i (RT = 8 9 min.), 514ii (RT = 8.9 min.) y 514iii (RT = 9.6 min.). Las mismas muestras se analizaron por CLAR quiral (Chiralpak AD. heptano:etanol 85:15, 0.5 mL/min.) para determinar el % ee de compuestos 514i (RT = 32.2 min.) compuesto 514ii (TR = 34.8 min.) en este sistema.

Tabla 16.

Cepa	SC	ATCC	Tiempo	Comp.472	Comp.514i	Comp.514i	Comp.514iii
			días	mg/ml	mg/ml	ee %	mg/ml
1.Mucor rouxii	13920	24905	3	0.30	0.01	100.00	0.000
			6	0.27	0.01	100.00	0.000
2.Streptomyces griseus	13971	13273	3	0.29	0.01	100.00	0.000
			6	0.30	0.01	100.00	0.000
3.Cunninghamella echinulata	16027	9244	3	0.34	0.02	100.00	0.002
			6	0.06	0.02	100.00	0.001
			10	0.16	0.02	100.00	0.001

Ejemplo 515

[3aR-(3aα,4β,5β,7β,7aα)]-4-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo (515)



Se llevó a cabo la transformación microbiana del compuesto 472 al compuesto 515 en una escala de 3 L en un fermentador de 5 L, usando *Cunninghamella echinulata* SC 16027 (ATCC 9244) y un medio que consistió de lo siguiente: 0.5% de nutrisoya tostada, 2% glucosa, 0.5% extracto de levadura, 0.5% K_2HPO_4, 0.5% NaCl, ajustado a un pH de 7 con HCl 1N (R. V. Smith y J. P. Rosazza, Arch. Biochem. Biophys., 161, 551-558 (1974)). El fermentador se formó en lotes con 0.05% de antiespuma SAG antes de la esterilización. Se preparó el

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inóculo de esporas para lavar las esporas desde un cultivo en superficie de agar de plano inclinado de 10 días, de *Cunninghamella echinulata* SC 16027 (ATCC 9244) con 0.9% de solución salina/0.1% de Tween 80. La etapa del inóculo se preparó al agregar 1 mL de inóculo de esporas dentro de 100 mL del medio en un matraz de 500 mL, después se hicieron crecer los cultivos a 28°C a 200 rpm por 1 día. Se mezcló 10% del inóculo del matraz en un mezclador estéril Waring y se usó para inocular el fermentador estéril, conteniendo 3 L de medio estéril. El fermentador se corrió a 28°C a 600 rpm y 1 vvm de aereación. Se agregó una solución estéril de tres antibióticos al fermentador después de la inoculación; 12 mg de cloruro de tetraciclina, 12 mg de sulfato de canamicina, y 60 mg de hidrato de cefalexina en 10 mL de agua desionizada. Después de 22 horas de crecimiento en el fermentador, se agregó una solución de un substrato estéril conteniendo 0.75 g de compuesto 472 disuelto en 30 mL de metanol, esta etapa se repitió dos horas después para un total de 0.5 g/L de compuesto 472 en la bioconversión. Las condiciones de fermentación se mantuvieron a 28°C a 600 rpm y 1 vvm de aereación. Se mantuvo un pH de 6.5 por la adición automática de 10% de H_2SO_4 o 10% de NaOH. Periódicamente, se tomaron muestras asépticas de 10 mL, y se extrajeron con dos porciones de 10 mL de acetato de etilo. La capa de acetato de etilo se aisló, se secó bajo una corriente de nitrógeno a

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40°C, y el residuo se disolvió en 2.0 mL de aCLohol isopropílico. Las muestras se analizaron por CLAR de fase inversa (método a continuación) para determinar la relación de compuesto 472 y del compuesto producto 515. Además, se analizó cada muestra por CLAR quiral (método a continuación) con objeto de determinar el % ee del compuesto 515. Durante el proceso de bioconversión, se alimentó una solución estéril de 30% de cerelosa y 1.5% de extracto de levadura a la reacción a ~5 mL /hora. Después de 114 h desde el momento de la adición del substrato, el análisis por fase inversa de CLAR, indicó la producción de un rendimiento del 78% de compuesto 515. El análisis CLAR quiral medido como el % e.e. de compuesto 515 a 94.9%. El proceso anterior se repitió en otra bioconversión de 3L, y la reacción se llevó a cabo a 28°C a 600 rpm, 1 vvm de aereación, con 0.5 g/L de entrada del compuesto 472. Después de 44 h, esta reacción dio un rendimiento del 80% de compuesto 515 con 95% e.e. El caldo se filtró a través de una almohadilla HyFlo™ para proporcionar un caldo de fermentación clarificado. El compuesto 515 se adsorbió completamente sobre 55 g de XAD-16 y se extrajo nuevamente en una mezcla 1:1 de EtOAc y acetona (3 X 100 mL) o éter de metil-tert-butilo (3 X 100 mL). El solvente se separó in vacuo y el residuo resultante fue purificado por una almohadilla de sílice (5 g), eluyendo con EtOAc. Las fracciones deseadas se recolectaron y trataron con carbón

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activado (0.5 g) para decolorar la solución y el solvente se eliminó in vacuo para producir 1.27 g de compuesto 515. La re-cristalización de este material de EtOAc/heptano (10 mL/20 mL) resultó en 950 mg de compuesto cristalino 515 que tiene un 97% de pureza por CLAR de fase inversa y 95% ee por CLAR quiral. CLAR de Fase Inversa: columna YMC Pak ODS-A C18, 4.6 x 50 mm, eluyendo con un gradiente de: 0 min. 20% acetonitrilo/80% 0.1% TFA en agua, 12 min. 90% acetonitrilo/10% 0.1% TFA en agua, 12.01-15 min. 20% acetonitrilo/80% 0.1% TFA en agua, observando a 250 nm, 40°C. 5 µL volumen de inyección). Compuesto 515: RT = 8.86 min. CLAR quiral: columna CHIRALPAK OD 25 x 0.46 cm; elución isocrática con 15% etanol/85% heptano a 0.5 mL/min., 18°C, observando a 220 nm, volumen de inyección: 20 µL. Compuesto 515: TR = 36.5 min.

En un proceso de recuperación alterno, el caldo de fermentación (1L) de la reacción de biohidroxilación anterior, se filtró y la torta de las células se lavó con 100 mL de agua. Se extrajo un caldo transparente con acetato de etilo (2 X 600 mL) y la torta de las células se extrajo con 400 mL de acetato de etilo. Las capas combinadas de acetato de etilo se concentraron y el residuo resultante se disolvió en 5 mL de 1:1 heptano/acetato de etilo y se cargó en una almohadilla de gel de sílice (70 g en 250 mL de filtro aglomerado de vidrio).

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La almohadilla de gel de sílice se eluyó con un gradiente de 80 hasta 90% EtOAc/heptano. Las fracciones se recolectaron y se acumularon las fracciones que contenien el compuesto 515. El solvente se separó in vacuo y se cristalizó el producto resultante a partir de EtOAc/heptano para dar un rendimiento del 90% de compuesto 515 con 98% de pureza por CLAR de fase inversa y 95% ee por CLAR quiral. CLAR de Fase Inversa: columna YMC Pak ODS-A C18, 4.6 x 50 mm, eluyendo con un gradiente de: 0 min. 20% acetonitrilo/80% 0.1% TFA en agua, 12 min. 90% acetonitrilo/10% 0.1% TFA en agua, 12.01-15 min. 20% acetonitrilo/80% 0.1% TFA en agua, observando a 250 nm, 40°C, 5 µL volumen de inyección). Compuesto 472: RT = 11.12 min. Compuesto 515: TR = 8.86 min. CLAR quiral: columna CHIRALPAK OD 25x0.46 cm; elución isocrática con 15% etanol/85% heptano a 0.5 mL/min., 18°C, observando a 220 nm, volumen de inyección: 20 µL. Compuesto 472: TR = 27.4 min. Compuesto 515: TR = 36.5 min. Compuesto (514iii) TR = 39.1 min.

Ejemplo 516

4-(2,5-Dioxo-2,5-dihidro-pirrol-1-il)-2-trifluorometilbenzonitrilo (516B)

El siguiente ejemplo demuestra la preparación de un intermediario útil para la preparación de los compuestos de la fórmula I de la presente invención.

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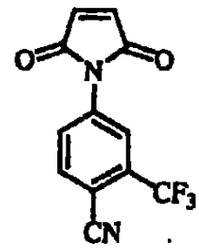
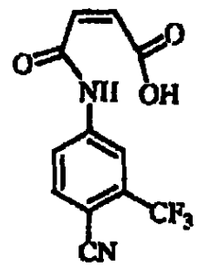


A. Ácido 3-(4-Ciano-3-trifluorometilfeni(Larbamoil)acrílico (516A)



5-amino-2-cianobenzotrifluoruro (210.6 mmoles; 40.00 g) y acetato de butilo (80 mL) se agregaron a un matraz de fondo redondo de 250 mL, seguido por la adición de anhidrido maleico (231.9 mmoles, 23.20 g). La suspensión resultante se calentó a 60°C por 3.5 h. La mezcla de reacción se enfrió hasta 25°C y después se agregó heptano (160 mL) gota a gota durante un periodo de 25 minutos. La suspensión resultante se filtró y se lavó con una mezcla de 4:1, heptano:acetato de butilo (30 mL) y heptano (45 mL). La torta se secó in vacuo para dar 60 g (95% rendimiento) de compuesto 516A.

B. 4-(2,5-Dioxo-2,5-dihidro-pirrol-1-il)-2-trifluorometil-benzonitrilo (516B)

El compuesto 516A (17.42 mmoles, 5.000 g) se agregó

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al matraz de reacción seguido por la adición de bromuro de zinc (17.58 mmoles, 3.960 g) y después se agregó tolueno (50.00 mL, 43.25 g) a la mezcla. La suspensión resultante se agitó por 20 min. Se agregó hexametildisilazano (26.35 mmoles, 5.560 mL, 4.253 g) a esta suspensión que después se calentó a 60°C por 4.5 h. La mezcla de reacción se diluyó con EtOAc (25 mL) y después se vació en una solución de HCl 1N (30 mL) a 25°C. La fase orgánica se recolectó y la fase acuosa se extrajo con EtOAc (15 mL). La fase orgánica se aisló, se combinó con la fase orgánica previa y se lavó consecutivamente con $NaHCO_3$ saturado (15 mL). Una mezcla 1:1 de agua: solución de salmuera (15 mL) y salmuera (15 mL). La solución resultante se secó sobre $MgSO_4$, se filtró y se concentró in vacuo hasta una suspensión de 50 mL. Se agregó heptano (125 mL) gota a gota a esta suspensión con agitación. La suspensión espesa resultante se filtró y se lavó con una mezcla de 2:1 heptano:tolueno (15 mL) y después heptano (15 mL) para dar 4 g (85% rendimiento) de compuesto 516B. CLAR: 100% a 2.11 min. (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, eluyendo con 10-90% metanol acuoso durante 4 min. conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm).

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Ejemplos 517 al 746

Los compuestos adicionales de la presente invención se prepararon por procedimientos análogos a aquellos antes descritos. Los compuestos de los Ejemplos 517 al 746 tienen las estructuras que se muestran en la siguiente Tabla 17.

La Tabla 17 también proporciona el nombre del compuesto, tiempo de retención/masa molecular, y el procedimiento empleado para la preparación de estos compuestos. Las técnicas de cromatografía usadas para determinar los tiempos de retención de los compuestos de la Tabla 17 son como siguen: CL y CLEM se describieron en los Ejemplos 439 al 454 (Tabla 9). La masa molecular de los compuestos enlistados en la Tabla 17, en donde se proporcionan, se determinaron por EM (ES) por la fórmula m/z.

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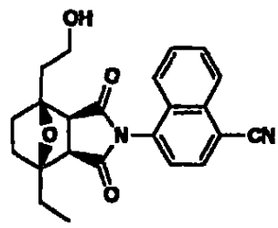
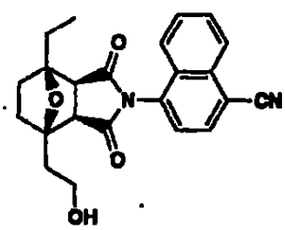
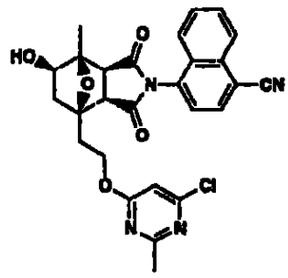
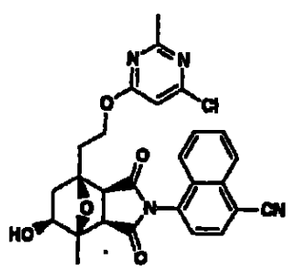
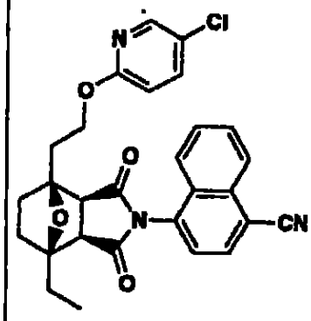
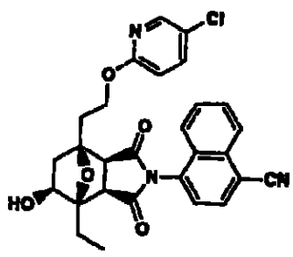
EJ. No.	Estructura del compuesto	Nombre del compuesto	Tiempo de retención Min./Masa molecular	Pro del Ej.
517		[3aR-(3aα,4β,7β,7aα)]-4-[4-Etiloctahidro-7-(2-hidroxietil)-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	2.84 CL $[M+H]^+$= 391.16	245 y 461
518		[3aS-(3aα,4β,7β,7aα)]-4-[4-Etiloctahidro-7-(2-hidroxietil)-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	2.84 CL $[M+H]^+$= 391.16	245 y 461

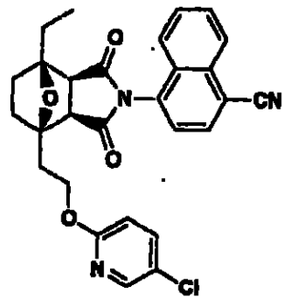
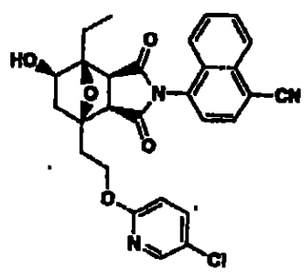
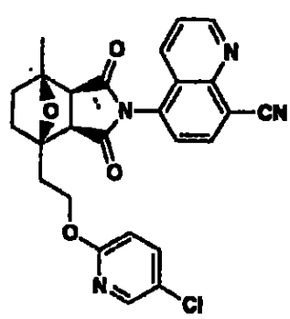
1030

519		[3aS-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[(6-Cloro-2-metil-4-pirimidinil)oxi]etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.04 CL $[M+H]^+$= 519.0	243 y 244
520		[3aR-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[(6-Cloro-2-metil-4-pirimidinil)oxi]etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.04 CL $[M+H]^+$= 519.0	243 y 244

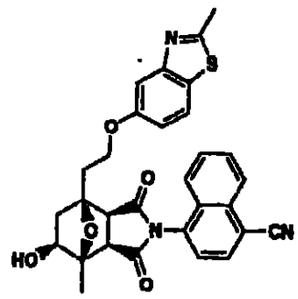
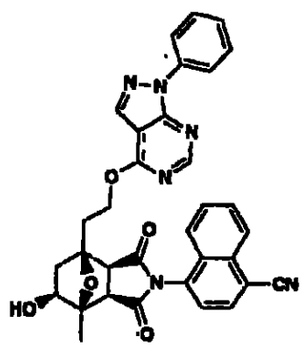
1031

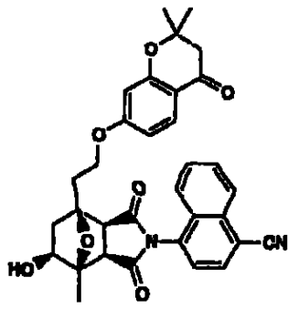
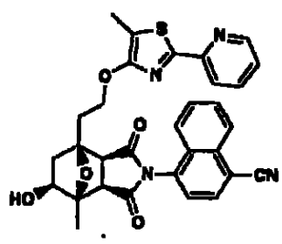
521		[3aR-(3aα,4β,7β,7aα)]-4-[4-[2-[(5-Cloro-2-piridinil)oxi]etil]-7-etiloctahidro-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.90 CL $[M+H]^+$= 502.28	245 y 461
522		[3aR-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[(5-Cloro-2-piridinil)oxi]etil]-4-etiloctahidro-5-hidroxi-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.37 CL $[M+H]^+$= 518.28	435, 499 y 500

1032

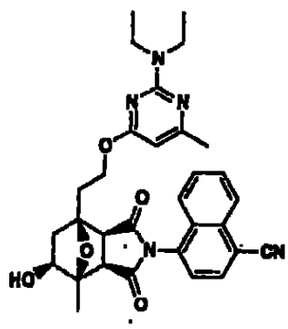
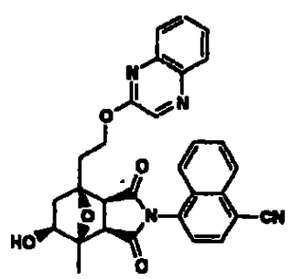
523		[3aS-(3aα,4β,7β,7aα)]-4-[4-[2-[(5-Cloro-2-piridinil)oxi]etil]-7-etiloctahidro-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.90 CL $[M+H]^+$= 502.27	245 y 461
524		[3aS-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[(5-Cloro-2-piridinil)oxi]etil]-4-etiloctahidro-5-hidroxi-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.40 CL $[M+H]^+$= 518.27	435, 499 y 500
525		(3aα,4β,7β,7aα)]-5-[4-[2-[(5-cloro-2-piridinil)oxi]etil]octa hidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-8-quinolincarbonitrilo	3.32 CL $[M+H]^+$= 489.26	467

1033

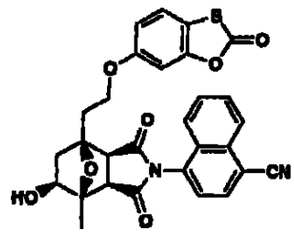
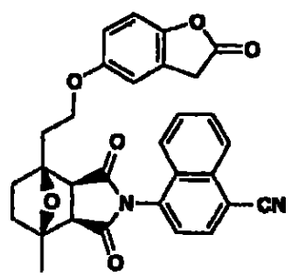
526		[3aR-(3aα,4β,5β,7β,7aα)]-4-[Octahidro-5-hidroxi-4-metil-7-[2-[(2-metil-5-benzotiazolil)oxi]etil]-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.36 CL $[M+H]^+$= 540.0	243 y 244
527		[3aR-(3aα,4β,5β,7β,7aα)]-4-[Octahidro-5-hidroxi-4-metil-1,3-dioxo-7-[2-[(1-fenil-1H-pirazolo[3,4-d]pirimidin-4-il)oxi]etil]-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.35 CL $[M+OAc]^-$= 644.8	243 y 244

528		[3aR-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[(3,4-Dihidro-2,2-dimetil-4-oxo-2H-1-benzopiran-7-il)oxi]etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.37 CL [M+OAc]$^-$= 391.16	243 y 244
529		[3aR-(3aα,4β,5β,7β,7aα)]-4-[Octahidro-5-hidroxi-4-metil-7-[2-[[5-metil-2-(2-piridinil)-4-tiazolil]oxi]etil]-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.47 CL [M+H]$^+$= 566.9	243 y 244

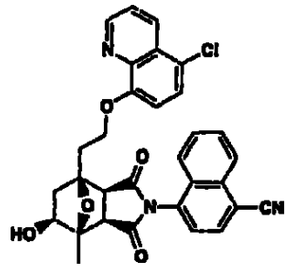
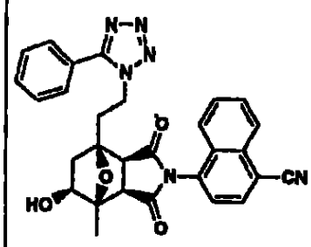
1035

530		[3aR-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[[2-(Dietilamino)-6-metil-4-pirimidinil]oxi]etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.47 CL $[M+H]^+$= 556.1	243 y 244
531		[3aR-(3aα,4β,5β,7β,7aα)]-4-[Octahidro-5-hidroxi-4-metil-1,3-dioxo-7-[2-(2-quinoxaliniloxi)etil]-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.39 CL $[M+H]^+$= 520.6	243 y 244

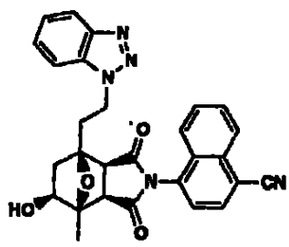
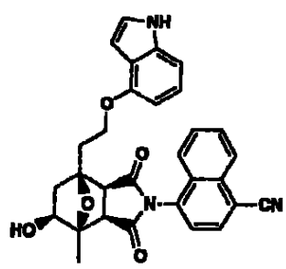
1036

532		[3aR-(3aα,4β,5β,7β,7aα)]-4-[Octahidro-5-hidroxi-4-metil-1,3-dioxo-7-[2-[(2-oxo-1,3-benzoxatiol-5-il)oxi]etil]-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.35 CL [M+OAc]⁻= 600.8	243 y 244
533		(3aα,4β,7β,7aα)]-4-[4-[2-[(2,3-Dihidro-2-oxo-5-benzofuranil)oxi]etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.28 CL [M+OAc]⁻= 566.6	223 y 250

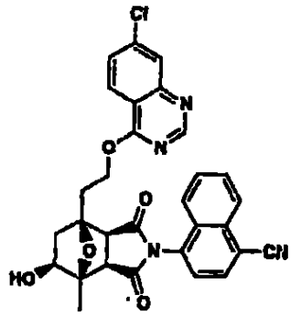
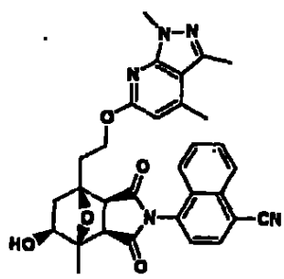
1037

534		[3aR-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[(5-Cloro-8-quinolinil)oxi]etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.18 CL [M+H]$^{+}$= 553.6	243 y 244
535		[3aR-(3aα,4β,5β,7β,7aα)]-4-[Octahidro-5-hidroxi-4-metil-1,3-dioxo-7-[2-(5-fenil-1H-tetrazol-1-il)etil]-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.32 CL [M+H]= 521.5	243 y 244

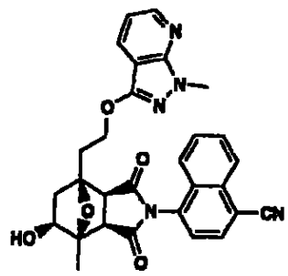
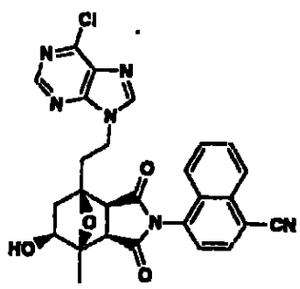
1038

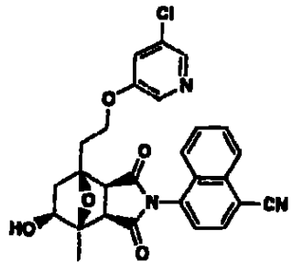
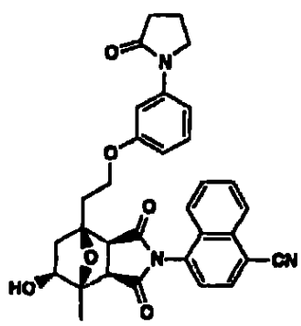
536		[3aR-(3aα,4β,5β,7β,7aα)]-4-[7-[2-(1H-1,2,3-Benzotriazol-1-il)etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.15 CL $[M+H]^+$= 493.8	243 y 244
537		[3aR-(3aα,4β,5β,7β,7aα)]-4-[Octahidro-5-hidroxi-7-[2-(1H-indol-4-iloxi)etil]-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.05 CL $[M]^+$= 507.6	243 y 244

1039

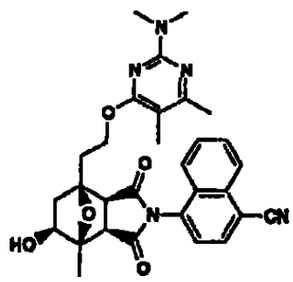
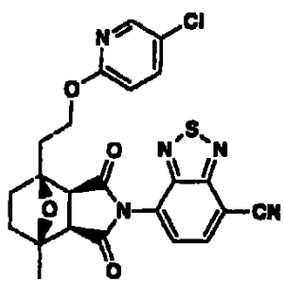
538		[3aR-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[(7-Cloro-4-quinazolinil)oxi]etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.33 CL $[M+H]^+$= 555.2	243 y 244
539		[3aR-(3aα,4β,5β,7β,7aα)]-4-[Octahidro-5-hidroxi-4-metil-1,3-dioxo-7-[2-[(1,3,4-trimetil-1H-pirazolo[3,4-b]piridin-6-il)oxi]etil]-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.48 CL $[M+H]^+$= 552.2	243 y 244

1040

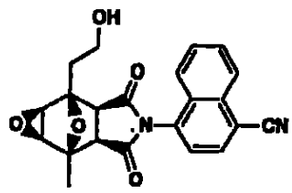
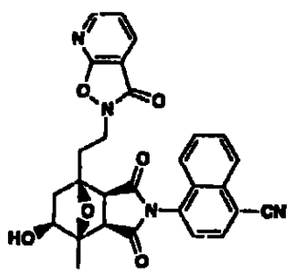
540		[3aR-(3aα,4β,5β,7β,7aα)]-4-[Octahidro-5-hidroxi-4-metil-7-[2-[(1-metil-1H-pirazolo[3,4-b]piridin-3-il)oxi]etil]-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.08 CL $[M+H]^+$= 524.2	243 y 244
541		[3aR-(3aα,4β,5β,7β,7aα)]-4-[7-[2-(6-Cloro-9H-purin-9-il)etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	2.70 CL $[M+H]^+$= 529.0	243 y 244

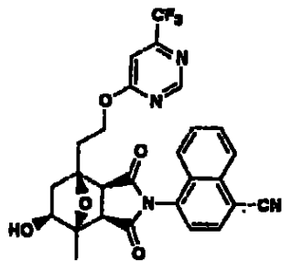
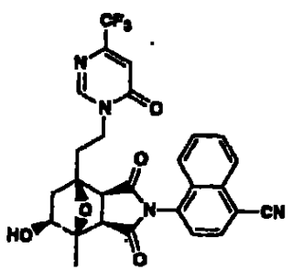
542		[3aR-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[(5-Cloro-3-piridinil)oxi]etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.17 CL $[M+H]^+$= 504.1	243 y 244
543		[3aR-(3aα,4β,5β,7β,7aα)]-4-[Octahidro-5-hidroxi-4-metil-1,3-dioxo-7-[2-[3-(2-oxo-1-pirrolidinil)fenoxi]etil]-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.10 CL $[M+H]^+$= 552.3	243 y 244

1042

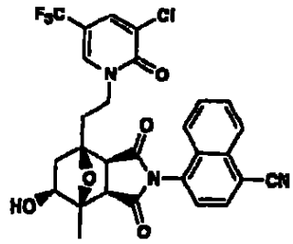
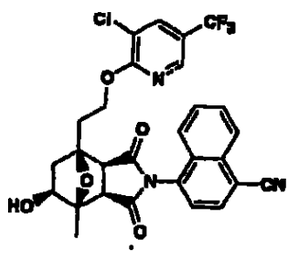
544		[3aR-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[[2-(Dimetilamino)-5,6-dimetil-4-pirimidinil]oxi]etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	2.40 CL $[M+H]^+$= 542.3	243 y 244
545		(3aα,4β,7β,7aα)-7-[4-[2-[(5-Cloro-2-piridinil)oxi]etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2,1,3-benzotiadiazol-4-carbonitrilo	3.52 CL $[M+H]^+$= 495.6	424A, 204, 482F y 482G

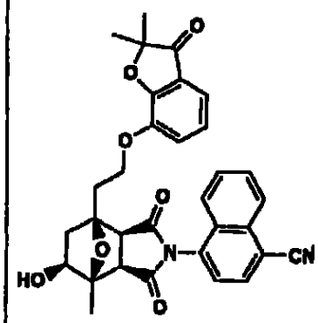
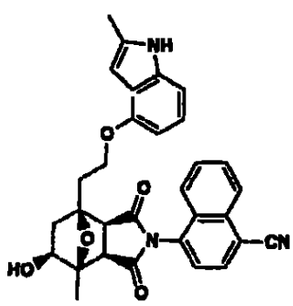
1043

546		(1aα,2β,2aα,5aα,6β,6aα)-4-[Octahidro-2-(2-hidroxietil)-6-metil-3,5-dioxo-2,6-epoxi-4H-oxireno[f]isoindol-4-il]-1-naftalencarbonitrilo	2.36 CL $[M+H]^+$= 391.31	460 y 228
547		[3aR-(3aα,4β,5β,7β,7aα)]-4-[Octahidro-5-hidroxi-4-metil-1,3-dioxo-7-[2-(3-oxoisoxazolo[5,4-b]piridin-2(3H)-il)etil]-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	2.92 CL $[M+OAc]^-$= 568.6	243 y 244

548		[3aR-(3aα,4β,5β,7β,7aα)]-4-[Octahidro-5-hidroxi-4-metil-1,3-dioxo-7-{2-[[6-(trifluorometil)-4-pirimidinil]oxi]etil]-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.18 CL [M+OAc]⁻= 596.7	243 y 244
549		[3aR-(3aα,4β,5β,7β,7aα)]-4-[Octahidro-5-hidroxi-4-metil-1,3-dioxo-7-[2-[6-oxo-4-(trifluorometil)-1(6H)-pirimidinil]etil]-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	2.94 CL [M+OAc]⁻= 596.5	243 y 244

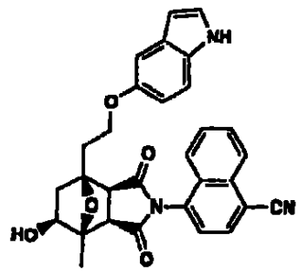
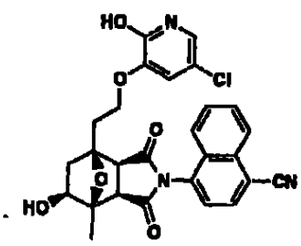
1045

550		[3aR-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[3-Cloro-2-oxo-5-(trifluorometil)-1(2H)-piridinil]etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.39 CL [M+OAc]⁻= 629.3	243 y 244
551		[3aR-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[[3-Cloro-5-(trifluorometil)-2-piridinil]oxi]etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.76 CL [M+OAc]⁻= 629.6	243 y 244

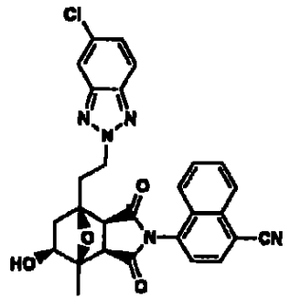
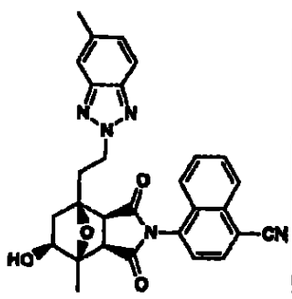
552		[3aR-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[(2,3-Dihidro-2,2-dimetil-3-oxo-7-benzofuranil)oxi]etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.26 CL $[M+OAc]^-$= 611.5	243 y 244
553		[3aR-(3aα,4β,5β,7β,7aα)]-4-[Octahidro-5-hidroxi-4-metil-7-[2-[(2-metil-1H-indol-4-il)oxi]etil]-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.16 CL $[M+H]^+$= 522.5	243 y 244

1046

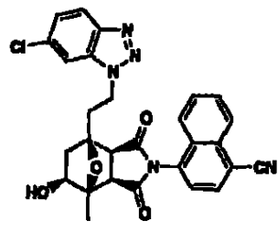
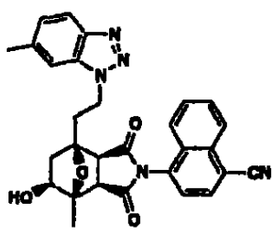
1047

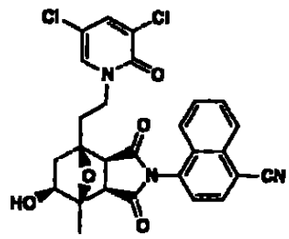
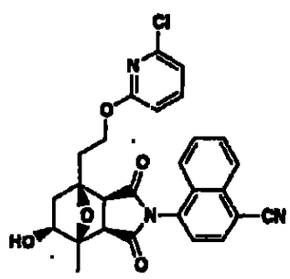
554		[3aR-(3aα,4β,5β,7β,7aα)]-4-[Octahidro-5-hidroxi-7-[2-(1H-indol-5-iloxi)etil]-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.03 CL $[M+H]^+$= 506.3	243 y 244
555		[3aR-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[(5-Cloro-1,2-dihidro-2-oxo-3-piridinil)oxi]etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	2.85 CL $[M+H]^+$= 520.5	243 y 244

1048

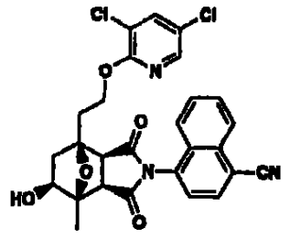
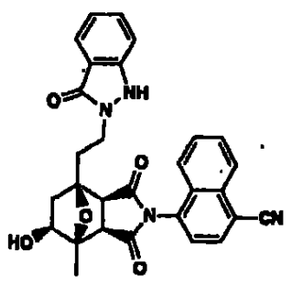
556		[3aR-(3aα,4β,5β,7β,7aα)]-4-[7-[2-(5-Cloro-2H-1,2,3-benzotriazol-2-il)etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.53 CL [M+OAc]⁻= 586.3	243 y 244
557		[3aR-(3aα,4β,5β,7β,7aα)]-4-[Octahidro-5-hidroxi-4-metil-7-[2-(5-metil-2H-1,2,3-benzotriazol-2-il)etil]-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.35 CL [M+H]⁺= 508.5	243 y 244

1049

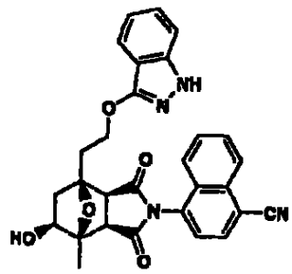
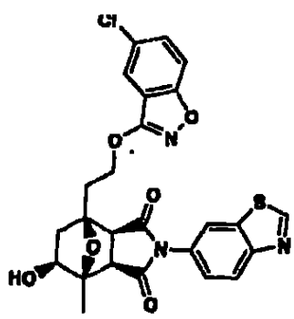
558		[3aR-(3aα,4β,5β,7β,7aα)]-4-[7-[2-(6-Cloro-1H-1,2,3-benzotriazol-1-il)etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.32 CL $[M+H]^+$= 528.3	243 y 244
559		[3aR-(3aα,4β,5β,7β,7aα)]-4-[Octahidro-5-hidroxi-4-metil-7-[2-(6-metil-1H-1,2,3-benzotriazol-1-il)etil]-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	2.97 CL $[M+H]^+$= 508.4	243 y 244

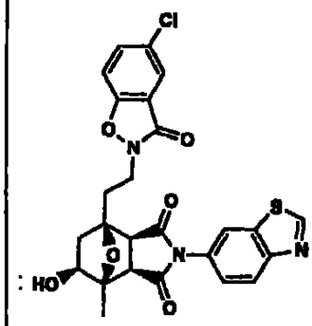
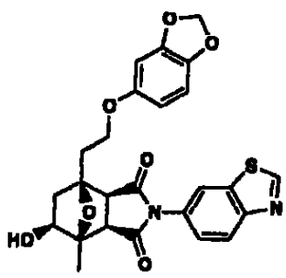
560		[3aR-(3aα,4β,5β,7β,7aα)]-4-[7-[2-(3,5-Dicloro-2-oxo-1(2H)-piridinil)etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.22 CL $[M+H]^+$= 538.3	243 y 244
561		[3aR-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[(6-Cloro-2-piridinil)oxi]etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.30 CL $[M+H]^+$= 504.3	243 y 244

1051

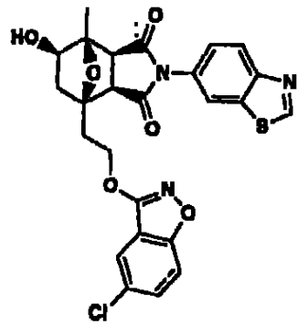
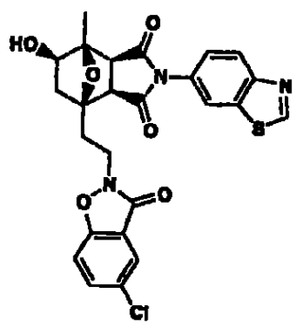
562		[3aR-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[(3,5-Dicloro-2-piridinil)oxi]etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.67 CL $[M+H]^+$= 596.3	243 y 244
563		[3aR-(3aα,4β,5β,7β,7aα)]-4-[7-[2-(1,3-Dihidro-3-oxo-2H-indazol-2-il)etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	2.82 CL $[M+H]^+$= 509.1	243 y 244

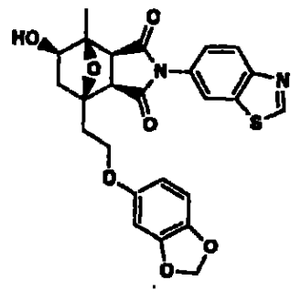
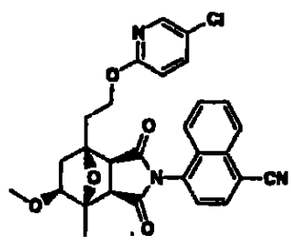
1052

564		[3aR-(3aα,4β,5β,7β,7aα)]-4-[Octahidro-5-hidroxi-7-[2-(1H-indazol-3-iloxi)etil]-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.19 CL $[M+H]^+$= 509.2	243 y 244
565		[3aR-(3aα,4β,5β,7β,7aα)]-2-(6-Benzotiazolil)-7-[2-[(5-cloro-1,2-benzisoxazol-3-il)oxi]etil]hexahidro-5-hidroxi-4-metil-4,7-epoxi-1H-isoindol-1,3(2H)-diona	3.21 CL $[M+H]^+$= 526.2	481

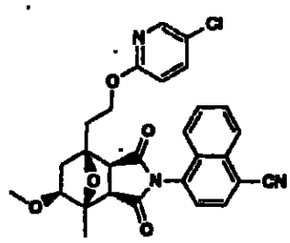
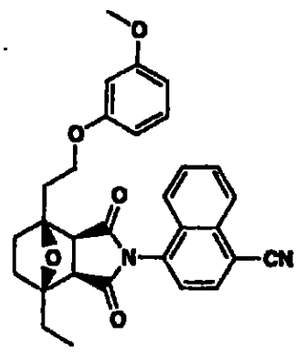
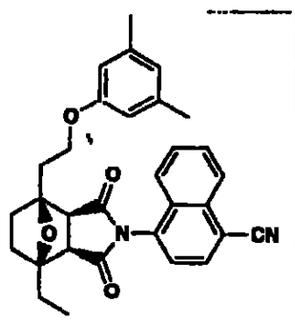
566		[3aR-(3aα,4β,5β,7β,7aα)]-2-(6-Benzotiazolil)-7-[2-(5-cloro-3-oxo-1,2-benzisoxazol-2(3H)-il)etil]hexahidro-5-hidroxi-4-metil-4,7-epoxi-1H-isoindol-1,3(2H)-diona	2.81 CL $[M+H]^+$= 526.2	481
567		[3aR-(3aα,4β,5β,7β,7aα)]-7-[2-(1,3-Benzodioxol-5-iloxi)etil]-2-(6-benzotiazolil)hexahidro-5-hidroxi-4-metil-4,7-epoxi-1H-isoindol-1,3(2H)-diona	2.80 CL $[M+H]^+$= 495.2	481

1054

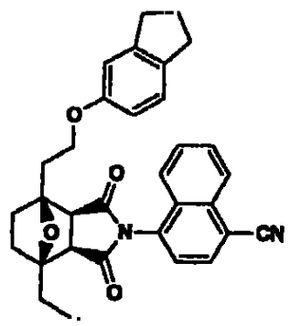
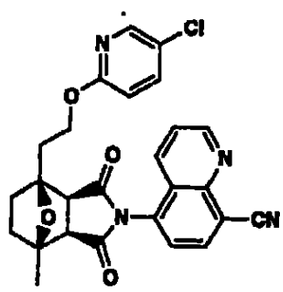
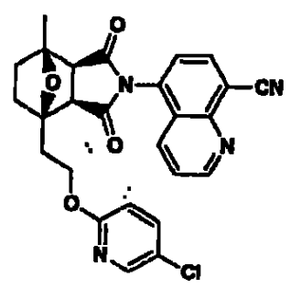
568		[3aS-(3aα,4β,5β,7β,7aα)]-2-(6-Benzotiazolil)-7-[2-[(5-cloro-1,2-benzisoxazol-3-il)oxi]etil]hexahidro-5-hidroxi-4-metil-4,7-epoxi-1H-isoindol-1,3(2H)-diona	3.21 CL $[M+H]^+$= 526.1	481
569		[3aS-(3aα,4β,5β,7β,7aα)]-2-(6-Benzotiazolil)-7-[2-(5-cloro-3-oxo-1,2-benzisoxazol-2(3H)-il)etil]hexahidro-5-hidroxi-4-metil-4,7-epoxi-1H-isoindol-1,3(2H)-diona	2.84 CL $[M+H]^+$= 391.16	481

570		[3aS-(3aα,4β,5β,7β,7aα)]-7-[2-(1,3-Benzodioxol-5-iloxi)etil]-2-(6-benzotiazolil)hexahidro-5-hidroxi-4-metil-4,7-epoxi-1H-isoindol-1,3(2H)-diona	2.82 CL $[M+H]^+$= 495.2	481
571		(3aα,4β,5β,7β,7aα)-4-[7-[2-[(5-Cloro-2-piridinil)oxi]etil]octahidro-5-metoxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.64 y 3.76 atropisómero CLEM $[M+H]^+$= 518.19	491

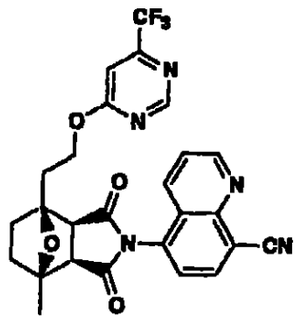
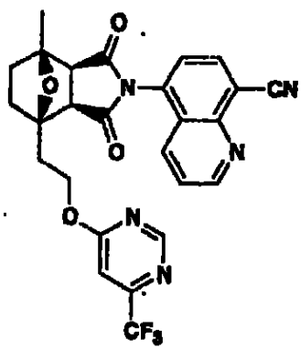
1056

572		[3aR-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[(5-Cloro-2-piridil)oxi]etil]octahidro-5-metoxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.50 CL $[M+H]^+$= 518.28	491
573		[3aR-(3aα,4β,7β,7aα)]-4-[4-Etiloctahidro-7-[2-(3-metoxifenoxi)etil]-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	7.49 y 7.75 atropisómeros CL HRMS $[M+CH_3-CO_2]^-$ = 555.2144	245C, 461 y 462
574		[3aR-(3aα,4β,7β,7aα)]-4-[4-[2-(3,5-Dimetilfenoxi)etil]-7-etiloctahidro-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	8.10 y 8.31 atropisómeros HRMS $[M+CH_3CO_2]^-$= 553.2363	245C, 461 y 462

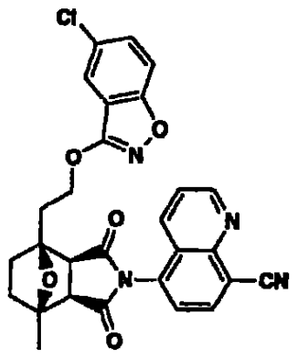
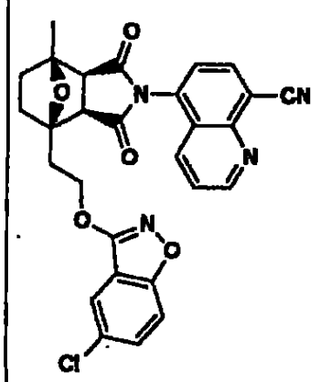
1057

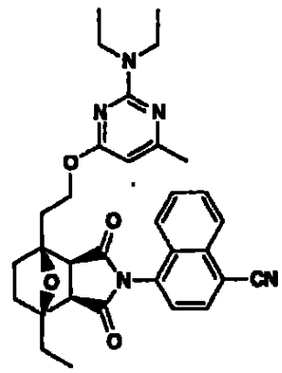
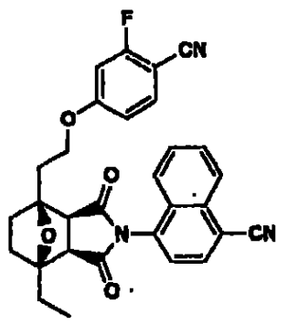
575		[3aR-(3aα,4β,7β,7aα)]-4-[4-[2-[(2,3-Dihidro-1H-inden-5-il)oxi]etil]-7-etiloctahidro-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	8.17 y 8.37 atropisómeros HRMS $[M+CH_3CO_2]^-$= 565.2326	245C, 461 y 462
576		[3aR-(3aα,4β,7β,7aα)]-5-[4-[2-[(5-Cloro-2-piridinil)oxi]etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-8-quinolincarbonitrilo	3.45 CL $[M+H]^+$= 489.0	467 y 487
577		[3aS-(3aα,4β,7β,7aα)]-5-[4-[2-[(5-Cloro-2-piridinil)oxi]etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-8-quinolincarbonitrilo	3.45 CL $[M+H]^+$= 488.99	467 y 487

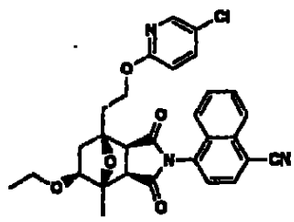
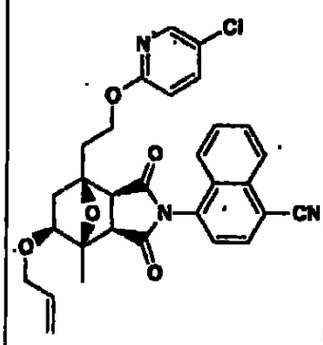
1058

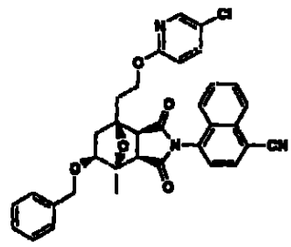
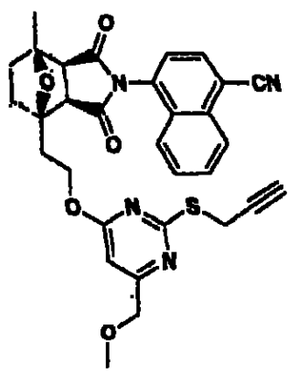
578		[3aR-(3aα,4β,7β,7aα)]-5-[Octahidro-4-metil-1,3-dioxo-7-[2-[[6-(trifluorometil)-4-pirimidinil]oxi]etil]-4,7-epoxi-2H-isoindol-2-il]-8-quinolincarbonitrilo	3.25 CL $[M+H]^+$= 524.0	467 y 487
579		[3aS-(3aα,4β,7β,7aα)]-5-[Octahidro-4-metil-1,3-dioxo-7-[2-[[6-(trifluorometil)-4-pirimidinil]oxi]etil]-4,7-epoxi-2H-isoindol-2-il]-8-quinolincarbonitrilo	3.45 CL $[M+H]^+$= 523.98	467 y 487

1059

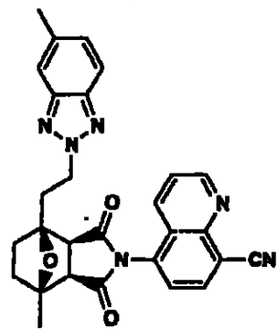
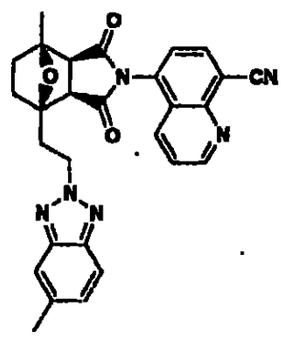
580		[3aR-(3aα,4β,7β,7aα)]-5-[4-[2-[(5-Cloro-1,2-benzisoxazol-3-il)oxi]etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-8-quinolincarbonitrilo	3.66 CL $[M+H]^+$= 529.16	467 y 487
581		[3aS-(3aα,4β,7β,7aα)]-5-[4-[2-[(5-Cloro-1,2-benzisoxazol-3-il)oxi]etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-8-quinolincarbonitrilo	3.66 CL $[M+H]^+$= 529.16	467 y 487

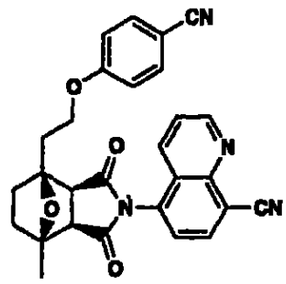
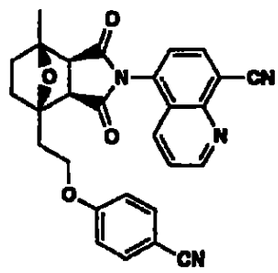
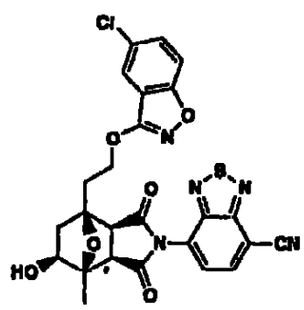
582		[3aR-(3aα,4β,7β,7aα)]-4-[4-[2-[[2-(Dietilamino)-6-metil-4-pirimidinil]oxi]etil]-7-etiloctahidro-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	5.85 y 6.06 atropisómeros CL $[M+H]^+$= 554.26	245C, 461 y 462
583		[3aR-(3aα,4β,7β,7aα)]-4-[4-[2-(4-Ciano-3-fluorofenoxi)etil]-7-etiloctahidro-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	7.23 y 7.50 atropisómeros HRMS $[M-H]^-$= 508.1682	245C, 461 y 462

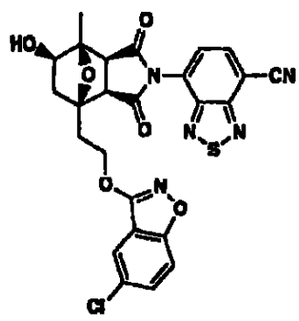
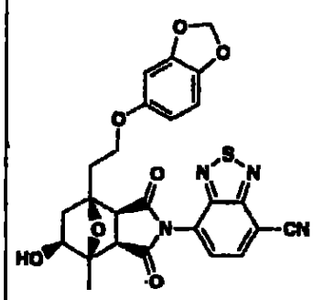
584		[3aR-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[(5-Cloro-2-piridinil)oxi]etil]-5-etiloctahidro-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.60 CL $[M+H]^+$= 532.23	223, 495 y 496
585		[3aR-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[(5-Cloro-2-piridinil)oxi]etil]octahidro-4-metil-1,3-dioxo-5-(2-propeniloxi)-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.68 CL $[M+H]^+$= 544.23	491

586		[3aR-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[(5-Cloro-2-piridinil)oxi]etil]octahidro-4-metil-1,3-dioxo-5-(fenilmetoxi)-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.63 CL $[M+H]^+$= 594.26	491
587		[3aS-(3aα,4β,7β,7aα)]-4-[Octahidro-4-[2-[[6-(metoximetil)-2-(2-propiniltio)-4-pirimidinil]oxi]etil]-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	4.02 CL $[M+H]^+$= 567.31	491

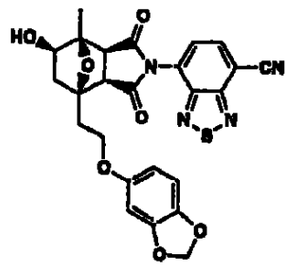
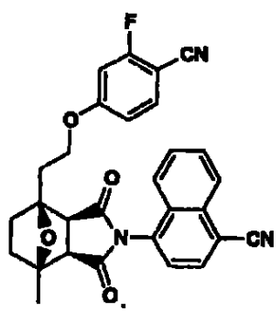
1063

588		[3aR-(3aα,4β,7β,7aα)]-5-[Octahidro-4-metil-7-[2-(5-metil-2H-1,2,3-benzotriazol-2-il)etil]-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-8-quinolincarbonitrilo	3.37 CL $[M+H]^+$= 493.24	467 y 487
589		[3aS-(3aα,4β,7β,7aα)]-5-[Octahidro-4-metil-7-[2-(5-metil-2H-1,2,3-benzotriazol-2-il)etil]-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-8-quinolincarbonitrilo	3.37 CL $[M+H]^+$= 493.24	467 y 487

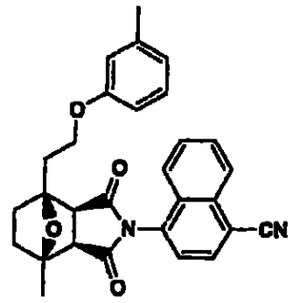
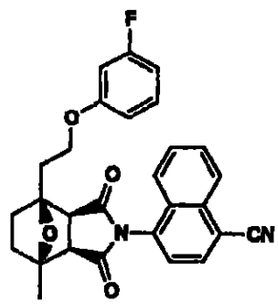
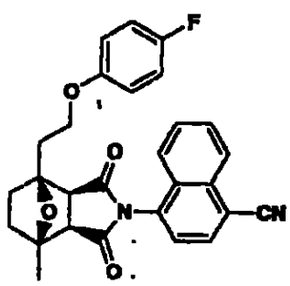
590		[3aR-(3aα,4β,7β,7aα)]-5-[4-[2-(4-Cianofenoxi)etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-8-quinolincarbonitrilo	3.14 CL $[M+H]^+$= 479.22	467 y 487
591		[3aS-(3aα,4β,7β,7aα)]-5-[4-[2-(4-Cianofenoxi)etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-8-quinolincarbonitrilo	3.14 CL $[M+H]^+$= 479.22	467 y 487
592		[3aR-(3aα,4β,5β,7β,7aα)]-7-[7-[2-[(5-Cloro-1,2-benzisoxazol-3-il)oxi]etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2,1,3-benzotiadiazol-4-carbonitrilo	3.38 CL $[M+H]^+$= 552.12	482

593		[3aS-(3aα,4β,5β,7β,7aα)]-7-[7-[2-[(5-Cloro-1,2-benzisoxazol-3-il)oxi]etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2,1,3-benzotiadiazol-4-carbonitrilo	3.39 CL $[M+H]^+$= 552.10	482
594		[3aR-(3aα,4β,5β,7β,7aα)]-7-[7-[2-(1,3-Benzodioxol-5-iloxi)etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2,1,3-benzotiadiazol-4-carbonitrilo	3.00 CL $[M+H]^+$= 521.15	482

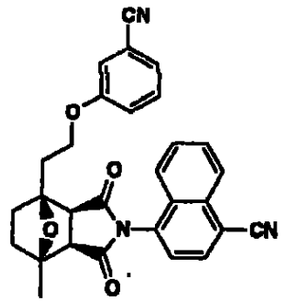
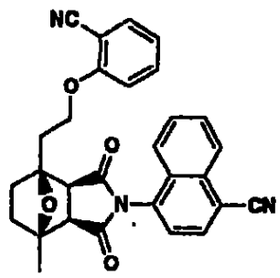
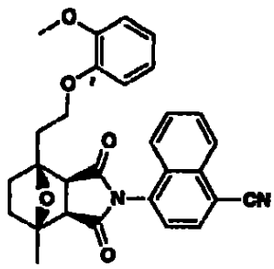
1066

595		[3aS-(3aα,4β,5β,7β,7aα)]-7-[7-[2-(1,3-Benzodioxol-5-iloxi)etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2,1,3-benzotiadiazol-4-carbonitrilo	2.99 CL $[M+H]^+$= 521.14	482
596		[3aS-(3aα,4β,7β,7aα)]-4-[4-[2-(4-Ciano-3-fluorofenoxi)etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.76 CLEM $[M+H]^+$= 496.2	496

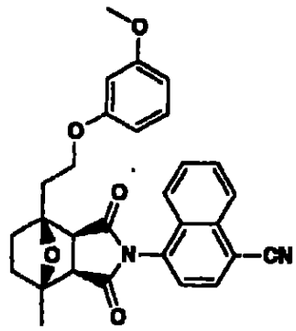
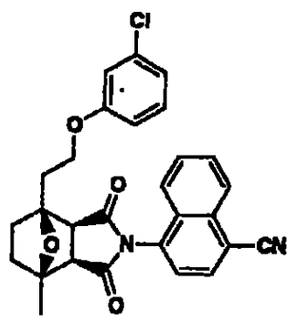
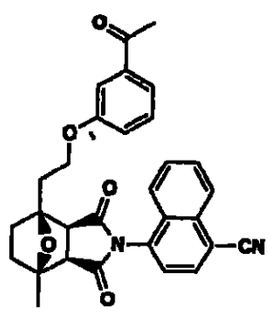
1067

597		[3aR-(3aα,4β,7β,7aα)]-4-[Octahidro-4-metil-7-[2-(3-metilfenoxi)etil]-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	1.79 CLEM $[M+H]^+$= 467.2	496
598		[3aR-(3aα,4β,7β,7aα)]-4-[4-[2-(3-Fluorofenoxi)etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	2.01 CLEM $[M+H]^+$= 471.2	496
599		[3aR-(3aα,4β,7β,7aα)]-4-[4-[2-(4-Fluorofenoxi)etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	1.98 CLEM $[M+H]^+$= 471.2	496

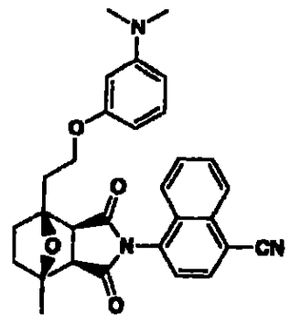
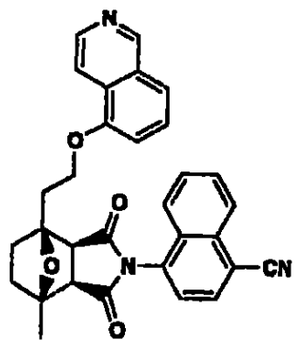
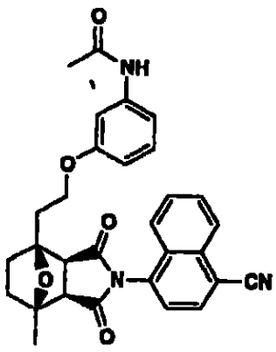
1068

600		[3aR-(3aα,4β,7β,7aα)]-4-[4-[2-(3-Cianofenoxi)etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	1.88 CLEM $[M+H]^+$= 478.2	496
601		[3aR-(3aα,4β,7β,7aα)]-4-[4-[2-(2-Cianofenoxi)etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.42 CLEM $[M+H]^+$= 478.2	496
602		[3aR-(3aα,4β,7β,7aα)]-4-[Octahidro-4-[2-(2-metoxifenoxi)etil]-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	1.83 CLEM $[M+H]^+$= 483.2	496

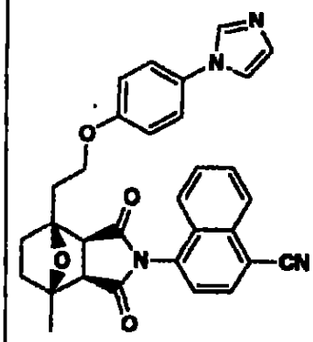
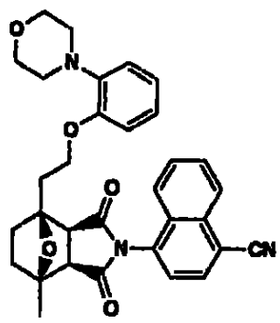
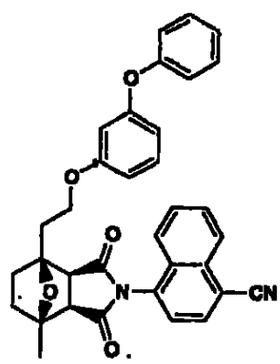
1069

603		[3aR-(3aα,4β,7β,7aα)]-4-[Octahidro-4-[2-(3-metoxifenoxi)etil]-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	2.14 CLEM $[M+H]^+$= 483.2	496
604		[3aR-(3aα,4β,7β,7aα)]-4-[4-[2-(3-Clorofenoxi)etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	2.09 CLEM $[M+H]^+$= 487.2	496
605		[3aR-(3aα,4β,7β,7aα)]-4-[4-[2-(3-Acetilfenoxi)etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	2.20 CLEM $[M+H]^+$= 495.2	496

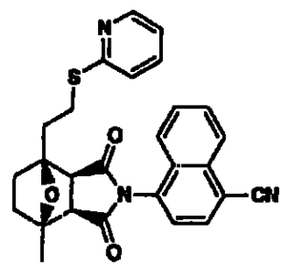
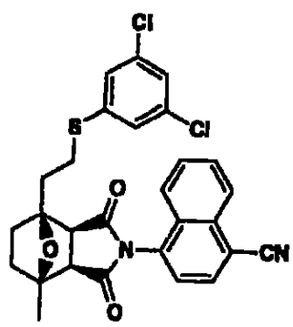
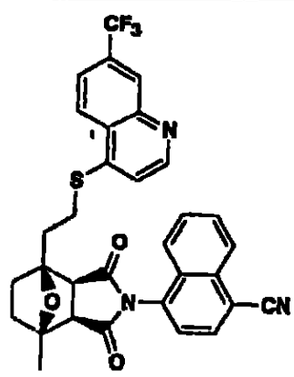
1070

606		[3aR-(3aα,4β,7β,7aα)]-4-[4-[2-[3-(Dimetilamino)fenoxi]etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	1.94 CLEM $[M+H]^+$= 496.2	496
607		[3aR-(3aα,4β,7β,7aα)]-4-[Octahidro-4-[2-(5-isoquinoliniloxi)etil]-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	1.89 CLEM $[M+H]^+$= 504.2	496
608		N-[3-[2-[3aR-(3aα,4β,7β,7aα)]-2-(4-Ciano-1-naftalenil)octahidro-7-metil-1,3-dioxo-4,7-epoxi-4H-isoindol-4-il]etoxi]fenilacetamida	1.97 CLEM $[M+H]^+$= 510.6	496

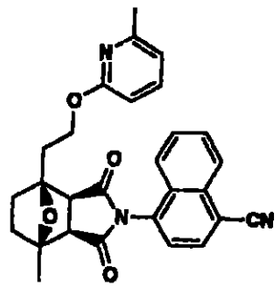
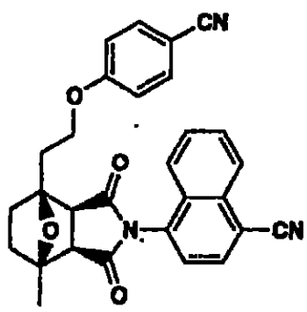
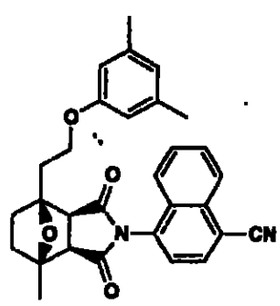
1071

609		[3aR-(3aα,4β,7β,7aα)]-4-[Octahidro-4-[2-[4-(1H-imidazol-1-il)fenoxi]etil]-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.81 CLEM $[M+H]^+$= 519.6	496
610		[3aR-(3aα,4β,7β,7aα)]-4-[Octahidro-4-metil-7-[2-[2-(4-morfolinil)fenoxi]etil]-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	2.16 CLEM $[M+H]^+$= 538.2	496
611		[3aR-(3aα,4β,7β,7aα)]-4-[Octahidro-4-metil-1,3-dioxo-7-[2-(3-fenoxifenoxi)etil]-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	1.89 CLEM $[M+H]^+$= 545.2	496

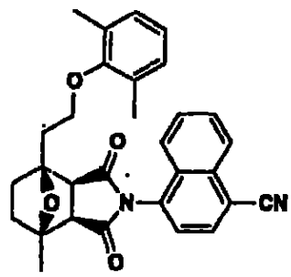
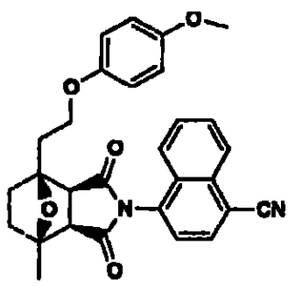
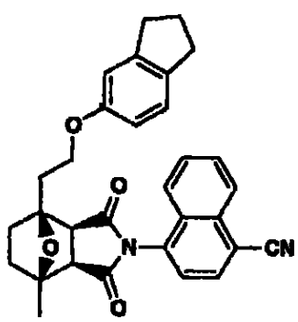
1072

612		[3aR-(3aα,4β,7β,7aα)]-4-[Octahidro-4-metil-1,3-dioxo-7-[2-(2-piridiniltio)etil]-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	1.91 CLEM $[M+H]^+$= 469.6	496
613		[3aR-(3aα,4β,7β,7aα)]-4-[4-[2-[(3,5-Diclorofenil)tio]etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	1.53 CLEM $[M+H]^+$= 537.1	496
614		[3aR-(3aα,4β,7β,7aα)]-4-[Octahidro-4-metil-1,3-dioxo-7-[2-[[7-(trifluorometil)-4-quinolinil]tio]etil]-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	1.49 CLEM $[M+H]^+$= 588.2	496

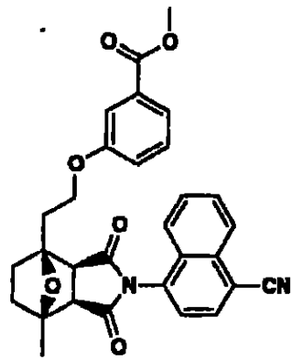
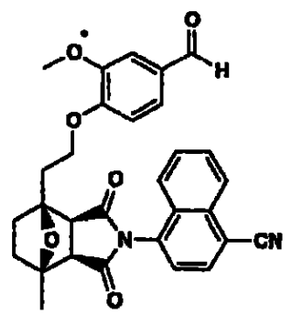
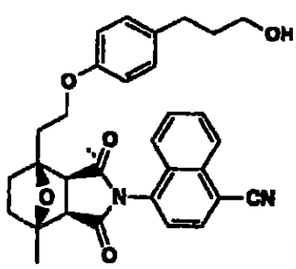
1073

615		[3aR-(3aα,4β,7β,7aα)]-4-[Octahidro-4-metil-7-[2-[(6-metil-2-piridinil)oxi]etil]-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	1.79 CLEM $[M+H]^+$= 467.5	496
616		[3aR-(3aα,4β,7β,7aα)]-4-[4-[2-(4-Cianofenoxi)etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	1.98 CLEM $[M+H]^+$= 478.2	496
617		[3aR-(3aα,4β,7β,7aα)]-4-[4-[2-(3,5-Dimetilfenoxi)etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	1.80 CLEM $[M+H]^+$= 481.2	496

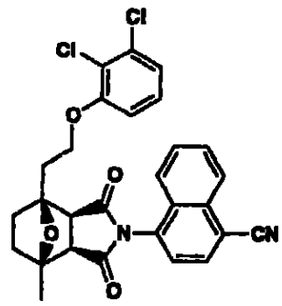
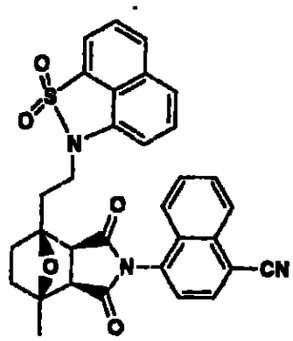
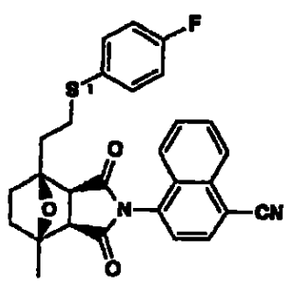
1074

618		[3aR-(3aα,4β,7β,7aα)]-4-[4-[2-(2,6-Dimetilfenoxi)etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	1.88 CLEM $[M+H]^+$= 481.2	496
619		[3aR-(3aα,4β,7β,7aα)]-4-[Octahidro-4-[2-(4-metoxifenoxi)etil]-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	1.50 CLEM $[M+H]^+$= 483.2	496
620		[3aR-(3aα,4β,7β,7aα)]-4-[4-[2-[(2,3-Dihidro-1H-inden-5-il)oxi]etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	2.14 CLEM $[M+H]^+$= 493.3	496

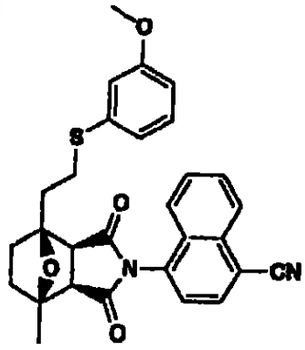
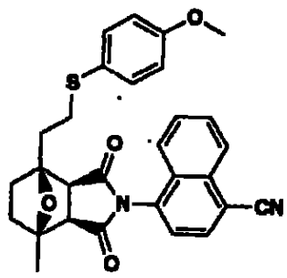
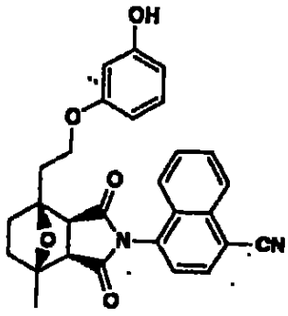
1075

621		Éster de metilo del ácido 3-[2-[[3aR-(3aα,4β,7β,7aα)]-2-(4-Ciano-1-naftalenil)octahidro-7-metil-1,3-dioxo-4,7-epoxi-4H-isoindol-4-il]etoxi]benzoico	3.99 CLEM $[M+H]^+$= 511.2	496
622		[3aR-(3aα,4β,7β,7aα)]-4-[4-[2-(4-Formil-2-metoxifenoxi)etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	2.01 CLEM $[M+H]^+$= 511.2	496
623		[3aR-(3aα,4β,7β,7aα)]-4-[Octahidro-4-[2-[4-(3-hidroxipropil)fenoxi]etil]-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	1.93 CLEM $[M+H]^+$= 511.3	496

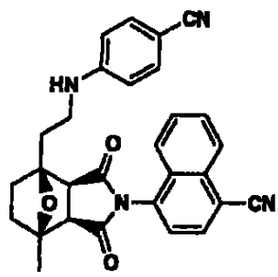
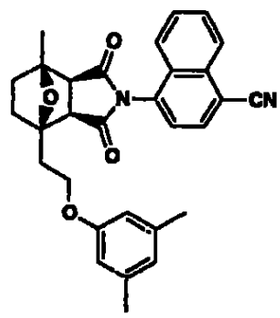
1076

624		[3aR-(3aα,4β,7β,7aα)]-4-[4-[2-(2,3-Diclorofenoxi)etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	1.79 CLEM $[M+H]^+$= 521.1	496
625		[3aR-(3aα,4β,7β,7aα)]-4-[4-[2-(1,1-Dióxido-2H-nafto[1,8-cd]isotiazol-2-il)etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	1.69 CLEM $[M+H]^+$= 564.2	496
626		[3aR-(3aα,4β,7β,7aα)]-4-[4-[2-[(4-fluorofenil)tio]etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	2.03 CLEM $[M+H]^+$= 487.2	496

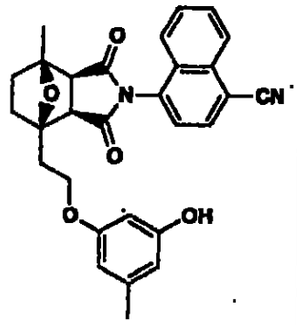
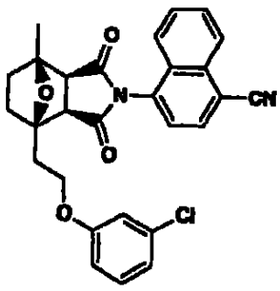
1077

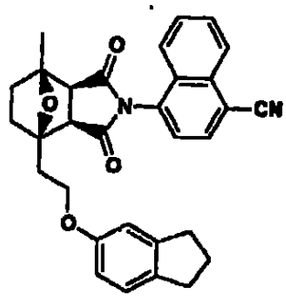
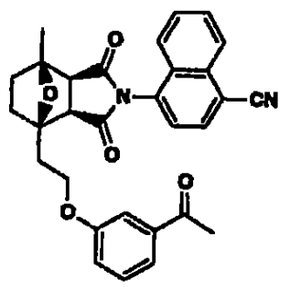
627		[3aR-(3aα,4β,7β,7aα)]-4-[Octahidro-4-[2-[(3-metoxifenil)tio]etil]-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	2.02 CLEM $[M+H]^+$= 499.2	496
628		[3aR-(3aα,4β,7β,7aα)]-4-[Octahidro-4-[2-[(4-metoxifenil)tio]etil]-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	1.99 CLEM $[M+H]^+$= 499.2	496
629		[3aR-(3aα,4β,7β,7aα)]-4-[Octahidro-4-[2-(3-Hidroxifenoxi)etil]-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	2.27 CLEM $[M+H]^+$= 469.2	496

1078

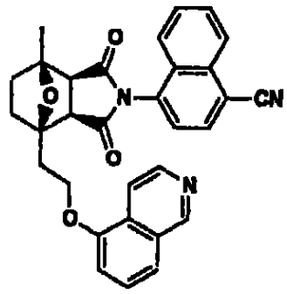
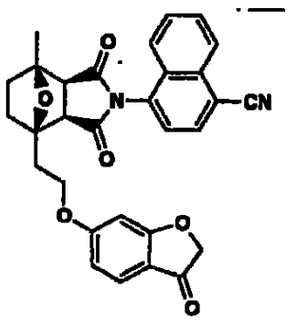
630		[3aR-(3aα,4β,7β,7aα)]-4-[4-[2-[(4-Cianofenil)amino]etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.56 CLEM $[M+H]^+$= 477.2	496
631		[3aS-(3aα,4β,7β,7aα)]-4-[4-[2-(3,5-Dimetilfenoxi)etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	4.10 CLEM $[M+H]^+$= 481.2	496

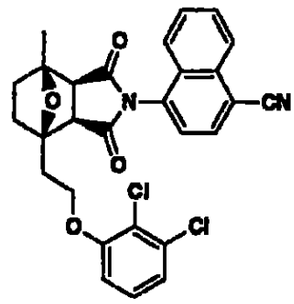
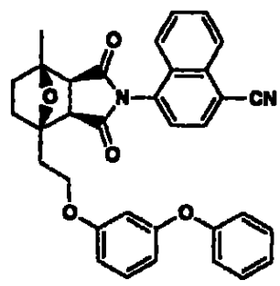
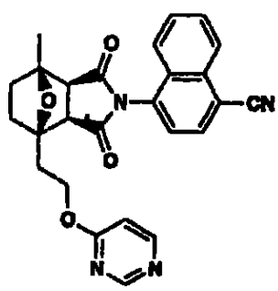
1079

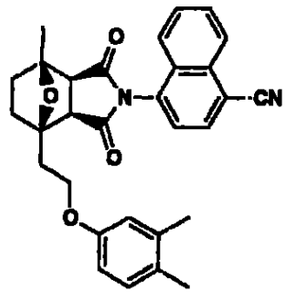
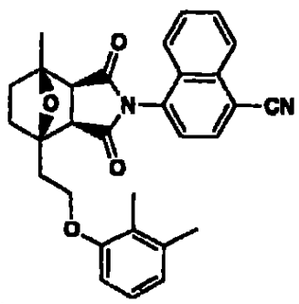
632		[3aS-(3aα,4β,7β,7aα)]-4-[Octahidro-4-[2-(3-hidroxi-5-metilfenoxi)etil]-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.56 CLEM $[M+H]^+$= 483.2	496
633		[3aS-(3aα,4β,7β,7aα)]-4-[4-[2-(3-Clorofenoxi)etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	4.03 CLEM $[M+H]^+$= 487.1	496

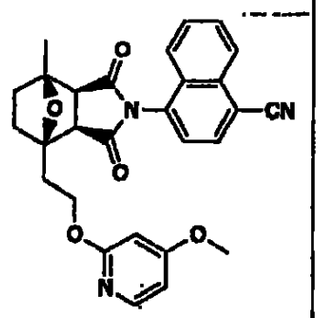
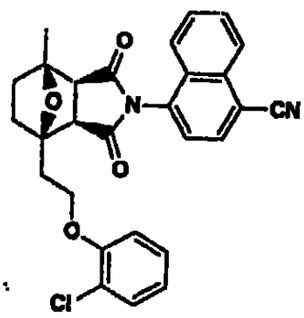
634		[3aS-(3aα,4β,7β,7aα)]-4-[4-[2-[(2,3-Dihidro-1H-inden-5-il)oxi]etil]octahidro-7- metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	4.15 CLEM $[M+H]^+$= 493.2	496
635		[3aS-(3aα,4β,7β,7aα)]-4-[4-[2-(3-Acetilfenoxi)etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.65 CLEM $[M+H]^+$= 495.2	496

1081

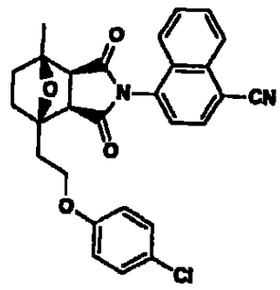
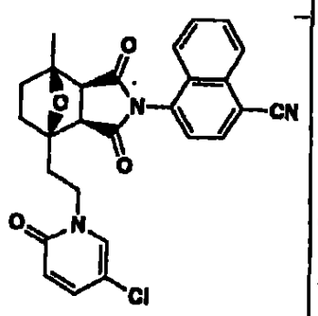
636		[3aS-(3aα,4β,7β,7aα)]-4-[octahidro-4-[2-(5-isoquinoliniloxi)etil]-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo, trifluoroacetato (1:1)	3.67 CLEM $[M+H]^+$= 504.2	496
637		[3aS-(3aα,4β,7β,7aα)]-4-[4-[2-[(2,3-Dihidro-3-oxo-6-benzofuranil)oxi]etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	2.90 CLEM $[M+H]^+$= 509.2	496

638		[3aS-(3aα,4β,7β,7aα)]-4-[4-[2-(2,3-Diclorofenoxi)etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	2.80 CLEM $[M+H]^+$= 521.1	496
639		[3aS-(3aα,4β,7β,7aα)]-4-[Octahidro-4-metil-1,3-dioxo-7-[2-(3-fenoxifenoxi)etil]-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.54 CLEM $[M+H]^+$= 545.2	496
640		[3aS-(3aα,4β,7β,7aα)]-4-[Octahidro-4-metil-1,3-dioxo-7-[2-(4-pirimidiniloxi)etil]-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	4.13 CLEM $[M+H]^+$= 455.2	496

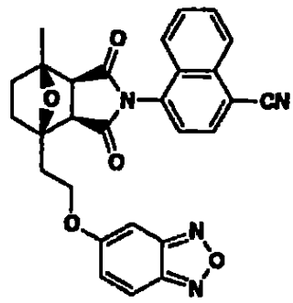
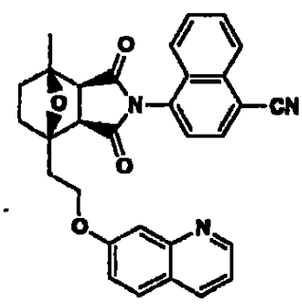
641		[3aS-(3aα,4β,7β,7aα)]-4-[4-[2-(3,4-Dimetilfenoxi)etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	4.19 CLEM $[M+H]^+$= 481.2	496
642		[3aS-(3aα,4β,7β,7aα)]-4-[4-[2-(2,3-Dimetilfenoxi)etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	2.80 CLEM $[M+H]^+$= 481.2	496

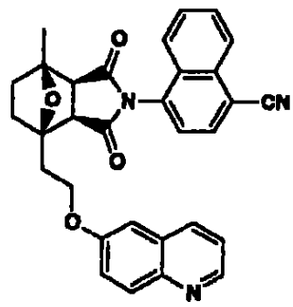
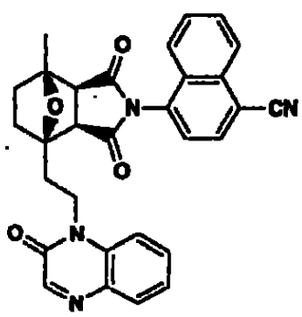
643		[3aS-(3aα,4β,7β,7aα)]-4-[Octahidro-4-[2-[(4-metoxi-2-piridinil)oxi]etil]-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	2.72 CLEM $[M+H]^+$= 484.2	496
644		[3aS-(3aα,4β,7β,7aα)]-4-[4-[2-(2-Clorofenoxi)etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	2.63 CLEM $[M+H]^+$= 487.1	496

1085

645		[3aS-(3aα,4β,7β,7aα)]-4-[4-[2-(4-Clorofenoxi)etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	4.07 CLEM $[M+H]^+$= 487.1	496
646		[3aS-(3aα,4β,7β,7aα)]-4-[4-[2-(5-Cloro-2-oxo-1(2H)-piridinil)etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	4.13 CLEM $[M+H]^+$= 488.1	496

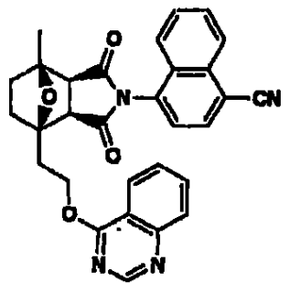
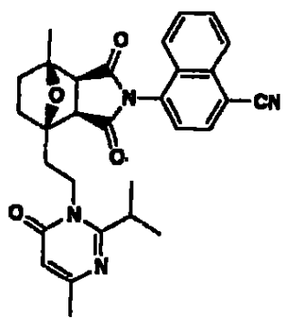
1086

647		[3aS-(3aα,4β,7β,7aα)]-4-[4-[2-(2,1,3-Benzoxadiazol-5-iloxi)etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.15 CLEM $[M+H]^+$= 495.2	496
648		[3aS-(3aα,4β,7β,7aα)]-4-[Octahidro-4-metil-1,3-dioxo-7-[2-(7-quinoliniloxi)etil]-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo, trifluoroacetato (1:1)	3.93 CLEM $[M+H]^+$= 504.2	496

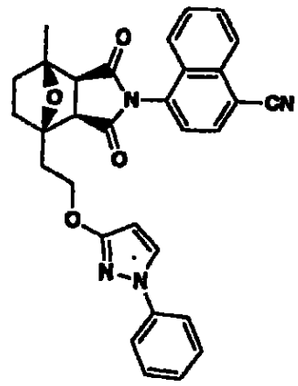
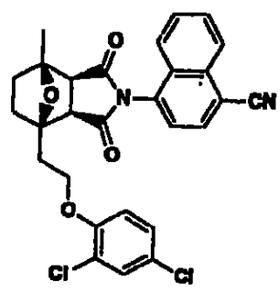
649		[3aS-(3aα,4β,7β,7aα)]-4-[Octahidro-4-metil-1,3-dioxo-7-[2-(6-quinoliniloxi)etil]-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo, trifluoroacetato (1:1)	4.01 CLEM $[M+H]^+$= 504.2	496
650		[3aS-(3aα,4β,7β,7aα)]-4-[Octahidro-4-metil-1,3-dioxo-7-[2-(2-oxo-1(2H)-quinoxalinil)etil]-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo, trifluoroacetato (1:1)	3.33 CLEM $[M+H]^+$= 505.2	496

1088

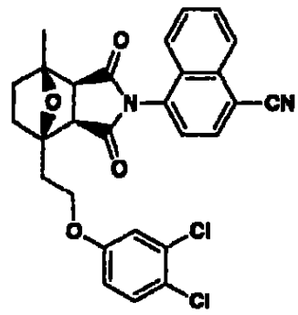
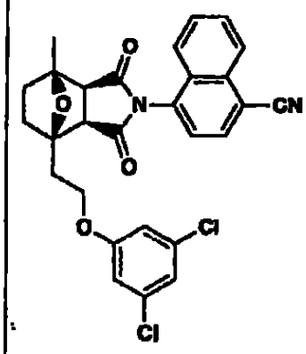
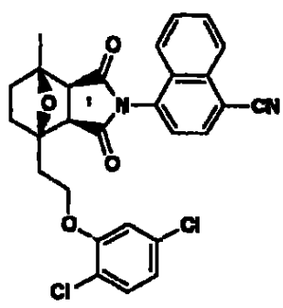
1287

651		[3aS-(3aα,4β,7β,7aα)]-4-[Octahidro-4-metil-1,3-dioxo-7-[2-(4-quinazoliniloxi)etil]-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo, trifluoroacetato (1:1)	3.39 CLEM $[M+H]^+$= 505.2	496
652		[3aS-(3aα,4β,7β,7aα)]-4-[Octahidro-4-metil-7-[2-[4-metil-2-(1-metiletil)-6-oxo-1(6H)-pirimidinil]etil]-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.72 CLEM $[M+H]^+$= 511.3	496

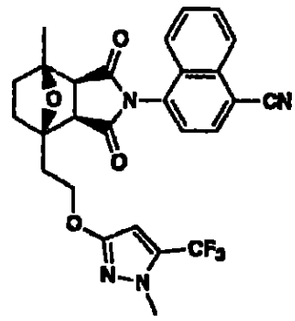
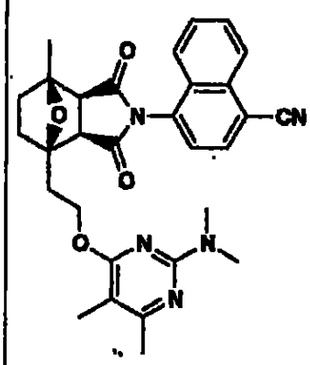
1089

653		[3aS-(3aα,4β,7β,7aα)]-4-[Octahidro-4-metil-1,3-dioxo-7-[2-[(1-fenil-1H-pirazol-3-il)oxi]etil]-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo, trifluoroacetato (1:1)	3.48 CLEM $[M]^+$= 519.2	496
654		[3aS-(3aα,4β,7β,7aα)]-4-[4-[2-(2,4-Diclorofenoxi)etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	2.85 CLEM $[M+H]^+$= 521.1	496

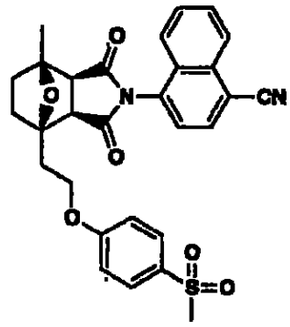
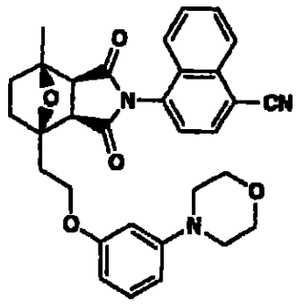
1090

655		[3aS-(3aα,4β,7β,7aα)]-4-[4-[2-(3,4-Diclorofenoxi)etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	2.86 CLEM $[M+H]^+$= 521.1	496
656		[3aS-(3aα,4β,7β,7aα)]-4-[4-[2-(3,5-Diclorofenoxi)etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.47 CLEM $[M+H]^+$= 521.1	496
657		[3aS-(3aα,4β,7β,7aα)]-4-[4-[2-(2,5-Diclorofenoxi)etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.33 CLEM $[M+H]^+$= 521.1	496

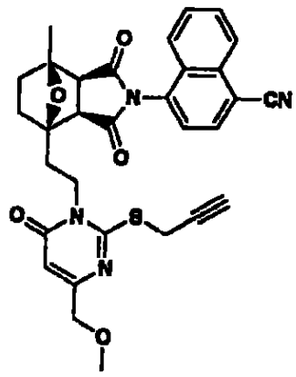
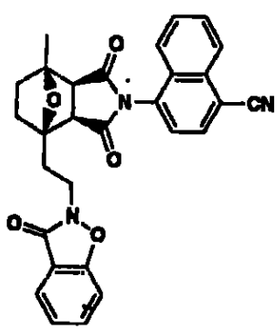
1091

658		[3aS-(3aα,4β,7β,7aα)]-4-[Octahidro-4-metil-7-[2-[[1-metil-5-(trifluorometil)-1H-pirazol-3-il]oxi]etil]-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo, trifluoroacetato (1:1)	3.87 CLEM $[M+H]^+$= 525.2	496
659		[3aS-(3aα,4β,7β,7aα)]-4-[4-[2-[[2-(Dimetilamino)-5,6-dimetil-4-pirimidinil]oxi]etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo, trifluoroacetato (1:1)	2.71 CLEM $[M+H]^+$= 526.2	496

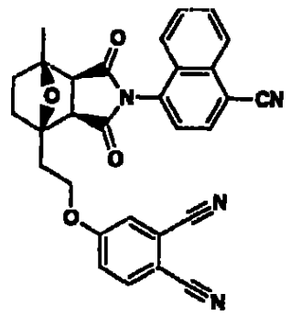
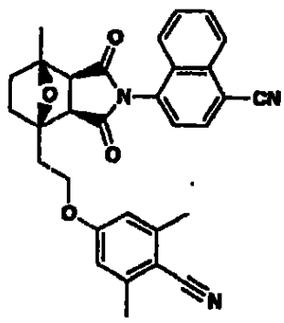
1092

660		[3aS-(3aα,4β,7β,7aα)]-4-[Octahidro-4-metil-7-[2-[4-(metilsulfonil)fenoxi]etil]-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	2.91 CLEM $[M+H]^+$= 531.2	496
661		[3aS-(3aα,4β,7β,7aα)]-4-[Octahidro-4-metil-7-[2-[3-(4-morfolin)fenoxi]etil]-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo, trifluoroacetato (1:1)	3.78 CLEM $[M+H]^+$= 538.2	496

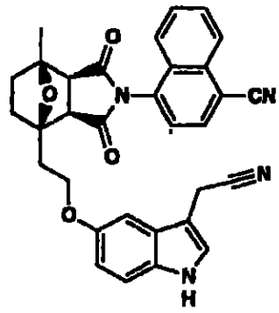
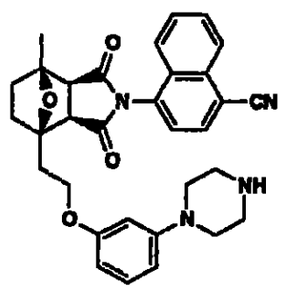
1093

662		[3aS-(3aα,4β,7β,7aα)]-4-[Octahidro-4-[2-[4-(metoximetil)-6-oxo-2-(2-propiniltio)-1(6H)-pirimidinil]etil]-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo, trifluoroacetato (1:1)	4.18 CLEM $[M+H]^+$= 569.2	496
663		[3aS-(3aα,4β,7β,7aα)]-4-[Octahidro-4-metil-1,3-dioxo-7-[2-(3-oxo-1,2-benzisoxazol-2(3H)-il)etil]-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	4.18 CLEM $[M+H]^+$= 494.2	496

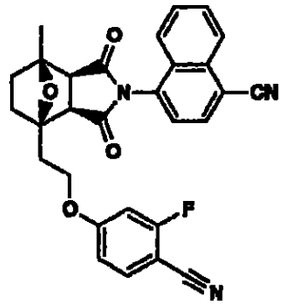
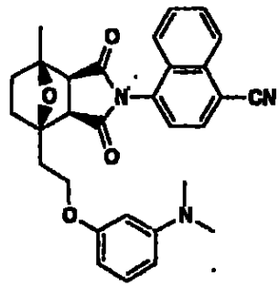
1094

664		[3aS-(3aα,4β,7β,7aα)]-4-[2-[2-(4-Ciano-1-naftalenil)octahidro-7-metil-1,3-dioxo-4,7-epoxi-4H-isoindol-4-il]etoxi]-1,2-benzendicarbonitrilo	4.30 CLEM $[M+H]^+$= 503.1	496
665		[3aS-(3aα,4β,7β,7aα)]-4-[4-[2-(4-Ciano-3,5-dimetilfenoxi)etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	4.13 CLEM $[M+H]^+$= 506.2	496

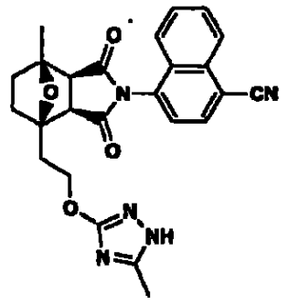
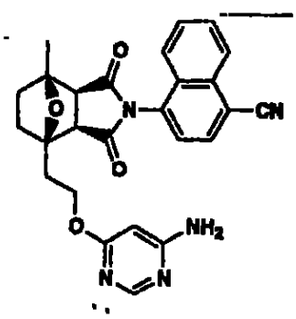
1095

666		[3aS-(3aα,4β,7β,7aα)]-5-[2-[2-(4-Ciano-1-naftalenil)octahidro-7-metil-1,3-dioxo-4,7-epoxi-4H-isoindol-4-il]etoxi]-1H-indol-3-acetonitrilo, trifluoroacetato (1:1)	3.36 CLEM $[M+H]^+$= 531.2	496
667		[3aS-(3aα,4β,7β,7aα)]-4-[Octahidro-4-metil-1,3-dioxo-7-[2-[3-(1-piperazinil)fenoxi]etil]-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo, trifluoroacetato (1:1)	3.81 CLEM $[M+H]^+$= 537.2	496

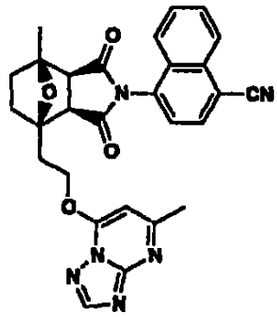
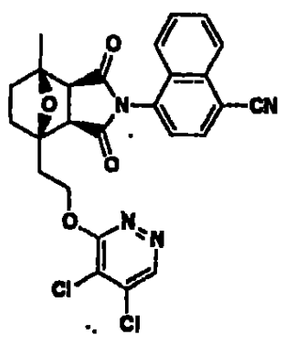
1096

668		[3aS-(3aα,4β,7β,7aα)]-4-[4-[2-(4-Ciano-3-fluorofenoxi)etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	2.89 CLEM $[M+H]^+$= 496.2	496
669		[3aS-(3aα,4β,7β,7aα)]-4-[4-[2-[3-(Dimetilamino)fenoxi]etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo, trifluoroacetato (1:1)	3.37 CLEM $[M+H]^+$= 496.2	496

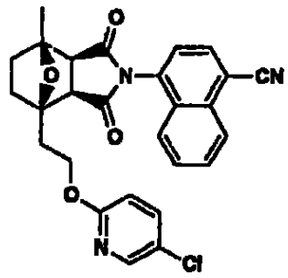
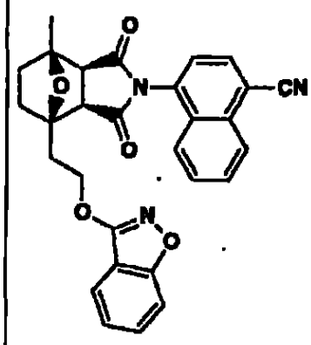
1097

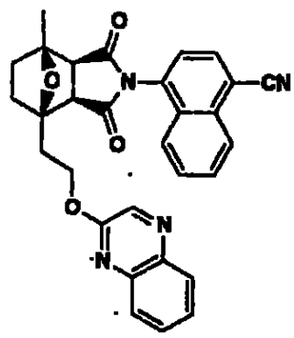
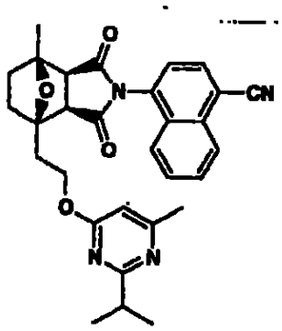
670		[3aS-(3aα,4β,7β,7aα)]-4-[Octahidro-4-metil-7-[2-[(5-metil-1H-1,2,4-triazol-3-il)oxi]etil]-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo, trifluoroacetato (1:1)	3.26 CLEM $[M+H]^+$= 458.2	496
671		[3aS-(3aα,4β,7β,7aα)]-4-[4-[2-[(6-Amino-4-pirimidinil)oxi]etil] octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo, trifluoroacetato (1:1)	2.97 CLEM $[M+H]^+$= 470.2	496

1098

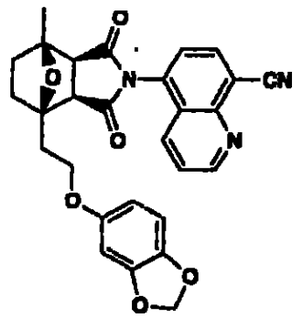
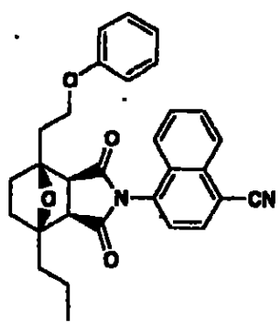
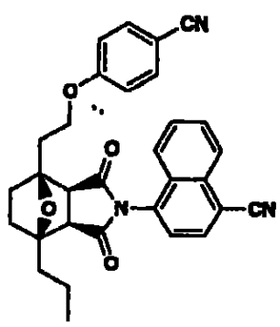
672		[3aS-(3aα,4β,7β,7aα)]-4-[Octahidro-4-metil-7-[2-[(5-metil[1,2,4]triazol[1,5-a]pirimidin-7-il)oxi]etil]-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo, trifluoroacetato (1:1)	3.45 CLEM $[M+H]^+$= 509.2	496
673		[3aS-(3aα,4β,7β,7aα)]-4-[4-[2-[(4,5-Dicloro-3-piridazinil)oxi]etil] octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.79 CLEM $[M+H]^+$= 523.1	496

1099

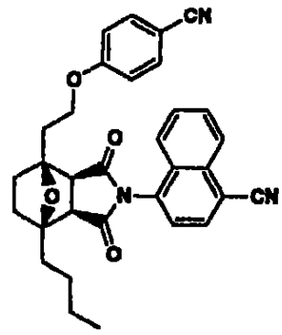
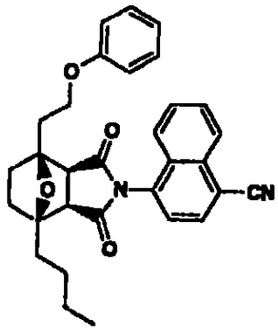
674		[3aS-(3aα,4β,7β,7aα)]-4-[4-[2-[(5-Cloro-2-piridinil)oxi]etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.86 CLEM $[M+H]^+$= 488.4	496
675		[3aS-(3aα,4β,7β,7aα)]-4-[4-[2-(1,2-Benzisoxazol-3-iloxi)etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.78 CLEM $[M+H]^+$= 494.41	496

676		[3aS-(3aα,4β,7β,7aα)]-4-[Octahidro-4-metil-1,3-dioxo-7-[2-(2-quinoxaliniloxi)etil]-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.83 CLEM $[M+H]^+$= 505.43	496
677		[3aS-(3aα,4β,7β,7aα)]-4-[Octahidro-4-metil-7-[2-[[6-metil-2-(1-metiletil)-4-pirimidinil]oxi]etil]-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.52 CLEM $[M+H]^+$= 511.49	496

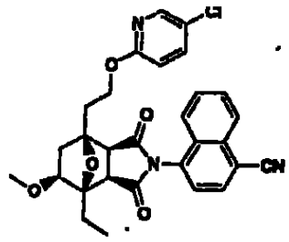
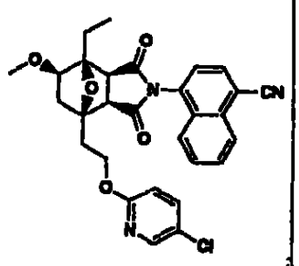
1101

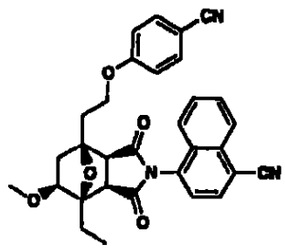
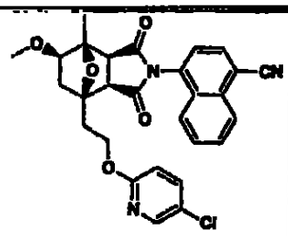
678		[3aS-(3aα,4β,7β,7aα)]-5-[4-[2-(1,3-Benzodioxol-5-iloxi)etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-8-quinolincarbonitrilo	3.327 CL $[M+H]^+$= 498.24	467 y 487
679		[3aR-(3aα,4β,7β,7aα)]-4-[Octahidro-1,3-dioxo-4-(2-fenoxietil)-7-propil-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	7.77 y 8.01 atropisómeros CL $[M+H]^+$= 481.4	501
680		[3aR-(3aα,4β,7β,7aα)]-4-[4-[2-(4-Cianofenoxi)etil]octahidro-1,3-dioxo-7-propil-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	7.42 y 7.68 atropisómeros CL $[M+H]^+$= 506.38	501

1102

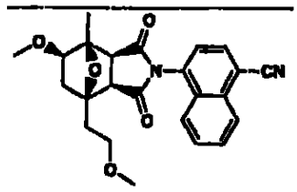
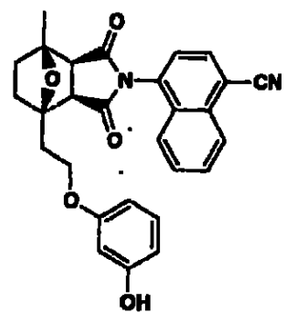
681		[3aR-(3aα,4β,7β,7aα)]-4-[4-Butil-7-[2-(4-cianofenoxi)etil]octahidro-1,3-dioxo-7-propil-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	7.69 y 7.92 atropisómeros CL $[M+H]^+$= 520.38	502
682		[3aR-(3aα,4β,7β,7aα)]-4-[4-Butiloctahidro-1,3-dioxo-7-(2-fenoxietil)-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	8.02 y 8.23 atropisómeros CL $[M+H]^+$= 495.33	502

1103

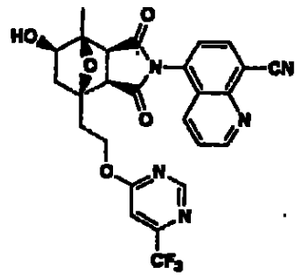
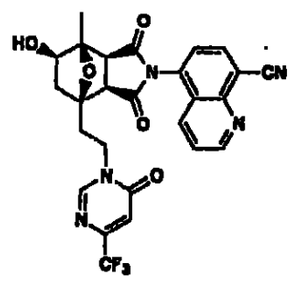
683		[3aR-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[(5-Cloro-2-piridinil)oxi]etil]-4-etiloctahidro-5-metoxi-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo, trifluoroacetato (1:1)	7.31 y 7.55 atropisómeros CL $[M+H]^+$= 532.3	504
684		[3aS-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[(5-Cloro-2-piridinil)oxi]etil]-4-etiloctahidro-5-metoxi-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo, trifluoroacetato (1:1)	7.31 y 7.55 atropisómeros CL $[M+H]^+$= 532.3	504

685		[3aR-(3aα,4β,5β,7β,7aα)]-4-[7-[2-(4-Cianofenoxi)etil]-4-etiloctahidro-5-metoxi-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	6.84 y 7.10 atropisómeros CL $[M+H]^+$= 522.33	504
686		[3aS-(3aα,4β,5β,7β,7aα)]-4-[7-[2-[(5-Cloro-2-piridinil)oxi]etil]octahidro-5-metoxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.37 y 3.52 atropisómeros CL $[M+H]^+$= 518.16	491

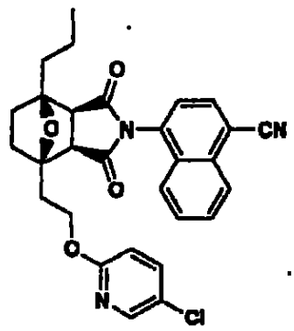
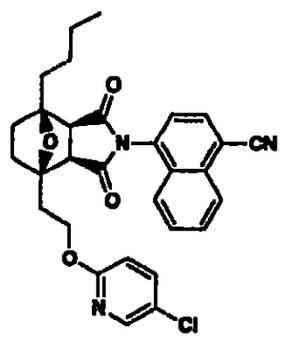
1105

687		[3aS-(3aα,4β,5β,7β,7aα)]-4-[Octahidro-5-metoxi-7-(2-metoxietil)-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	2.57 y 2.75 atropisómeros CL $[M+H]^+$= 421.18	491
688		[3aS-(3aα,4β,7β,7aα)]-4-[Octahidro-4-[2-(3-hidroxifenoxi)etil]-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.38 CLEM $[M+H]^+$= 469.38	496

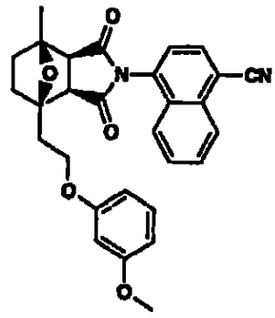
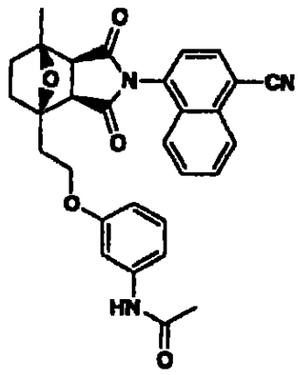
1106

689		[3aS-(3aα,4β,5β,7β,7aα)]-5-[Octahidro-5-hidroxi-4-metil-1,3-dioxo-7-[2-[[6-(trifluorometil)-4-pirimidinil]oxi]etil]-4,7-epoxi-2H-isoindol-2-il]-8-quinolincarbonitrilo	2.833 CL $[M+H]^+$= 540.17	485, 486, 487 y 488
690		[3aS-(3aα,4β,5β,7β,7aα)]-5-[Octahidro-5-hidroxi-4-metil-1,3-dioxo-7-[2-[6-oxo-4-(trifluorometil)-1(6H)-pirimidinil]etil]-4,7-epoxi-2H-isoindol-2-il]-8-quinolincarbonitrilo	2.59 CL $[M+H]^+$= 540.16	485, 486, 487 y 488

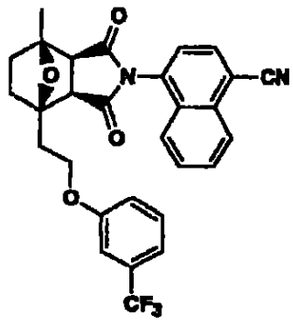
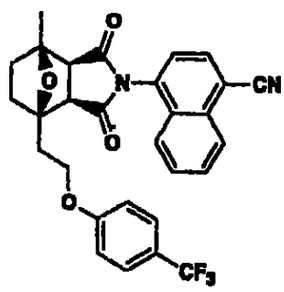
1107

691		[3aS-(3aα,4β,7β,7aα)]-4-[4-[2-[(5-Cloro-2-piridinil)oxi]etil]octahidro-1,3-dioxo-7-propil-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	7.91 y 8.15 atropisómeros CL $[M+H]^+$= 516.25	501
692		[3aS-(3aα,4β,7β,7aα)]-4-[4-Butil-7-[2-[(5-cloro-2-piridinil)oxi]etil]octahidro-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	8.18 y 8.39 atropisómeros CL $[M+H]^+$= 530.28	502

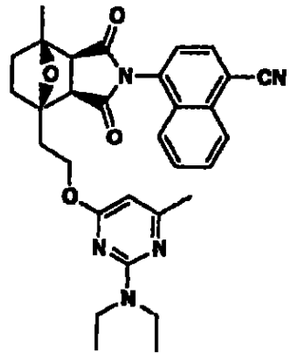
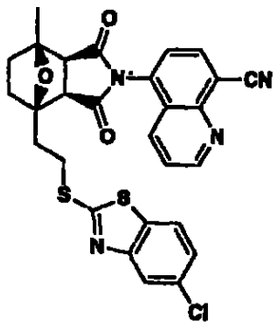
1108

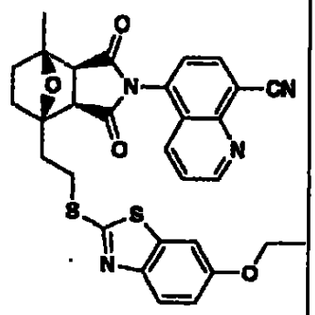
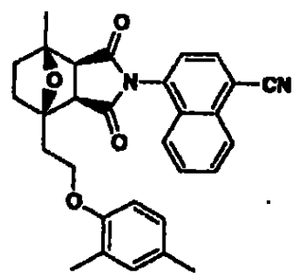
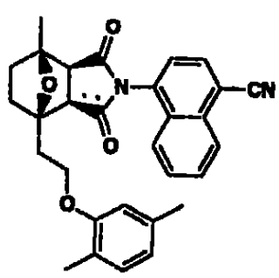
693		[3aS-(3aα,4β,7β,7aα)]-4-[Octahidro-4-[2-(3-metoxifenoxi)etil]-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.97 CLEM $[M+H]^+$= 483.1	496
694		N-[3-[2-[3aS-(3aα,4β,7β,7aα)]-2-(4-Ciano-1-naftalenil)octahidro-7-metil-1,3-dioxo-4,7-epoxi-4H-isoindol-4-il]etoxi]fenilacetamida	3.42 CLEM $[M+H]^+$= 510.1	496

1109

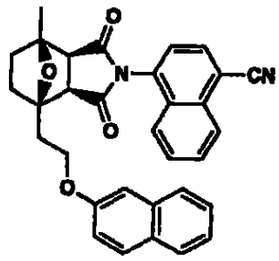
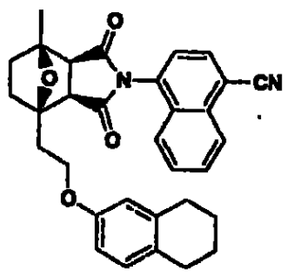
695		[3aS-(3aα,4β,7β,7aα)]-4-[Octahidro-4-metil-1,3-dioxo-7-[2-[3-(trifluorometil)fenoxi]etil]-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.83 CLEM $[M+H]^+$= 521.1	496
696		[3aS-(3aα,4β,7β,7aα)]-4-[Octahidro-4-metil-1,3-dioxo-7-[2-[4-(trifluorometil)fenoxi]etil]-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.86 CLEM $[M+H]^+$= 521.2	496

1110

697		[3aS-(3aα,4β,7β,7aα)]-4-[4-[2-[[2-(Dietilamino)-6-metil-4-pirimidinil]oxi]etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.63 CLEM $[M+H]^+$= 540.2	496
698		[3aS-(3aα,4β,7β,7aα)]-4-[4-[2-[(5-Cloro-2-benzotiazolil)tio]etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	4.15 CLEM $[M+H]^+$= 560.0	496

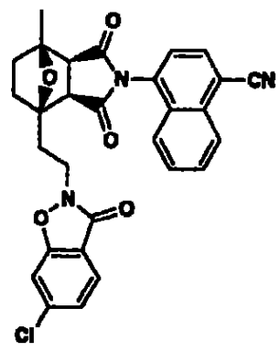
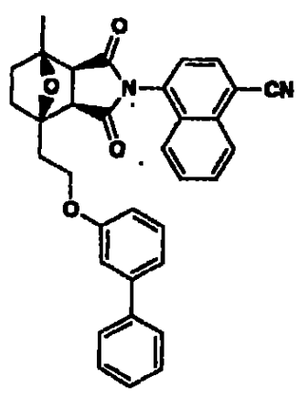
699		[3aS-(3aα,4β,7β,7aα)]-4-[4-[2-[(6-Etoxi-2-benzotiazolil)tio]etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	4.15 CLEM $[M+H]^+$= 570.1	496
700		[3aS-(3aα,4β,7β,7aα)]-4-[4-[2-(2,4-Dimetilfenoxi)etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.71 CLEM $[M+H]^+$= 481.2	496
701		[3aS-(3aα,4β,7β,7aα)]-4-[4-[2-(2,5-Dimetilfenoxi)etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.79 CLEM $[M+H]^+$= 481.2	496

1112

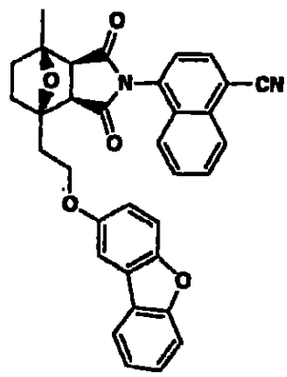
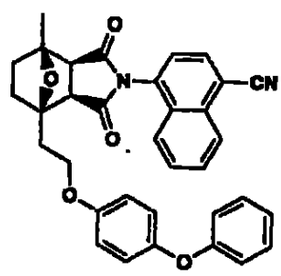
702		[3aS-(3aα,4β,7β,7aα)]-4-[Octahidro-4-metil-7-[2-(2-naftaleniloxi)etil]-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	2.66 CLEM $[M+H]^+$= 503.2	496
703		[3aS-(3aα,4β,7β,7aα)]-4-[Octahidro-4-metil-1,3-dioxo-7-[2-[(5,6,7,8-tetrahidro-2-naftalenil)oxi]etil]-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	2.72 CLEM $[M+H]^+$= 507.2	496

1113

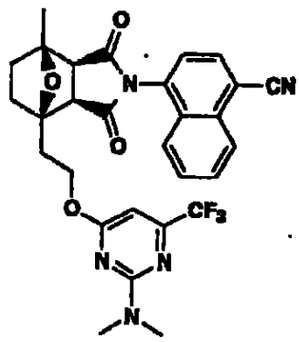
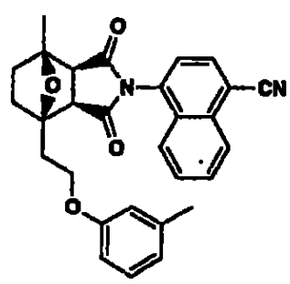
1771

704		[3aS-(3aα,4β,7β,7aα)]-4-[4-[2-(6-Cloro-3-oxo-1,2-benzisoxazol-2(3H)-il)etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	2.71 CLEM $[M+H]^+$= 528.1	496
705		[3aS-(3aα,4β,7β,7aα)]-4-[4-[2-([1'1-Bifenil]-3-iloxi)etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.03 CLEM $[M+H]^+$= 529.2	496

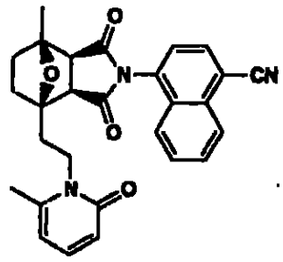
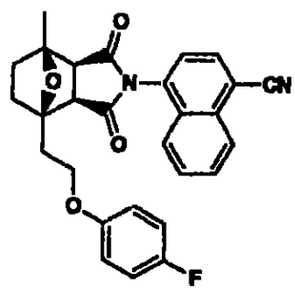
1114

706		[3aS-(3aα,4β,7β,7aα)]-4-[4-[2-(2-Dibenzofuraniloxi)etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.51 CLEM $[M+H]^+$= 543.2	496
707		[3aS-(3aα,4β,7β,7aα)]-4-[Octahidro-4-metil-1,3-dioxo-7-[2-(4-fenoxifenoxi)etil]-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.73 CLEM $[M+H]^+$= 545.2	496

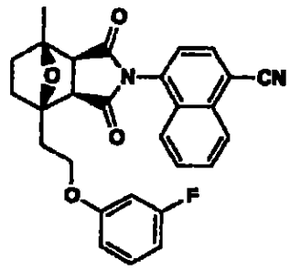
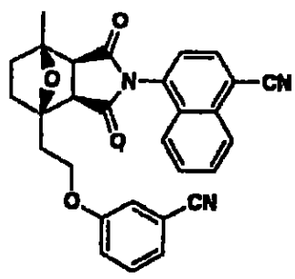
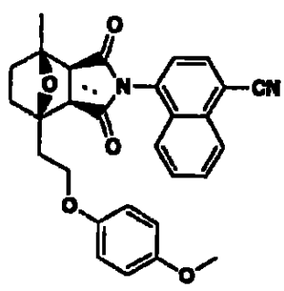
1115

708		[3aS-(3aα,4β,7β,7aα)]-4-[4-[2-[[2-(Dimetilamino)-6-(trifluorometil)-4-pirimidinil]oxi]etil] octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo, trifluoroacetato (1:1)	4.15 CLEM $[M+H]^+$= 566.2	496
709		[3aS-(3aα,4β,7β,7aα)]-4-[Octahidro-4-metil-7-[2-(3-metilfenoxi)etil]-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.17 CLEM $[M+H]^+$= 466.5	496

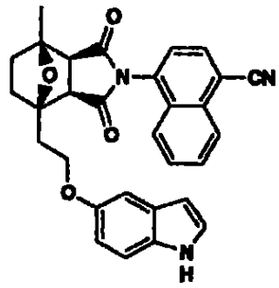
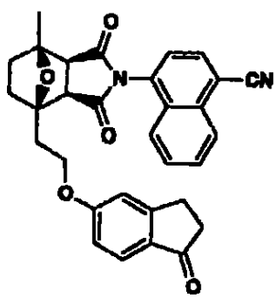
1116

710		[3aS-(3aα,4β,7β,7aα)]-4-[Octahidro-4-metil-7-[2-(6-metil-2-oxo-1(2H)-piridinil)etil]-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.41 CLEM $[M+H]^+$= 468.2	496
711		[3aS-(3aα,4β,7β,7aα)]-4-[4-[2-(4-Fluorofenoxi)etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	4.10 CLEM $[M+H]^+$= 471.2	496

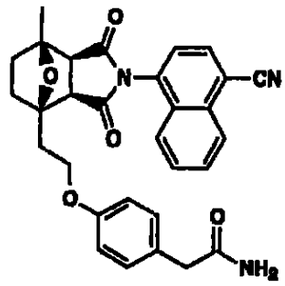
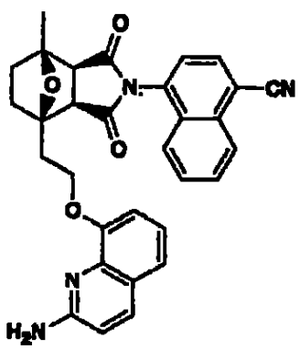
1117

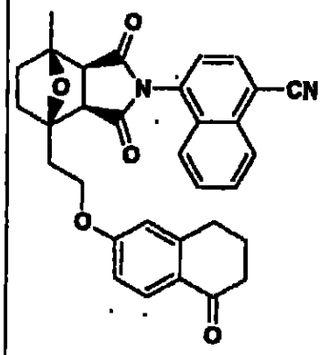
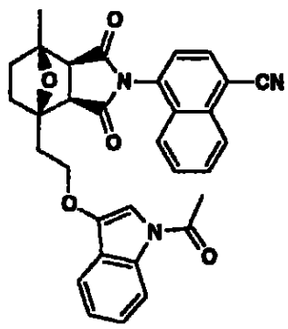
712		[3aS-(3aα,4β,7β,7aα)]-4-[4-[2-(3-Fluorofenoxi)etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.56 CLEM $[M+H]^+$= 471.2	496
713		[3aS-(3aα,4β,7β,7aα)]-4-[4-[2-(3-Cianofenoxi)etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	4.28 CLEM $[M+H]^+$= 478.2	496
714		[3aS-(3aα,4β,7β,7aα)]-4-[Octahidro-4-[2-(4-metoxifenoxi)etil]-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.58 CLEM $[M+H]^+$= 483.2	496

1118

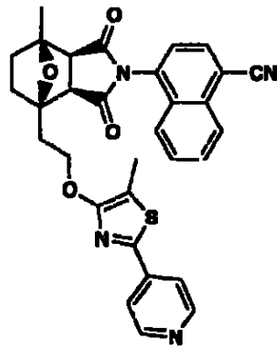
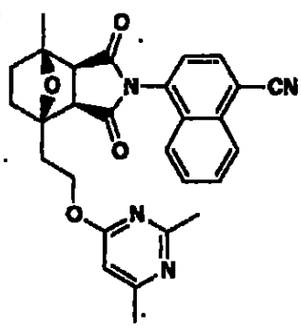
715		[3aS-(3aα,4β,7β,7aα)]-4-[Octahidro-4-[2-(1H-indol-5-iloxi)etil]-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.40 CLEM $[M+H]^+$= 492.2	496
716		[3aS-(3aα,4β,7β,7aα)]-4-[4-[2-[(2,3-Dihidro-1-oxo-1H-inden-5-il)oxi]etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.20 CLEM $[M+H]^+$= 507.2	496

1119

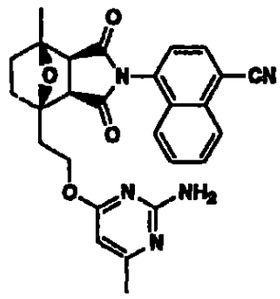
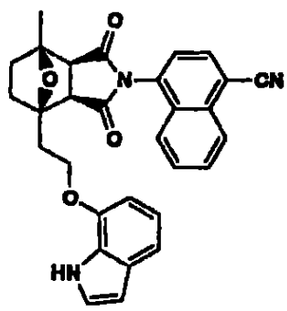
717		[3aS-(3aα,4β,7β,7aα)]-4-[2-[2-(4-Ciano-1-naftalenil)octahidro-7-metil-1,3-dioxo-4,7-epoxi-4H-isoindol-4-il]etoxi]benzenacetamida	3.26 CLEM $[M+H]^+$= 510.2	496
718		[3aS-(3aα,4β,7β,7aα)]-4-[4-[2-[(2-Amino-8-quinolinil)oxi]etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo, trifuoroacetato (1:1)	2.77 CLEM $[M+H]^+$= 519.2	496

719		[3aS-(3aα,4β,7β,7aα)]-4-[Octahidro-4-metil-1,3-dioxo-7-[2-[(5,6,7,8-tetrahidro-5-oxo-2-naftalenil)oxi]etil]-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	2.88 CLEM $[M+H]^+$= 521.2	496
720		[3aS-(3aα,4β,7β,7aα)]-1-Acetil-3-[2-[2-(4-ciano-1-naftalenil)octahidro-7-metil-1,3-dioxo-4,7-epoxi-4H-isoindol-4-il]etoxi]-1H-indol	4.03 CLEM $[M+H]^+$= 534.2	496

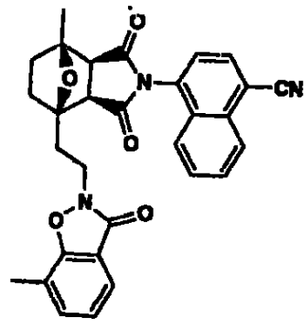
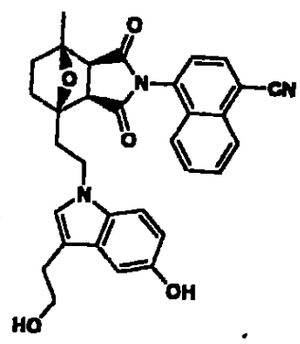
1121

721		[3aS-(3aα,4β,7β,7aα)]-4-[Octahidro-4-metil-7-[2-[[5-metil-2-(4-piridinil)-4-tiazolil]oxi]etil]-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo, trifuoroacetato (1:1)	4.02 CLEM $[M+H]^+$= 551.2	496
722		[3aS-(3aα,4β,7β,7aα)]-4-[4-[2-[(2,6-Dimetil-4-pirimidinil)oxi]etil] octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.74 CLEM $[M+H]^+$= 483.2	496

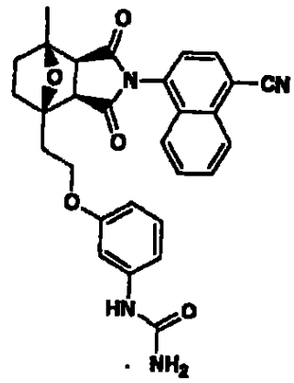
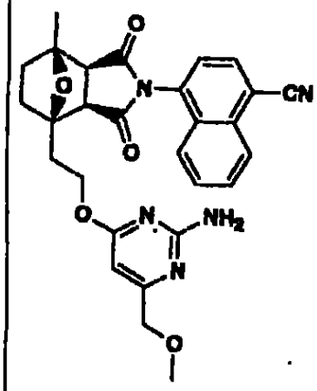
1122

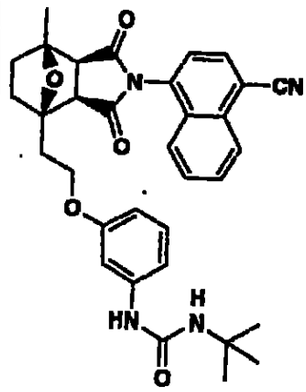
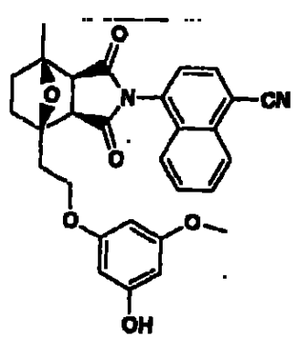
723		[3aS-(3aα,4β,7β,7aα)]-4-[4-[2-[(2-Amino-6-metil-4-pirimidinil)oxi]etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.71 CLEM $[M+H]^+$= 484.2	496
724		[3aS-(3aα,4β,7β,7aα)]-4-[Octahidro-4-[2-(1H-indol-7-iloxi)etil]-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	4.23 CLEM $[M+H]^+$= 492.2	496

1123

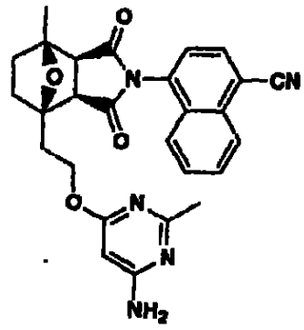
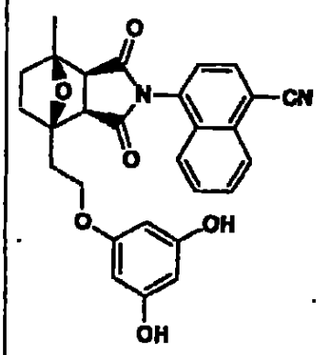
725		[3aS-(3aα,4β,7β,7aα)]-4-[Octahidro-4-metil-7-[2-(7-metil-3-oxo-1,2-benzisoxazol-2(3H)-il)etil]-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.02 CLEM $[M+H]^+$= 508.2	496
726		[3aS-(3aα,4β,7β,7aα)]-4-[Octahidro-4-[2-[5-hidroxi-3-(2-hidroxietil)-1H-indol-1-il]etil]-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	2.94 CLEM $[M+H]^+$= 536.2	496

1124

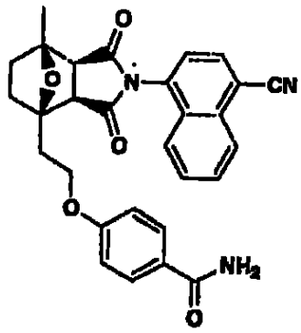
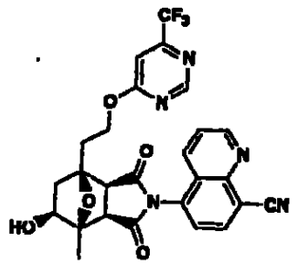
727		N-[3-[2-[[3aS-(3aα,4β,7β,7aα)]-2-(4-Ciano-1-naftalenil)octahidro-7-metil-1,3-dioxo-4,7-epoxi-4H-isoindol-4-il]etoxi]fenil]urea	4.26 CLEM $[M+H]^+$= 511.2	496
728		[3aS-(3aα,4β,7β,7aα)]-4-[4-[2-[[2-Amino-6-(metoximetil)-4-pirimidinil]oxi]etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	4.18 CLEM $[M+H]^+$= 514.2	496

729		N-[3-[2-[[3aS-(3aα,4β,7β,7aα)]-2-(4-Ciano-1-naftalenil)octahidro-7-metil-1,3-dioxo-4,7-epoxi-4H-isoindol-4-il]etoxi]fenil]-N'-(1,1-dimetiletil)urea	3.13 CLEM $[M+H]^+$= 567.2	496
730		[3aS-(3aα,4β,7β,7aα)]-4-[Octahidro-4-[2-(3-hidroxi-5-metoxifenoxi)etil]-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	4.22 CLEM $[M+H]^+$= 499.2	496

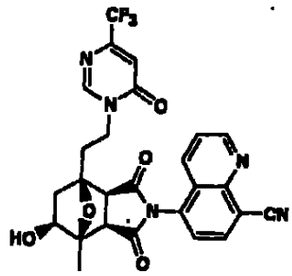
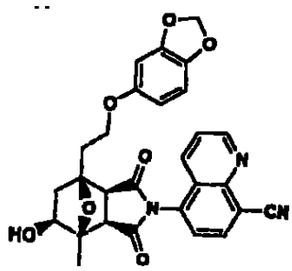
1120

731		[3aS-(3aα,4β,7β,7aα)]-4-[4-[2-[(6-Amino-2-metil-4-pirimidinil)oxi]etil] octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	4.19 CLEM $[M+H]^+$= 484.2	496
732		[3aS-(3aα,4β,7β,7aα)]-4-[4-[2-(3,5-Dihidroxifenoxi)etil] octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.73 CLEM $[M+H]^+$= 485.1	496

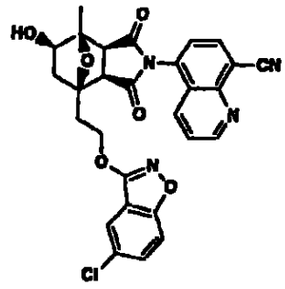
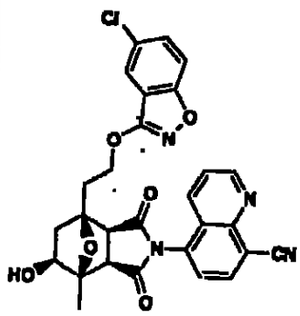
1127

733		[3aS-(3aα,4β,7β,7aα)]-4-[2-[2-(4-ciano-1-naftalenil)octahidro-7-metil-1,3-dioxo-4,7-epoxi-4H-isoindol-4-il]etoxi]benzamida	4.11 CLEM $[M+H]^+$= 496.2	496
734		[3aR-(3aα,4β,5β,7β,7aα)]-5-[Octahidro-5-hidroxi-4-metil-1,3-dioxo-7-[2-[[6-(trifluorometil)-4-pirimidinil]oxi]etil-4,7-epoxi-2H-isoindol-2-il]-8-quinolincarbonitrilo	2.847 CL $[M+H]^+$= 540.14	485, 486, 487 y 488

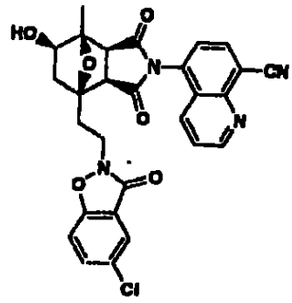
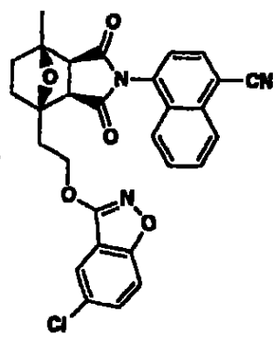
1123

735		[3aR-(3aα,4β,5β,7β,7aα)]-5-[Octahidro-5-hidroxi-4-metil-1,3-dioxo-7-[2-[6-oxo-4-(trifluorometil)-1(6H)-piridinil]etil]-4,7-epoxi-2H-isoindol-2-il]-8-quinolincarbonitrilo	2.577 CLEM $[M+H]^+$= 540.14	485, 486, 487 y 488
736		[3aR-(3aα,4β,5β,7β;7aα)]-5-[7-[2-(1,3-Benzodioxol-5-iloxi)etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-8-quinolincarbonitrilo	2.867 CLEM $[M+H]^+$= 514.16	485, 486, 487 y 488

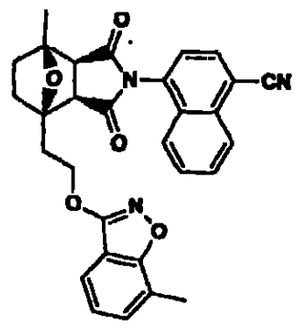
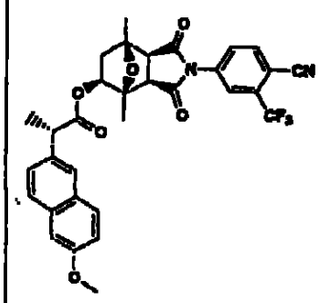
1129

737		[3aS-(3aα,4β,5β,7β,7aα)]-5-[7-[2-[(5-Cloro-1,2-benzisoxazol-3-il)oxi]etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-8-quinolincarbonitrilo	3.24 CLEM $[M+H]^+$= 545.12	485, 486, 487 y 488
738		[3aR-(3aα,4β,5β,7β,7aα)]-5-[7-[2-[(5-Cloro-1,2-benzisoxazol-3-il)oxi]etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-8-quinolincarbonitrilo	3.25 CLEM $[M+H]^+$= 545.12	485, 486, 487 y 488

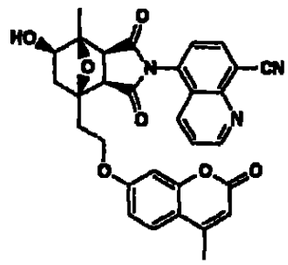
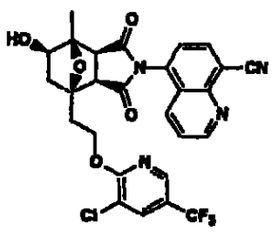
1130

739		[3aS-(3aα,4β,5β,7β,7aα)]-5-[7-[2-(5-Cloro-3-oxo-1,2-benzisoxazol-2(3H)-il)etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-8-quinolincarbonitrilo	2.863 CLEM $[M+H]^+$= 545.12	485, 486, 487 y 488
740		[3aS-(3aα,4β,7β,7aα)]-4-[4-[2-[(6-Cloro-1,2-benzisoxazol-3-il)oxi]etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	4.04 CLEM $[M+H]^+$= 528.1	496

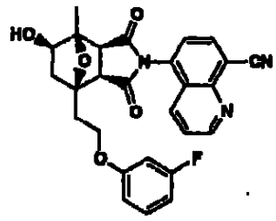
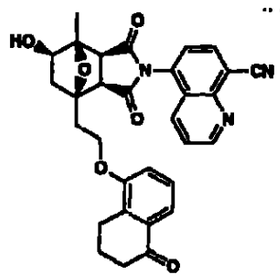
1131

741		[3aS-(3aα,4β,7β,7aα)]-4-[Octahidro-4-metil-7-[2-[(7-metil-1,2-benzisoxazol-3-il)oxi]etil]-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo	3.94 CLEM $[M+H]^+$= 508.1	496
742		Éster de [3aR-(3aα,4β,5β,7β,7aα)]-2-[4-ciano-3-(trifluorometil)fenil]octahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-1H-isoindol-5-ilo del ácido (αS)-6-Metoxi-α-metil-2-naftalenacético	$[M-H]^-$= 591.3	483

1132

743		[3aS-(3aα,4β,5β,7β,7aα)]-5-[Octahidro-5-hidroxi-4-metil-7-[2-[(4-metil-2-oxo-2H-1-benzopiran-7-il)oxi]etil]-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-8-quinolincarbonitrilo	2.89 CLEM $[M+H]^+$= 552.19	485, 486, 487 y 488
744		[3aS-(3aα,4β,5β,7β,7aα)]-5-[7-[2-[[3-Cloro-5-(trifluorometil)-2-piridinil]oxi]etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-8-quinolincarbonitrilo	3.46 CLEM $[M+H]^+$= 573.12	485, 486, 487 y 488

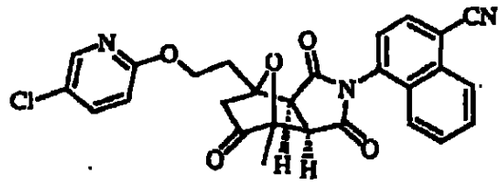
1133

745		[3aS-(3aα,4β,5β,7β,7aα)]-5-[7-[2-(3-Fluorofenoxi)etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-8-quinolincarbonitrilo	3.05 CLEM $[M+H]^+$= 488.03	485, 486, 487 y 488
746		[3aS-(3aα,4β,5β,7β,7aα)]-5-[Octahidro-5-hidroxi-4-metil-1,3-dioxo-7-[2-[(5,6,7,8-tetrahidro-5-oxo-1-naftalenil)oxi]etil]-4,7-epoxi-2H-isoindol-2-il]-8-quinolincarbonitrilo	2.98 CLEM $[M+H]^+$= 538.23	485, 486, 487 y 488

1134

Ejemplo 747

[3aR-(3aα,4β,7β,7aα)]-4-[7-[2-[(5-Cloro-2-piridinil)oxi]etil]octahidro-4-metil-1,3,5-trioxo-4,7-epoxi-2H-isoindol-2-il]-1-naftalencarbonitrilo (747)



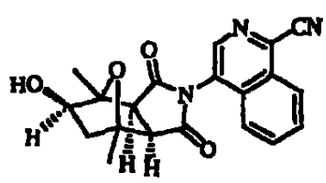
El peryodinano Dess-Martin (122 mg, 0.29 mmol, preparado como se describe en Ishiharaa, J., T. Fukuzakia, et al. Tetrahedron Letters 40(10), 1907-1910 (1999)) se agregó a una solución del compuesto 490A (120 mg, 0.24 mmol) en diclorometano (2.5 mL) bajo nitrógeno y la mezcla se agitó por 4h. La reacción se concentró a la mitad bajo una corriente de nitrógeno y se aplicó sobre un cartucho instantáneo (Jones 2 g) con celite en la parte superior y se eluyó con cloroformo:heptano (9:1) hasta cloroformo:acetona (4:1) para dar 148 mg de un sólido blanco todavía impuro. El sólido se disolvió en diclorometano (5 mL) y heptano (3 mL) y el precipitado se filtró sobre 1 g de sílice y se eluyó con diclorometano hasta cloroformo:acetona (4:1). Las fracciones 3-9 (58.8 mg de sólido blanco) fueron casi puras y las fracciones 10-13 (68 mg espuma blanca) estuvieron todavía impuras. Las fracciones 3-9 se purificaron sobre sílice (1 g) usando heptano a heptano:acetato de etilo (1:1) como eluyente para dar 35.8 mg (30% de rendimiento) del compuesto 747 como

1135

un sólido blanco. Las fracciones 10-13 se purificaron al agregar ~400 mg de sílice a una solución en exceso del compuesto crudo 747 en acetato de etilo y heptano y concentrándolas. La sílice se puso después en la parte superior de una columna preacondicionada (heptano) de sílice (1 g) y se eluyó con un gradiente de heptano a heptano acetato de etilo (1:1) para dar 36.7 mg adicionales (31% rendimiento) del compuesto 747 como un sólido blanco. CLAR: 94% a 3.46 y 3.59 min. (atropisómeros, tiempo de retención) (YMC S5 ODS 4.6 X 50 mm, 4 mL min., 4 min. gradiente 100% A hasta 100% B (A: 10% metanol, 89.1% agua, 0.1% TFA; B: 10% agua, 89.1% metanol, 0.1% TFA, 4 mL/min., observando a 220 nm). MS (ES): m/z 502.11 $[M+H]^+$.

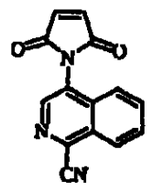
Ejemplo 748

(3aα,4β,5β,7β,7aα)-4-[Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-isoquinolinocarbonitrilo (748D)



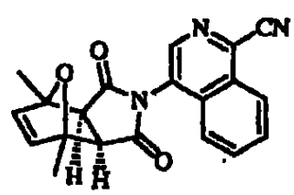
A. 4-(2,5-Dioxo-2,5-dihidro-pirrol-1-il)-isoquinolino-1-carbonitrilo (748A)

1136



Una mezcla de compuesto 470D (200 mg, 1.18 mmol) y anhidrido maleico (470 mg, 4.7 mmol) en ácido acético glacial (5 mL) se calentó a reflujo por 4 horas. Después de eliminar los volátiles in vacuo, el residuo se dividió entre acetato de etilo (50 mL) y agua (50 mL). La capa orgánica se lavó con una solución saturada de bicarbonato de sodio (2 x 50 mL) y salmuera (50 mL). Después de secar sobre sulfato de magnesio, la capa orgánica se filtró a través de un tapón de 1 x 5 cm de gel de sílice. El filtrado se concentró para dar 263 mg (90%) de 748a como un sólido blanco descolorido. CLAR: 99% a 1.12 min. (Phenomenex 5 micron ODS 4.6X30 mm, 10%-90% metanol acuoso durante un gradiente de 2 minutos con 0.1% TFA, detectando a 254 nm). MS (ES): m/z 250.2 $[M+H]^+$.

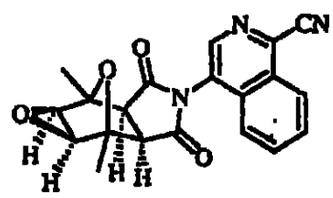
B. (3aα,4β;7β,7aα)-4-(1,3,3a,4,7,7a-Hexahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-1-isoquinolinocarbonitrilo (748B)



1137

Una mezcla de compuesto 748A (250 mg, 1 mmol) y 2,5-dimetilfurano (4 mL) se calentó a 60°C por 2 h. a 15 min., La mezcla de reacción se hizo homogénea. Se formó un precipitado a los 45 minutos. Después de enfriar hasta 25°C, la mezcla de reacción se diluyó con hexano y la torta filtro se lavó con etil éter:hexano, 1:1. El secado bajo alto vacío resultó en 270 mg (78%) de compuesto 748B como un sólido amarillo claro. ^{1}H RMN-400 MHz ($CDCl_3$): δ 8.55 (s, 1H), 8.54 (m, 1H), 7.86 (m, 3H), 6.45 (s, 2H), 3.18 (s, 2H), 1.81 (s, 6H).

C. (1aα,2β,2aα,5aα,6β,6aα)-4-[Octahidro-2,6-dimetil-3,5-dioxo-2,6-epoxi-4H-oxireno[f]isoindol-4-il]-1-isoquinolinocarbonitrilo (748C)



Se agregó m-CPBA, (70%, 110 mg, 0.45 mmol) a una solución de compuesto 748B (100 mg, 0.29 mmol) en 3 mL de diclorometano a 25°C. Después de 1 h, se agregó m-CPBA adicional, (70%, 110 mg, 0.45 mmol) y la mezcla de reacción se agitó 18 h adicionales. Después de dividir la mezcla de reacción entre acetato de etilo (30 mL) y agua (30 mL), la capa orgánica se lavó con solución saturada de bisulfito de

1138

sodio (30 mL), solución saturada de bicarbonato de sodio (2 x 30 mL) y salmuera (30 mL). La muestra se secó sobre sulfato de magnesio y concentración para resultar en 103 mg (98%) del compuesto 748C como un sólido blanco descolorido. CLAR: 99% a 1.09 y 1.22 min. (atropisómeros, tiempo de retención) (Phenomenex 5 micras ODS 4.6X30 mm, 10%-90% metanol acuoso durante un gradiente de 2 min. con 0.1% TFA, detectando a 254 nm). MS (ES): m/z 362.07 $[M+H]^+$.

D. (3aα,4β,5β,7β,7aα)-4-[Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-isoquinolinocarbonitrilo (748D)

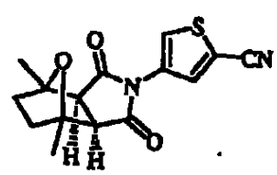
Una solución 0.5 M de cloruro de bis(ciclopentadienil)titanio en THF (1.2 mL, 0.6 mmol) se agregó gota a gota durante 20 min. a una suspensión bien agitada de compuesto 748C (103 mg, 0.29 mmol) en THF (2.5 mL) y 1,4-ciclohexadieno (1.2 mL) a 60°C. Después de agitar 1 h a 60°C, la mezcla de reacción se dividió entre HCl 1N (40 mL) y acetato de etilo (50 mL). El pH de la capa acuosa se ajustó hasta 7 con bicarbonato de sodio sólido. Después de extraer la capa acuosa con acetato de etilo, las capas orgánicas combinadas se secaron sobre sulfato de sodio. Se agregó carbón decolorante (~1 g) y la mezcla se dejó reposar por 18 h. La filtración y la concentración del filtrado in vacuo, resultaron en un aceite amarillo que se cromatografió sobre

1139

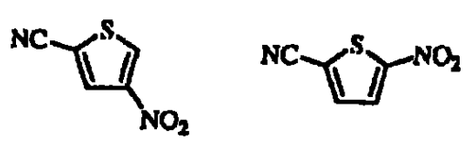
una columna de gel de sílice de 2.5 x 15 cm, usando diclorometano:acetona, 6:4 como la fase móvil. La concentración del producto conteniendo fracciones in vacuo dio un residuo parcialmente purificado que se sometió a cromatografía de capa delgada preparativa sobre gel de sílice, usando diclorometano:acetona 6.4 como la fase móvil. La extracción de la banda deseada con CH_2Cl_2, la filtración y la concentración del filtrado in vacuo resultaron en 3 mg (31%) de compuesto 748D como un sólido blanco descolorido. Condiciones CLAR: 95% a 1.46 min (Phenomenex 5 micras ODS 4 6X30 mm, 10%-90% metanol acuoso durante un gradiente de 2 minutos con 0.1% TTA, detectando a 254 nm). MS (ES): m/z 364.19 $[M+H]^+$

Ejemplo 749

(3aα,4β,7β,7α)-4-[Octahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2-tiofencarbonitrilo (749C)



A. 2-Ciano-4-nitrotiofeno (749Ai) y 2-Ciano-5-nitrotiofeno (749Aii)

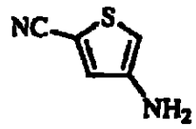


1140

Se agregó lentamente ácido nítrico fumante (21 mL) al ácido acético glacial (105 mL) y la mezcla se enfrió después en un baño de hielo. 2-Cianotiofeno (7.98 g. 73.1 mmol) se disolvió en 20 mL de anhidrido acético y se agregó gota a gota a la mezcla ácida anterior, de manera que la temperatura no superara 25°C. Al terminar la adición, la mezcla de reacción se calentó hasta 22°C y se agitó por 48 h. La reacción se vació sobre 400 mL de hielo y se extrajo con 200 mL de dietil éter. La capa de éter se aisló, se lavó con agua, seguida por salmuera y se secó sobre $MgSO_4$. La filtración y la concentración in vacuo dio un residuo color naranja, pegajoso, que fue purificado por cromatografía en columna usando 1:1 hexanos/ cloruro de metileno como el eluyente para dar 1.69 g (15%) de compuesto 749Ai como un sólido blanco y 1.71 g (15%) de compuesto 749Aii como una substancia cristalina amarilla. Compuesto 749Ai: CLAR: 0.73 minutos (tiempo de retención) (Columna Phenomenex 30 x 4.6 mm eluye con 10-90% metanol acuoso durante 2 minutos conteniendo 0.1% TFA, 5 mL/min., observando a 220 nm). Compuesto 749Aii: CLAR: 99% a 0.89 minutos (tiempo de retención) (Columna Phenomenex 30 x 4.6 mm eluyendo con 10-90% metanol acuoso durante 2 minutos conteniendo 0.1% TFA, 5 mL/min., observando a 220 nm).

1441

B. 4-Amino-2-cianotiofeno (749B)



A un matraz de 3 cuellos de 100 mL, se agregó el compuesto 749Ai (1.42 g, 9.21 mmol) disuelto en acetato de etilo (20 mL) seguido por una solución al 10% de ácido acético (20 mL). La mezcla bifásica se calentó a 65°C y se agregó después polvo de hierro (2.95 g, 52.9 mmol) en porciones durante 5 minutos. Después de agitar por 1.5 h a 65°C, la reacción se filtró a través de un lecho de Celite y la almohadilla se lavó con acetato de etilo. La capa orgánica se separó, se lavó con agua (3 x 20 mL), salmuera y se secó sobre $MgSO_4$. La filtración y la concentración in vacuo dio un residuo ámbar oscuro que fue purificado por cromatografía en columna usando 30% de dietil éter/cloruro de metileno como eluyente para dar 84 mg (73%) de compuesto 749B como un sólido café. CLAR: 93.4% a 0 26 minutos (tiempo de retención) (columna YMC S5 ODS 4.6 x 50 mm eluyendo con 10-90% metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm).

C. (3aα,4β,7β,7aα)-4-[Octahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2-tiofenocarbonitrilo (749C)

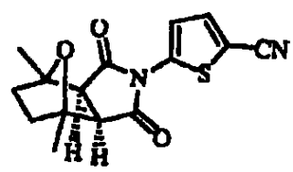
A un tubo Pyrex se agregó el compuesto 749B (0.06 g, 0.5 mmol), tolueno (1 mL), trietilamina (0.25 g, 0.35 mL, 2.5

1142

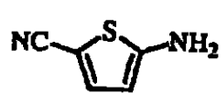
mmol), $MgSO_4$ (0.15 g, 1.3 mmol), y compuesto 20A. El tubo se selló con una tapa de teflón y se calentó durante la noche a 145°C. La reacción se enfrió, se diluyó con cloruro de metileno y se filtró a través de Celite. El filtrado se concentró in vacuo y el residuo se purificó por cromatografía en columna usando 10% de éter/cloruro de metileno como eluyente para dar 14 mg (95%) de compuesto 749C como un sólido cristalino amarillo claro. CLAR: 94.6% a 2.6 minutos (tiempo de retención) (columna YMC S5 ODS 4.6 x 50 mm eluyendo con 10-90% metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm. MS (ES): m/z 303.05 $[M+H]^+$.

Ejemplo 750

(3aα,4β,7β,7aα)-5-[Octahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2-tiofenocarbonitrilo (750B)



A. 5-Amino-2-cianotiofeno (750A)



A un matraz de 3 cuellos de 100 mL se agregó el compuesto 749Aii (1.63 g 10 1 mmol) disuelto en acetato de

1143

etilo (20 mL) seguido por una solución al 10% de ácido acético (20 mL). La mezcla bifásica se calentó a 65°C y después se agregó polvo de hierro (2.95 g, 52.9 mmol) en porciones durante 5 minutos. Después de agitar por 1.5 h a 65°C, La reacción se filtró a través de una cama de Celite y la almohadilla se lavó con acetato de etilo. La capa orgánica se separó, se lavó con agua (3 x 20 mL), salmuera y se secaron sobre $MgSO_4$. La filtración y la concentración in vacuo dio un residuo ámbar oscuro que fue purificado por cromatografía en columna usando 10% de dietil éter/cloruro de metileno como eluyente para dar 87 mg (66%) de compuesto 750A como un sólido café. CLAR: 94.2% a 1.05 minutos (tiempo de retención) (columna YMC S5 ODS 4.6 x 50 mm eluyendo con 10-90% metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm).

B. (3aα,4β,7β,7aα)-5-[Octahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2-tiofenocarbonitrilo (750B)

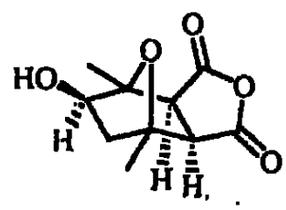
Se agregó a un tubo Pyrex el compuesto 750A (0.06 g, 0.5 mmol), tolueno (1 mL), trietilamina (0.25 g, 0.35 mL, 2.5 mmol), $MgSO_4$ (0.15 g. 1.3 mmol), y el compuesto 20B. El tubo se selló con una tapa de teflón y se calentó durante la noche a 145° C. La reacción se enfrió, se diluyó con cloruro de metileno y se filtró a través de Celite. El filtrado se concentró in vacuo y el residuo se purificó por cromatografía

1144

en columna usando 10% éter/cloruro de metileno como el eluyente para producir 143 mg (96%) de compuesto 750B como un sólido cristalino amarillo claro. CLAR: 92.7% a 2.93 minutos (tiempo de retención) (columna YMC S5 ODS 4.6 x 50 mm eluyendo con 10-90% metanol acuoso durante 4 minutos conteniendo 0.2% ácido fosfórico, 4 mL/min., monitoreando a 220 nm. MS (ES): m/z 303.21 $[M+H]^+$.

Ejemplo 751

[3aS-(3aα,4β,7β,7aα)]-Hexahidro-5-hidroxi-4,7-dimetil-4,7-epoxiisobenzofuran-1,3-diona (751)



A una solución del compuesto 471Dii (2.36 g, 6.21 mmol) en tetrahidrofurano (THF, 20 mL) se enfrió en un baño de hielo (~5°C) se agregó, en una porción, solución 1M NaOH acuosa (10 mL, 10 mmol). La mezcla de reacción amarillo claro resultante, se agitó por 30 min., después se acidificó por la adición de una solución HCl 1M acuoso (12 mL, 12 mmol) y se dividió entre agua (100 mL) y EtOAc (40 mL). La capa acuosa se separó y extrajo con EtOAc (25 mL). Las fases orgánicas se combinaron, se secaron rápidamente sobre sulfato de sodio y se filtraron, enjuagando con THF caliente para

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disolver algún producto sólido precipitado. Se filtró el concentrado in vacuo para dar el intermediario amido-ácido de anillo abierto, crudo como un sólido blanco. Una suspensión del material crudo suspendida en 60 mL de THF seco y 25 mL de HOAc glacial y se calentó con agitación hasta 60°C tiempo durante el cual la mezcla se hizo homogénea. Después de 9 h, la mezcla de reacción se enfrió y concentró in vacuo para dar un sólido amarillo pálido. El sólido se trituró con 30 mL de tolueno, se entibió (~50 °C), se dejó después enfriar a temperatura ambiente. El producto insoluble se recolectó en un embudo Buchner, se lavó con tolueno y se secó bajo vacío para resultar el compuesto 751 (75%) como un sólido blanco. 400 MHz ^{1}H RMN (DMSO-d_6) δ 1.34 (s, 3H), 1.34 (m, 1H), 1.45 (s, 3H), 2.32 (dd, J=7.3, 13.1, 1H), 3.20 (d, J=7.3, 1H), 3.28 (d, J=7.2, 1H), 3.79 (m, 1H), 5.11 (d, J=6.1, 1H); 100 MHz ^{13}C RMN (DMSO-d_6) δ 169.6, 86.7, 82.3, 72.8, 52.9, 50.3, 46.5, 16.0, 11.2. La estereoquímica absoluta del compuesto 751 se establece por la estereoquímica conocida del compuesto intermediario 471Dii y la retención de la configuración en ella. La estereoquímica absoluta es como se obtiene en la figura anterior.

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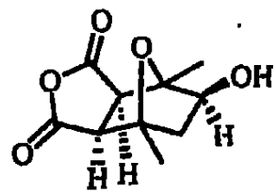
Ejemplo 752

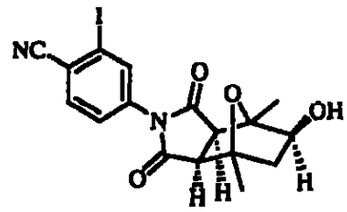
[3aR-(3aα,4β,7β,7aα)]-Hexahidro-5-hidroxi-4,7-dimetil-4,7-epoxiisobenzofuran-1,3-diona (752)



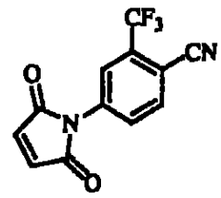
El compuesto 752 se sintetizó como se describe en el ejemplo 751 con la excepción de que el compuesto de partida 471Di se utilizó como el material de partida, más que el compuesto 471Dii. 400 MHz ^{1}H RMN (DMSO-d_6) δ 1.34 (s, 3H), 1.34 (m, 1H), 1.45 (s, 3H), 2.32 (dd, J=7.3, 13.1, 1H), 3.20 (d, J=7.3, 1H), 3.28 (d, J=7.2, 1H), 3.79 (m, 1H), 5.11 (d, J=6.1, 1H); 100 MHz ^{13}C RMN (DMSO-d_6) δ 169.6, 86.7, 82.3, 72.8, 52.9, 50.3, 46.5, 16.0, 11.2. La estereoquímica absoluta del compuesto 752 se establece por la estereoquímica conocida del compuesto intermediario 471Di y la retención de la configuración en ella. La estereoquímica absoluta es como se obtiene en la figura anterior.

Ejemplo 753

[3aR-(3aα,4β,5β,7β,7aα)]-4-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-yodobenzonitrilo (753G)



A. 4-(2,5-Dioxo-2,5-dihidro-pirrol-1-il)-2-trifluorometil-benzonitrilo (453A)



Una mezcla de 3-trifluorometil-4-ciano-anilina (24.0 g, 129 mmol) y anhidrido maleico (14.0 g, 143 mmol) en 50 mL de ácido acético se calentó a 115°C durante la noche. Se obtuvo un precipitado durante el periodo de calentamiento. La reacción se dejó reposar a temperatura ambiente por un periodo adicional durante la noche. El sólido se separó por filtración, la torta filtro se lavó con éter de dietilo y se secó para dar 21 g (79 mmol, 61%) del compuesto 753A como un sólido blanco descolorido. CLAR: 100% a 2.11 min. (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, se eluye con 10-90% metanol acuoso durante 4 min. conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm).

B. (3aα,4β,7β,7aα)]-4-(1,3,3a,4,7,7a-Hexahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo (753B)

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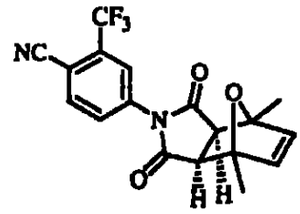
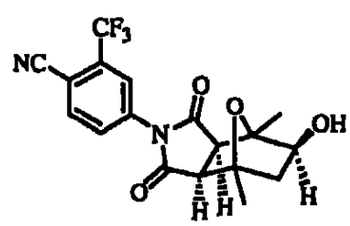


Una suspensión de 4-(2,5-dihidro-2,5-2,5-dioxo-1H-pirrol-1-il)-2-trifluorometil-benzonitrilo (15.0g, 56.35 mmol) y 2,5-dimetilfurano (32.5g, 338 mmol) se agitó a 60°C por 3h, seguido por la agitación continua por otras 14h a 23°C. La mezcla se diluyó con tolueno frío (~5°C) (15 mL) y el sólido blanco descolorido resultante se recolectó por filtración mientras estaba frío. La torta filtro se lavó con tolueno frío (20 mL) y se secó a 23°C en un horno al vacío por 24 h para proporcionar el compuesto 753B (18.6g, 91% rendimiento) con una pureza de 98.7% como se califica por CLAR.

C. [3aR-(3aα,4β,5β,7β,7aα)]-4-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo (753C)



Una suspensión espesa del compuesto 753B (5.0g, 13.81 mmol), dímero de cloruro de alilpaladio (10 mg, 0.027 mmol) y

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(R)-2-metoxi-2'-difenilfosfino-1,1'-binaftilo (R-MOP, 26mg, 0.055 mmol) en THF (14 mL) se purgó con nitrógeno y se enfrió hasta 10°C. A la mezcla anterior, se agregó triclorosilano (3.7g, 27.62 mmol) lentamente durante un periodo de 10 min. y la mezcla heterogénea resultante se agitó por 24 h a 10°C. La mezcla se diluyó con THF (85 mL) y se enfrió además hasta -20°C. A la mezcla anterior se agregó una solución de trietilamina (9.76g, 96.67 mmol) en etanol (6.35g, 138.1 mmol), lentamente manteniendo la temperatura <25°C y se agitó por otras 2 h a temperatura ambiente. El sólido blanco se filtró y la torta filtro se lavó con THF (50 mL) y el filtrado se evaporó bajo presión reducida. El residuo aceitoso se disolvió en acetato de etilo (100 mL) y se agitó a 23°C en presencia de ácido tritiocianúrico (TMT, 500mg) y carbón mineral (500mg) por 5h. La suspensión espesa se filtró a través de una almohadilla de celite y gel de sílice y el filtrado se evaporó bajo presión reducida. El residuo se disolvió en una mezcla de THF (175 mL) y metanol (125 mL), y a esta mezcla se agregó fluoruro de potasio anhidro (2.0g, 34.5 mmol), carbonato ácido de potasio (6.9g, 69 mmol), seguido por el aducto de peróxido de hidrógeno-urea (6.5g, 69 mmol). Esta suspensión se agitó a temperatura ambiente por 14 h y se agregó una cantidad adicional de fluoruro de potasio (800 mg, 13.81 mmol), carbonato ácido de potasio (1.38 g, 13.81 mmol) y aducto de peróxido de hidrógeno-urea (2.59 g,

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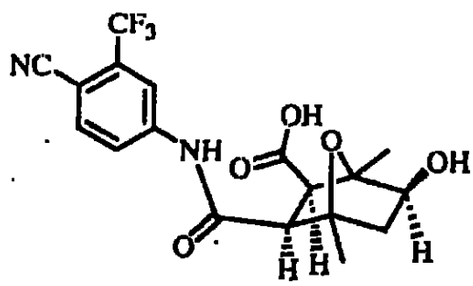
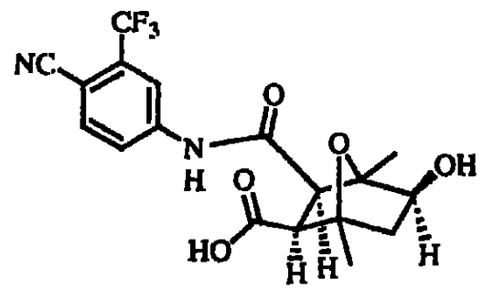
27.62 mmol). La agitación continuó por otras 12 h y la suspensión espesa se filtró y la torta filtro se lavó con acetato de etilo (100 mL). El filtrado se lavó consecutivamente con sulfito ácido de sodio acuoso al 10% (50 mL x 2), agua (50 mL) y salmuera (50 mL). El solvente se evaporó bajo presión reducida para proporcionar una espuma café claro. La cromatografía en columna de esta espuma usando gel de sílice y EtOAc-heptano (2:3) resultó en el compuesto 753C (4.72g, 90%, >99% puro por CLAR) como un sólido blanco descolorido. Este material tiene una pureza enantiomérica de >96% ee por CLAR quiral y CL-EM: m/z 379 ($M+H^-$). La estereoquímica absoluta del compuesto 753C se estableció por comparación con el material existente de estereoquímica conocida como se describe en el Ejemplo 483.

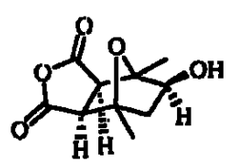
D. Ácido [1S-(1β,2α,3α,4β,6β)]-3-[[(4-Ciano-3-(trifluorometil)fenil)amino]carbonil]-6-hidroxi-1,4-dimetil-7-oxa-biciclo[2.2.1]heptano-2-carboxílico y ácido [1R-(1β,2α,3α,4β,5β)]-3-[[(4-Ciano-3-(trifluorometil)fenil)amino]carbonil]-5-hidroxi-1,4-dimetil-7-oxa-biciclo[2.2.1]heptano-2-carboxílico (753Di y 753Dii)





El compuesto 753C (25.0 g, 65.7 mmol) se disolvió en THF (100 mL) a 22°C y se agregó 1 N NaOH (100 mL). Después de 1 h, se agregó THF (100 mL), HCl 1 N (110 mL) y salmuera (100 mL). La mezcla se extrajo después una vez con EtOAc (200 mL) y dos veces con 1:1 THF/EtOAc (200 mL). Los compuestos orgánicos combinados se secaron sobre $MgSO_4$ anhidro, se filtraron y concentraron in vacuo para dar los compuestos 753Di y 753Dii (1:1 por CLAR) como un sólido blanco. No fue necesaria purificación. CLAR: 100% a 2.217 y 2.413 min. (tiempo de retención) (columna YMC S5 ODS-A 4.6 x 50 mm se eluye con 10-90% metanol acuoso durante 4 min., contiene 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm).

E. [3aR-(3aα,4β,7β,7aα)]-Hexahidro-5-hidroxi-4,7-dimetil-4,7-epoxiisobenzofuran-1,3-diona (753E)

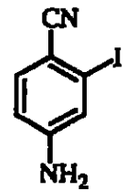


1152

Los compuestos 753Di y 753Dii se suspendieron en una mezcla de THF (500 mL) y AcOH (200 mL) y se calentaron hasta 60°C por 16 h. La reacción se hizo homogénea después de 4 h. La reacción se enfrió a 22°C y se concentró in vacuo. Se agregó después tolueno (200 mL) y la mezcla se calentó hasta 90°C por 4 h hasta que se había disuelto todo el producto. La mezcla se enfrió después hasta 22°C y se dejó reposar por 20 h. El compuesto 753E se precipita de la solución durante un periodo de 20 h. El sólido resultante se filtró y enjuagó con tolueno, seguido por secado in vacuo. Se obtuvo un rendimiento de 11.93 g del compuesto crudo 753E como un sólido blanco descolorido. El compuesto crudo 753E (10 g) se disolvió en 350 ml de EtOAc tibio (La solución estaba turbia), y después se agregaron 5 g de carbón decolorante y la mezcla se agitó a temperatura ambiente por 40 min. Después de filtrar a través de celite, la torta filtro se lavó con EtOAc caliente (2 x 50 ml). La concentración del filtrado resultó en un sólido blanco descolorido que se disolvió en 40 ml de acetonitrilo caliente. Después de agregar cuidadosamente 200 ml de éter de etilo, se agregaron 300 ml de hexano y el matraz se dejó reposar 18 hrs a temperatura ambiente. La filtración y secado resultaron en 8.32 g del compuesto 753E como un sólido cristalino incoloro. ^{1}H RMN(DMSO-d^6): δ = 5.11 (d, 1H, J = 6.0 Hz), 3.78 (dd, 1H, J = 7.2, 30.6 Hz), 3.27 (d, 1 H, J = 7.2 Hz), 3.20 (d, 1 H, J =

7.3 Hz), 2.27 (dd, 1H, J = 7.3, 13.1 Hz), 1.44 (s, 3H), 1.33 (s, 3 H) y 1.32 ppm (m, 1H).

F. 4-Amino-2-yodo-benzonitrilo (753F)



El 2-yodo-4-nitro-benzonitrilo (1.00 g, 3.65 mmol, se preparó por el método dado en J. Med. Chem. 2000, 43, 3344-47) se disolvió en THF (20 mL) a 60°C con agitación mecánica. Se agregó después EtOH (25 mL), seguido de NH_4Cl acuoso (0.293 g, 5.48 mmol en 20 mL H_2O). Se agregó después polvo de hierro (malla 325, 0.815 g, 14.6 mmol) con agitación vigorosa. Después de 2 h, la reacción estaba completa. Se enfrió a 22°C y se filtró a través de celite enjuagando con EtOAc. La mezcla se concentró después hasta ~20 mL y después se diluyó con EtOAc (200 mL) y se lavó una vez con 1 N NaOH (50 mL), una vez con salmuera (50 mL) y se secó sobre $MgSO_4$ anhidro, para dar compuesto el 753F (0.710 g) como un sólido amarillo claro. No se necesitó purificación adicional. CLAR: 99% a 2.147 min. (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, se eluye con 10-90% metanol acuoso durante 4 min. conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm).

G. [3aR-(3aα,4β,5β,7β,7aα)]-4-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-yodobenzonitrilo (753G)

Una mezcla del compuesto 753E (1.60 g, 7.57 mmol), compuesto 753F (1.32 g, 5.41 mmol), mallas moleculares de 4Å (2.0 g) en dimetilacetamida (8 mL) se agitó en un baño de aceite a 175°C por 4 h. La mezcla obscura resultante se enfrió, se diluyó con EtOAc (50 mL) se filtró después para retirar las mallas y se enjuagó con EtOAc. El filtrado se dividió entre EtOAc (50 mL) y agua (75 mL). La fase orgánica se separó, se lavó con agua (2 x 75 mL), salmuera (50 mL), después se diluyó con tetrahidrofurano (20 mL), se secó sobre sulfato de sodio y concentró in vacuo para dar una espuma sólida. El material crudo se trituró con éter de dietilo (100 mL) después se agitó por 1.5 h. El precipitado sólido se recolectó en un embudo Buchner, y después se suspendió en éter de dietilo (50 mL) y se agitó por 16 h. El sólido resultante se recolectó en un embudo Buchner, se enjuagó con éter de dietilo y se secó bajo vacío (90°C) para resultar el compuesto 753G (67%) como un sólido blanco descolorido. CLAR: 96% a 3.00 min. (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, se eluye con 10-90% metanol acuoso durante 4 min. conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). MS (ES): m/z 438.90 $[M+H]^+$. La estereoquímica absoluta del compuesto 753G se establece por la

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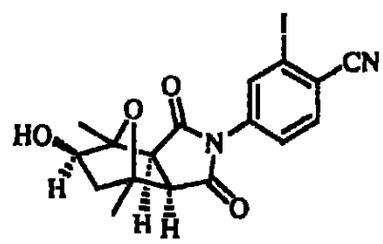
estereoquímica conocida del compuesto intermediario 753C y la retención de la configuración en ella. La estereoquímica absoluta es como se obtiene en la figura anterior y resulta por la nomenclatura.

Ejemplo 754

[3aS-(3aα,4β,5β,7β,7aα)]-4-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-yodobenzonitrilo (754)



Una mezcla del compuesto 751 (850 mg, 4.01 mmol), 4-ciano-3-yodo-anilina (975 mg, 4.01 mmol), mallas moleculares de 4Å (1.2 g) en dimetilacetamida (4.5 mL) se agitó en un baño de aceite a 175°C por 4 h. La mezcla obscura resultante se enfrió, se filtró para retirar las mallas y se enjuagó con EtOAc. El filtrado se dividió entre EtOAc (50 mL) y agua (50 mL). La fase orgánica se separó, se lavó con agua (2 x 50 mL), salmuera (25 mL), se secó sobre sulfato de sodio y se concentró in vacuo. El material crudo se disolvió en tetrahidrofurano y se purificó por cromatografía instantánea por gel de sílice, se eluye con 1:4 acetona/cloruro de metileno para dar un sólido blanco impuro. El material impuro

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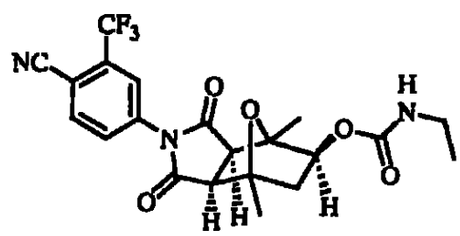
se suspendió en éter de dietilo (75 mL), se agitó por 18 h, después se recolectó en un embudo Buchner para resultar 650 mg (37%) del compuesto 754 como un sólido blanco. CLAR: 100% a 2.90 min. (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, se eluye con 10-90% metanol acuoso durante 4 min. conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). MS (ES): m/z 438.95 $[M+H]^+$. La estereoquímica absoluta del compuesto 754 se establece por la estereoquímica conocida del compuesto intermediario 751 y la retención de la configuración en ella. La estereoquímica absoluta es como se obtiene en la figura anterior y resulta de la nomenclatura.

Ejemplo 755



Una solución del compuesto 471Di (80 mg, 0.21 mmol), etil isocianato (30 mg, 0.43 mmol) y 4-dimetiaminopiridina (5 mg, 0.04 mmol) en tetrahidrofurano seco (1 mL) se calentó hasta 55°C por 2 h, después se agregó etil isocianato adicional (30 mg) y se calentó por otras 2 h. Se agregó una porción final de EIC (30 mg), y entonces después de 16 h la mezcla de reacción se enfrió, se concentró in vacuo y se purificó por cromatografía instantánea por gel de sílice

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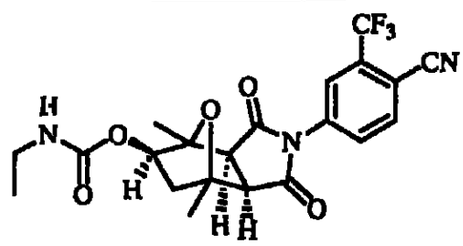
sobre SiO_2, se eluye con 2:1 EtOAc/heptano para dar 80 mg (86%) del compuesto 755 como un sólido blanco. CLAR: 94% a 3.51 min. (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, se eluye con 10-90% metanol acuoso durante 4 min. conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). MS (ES): m/z 452.29 $[M+H]^+$ La estereoquímica absoluta del compuesto 755 se establece por la estereoquímica conocida del compuesto intermediario 471Di y la retención de la configuración en ella. La estereoquímica absoluta es como se obtiene en la figura anterior y resulta de la nomenclatura.

Ejemplo 756



Una solución del compuesto 471Dii (80 mg, 0.21 mmol), etil isocianato (100 mg, 1.4 mmol) y 4-dimetiaminopiridina (8 mg, 0.07 mmol) en tetrahidrofurano seco (2 mL) se calentó hasta 60°C por 16 h, después se enfrió, se agregó MeOH y la solución se concentró in vacuo. La mezcla de reacción se purificó por cromatografía instantánea por gel de sílice, se eluye con 2:1 EtOAc/heptano para dar 84 mg (90%) del compuesto 756 como una espuma de un sólido blanco. CLAR: 94% a 3.54 min. (tiempo de retención) (Columna YMC S5 ODS, 4.6 x

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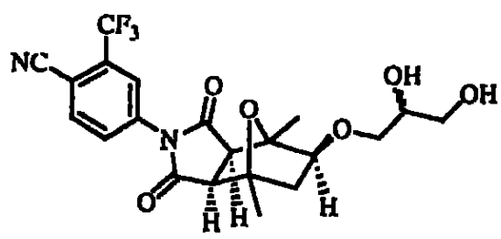
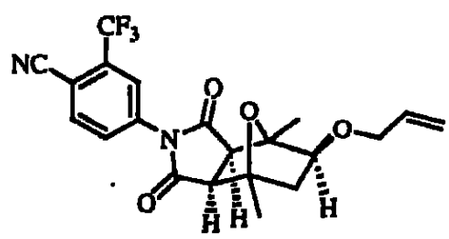
50 mm, se eluye con 10-90% metanol acuoso durante 4 min. conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). MS (ES): m/z 452.34 $[M+H]^+$. La estereoquímica absoluta del compuesto 756 se establece por la estereoquímica conocida del compuesto intermediario 471Dii y la retención de la configuración en ella. La estereoquímica absoluta es como se obtiene en la figura anterior y resulta de la nomenclatura.

Ejemplo 757



A. (757A)



Una mezcla del compuesto 471Di (620 mg, 1.63 mmol), óxido de plata(I) (3.78 g, 16.3 mmol), yoduro de alilo (2.74 g, 16.3 mmol) y MeCN seco (15 mL) se agitó rápidamente a 75-80°C por 7.5 h. La mezcla resultante se enfrió y filtró a través de una almohadilla de Celite enjuagando con EtOAc. El filtrado se concentró in vacuo y el material crudo se

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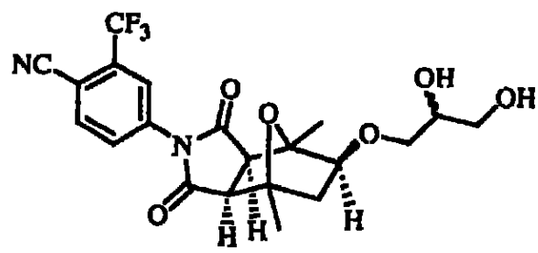
purificó por cromatografía instantánea por gel de sílice sobre SiO_2 se eluye con 1:1 EtOAc/heptano para dar 570 mg (83%) del compuesto 757A como un vidrio. CLAR: 96% a 3.72 min. (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, se eluye con 10-90% metanol acuoso durante 4 min. conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). MS (ES): m/z 421.27 $[M+H]^+$.

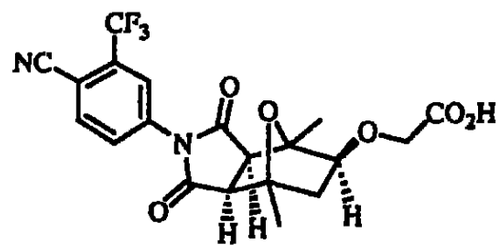
B. (757B)



A una mezcla del compuesto 757A (85mg, 0.20 mmol), N-óxido de 4-metilmorfolina (26mg, 0.22 mmol) y acetona (1.6 mL) a temperatura ambiente se agregó agua (0.4 mL) y después una solución de tetróxido de osmio al 2.5% en t-butanol (17 mg, 0.002 mmol). La mezcla de reacción se agitó por 5 h, después se filtró a través de una almohadilla de Florosil. Se filtró el concentrado in vacuo y el residuo se dividió entre EtOAc y solución acuosa 1M de HCl. La fase orgániça se separó, se secó sobre sulfato de sodio, se concentró in vacuo y el material crudo se purificó por cromatografía instantánea por gel de sílice sobre SiO_2, se eluye con 2:1 acetona/heptano para dar el compuesto 757B (52 mg, 55%) como

un sólido blanco. CLAR: 100% a 3.11 min. (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, se eluye con 10-90% metanol acuoso durante 4 min. conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). MS (ES): m/z 455 $[M+H]^+$. La estereoquímica absoluta del compuesto 757B se establece por la estereoquímica conocida del compuesto intermediario 471Di y la retención de la configuración en ella. La estereoquímica absoluta es como se obtiene en la figura anterior y resulta de la nomenclatura.

Ejemplo 758



A una solución del compuesto 757A (45 mg, 0.11 mmol), tetracloruro de carbono (0.50 mL), acetonitrilo (0.5 mL) y agua (0.75 mL) a temperatura ambiente, se agregó peryodato de sodio (94 mg, 0.44 mmol), entonces después de varios minutos, hidrato del cloruro de rutenio(III) (50 mg, 0.24 mmol). Después de 30 min. la mezcla obscura se dividió entre cloruro de metileno (20 mL) y agua (20 mL). La mezcla se filtró para retirar los sólidos, después la fase orgánica se separó, se secó sobre sulfato de sodio y se concentró in vacuo. El material crudo se purificó por cromatografía instantánea por

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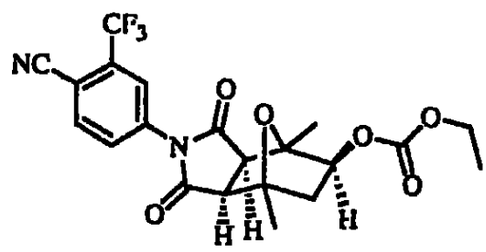
gel de sílice sobre SiO_2 se eluye con 1:20 MeOH/EtOAc, después 1:5:100 HOAc/MeOH/EtOAc para dar el compuesto 758 (19 mg, 36%) como una espuma de un sólido blanco. CLAR: 99% a 3.31 min. (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, se eluye con 10-90% metanol acuoso durante 4 min. conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). MS (ES): m/z 437.23 $[M-H]^-$. La estereoquímica absoluta del compuesto 758 se establece por la estereoquímica conocida del compuesto intermediario 471Di y la retención de la configuración en ella. La estereoquímica absoluta es como se obtiene en la figura anterior y resulta de la nomenclatura.

Ejemplo 759



A una solución del compuesto 471Di (100 mg, 0.26 mmol) y trietilamina (50 mg, 0.50 mmol) en cloruro de metileno seco (3 mL) enfriado en un baño de hielo se agregó cloroformiato de etilo (40 µL, 0.40 mmol). La reacción se entibió hasta temperatura ambiente por 2 h y se agregó una porción adicional de cloroformiato de etilo (40 µL), trietilamina (50 mg), 4-dimetilaminopiridina (10 mg, 0.08 mmol). La mezcla de

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reacción se agitó por 18 h a temperatura ambiente, después se dividió entre 25 mL de EtOAc y 25 mL de una solución acuosa 1M de HCl. La fase orgánica se separó, se lavó con 1M HCl acuoso (2 x 25 mL), salmuera (1 x 25 mL), se secó (sulfato de sodio) y se concentró in vacuo. La purificación por cromatografía instantánea por gel de sílice se eluye con 1:1 EtOAc/heptano, seguida por recristalización (EtOAc/heptano) resultó en 76 mg (65%) del compuesto 759 como un sólido blanco. CLAR: 100% a 3.85 min. (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, se eluye con 10-90% metanol acuoso durante 4 min. conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). MS (ES): m/z 453.01 $[M+H]^+$. La estereoquímica absoluta del compuesto 759 se establece por la estereoquímica conocida del compuesto intermediario 471Di y la retención de la configuración en ella. La estereoquímica absoluta es como se obtiene en la figura anterior y resulta de la nomenclatura.

Ejemplo 760

[3aS-(3aα,4β,5β,7β,7aα)]-2-(4-Cloro-2-metil-3-(trifluorometil)fenil)hexahidro-5-hidroxi-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3(2H)-diona (760D)

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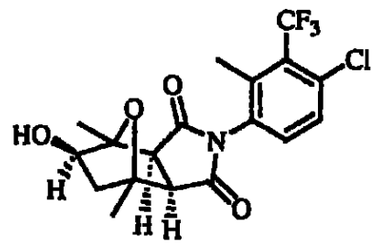
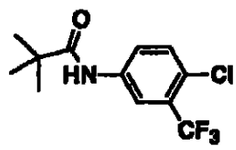
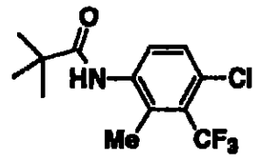


A. N-(4-Cloro-3-trifluorometilfenil)-2,2-dimetilpropionamida (760A)



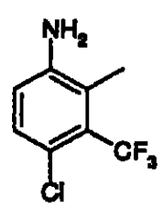
A una solución de 4-cloro-3-(trifluorometil)anilina comercialmente disponible (15.0 g, 76.7 mmol) en THF anhidro (200 mL) enfriada hasta 0-5 °C se agregó trietilamina (11.7 mL, 84.4 mmol), seguida por cloruro de pivaloilo (10.4 mL, 84.4 mmol) durante 30 min. El baño de hielo se retiró y la mezcla se agitó a temperatura ambiente por 1 h. La mezcla se diluyó con éter y se filtró. El filtrado se lavó con agua (2X) y salmuera, se secó sobre $MgSO_4$, se filtró y concentró. El residuo se trituró con hexanos y el sólido se filtró y se secó in vacuo para resultar el compuesto 760A (20.4 g, 95%); MS (ES): m/z = 280 $[M+1]^+$.

B. N-(4-Cloro-2-metil-3-trifluorometilfenil)-2,2-dimetil-propionamida (760B)



A una solución de N-(4-cloro-3-trifluorometilfenil)-2,2-dimetilpropionamida (2.29 g, 8.19 mmol) en THF anhidro (25 mL) enfriada hasta 0-5°C se agregó una solución 1.6 M de n-butillitio en hexanos (12.3 mL, 19.7 mmol) lentamente de manera que la temperatura de reacción se mantuvo debajo de 5°C. La solución se agitó a 0-5°C por 1.5 h. Una solución de yodometano (0.56 mL, 9.01 mmol) en éter de petróleo (2 mL) se agregó durante 20 min. mientras se mantenía la temperatura debajo de 5°C. La suspensión se agitó a 0-5°C por 1 h y se diluyó con agua y éter. La capa acuosa se extrajo con éter y las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre $MgSO_4$, se filtraron y concentraron. El residuo se cromatografió (gel de sílice), se eluye con CH_2Cl_2 para resultar el compuesto 760B (1.60 g, 67%). MS (ES): m/z = 294 $[M+1]^+$.

C. 4-Cloro-2-metil-3-trifluorometilanilina (760C)



1165

N-(4-Cloro-2-metil-3-trifluorometilfenil)-2,2-dimetil-propionamida 1.0 g, 3.4 mmol) se agregó a una mezcla 1:1 (15 mL) de HCl concentrado y etanol y se calentó a reflujo durante la noche. La reacción se enfrió y se concentró in vacuo para dar un sólido color marrón que se dividió después entre EtOAc y $NaHCO_3$ saturado. La capa orgánica se separó, se lavó con agua, salmuera, se secó (Na_2SO_4), se filtró y concentró para dar el compuesto 760C (0.54g, 76%) como un sólido café aceitoso.

D. [3aS-(3aα,4β,5β,7β,7aα)]-2-(4-Cloro-2-metil-3-(trifluorometil)fenil)hexahidro-5-hidroxi-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3(2H)-diona (760D)

A un tubo Pyrex que se sella, se agregó 4-cloro-2-metil-3-trifluorometilanilina (0.1g, 0.48 mmol), el compuesto 751 (0.15g, 0.72 mmol), TEA (0.24g, 0.33 mL, 2.4 mmol), $MgSO_4$ (0.14g, 1.2 mmol), y tolueno (0.5 mL). La reacción se calentó en el tubo sellado a 150°C por 18 h. La reacción enfriada se diluyó con EtOAc, se filtró, se concentró y se purificó por CCD Prep usando CH_2Cl_2 como eluyente para dar el compuesto 760D (0.078g, 40%) como un sólido blanco descolorido. CLAR: 90% a 3.26 min. (Columna YMC S5 ODS) se eluye con 10-90% metanol acuoso conteniendo 0.2% ácido fosfórico durante un gradiente de 4 min. observando a 220 nm. MS (ES): m/z 404.01 $[M+H]^+$. La estereoquímica absoluta del compuesto 760D se

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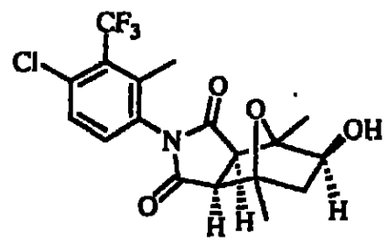
establece por la estereoquímica conocida del compuesto intermediario 751 y la retención de la configuración en ella. La estereoquímica absoluta es como se obtiene en la figura anterior y resulta de la nomenclatura.

Ejemplo 761

[3aR-(3aα,4β,5β,7β,7aα)]-2-(4-Cloro-2-metil-3-(trifluorometil)fenil)hexahidro-5-hidroxi-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3(2H)-diona (761)



A un tubo Pyrex que se sella, se agregó el compuesto 760C (0.1g, 0.48 mmol), compuesto 752 (0.15g, 0.72 mmol), TEA (0.24g, 0.33 mL, 2.4 mmol), $MgSO_4$ (0.14g, 1.2 mmol), y tolueno (0.5 mL). La reacción se calentó en el tubo sellado a 150°C por 18 h. La reacción enfriada se diluyó con EtOAc, se filtró, se concentró y se purificó por CCD-Prep en SiO_2 usando CH_2Cl_2 como eluyente para dar el compuesto 761 (0.056g, 29%) como un sólido blanco descolorido. CLAR: 90% a 3.27 min. (Columna YMC S5 ODS) se eluye con 10-90% metanol acuoso conteniendo 0.2% ácido fosfórico durante un gradiente de 4 min. observando a 220 nm. MS (ES): m/z 403.91 $[M+H]^+$. La estereoquímica absoluta del compuesto 761 se establece por la

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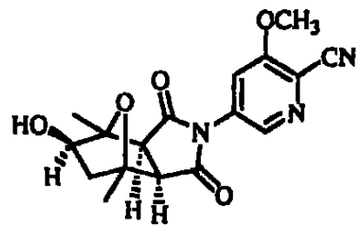
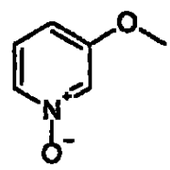
estereoquímica conocida del compuesto intermediario 752 y la retención de la configuración en ella. La estereoquímica absoluta es como se obtiene en la figura anterior y resulta de la nomenclatura.

Ejemplo 762

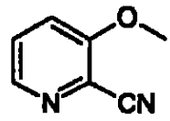


A. 3-Metoxipiridina-1-óxido (762A)



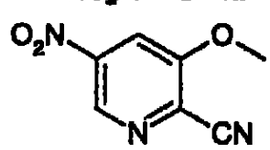
La 3-Metoxipiridina (20.08g, 209 mmol) se disolvió en 100 mL de ácido acético. Se agregó 30% de H_2O_2 (28.3 mL, 275 mmol) y la mezcla de reacción se calentó a 70°C por seis h. La mezcla de reacción enfriada se concentró y el residuo se disolvió en CH_2Cl_2 y se agitó durante la noche con 20 g de carbonato de potasio sólido. La mezcla se filtró y concentró para dar el compuesto 762A (25.2g, 100%) como un sólido amarillo claro que se caracteriza por ^1H RMN y se lleva a la etapa siguiente.

B. 2-Ciano-3-metoxipiridina (762B)



3-Metoxipiridina-1-óxido (25.2g, 209 mmol) se disolvió en acetonitrilo (260mL). Se agregaron trimetilsilicianuro (66.35g, 669 mmol) y trietilamina (45.13g, 446 mmol) y la mezcla de reacción se calentó a reflujo durante la noche. La solución enfriada se concentró in vacuo para dar un sólido café que se dividió entre CH_2Cl_2 y Na_2CO_3 3M. La capa orgánica se separó, se lavó con salmuera, se secó ($MgSO_4$), se filtraron y concentraron in vacuo. El residuo se purificó por cromatografía en gel de sílice usando 1:1 EtOAc/hexanos como eluyente. El compuesto 762B se aisló (17.63g, 63%) como un sólido amarillo claro. CLAR: 96.2% a 1.37 min. (Columna YMC S5 ODS) se eluye con 10-90% metanol acuoso conteniendo 0.2% ácido fosfórico durante un gradiente de 4 min., observando a 220 nm. MS (ES): m/z 134.88 $[M+H]^+$.

C. 2-Ciano-3-metoxi-5-nitropiridina (762C)



La 2-Ciano-3-metoxipiridina (17.63g, 131.4 mmol) se disolvió en CH_2Cl_2 (400 mL) y enfrió en un baño de hielo. Se disolvieron nitrato de tetrabutilamonio (52.02g, 170.8 mmol) y anhídrido trifluoroacético (35.88g, 170.8 mmol) en 200 mL

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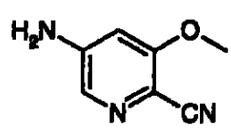
de CH_2Cl_2 y se agregó en una corriente delgada por medio de un embudo de adición. La mezcla se entibió hasta 23°C y se agitó por 60 h. La mezcla de reacción se agitó por una hora con bicarbonato de sodio saturado. La capa orgánica se separó, se lavó con salmuera, se secó ($MgSO_4$), se filtró, se concentró in vacuo, y se purificó por cromatografía en columna sobre gel de sílice usando CH_2Cl_2 como eluyente para dar el compuesto 762C (18.07g, 79%) como un sólido amarillo claro cristalino. CLAR: 100% a 1.67 min. (Columna YMC S5 ODS) se eluye con 10-90% metanol acuoso conteniendo 0.2% ácido fosfórico durante un gradiente de 4 min. observando a 220 nm. MS (ES): m/z 179.93 $[M+H]^+$.

D. 5-Amino-2-ciano-3-metoxipiridina (762D)



La 2-Ciano-3-metoxi-5-nitropiridina (1.0g, 5.6 mmol) se disolvió en 1:1 EtOAc/ AcOH (10 mL) y se calentó hasta 65°C. Se agregó polvo de hierro (1.61g, 28 mmol, malla 325) y la mezcla se agitó por dos horas. La mezcla se filtró a través de Celite y el filtrado se concentró in vacuo. El residuo se dividió entre EtOAc y bicarbonato de sodio saturado acuoso. La capa orgánica se separó, se lavó con salmuera, se secó ($MgSO_4$), se filtró y concentró. El residuo se purificó por SiO_2 CCD-prep usando CH_2Cl_2 como el eluyente para dar el

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compuesto 762D (0.805 g, 97%) como un sólido blanco descolorido. CLAR: 100% a 1.31 min. (Columna YMC S5 ODS) se eluye con 10-90% metanol acuoso conteniendo 0.2% ácido fosfórico durante un gradiente de 4 min. observando a 220 nm. MS (ES): m/z 149.90 $[M+H]^+$.

E. (762E)

5-Amino-2-ciano-3-metoxipiridina (0.1g, 0.67 mmol), mallas moleculares de 4Å (0.4 g), el compuesto 751 (0.142 g, 0.67 mmol), y N,N-dimetilacetamida (0.67 mL) se combinaron en un tubo Pirex que se sella y se calentaron a 170°C por 1 h. La mezcla de reacción enfriada se diluyó con EtOAc y se filtró. El filtrado se lavó 3x con 1:1 NH_4Cl saturado / agua y después salmuera. El filtrado se secó sobre Na_2SO_4, se filtró, se concentró y se purificó por CCD-prep usando 4:1 cloroformo/acetona como el eluyente para dar el compuesto 762E (0.062g, 27%) como un sólido blanco. CLAR: 94% a 1.85 min. (Columna YMC S5 ODS) se eluye con 10-90% metanol acuoso conteniendo 0.2% ácido fosfórico durante un gradiente de 4 min. observando a 220 nm. MS (ES): m/z 344.02 $[M+H]^+$. La estereoquímica absoluta del compuesto 762E se establece por la estereoquímica conocida del compuesto intermediario 751 y la retención de la configuración en ella. La estereoquímica absoluta es como se obtiene en la figura anterior y resulta de la nomenclatura.

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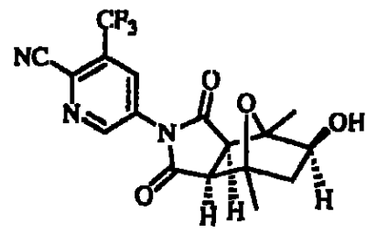
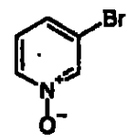
Ejemplo 763

[3aR-(3aα,4β,5β,7β,7aa)]-5-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-3-(trifluorometil)-2-piridincarbonitrilo (763F)

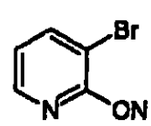


A. 3-Bromopiridina-1-óxido (763A)



Se agregaron 3-Bromopiridina (11.06g, 70 mmol), 30% H_2O_2 (14 mL, 140 mmol), y metiltrioxorenio (0.035g, 0.14 mmol) a 28 mL de CH_2Cl_2 y se agitó a temperatura ambiente durante la noche. Se agregó una porción de 25 mg de dióxido de manganeso y la reacción se agitó hasta que estuvo completa la evolución del oxígeno (~1 h). La capa orgánica se separó, se lavó con salmuera, se secó sobre $MgSO_4$, se filtró, y se concentró in vacuo para dar el compuesto 673A (9.84g (81%) como un aceite amarillo.

B. 3-Bromo-2-cianopiridina (763B)



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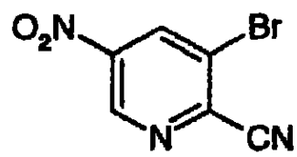
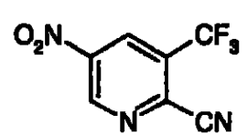
El 3-Bromopiridina-1-óxido se convirtió al compuesto 763B como se describe en el ejemplo 762B. El producto crudo se purificó por cromatografía de gel de sílice usando CH_2Cl_2 como eluyente para dar el compuesto 763B (6.64g, 65%) como un sólido blanco descolorido. El producto se caracterizó por ^1H RMN.

C. 3-Bromo-2-ciano-5-nitropiridina (763C)



La 3-Bromo-2-cianopiridina se convirtió al compuesto 763C como se describe en el ejemplo 762C. El producto crudo se purificó por cromatografía de gel de sílice usando 20% hexanos / CH_2Cl_2 como eluyente para dar el compuesto 763C (1.27g, 16%) como un sólido blanco descolorido. El producto se caracterizó por ^1H RMN.

D. 2-Ciano-5-nitro-3-trifluorometilpiridina (763D)



La 3-Bromo-2-ciano-5-nitropiridina (0.23g, 1 mmol) se disolvió en DMF (3 mL). Se agregaron yoduro de cobre (0.023g, 0.12 mmol) y metil 2,2-difluoro-2-(fluorosulfonil)acetato

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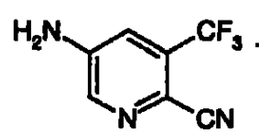
(0.1g, 0.5 mmol) y la mezcla de reacción se calentó a 80°C por 7 h. Se agregó metil 2,2-difluoro-2-(fluorosulfonil)acetato adicional (0.05 g, 0.25 mmol) y se continuó el calentamiento a 80°C por 8 h adicionales. La mezcla de reacción enfriada se vació en agua para dar un aceite oscuro. Se decantó el agua y el aceite se disolvió en EtOAc y se lavó con agua y salmuera. La capa orgánica se secó sobre $MgSO_4$, se filtró, y se concentró in vacuo. El residuo se purificó por cromatografía de gel de sílice usando CH_2Cl_2 como eluyente para el compuesto 763D (0.065g, 43%) como un aceite amarillo. CLAR: 90% a 2.09 min. (Columna YMC S5 ODS) se eluye con 10-90% metanol acuoso conteniendo 0.2% ácido fosfórico durante un gradiente de 4 min. observando a 220 nm.

E. 5-Amino-2-ciano-3-trifluorometilpiridina (763E)



La 2-Ciano-5-nitro-3-trifluorometilpiridina (0.065g, 0.3 mmol) reaccionó de la misma forma como se describe en el ejemplo 762D para dar el compuesto deseado 763E (0.046g, 82%) como un sólido color oro después de la trituración con éter. CLAR: 100% a 2.07 min. (Columna YMC S5 ODS) se eluye con 10-90% metanol acuoso conteniendo 0.2% ácido fosfórico durante

1174

un gradiente de 4 min. observando a 220 nm. MS (ES): m/z 187.82 $[M+H]^+$.

F. [3aR-(3aα,4β,5β,7β,7aα)]-5-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-3-(trifluorometil)-2-piridincarbonitrilo (763F)

La 5-Amino-2-ciano-3-trifluorometilpiridina (0.044g, 0.24 mmol) reaccionó con el compuesto 752 (0.087g, 0.41 mmol) de acuerdo con el procedimiento descrito por la síntesis del compuesto 762. El producto crudo se purificó por SiO_2 CCD-prep usando 15% acetona / $CHCl_3$ como eluyente para dar el compuesto 763F (0.058g, 65%) como un sólido blanco descolorido. CLAR: 92% a 2.58 min. (Columna YMC S5 ODS) se eluye con 10-90% metanol acuoso conteniendo 0.2% ácido fosfórico durante un gradiente de 4 min. observando a 220 nm. MS (ES): m/z 382.33 $[M+H]^+$. La estereoquímica absoluta del compuesto 763F se establece por la estereoquímica conocida del compuesto intermediario 752 y la retención de configuración en ella. La estereoquímica absoluta es como se obtiene en la figura anterior y resulta de la nomenclatura.

1175

Eugenio Perez

De: Michael Ervin [MAErvinAssoc@austin.rr.com]
Enviado: Miércoles, 09 de Junio de 2004 09:59 a.m.
Para: Ing. Eugenio Perez P
Asunto: Re: Best way for filing a PCT patent application in Mexico

Dear Mr. Perez

One question on the Power of Attorney form. The invention will not be assigned to a company so do we just ignore all the questions having to do with the company on the notarial certification?

Regards

Mike Ervin

From: "Ing. Eugenio Perez P" <eugenioperez@uhthoff.com.mx>
Reply-To: eugenioperez@uhthoff.com.mx
Date: Tue, 08 Jun 2004 13:03:50 -0500
To: maervinassoc@austin.rr.com
Subject: Best way for filing a PCT patent application in Mexico

M.A. ERVIN & ASSOCIATES

RE: Best way for filing a PCT patent application in Mexico - Our Ref: EPP*bge

Attention: Mr. Mike Ervin

Dear Sir:

Please see the enclosed documents.

Very truly yours,
EUGENIO PEREZ P.
UHTHOFF GOMEZ VEGA & UHTHOFF
Hamburgo 260, Col. Juárez
06600 - México, D.F.
Tel. +5255 5533 5060 ext.247
mailbox@uhthoff.com.mx
personal e-mail eugenioperez@uhthoff.com.mx

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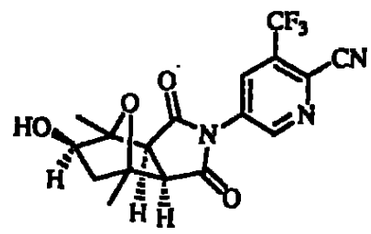
Ejemplo 764

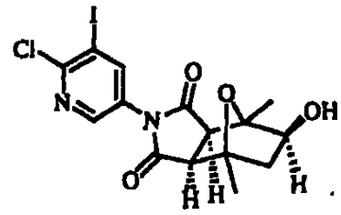
[3aS-(3aα,4β,5β,7β,7aα)]-5-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-3-(trifluorometil)-2-piridincarbonitrilo (764)



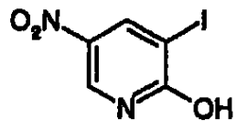
La 5-Amino-2-ciano-3-trifluorometilpiridina (0.2g, 1.07 mmol) reaccionó con el compuesto 751 (0.386g, 1.82 mmol) según el procedimiento descrito en el ejemplo 763F. El producto crudo se purificó por SiO_2 CCD-prep usando 15% acetona / $CHCl_3$ como el eluyente para dar el compuesto 764 (0.293g, 72%) como un sólido blanco descolorido. CLAR: 92% a 2.58 min. (Columna YMC S5 ODS) se eluye con 10-90% metanol acuoso conteniendo 0.2% ácido fosfórico durante un gradiente de 4 min. observando a 220 nm. EM (ES): m/z 382.23 $[M+H]^+$. La estereoquímica absoluta del compuesto 764 se establece por la estereoquímica conocida del compuesto intermediario 751 y la retención de la configuración en ella. La estereoquímica absoluta es como se obtiene en la figura anterior y resulta de la nomenclatura.

Ejemplo 765

(765D)

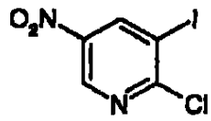


A. 2-Hidroxi-3-yodo-5-nitropiridina (765A)



Se suspendió la 2-Hidroxi-5-nitropiridina (7.0g, 50 mmol) en 100 mL de ácido sulfúrico al 20%, y se trató después con yodato de potasio (4.2g, 19.6 mmol) disuelto en 10 mL de agua. La mezcla se calentó hasta 100 °C y el yoduro de potasio (8.0g, 48.2 mmol) disuelto en 20 mL de agua se agregó gota a gota durante una hora. La mezcla de reacción cambia a un rojo púrpura y se forma un precipitado. Después de 0.5 h, la mezcla de reacción se enfrió y se filtró. El sólido se agitó por 15 min. con 10% de una solución de meta-bisulfito de sodio, se filtró, se lavó con agua y se secó a 80°C durante la noche sobre una bomba de vacío para dar el compuesto deseado 765A (12.32 g, 92%) como un sólido amarillo. El producto se caracterizó por ^{1}H RMN.

B. 2-Cloro-3-yodo-5-nitropiridina (765B)



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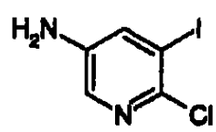
La 2-Hidroxi-3-yodo-5-nitropiridina (2.55g, 9.5 mmol), pentacloruro de fósforo (2.60g, 12 mmol) y oxicloruro de fósforo (2 mL) se combinaron en un matraz bajo nitrógeno y se calentaron hasta 140°C por 45 min. La mezcla de reacción enfriada se vació sobre hielo para dar un sólido que se dividió entre CH_2Cl_2 y agua. La capa orgánica se separó, se lavó con salmuera, se secó ($MgSO_4$), se filtró, y el solvente se separó in vacuo para dar el compuesto 765B (2.25 g, 83%) como un sólido amarillo. CLAR: 98.5% a 2.75 min. (Columna YMC S5 ODS) se eluye con 10-90% metanol acuoso conteniendo 0.2% ácido fosfórico durante un gradiente de 4 min. observando a 220 nm.

C. 5-Amino-2-cloro-3-yodopiridina (765C)



La 2-Cloro-3-yodo-5-nitropiridina (0.25g, 0.88 mmol) reaccionó con polvo de hierro (0.25g, 4.4 mmol) en la forma descrita en el ejemplo 762D. La separación del solvente in vacuo dio el compuesto 765C (0.172g, 77%), como un sólido dorado amarillo. CLAR: 100% a 2.32 min. (Columna YMC S5 ODS) se eluye con 10-90% metanol acuoso conteniendo 0.2% ácido fosfórico durante un gradiente de 4 min. observando a 220 nm. EM (ES): m/z 255.03 $[M+H]^+$.

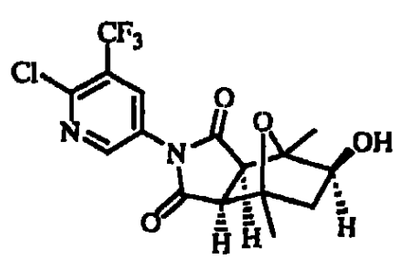
1179

D. (765D)

5-Amino-2-cloro-3-yodopiridina (0.06g, 0.24 mmol) y el compuesto 752 (0.085g, 0.4 mmol) reaccionaron como se describió previamente en el ejemplo 762E. El producto crudo obtenido después de la preparación se purificó por SiO_2 CCD-prep usando 10% acetona/$CHCl_3$ como eluyente para dar el compuesto 765D (0.067g, 62%) como una espuma blanca descolorida. CLAR: 95% a 2.65 min. (Columna YMC S5 ODS) se eluye con 10-90% metanol acuoso conteniendo 0.2% ácido fosfórico durante un gradiente de 4 min. observando a 220 nm. EM (ES): m/z 448.96 $[M+H]^+$. La estereoquímica absoluta del compuesto 765D se establece por la estereoquímica conocida del compuesto intermediario 752 y la retención de la configuración en ella. La estereoquímica absoluta es como se obtiene en la figura anterior y resulta de la nomenclatura.

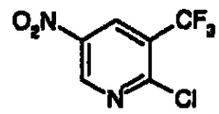
Ejemplo 766

[3aR-(3aα,4β,5β,7β,7aα)]-2-(4-Cloro-3-(trifluorometil)piridinil)hexahidro-5-hidroxi-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3(2H)-diona (766C)



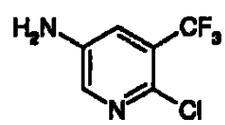
1180

A. 2-Cloro-5-nitro-3-trifluorometilpiridina (766A)



2-Cloro-3-yodo-5-nitropiridina (1.0g, 3.5 mmol), metil 2,2-difluoro-2-(fluorosulfonil)acetato (0.35g, 1.82 mmol), y yoduro de cobre (0.083g, 0.44 mmol) reaccionaron en DMF (10 mL) según el método descrito en el ejemplo 763D. El producto crudo se purificó por cromatografía de gel de sílice usando 30% CH_2Cl_2 / hexano como el eluyente para dar el compuesto 766A (0.278g, 35%) como un aceite incoloro. El producto se caracterizó por ^1H RMN y ^{19}F RMN.

B. 5-Amino-2-cloro-3-trifluorometilpiridina (766B)



La 2-Cloro-5-nitro-3-trifluorometilpiridina (0.16g, 0.68 mmol) y polvo de hierro (0.2g, 3.42 mmol, Malla 325) reaccionaron como se describe en el ejemplo 762D. La purificación del producto crudo por CCD-prep usando 10% éter / CH_2Cl_2 como eluyente dio el compuesto 766B (0.098g, 73%) como un sólido amarillo. CLAR: 89% a 2.52 min. (Columna YMC S5 ODS) se eluye con 10-90% metanol acuoso conteniendo 0.2% ácido fosfórico durante un gradiente de 4 min. observando a 220 nm. EM (ES): m/z 197.01 $[M+H]^+$.

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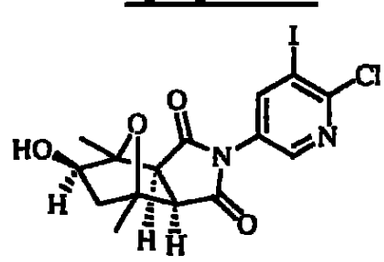
c. [3aR-(3aα,4β,5β,7β,7aα)]-2-(4-Cloro-3-(trifluorometil)piridinil)hexahidro-5-hidroxi-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3(2H)-diona (766C)

5-Amino-2-cloro-3-trifluorometilpiridina (0.045g, 0.23 mmol) y el compuesto 751 (0.085g, 0.4 mmol) reaccionaron como se describe en el ejemplo 762E. Después de la preparación, el producto crudo se purificó por CCD-prep usando 10% acetona/$CHCl_3$ como el eluyente para dar el compuesto 766C (0.038g, 42%) como un sólido blanco descolorido. CLAR: 100% a 2.92 min (Columna YMC S5 ODS) se eluye con 10-90% metanol acuoso conteniendo 0.2% ácido fosfórico durante un gradiente de 4 min. observando a 220 nm. EM (ES): m/z 391.06 $[M+H]^+$. La estereoquímica absoluta del compuesto 766C se establece por la estereoquímica conocida del compuesto intermediario 751 y la retención de la configuración en ella. La estereoquímica absoluta es como se obtiene en la figura anterior y resulta de la nomenclatura.

Ejemplo 767



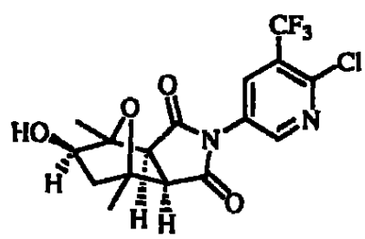
La 5-Amino-2-cloro-3-yodopiridina (0.06g, 0.24 mmol) y el compuesto 752 (0.085g, 0.4 mmol) reaccionaron como se

1182

describe en el ejemplo 762E. El producto crudo de reacción se purificó por CCD-prep usando 20% acetona/$CHCl_3$ como el eluyente para dar el compuesto 767 (0.061g, 58%) como un sólido amarillo. CLAR: 100% a 2.64 min. (Columna YMC S5 ODS) se eluye con 10-90% metanol acuoso conteniendo 0.2% ácido fosfórico durante un gradiente de 4 min. observando a 220 nm. EM (ES): m/z 449.02 $[M+H]^+$. La estereoquímica absoluta del compuesto 767 se establece por la estereoquímica conocida del compuesto intermediario 752 y la retención de la configuración en ella. La estereoquímica absoluta es como se obtiene en la figura anterior y resulta de la nomenclatura.

Ejemplo 768

[3aS-(3aα,4β,5β,7β,7aα)]-2-(4-Cloro-3-(trifluorometil)piridinil)hexahidro-5-hidroxi-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3(2H)-diona (768)



La 6-Cloro-5-trifluorometil-piridin-3-ilamina (0.045g, 0.23 mmol) y el compuesto 752 (0.085g, 0.4 mmol) reaccionaron como se describe en el ejemplo 762E. El producto crudo se purificó por SiO_2 CCD-prep usando 10% acetona/$CHCl_3$ como el eluyente para dar el compuesto 768 (0.048g, 54%) como un

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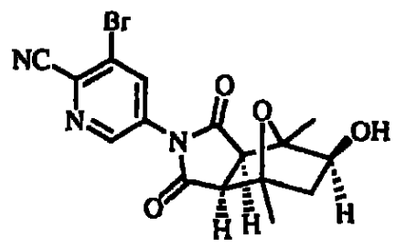
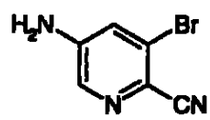
sólido blanco. CLAR: 100% a 2.91 min. (Columna YMC S5 ODS) se eluye con 10-90% metanol acuoso conteniendo 0.2% ácido fosfórico durante un gradiente de 4 min. observando a 220 nm. EM (ES): m/z 391.21 $[M+H]^+$. La estereoquímica absoluta del compuesto 768 se establece por la estereoquímica conocida del compuesto intermediario 752 y la retención de la configuración en ella. La estereoquímica absoluta es como se obtiene en la figura anterior y resulta de la nomenclatura.

Ejemplo 769



A. 5-Amino-3-bromo-2-cianopiridina (769A)



3-Bromo-2-ciano-5-nitropiridina (0.4g, 1.75 mmol) y polvo de hierro (0.51 g, 8.8 mmol, Malla 325) reaccionaron como se describe en el ejemplo 762D. El sólido crudo obtenido por trituración con éter se purificó por SiO_2 CCD-prep usando 4:1 CH_2Cl_2 / éter como eluyente para dar el compuesto 769A (0.16 g, (65%) como un sólido blanco descolorido. CLAR: 100% a 1.77 min. (Columna YMC S5 ODS) se eluye con 10-90% metanol

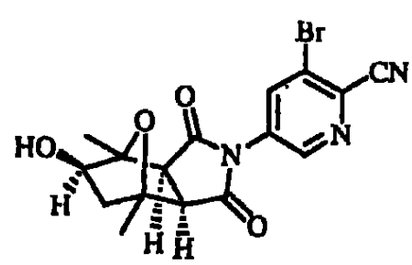
1184

acuoso conteniendo 0.2% ácido fosfórico durante un gradiente de 4 min. observando a 220 nm. EM (ES): m/z 197.93 $[M+H]^+$.

B. (769B)

La 5-Amino-3-bromo-2-cianopiridina (0.06g, 0.3 mmol) y el compuesto 752 (0.096 g, 0.45 mmol) reaccionaron como previamente en el ejemplo 762E. El producto crudo se purificó por SiO_2 CCD-prep usando 20% acetona/$CHCl_3$ como el eluyente para dar el compuesto 769B (0.036g, 30%) como un sólido blanco descolorido. CLAR: 100% a 2.29 min. (Columna YMC S5 ODS) se eluye con 10-90% metanol acuoso conteniendo 0.2% ácido fosfórico durante un gradiente de 4 min. observando a 220 nm. EM (ES): m/z 393.33 $[M+H]^+$. La estereoquímica absoluta del compuesto 769B se establece por la estereoquímica conocida del compuesto intermediario 752 y la retención de la configuración en ella. La estereoquímica absoluta es como se obtiene en la figura anterior y resulta de la nomenclatura.

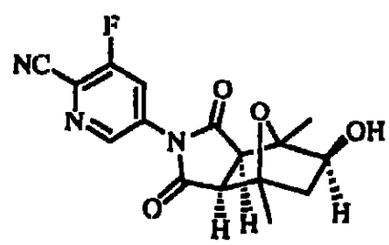
Ejemplo 770



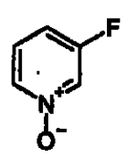
1185

La 5-Amino-3-bromo-2-cianopiridina (0.06g, 0.3 mmol) y el compuesto 751 (0.096g, 0.45 mmol) reaccionaron como previamente en el ejemplo 762E. El producto crudo se purificó por SiO_2 CCD-prep usando 20% acetona/$CHCl_3$ para dar el compuesto 770 (0.038g (31%) como un sólido blanco descolorido. CLAR: 99.2% a 2.28 min. (Columna YMC S5 ODS) se eluye con 10-90% metanol acuoso conteniendo 0.2% ácido fosfórico durante un gradiente de 4 min. observando a 220 nm. EM (ES): m/z 392.27 $[M]^+$. La estereoquímica absoluta del compuesto 770 se establece por la estereoquímica conocida del compuesto intermediario 751 y la retención de la configuración en ella. La estereoquímica absoluta es como se obtiene en la figura anterior y resulta de la nomenclatura.

Ejemplo 771



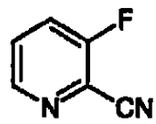
A. 3-Fluoropiridina-1-óxido (771A)



3-Fluoropiridina (9.71g, 100 mmol), 30% H_2O_2 (20 mL, 200 mmol), y metiltrioxorenio (0.13g, 0.5 mmol) reaccionaron en

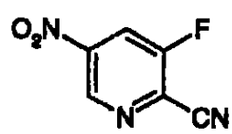
40 mL de CH_2Cl_2 según el mismo procedimiento descrito en el ejemplo 760C. La filtración y la concentración del solvente in vacuo dio el compuesto 771A (8.79g, 78%) como un sólido amarillo.

B. 2-Ciano-3-fluoropiridina (771B)



3-Fluoropiridina-1-óxido (10.0g, 88.4 mmol), trimetilsililcianuro (26.32g, 265.3 mmol), y trietilamina (17.89g, 177 mmol) reaccionaron en 90 mL de acetonitrilo utilizando el procedimiento descrito en el ejemplo 762B. La purificación del crudo por cromatografía de gel de sílice usando CH_2Cl_2 como eluyente da el compuesto 771B (7.5g, 70%) como un sólido amarillo claro.

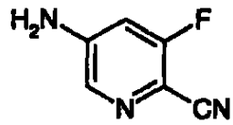
C. 2-Ciano-3-fluoro-5-nitropiridina (771C)



2-Ciano-3-fluoropiridina (6.5g, 53.2 mmol), nitrato de tetrabutilamonio (21.07 g, 69.2 mmol), y anhídrido trifluoroacético (14.53g, 69.2 mmol) reaccionaron en 245 mL de CH_2Cl_2 utilizando el procedimiento descrito en el ejemplo 762C. La purificación del crudo por cromatografía de gel de

sílice usando 20% hexanos/CH_2Cl_2 dio el compuesto 771C (0.12g, 1.3%) como un aceite amarillo.

D. 5-Amino-2-ciano-3-fluoropiridina (771D)



2-Ciano-3-fluoro-5-nitropiridina (0.12g, 0.72 mmol) y polvo de hierro (0.21g, 3.6 mmol, Malla 325) reaccionaron en 1:1 EtOAc/AcOH (10 mL) utilizando el procedimiento descrito en el ejemplo 762D. La trituración del producto crudo con éter dio el compuesto 771D (0.093g, 94%) como un sólido amarillo pálido. CLAR: 99% a 1.27 min. (Columna YMC S5 ODS) se eluye con 10-90% metanol acuoso conteniendo 0.2% ácido fosfórico durante un gradiente de 4 min. observando a 220 nm. EM (ES): m/z 138.02 $[M+H]^+$.

E. (771E)

La 5-Amino-2-ciano-3-fluoropiridina (0.45g, 0.33 mmol) y el compuesto 752 (0.104g, 0.49 mmol) reaccionaron en 0.33 mL de dimetilacetamida utilizando el procedimiento descrito en el ejemplo 762E. El residuo crudo se purificó por CCD-prep usando 20% acetona/$CHCl_3$ como el eluyente, produciendo el compuesto 771E (0.026g, 23%) como un sólido color durazno pálido. CLAR: 90.2% a 1.97 min. (Columna YMC S5 ODS) se eluye

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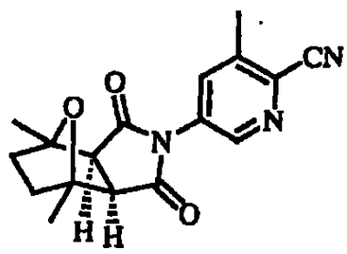
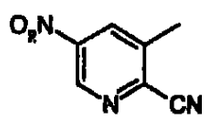
con 10-90% metanol acuoso conteniendo 0.2% ácido fosfórico durante un gradiente de 4 min. observando a 220 nm. EM (ES): m/z 332.2 $[M+H]^+$. La estereoquímica absoluta del compuesto 771E se establece por la estereoquímica conocida del compuesto intermediario 752 y la retención de la configuración en ella. La estereoquímica absoluta es como se obtiene en la figura anterior y resulta de la nomenclatura.

Ejemplo 772



A. 2-Ciano-3-metil-5-nitropiridina (772A)



La 2-ciano-3-metilpiridina comercialmente disponible (2.36g, 20 mmol), nitrato de tetrabutil amonio (6.7g, 22 mmol) y anhídrido trifluoroacético (4.20g, 20 mmol) reaccionaron en 65 mL de CH_2Cl_2 utilizando el procedimiento descrito en el ejemplo 762B. La purificación del crudo por cromatografía de gel de sílice usando 20% hexanos/CH_2Cl_2 como el eluyente da el compuesto 772A (1.05g (32%) como un sólido amarillo claro.

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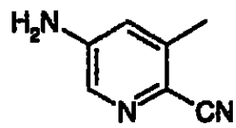
B. 5-Amino-2-ciano-3-metilpiridina (772B)



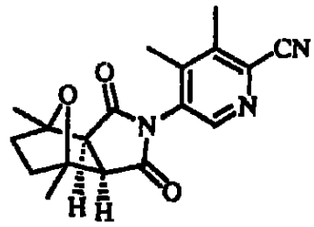
La 2-Ciano-3-metil-5-nitropiridina (0.2 g, 1.23 mmol) se disolvió en 6 mL de 90% etanol y cloruro de calcio (0.07g, 0.64 mmol) se agregó seguido por polvo de hierro (0.62g, 11.1 mmol, malla 325). La mezcla heterogénea se agitó por una hora. La mezcla se filtró a través de Celite y se concentró para dar el compuesto 772B (0.13g, 81%) como un sólido café claro.

C. (772C)

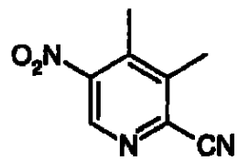
La 5-Amino-2-ciano-3-metilpiridina (0.067g, 0.5 mmol), el compuesto 20A (0.103g, 0.53 mmol), $MgSO_4$ (0.15g, 1.25 mmol), trietilamina (0.25g, 2.5 mmol) y 1 mL de tolueno se combinaron en un tubo sellado y se calentaron a 145°C por 16 h. La mezcla enfriada se diluyó con CH_2Cl_2, se filtró, y se purificó por cromatografía de gel de sílice usando 5% éter/ CH_2Cl_2 como el eluyente para dar el compuesto 772C (0.055g, 35%) como un sólido blanco descolorido. CLAR: 100% a 2.49 min (Columna YMC S5 ODS) se eluye con 10-90% metanol acuoso conteniendo 0.2% ácido fosfórico durante un gradiente de 4 min. observando a 220 nm. EM (ES): m/z 312.2 $[M+H]^+$.

1190

Ejemplo 773

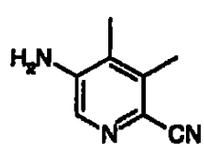


A. 2-Ciano-3,4-dimetil-5-nitropiridina (773A)



La 2-Ciano-3-metil-5-nitropiridina (0.33g, 2 mmol) se disolvió en 10 mL de THF y se enfrió en un baño de hielo seco/acetona bajo nitrógeno. Se agregó bromuro de metilmagnesio (1.33 mL, 4 mmol) por medio de una jeringa durante cinco minutos. La reacción se agitó por 2 h a -70°C. Se agregó DDQ (0.068g, 3 mmol) en 7 mL de THF y la mezcla se entibió a 25°C. El solvente se separó in vacuo y el residuo se purificó por cromatografía de gel de sílice usando CH_2Cl_2 como el eluyente para dar el compuesto 773A (0.15g, 42%) como un aceite rojo.

B. 5-Amino-2-ciano-3,4-dimetilpiridina (773B)



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2-Ciano-3,4-dimetil-5-nitropiridina (0.15g, 0.85 mmol), cloruro de calcio (0.05g, 0.42 mmol), y polvo de hierro (0.44g, 7.8 mmol, malla 325) reaccionaron como se describe en el ejemplo 772B. La purificación del producto crudo por cromatografía de gel de sílice usando 1:1 éter/ CH_2Cl_2 como el eluyente dio el compuesto 773B (0.054g, 50%) como un sólido amarillo.

C. (773C)

5-Amino-2-ciano-3,4-dimetilpiridina (0.05g, 0.34 mmol) y el compuesto 20A (0.1g, 0.5 mmol) reaccionaron como se describe en el ejemplo 772C. El producto crudo obtenido después de filtración a través de Celite se purificó por cromatografía de gel de sílice usando 10% éter/ CH_2Cl_2 como el eluyente para dar el compuesto 773C (0.33g, 30%). como un sólido amarillo. CLAR: 90% a 2.58 min. (Columna YMC S5 ODS) se eluye con 10-90% metanol acuoso conteniendo 0.2% ácido fosfórico durante un gradiente de 4 min. observando a 220 nm. EM (ES): m/z 326.22 $[M+H]^+$.

Ejemplo 774

[3aR-(3aα,4β,5α,7β,7aα)]-4-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo y [3aS-(3aα,4β,5α,7β,7aα)]-4-

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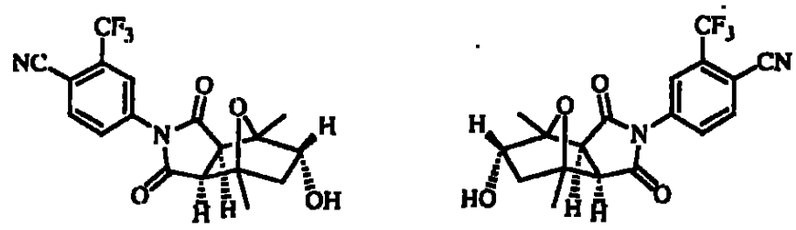
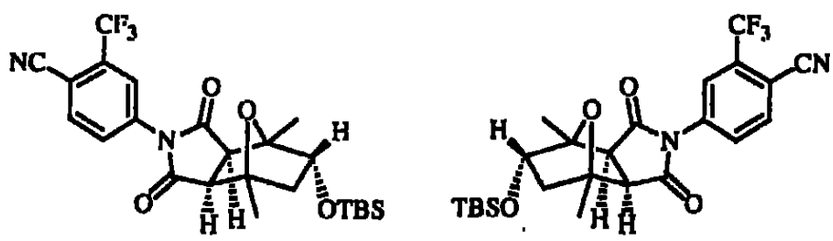
(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo (774Bi y 774Bii)



A. [3aR-(3aα,4β,5α,7β,7aα)]-4-[5-[[(1,1-Dimetiletil)dimetilsilil]oxi]octahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2-(trifluorometil)benzonitrilo y [3aS-(3aα,4β,5α,7β,7aα)]-4-[5-[[(1,1-Dimetiletil)dimetilsilil]oxi]octahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2-(trifluorometil)benzonitrilo (774Ai y 774Aii)



El compuesto racémico 222C se separó en sus enantiómeros por CLAR quiral preparativa de fase normal (columna CHIRALPAK AD 5x50 cm; se eluye con 7% EtOH en hexanos (isocrático) a 50 mL/min.) para dar el compuesto de elución más rápida 774Ai (18 min.) y el compuesto de elución más lenta 774Aii.

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B. [3aR-(3aα,4β,5α,7β,7aα)]-4-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo y [3aS-(3aα,4β,5α,7β,7aα)]-4-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo (774Bi y 774Bii)

El 774Ai y el 774Aii (0.12g, 0.25 mmol) fueron cada uno disueltos en 2 mL de THF y se agregó 2 mL de 10% HCl/MeOH y las reacciones se agitaron durante la noche a temperatura ambiente. Se agregó bicarbonato de sodio saturado y EtOAc y la capa orgánica se separó, se lavó con salmuera, se secó (Na_2SO_4), se filtró, y se concentró in vacuo para dar el compuesto 774Bi (0.084mg, 88%) y el compuesto 774Bii (0.076g, 82%) como sólidos blancos. Compuesto 774Bi: CLAR: 100% a 2.89 min. (Columna YMC S5 ODS) se eluye con 10-90% metanol acuoso conteniendo 0.2% ácido fosfórico durante un gradiente de 4 min. observando a 220 nm. EM (ES): m/z 381.19 [M+H]. Compuesto 774Bii: CLAR: 100% a 2.89 min. (Columna YMC S5 ODS) se eluye con 10-90% metanol acuoso conteniendo 0.2% ácido fosfórico durante un gradiente de 4 min. observando a 220 nm. EM (ES): m/z 381.16 $[M+H]^+$. La estereoquímica absoluta de los compuestos 774Bi y 774Bii no se ha establecido. Aunque cada compuesto representa un antípodo sencillo, la

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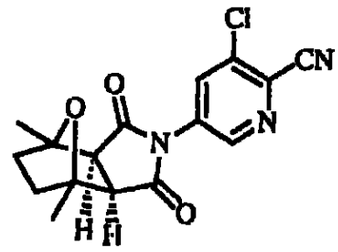
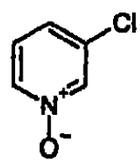
nomenclatura y estructura mostradas no reflejan la estereoquímica absoluta del compuesto.

Ejemplo 775

(775F)



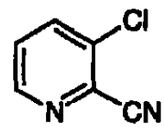
A. 3-Cloropiridina-1-óxido (775A)



La 3-cloropiridina comercialmente disponible (11.36g, 100 mmol) se disolvió en 60 mL de ácido acético y se agregó peróxido de hidrógeno al 30% (15 mL). La mezcla de reacción se calentó hasta 70°C por 16 h. La mezcla de reacción enfriada se diluyó con cloroformo y se agitó con carbonato de potasio sólido. La mezcla se filtró y el solvente se separó in vacuo para dar el compuesto 775A (10.21g, 79%) como un aceite amarillo-verdoso.

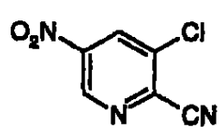
B. 3-Cloro-2-cianopiridina (775B)

1195



3-Cloropiridina-1-óxido (2.59g, 20 mmol), trimetilsilil cianuro (5.95g, 60 mmol), y trietilamina (4.05g, 40 mmol) se combinaron en 40 mL de acetonitrilo y reaccionaron como se describe en el ejemplo 763A. El solvente se separó in vacuo y el residuo se dividió entre CH_2Cl_2 y carbonato de potasio 3M. La capa orgánica se separó, se lavó con salmuera, se secó ($MgSO_4$), y se concentró in vacuo. La purificación del producto crudo por cromatografía de gel de sílice usando 5% éter/ CH_2Cl_2 como el eluyente dio el compuesto 775B (1.84 g, 67%) como un sólido cristalino blanco. CLAR: 100% a 1.64 min (Columna YMC S5 ODS) se eluye con 10-90% metanol acuoso conteniendo 0.2% ácido fosfórico durante un gradiente de 4 min. observando a 220 nm. EM (ES):m/z 139.0$[M+H]^+$.

C. 3-Cloro-2-ciano-5-nitropiridina (775C)



3-Cloro-2-cianopiridina (1.75g, 12.7 mmol), nitrato de tetrabutilamonio (5.02g, 16.5 mmol), y anhídrido trifluoroacético (3.15g, 15 mmol) se combinaron en 65 mL de CH_2Cl_2 y reaccionaron como se describe en el ejemplo 762C. El

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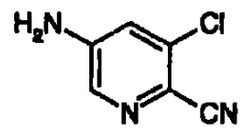
producto crudo se purificó por cromatografía de gel de sílice usando CH_2Cl_2 como el eluyente para dar el compuesto 775C (0.43g, 16%) como un sólido amarillo pálido.

D. 5-Amino-3-cloro-2-cianopiridina (775D)



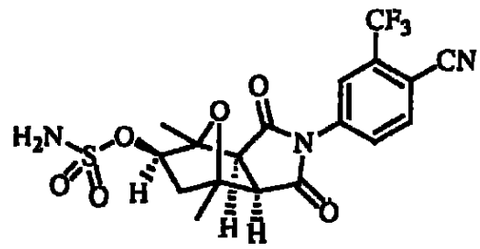
3-Cloro-2-ciano-5-nitropiridina (0.35g, 1.9 mmol), polvo de hierro (0.56g, 10 mmol, malla 325) y cloruro de calcio (0.06g, 0.55 mmol) se combinaron en 10 mL de 90% etanol y como se describe en el ejemplo 772B. La purificación del producto crudo por medio de cromatografía de gel de sílice usando 10% éter/ CH_2Cl_2 como el eluyente da el compuesto 775D (0.14g, 43%) como un sólido café claro. CLAR: 95.5% a 1.69 min. (Columna YMC S5 ODS) se eluye con 10-90% metanol acuoso conteniendo 0.2% ácido fosfórico durante un gradiente de 4 min. observando a 220 nm. EM (ES): m/z 154.03 $[M+H]^+$.

E. (775E)

La 5-Amino-3-cloro-2-cianopiridina (0.05g, 0.33 mmol) y el compuesto 20A (0.07g, 0.36 mmol) reaccionaron como se describe en el ejemplo 772C. El producto crudo obtenido después de la preparación se purificó por cromatografía de gel de sílice usando 5% éter/ CH_2Cl_2 para dar el compuesto 775E (0.054g, 50%) como un sólido blanco descolorido. CLAR:

97.6% a 2.86 min. (Columna YMC S5 ODS) se eluye con 10-90% metanol acuoso conteniendo 0.2% ácido fosfórico durante un gradiente de 4 min. observando a 220 nm. EM (ES): m/z 332.16 $[M+H]^+$.

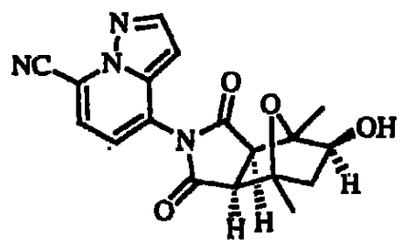
Ejemplo 776



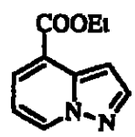
A una solución transparente del compuesto 741Di (190 mg, 0.5 mmol) en dioxano anhidro (3.5 mL) se agregó reactivo Burgess (143 mg, 0.6 mmol) a temperatura ambiente bajo argón. Después de que la mezcla se agitó a temperatura ambiente por 70 min., se agregó bis(ciclopentadienil) dicloruro de titanio (137 mg, 0.55 mmol). La mezcla se agitó a 100°C por 1 día, después se enfrió hasta temperatura ambiente. Se agregaron H_2O y una solución saturada acuosa de $KHSO_4$. La mezcla se extrajo con EtOAc (3X). Los extractos combinados se secaron sobre Na_2SO_4 y se concentraron bajo presión reducida. La purificación por cromatografía instantánea por gel de sílice se eluye con EtOAc/heptano (gradiente desde una relación de 1:4 hasta 1:0) dio el compuesto 776 (170 mg, 74%) como un sólido amarillo vidrioso. CLAR: 99% a 3.27 min. (tiempo de retención) (columna YMC S5 ODS-A 4.6 x 50 mm se eluye con 10-

90% metanol acuoso durante 4 min., contiene 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 458 $[M-H]^-$. La estereoquímica absoluta del compuesto 776 se establece por la estereoquímica conocida del compuesto intermediario 741Di y la retención de la configuración en ella. La estereoquímica absoluta es como se obtiene en la figura anterior y resulta de la nomenclatura.

Ejemplo 777



A. Éster de etilo del ácido Pirazol[1,5-a]piridin-4-carboxílico (777A)



A una solución transparente de éster de etilo del ácido 2-metil-nicotínico (50.6 g, 306 mmol) en cloruro de metileno anhidro (200 mL) se agregó O-mesitilenosulfonil hidroxilamina (73 g, 337 mmol; preparada de acuerdo con un procedimiento de la literatura descrito en Krause; J.G., Synthesis 1972, 140); en porciones a 0°C. La solución obtenida se agitó a 0°C por 15 min., y después a temperatura ambiente por 1 h. La concentración bajo presión reducida dio un sólido amarillo.

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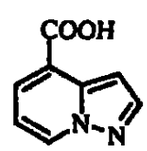
Después de que el sólido se disolvió en DMF anhidro (300 mL), se agregó N,N-dimetilformamida dimetil acetal (122 mL, 918 mmol) a 0°C. La mezcla se agitó a 0°C por 15 min., y después a 90°C por 3 h. La mezcla de reacción se concentró bajo presión reducida, se mezcló con H_2O (200 mL), y se extrajo con Et20 (3 x 180 mL). Las soluciones orgánicas combinadas se lavaron secuencialmente con salmuera (50 mL), HCl 1N acuoso (50 mL), y salmuera (50 mL), y se secaron sobre Na_2SO_4. La filtración a través de una columna de SiO_2, que se eluyó después con 30% EtOAc en heptano, dio el compuesto 777A (43.3 g, 74%) como un sólido amarillo. CLAR: 80% a 3.20 min. (tiempo de retención) más 20% correspondiente al éster de metilo a 2.83 min. (tiempo de retención) (columna YMC S5 ODS-A 4.6 x 50 mm se eluye con 10-90% metanol acuoso durante 4 min., contiene 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 191 $[M+H]^+$.

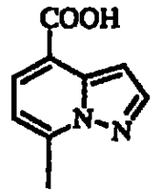
B. Ácido Pirazol[1,5-a]piridina-4-carboxílico (777B)



A una mezcla agitada de éster del ácido pirazolo[1,5-a]piridina-4-carboxílico (35.1 g, 185 mmol), KOH (85%, 25 g, 379 mmol), y MeOH (200 mL), enfriada hasta temperatura ambiente en un baño de agua, se agregó H_2O lentamente. La

mezcla de reacción obtenida se agitó a temperatura ambiente por 1.5 h y después se concentró bajo presión reducida para eliminar el MeOH. Se agregó una cantidad mínima de H_2O al residuo para hacer una solución transparente que se acidificó después hasta un pH=1 a 0°C con HCl acuoso (HCl concentrado, 11 mL; HCl 5N, 10 mL, después HCl 2N y 1N). Después del calentamiento en un baño de vapor, la mezcla se enfrió. El sólido se filtró, se lavó con H_2O, y se secó bajo vacío para dar el compuesto 777B (29 g, 97%) como un sólido amarillo. CLAR: 100% a 2.14 min. (tiempo de retención) (columna YMC S5 ODS-A de 4.6 x 50 mm se eluye con 10-90% metanol acuoso durante 4 min., contiene 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 163 $[M+H]^+$.

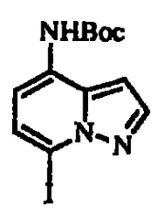
C. Ácido 7-yodo-pirazol[1,5-a]piridina-4-carboxílico (777C)



A una suspensión agitada de ácido pirazol[1,5-a]piridina-4-carboxílico (29 g, 179 mmol) en THF anhidro (1000 mL) enfriada a 0°C se agregó una solución de hexametildisilazida de litio (1M en THF, 200 mL, 200 mmol). Después de que la mezcla se agitó a 0°C por 30 min., se agregó una solución adicional de LHMDS (1M en THF, 320 mL, 320 mmol) a -4°C. Después de que la mezcla se agitó por 10

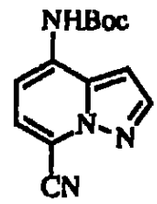
min., se agregó yodo (55 g, 215 mmol) en porciones. La mezcla de reacción se agitó a -4°C por 1.5 h, a temperatura ambiente por 1 h, y después se enfrió hasta 0°C. Se agregaron HCl acuoso (5N, 40 mL) y solución de NaS_2O_3 (10 g en 40 mL de H_2O). La mezcla se agitó a 0°C por 30 min., y después se concentró bajo presión reducida. La mezcla residual se mezcló con una solución de $NaHCO_3$ saturado (100 mL), éter de etilo (150 mL), y H_2O (130 mL). La solución de éter se separó y extrajo con H_2O (50 mL). Las soluciones acuosas combinadas se lavaron con éter de etilo (150 mL), se acidificaron hasta pH=1 con una solución acuosa saturada de $KHSO_4$, se calentó en un baño de vapor, y después se enfrió. El sólido se filtró, se lavó con H_2O, y después se secó después para dar el compuesto 777C (50 g, 97%) como un sólido amarillo. CLAR: 100% a 2.88 min. (tiempo de retención) (columna YMC S5 ODS-A de 4.6 x 50 mm se eluye con 10-90% metanol acuoso durante 4 min., contiene 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 289 $[M+H]^+$.

D. Éster de tert-butilo del ácido (7-yodo-pirazol[1,5-a]piridin-4-il)-carbámico (777D)



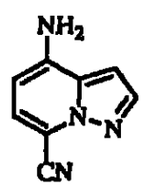
A una solución transparente de ácido 7-yodo-pirazol[1,5-a]piridina-4-carboxílico (23.4 g, 81.2 mmol) y diisopropiletilamina (65 mL) en tert-butanol (250 mL) y tolueno anhidro (200 mL) se agregó difenil fosforil azida (25 mL, 114 mmol) bajo argón. Después de que la mezcla se agitó a temperatura ambiente por 30 min., la temperatura se elevó lentamente hasta 90°C. La mezcla se agitó a 90°C durante la noche y se concentró bajo presión reducida para eliminar los solventes. El residuo se dividió entre EtOAc (200 mL) y una solución acuosa de NaOH (2N, 75 mL). La solución acuosa se separó y extrajo con EtOAc (100 mL). Las soluciones orgánicas combinadas se lavaron con solución acuosa de NaOH (1N, 75 mL), se secaron sobre Na_2SO_4, y concentraron bajo presión reducida. La purificación por cromatografía instantánea por gel de sílice se eluye con EtOAc/heptano (gradiente desde una relación de 0:1 a 1:1) dio un sólido de tono café. La recristalización en heptano con algo de EtOAc dio el compuesto 777D (19.6 g, 67%) como un sólido amarillo. CLAR: 95% a 3.83 min. (tiempo de retención) (columna YMC S5 ODS-A de 4.6 x 50 mm se eluye con 10-90% metanol acuoso durante 4 min., contiene 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 360 $[M+H]^+$.

E. Éster de tert-butilo del ácido (7-ciano-pirazol[1,5-a]piridin-4-il)-carbámico (777E)



Una mezcla de éster de tert-butilo del ácido (7-yodo-pirazol[1,5-a]piridin-4-il)-carbámico (36 mg, 0.1 mmol), cianuro de zinc (24 mg, 0.2 mmol), tetraquis(trifenilfosfino) paladio (0) (23 mg, 0.02 mmol), y DMF anhidro (1 mL) se desgasificó con argón. Después, la mezcla se agitó a 80°C por 4.5 h, se enfrió hasta temperatura ambiente, se mezcló con EtOAc (6 mL), y se filtró. Se filtró el concentrado bajo presión reducida. La purificación por cromatografía instantánea por gel de sílice se eluye con EtOAc/heptano (gradiente desde una relación 1:4 hasta 1:2) dio el compuesto 777E (24 mg, 93%) como un sólido blanco. CLAR: 93% a 3.64 min. (tiempo de retención) (columna YMC S5 ODS-A de 4.6 x 50 mm se eluye con 10-90% metanol acuoso durante 4 min., contiene 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 259 $[M+H]^+$.

F. 4-amino-pirazolo[1,5-a]piridina-7-carbonitrilo (777F)



1204

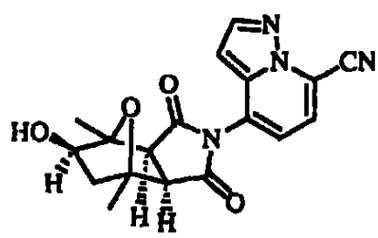
A una solución transparente de éster de tert-butilo del ácido (7-ciano-pirazol[1,5-a]piridin-4-il)-carbámico (3 g, 11.6 mmol) en cloruro de metileno (40 mL) se agregó TFA (8 mL). La mezcla se agitó a temperatura ambiente por 3 h, y después se concentró bajo presión reducida. El residuo se dividió entre EtOAc (100 mL) y una solución saturada de $NaHCO_3$ (50 mL). La solución acuosa se separó y extrajo con EtOAc (2x50 mL). Las soluciones orgánicas combinadas se secaron sobre Na_2SO_4, se filtró a través de una almohadilla de SiO_2, y se concentró bajo presión reducida. La cristalización en EtOAc y 95% EtOH dio el compuesto 777F (1.07 g, 58%) como un sólido amarillo oscuro. CLAR: 97% a 1.96 min. (tiempo de retención) (columna YMC S5 ODS-A de 4.6 x 50 mm se eluye con 10-90% metanol acuoso durante 4 min., contiene 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 159 $[M+H]^+$.

G. (777G)

Una mezcla de 4-amino-pirazol[1,5-a]piridina-7-carbonitrilo (135 mg, 0.85 mmol), compuesto 752 (225 mg, 1.06 mmol), polvo de malla molecular de 4Å (850 mg), y DMA (0.85 mL) se agitó bajo argón a temperatura ambiente por 10 min., a 170°C por 3 h, y después se enfrió hasta temperatura ambiente. El polvo de malla molecular se filtró completamente, y se filtró el concentrado bajo presión

reducida. La purificación por cromatografía instantánea por gel de sílice se eluye con EtOAc (gradiente con MeOH desde 0% hasta 5%) dio el compuesto 777G (98 mg, 33%) como un sólido amarillento. CLAR: 99% a 2.28 min. (tiempo de retención) (columna YMC S5 ODS-A de 4.6 x 50 mm se eluye con 10-90% metanol acuoso durante 4 min., contiene 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 353 $[M+H]^+$. La estereoquímica absoluta del compuesto 777G se establece por la estereoquímica conocida del compuesto intermediario 752 y la retención de la configuración en ella. La estereoquímica absoluta es como se obtiene en la figura anterior y resulta de la nomenclatura.

Ejemplo 778

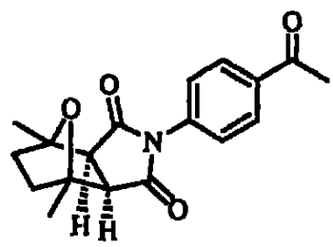


Una mezcla de 4-amino-pirazol[1,5-a]piridina-7-carbonitrilo (60 mg, 0.38 mmol), compuesto 751 (110 mg, 0.52 mmol), $MgSO_4$ (360 mg, 3 mmol), diisopropiletilamina (0.35 mL, 2 mmol), y tolueno anhidro (0.6 mL) se agitó a 135°C bajo argón por 20 h. La purificación por cromatografía instantánea por gel de sílice, se eluye con EtOAc (gradiente con MeOH desde 0% hasta 5%) dio el compuesto 778 (115 mg, 86%) como un

1206

sólido grisáceo. CLAR: 98% a 2.28 min. (tiempo de retención) (columna YMC S5 ODS-A de 4.6 x 50 mm se eluye con 10-90% metanol acuoso durante 4 min., contiene 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 353 $[M+H]^+$. La estereoquímica absoluta del compuesto 778 se establece por la estereoquímica conocida del compuesto intermediario 751 y la retención de la configuración en ella. La estereoquímica absoluta es como se obtiene en la figura anterior y resulta de la nomenclatura.

Ejemplo 779

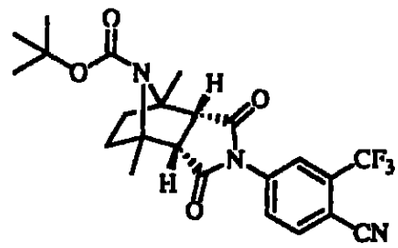


Una solución transparente del compuesto 20A (50 mg, 0.25 mmol), p-aminoacetofenona (68 mg, 0.5 mmol), y N,N-dimetilformamida dimetil acetal (0.065 mL, 0.49 mmol) en N,N-dimetilformamida anhidra(0.2 mL) se agitó a 100°C bajo argón por 18 h, y después se concentró. La purificación por cromatografía instantánea por gel de sílice sobre SiO_2, se eluye con EtOAc/heptano (gradiente desde una relación de 1:4 hasta 1:0) dio un sólido que se cristalizó en una mezcla de EtOAc y heptano para dar el compuesto 779 (11 mg, 14%) como un sólido blanco. CLAR: 98% a 2.89 min. (tiempo de retención)

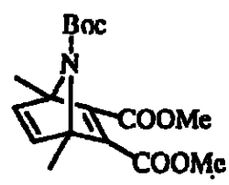
1207

(columna YMC S5 ODS-A de 4.6 x 50 mm se eluye con 10-90% metanol acuoso durante 4 min., contiene 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 314 $[M+H]^+$.

Ejemplo 780



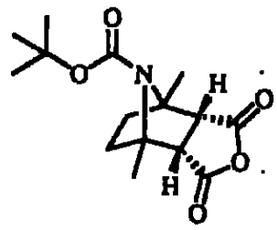
A. Éster de 2,3-dimetilo del éster de 7-tert-butilo del ácido 1,4-dimetil-7-aza-biciclo[2.2.1]hepta-2,5-dieno-2,3,7-tricarboxílico (780A)



Una mezcla de éster de tert-butilo crudo del ácido 2,5-dimetil-pirrol-1-carboxílico (preparado según la literatura (Haiser, H.-P.; et al. J. Org. Chem. 1984 49(22) 4203-4209); 500 mg) y dimetil acetilendicarboxilato (0.5 mL, casi 4 eq) se agitó a 120°C bajo argón por 2 h. La purificación por cromatografía instantánea por gel de sílice sobre SiO_2, se eluye con EtOAc/heptano (gradiente desde una relación de 1:20 hasta 1:2 ratio) y dio el compuesto 780A (166 mg, 50% rendimiento) como un líquido incoloro. CLAR: 90% a 3.67 min. (tiempo de retención) (columna YMC S5 ODS-A de 4.6 x 50 mm se

eluye con 10-90% metanol acuoso durante 4 min., contiene 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm).

B. (780B)



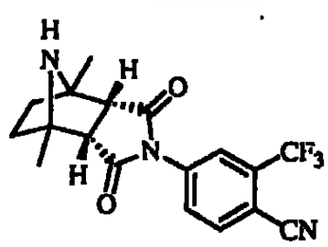
A una solución transparente de éster de 2,3-dimetilo del éster de 7-tert-butilo del ácido 1,4-dimetil-7-aza-biciclo[2.2.1]hepta-2,5-dieno-2,3,7-tricarboxílico (1.5 g, 4.4 mmol) en MeOH (10 mL) y H_2O (5 mL) se enfrió en agua con hielo y se agregó KOH (2.9 g, 44 mmol) en porciones. Se agregó después más H_2O (5 mL). Después de que la mezcla de reacción se agitó a temperatura ambiente por 1 h, se agregó hidrazina (1.4 mL, 44 mmol), HCl (solución acuosa 2N, 17mL, 34 mmol), y peróxido de hidrógeno (solución acuosa al 50%, 1.27mL, 22 mmol) secuencialmente a 0°C. La mezcla de reacción se agitó a temperatura ambiente por 3 h, y después se concentró bajo presión reducida para eliminar el MeOH. La solución acuosa obtenida se acidificó hasta un pH=1 con una solución acuosa saturada de $KHSO_4$ y se extrajo con EtOAc (3X). Los extractos combinados se secaron sobre Na_2SO_4, y concentraron bajo presión reducida para dar un sólido amarillo. El sólido amarillo anterior se disolvió en anhídrido acético (15 mL). La solución se agitó a 100°C por 1

h. La concentración bajo presión reducida dio 1.3 g (100%) del compuesto 780B como un sólido color naranja.

C. (780C)

Una mezcla del compuesto 780B (0.8g, 2.7 mmol), 4-amino-2-trifluorometilbenzonitrilo (0.5 g, 2.7 mmol), $MgSO_4$ (2.6 g, 22 mmol), diisopropiletilamina (2.35 mL, 13.5 mmol), y tolueno anhidro (2.9 mL) se agitó a 135°C bajo argón por 15 h. El sólido se filtró y se lavó con EtOAc. El filtrado se concentró bajo presión reducida. La purificación por cromatografía instantánea por gel de sílice, se eluye con EtOAc/heptano (gradiente desde una relación de 1:4 hasta 1:2) dio el compuesto 780C (1.03 g, 82%) como un sólido vidrioso. CLAR: 100% a 4.26 min. (tiempo de retención) (Columna YMC S5 ODS-A de 4.6 x 50 mm se eluye con 10-90% metanol acuoso durante 4 min., contiene 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 462.34 $[M-H]^-$.

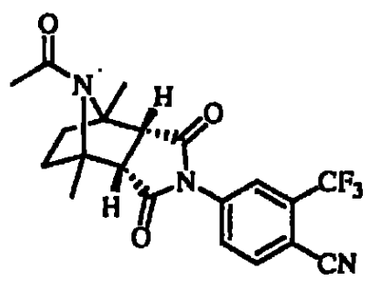
Ejemplo 781



A una solución del compuesto 780C (770 mg, 1.66 mmol) en cloruro de metileno (10 mL) se agregó ácido trifloroacético

(5 mL). La mezcla de reacción se agitó a temperatura ambiente por 40 min. La mezcla se concentró después bajo presión reducida, basificada con una solución saturada de $NaHCO_3$, y se extrajo con EtOAc (3X). Los extractos combinados se secaron sobre Na_2SO_4 y concentraron bajo presión reducida para dar el compuesto 781 (600 mg, 99%) como un sólido color naranja. CLAR: 100% a 2.55 min. (tiempo de retención) (Columna YMC S5 ODS-A de 4.6 x 50 mm se eluye con 10-90% metanol acuoso durante 4 min., contiene 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 364 $[M+H]^+$.

Ejemplo 782

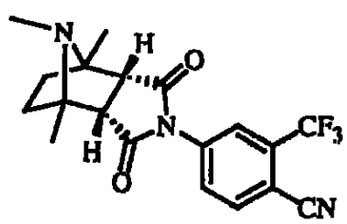


A una solución transparente del compuesto 781 (27 mg, 0.074 mmol) y trietilamina (0.061 mL, 0.44 mmol) en cloruro de metileno anhidro (3 mL) se agregó cloruro de acetilo (0.016 mL, 0.22 mmol) a 0°C bajo argón. Después de que la mezcla se agitó a 0°C por 30 min. y a temperatura ambiente por 30 min., se agregó una solución saturada de $NaHCO_3$. Después de que la mezcla se agitó por 15 min., la solución orgánica se separó, se secó sobre Na_2SO_4, y se filtró a través

de una almohadilla de SiO_2 que después se enjuagó con EtOAc. El filtrado se concentró bajo presión reducida. La cristalización en una mezcla de EtOAc y heptano dio el compuesto 782 (19 mg, 63%) como un sólido blanco. CLAR: 99% a 3.56 min. (tiempo de retención) (Columna YMC S5 ODS-A de 4.6 x 50 mm se eluye con 10-90% metanol acuoso durante 4 min., contiene 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 406 $[M+H]^+$.

Ejemplo 783

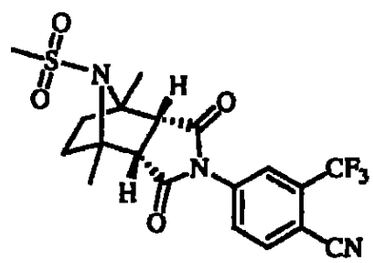
(3aα,4β,7β,7aα)-4-(Octahidro-4,7,8-trimetil-1,3-dioxo-4,7-imino-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo (783)



Una mezcla del compuesto 781 (180 mg, 0.5 mmol), formaldehido (solución acuosa al 37%, 0.11 mL, 1.5 mmol), $NaHB(OAc)_3$ (318 mg, 1.5 mmol), y 1,2-dicloroetano (9 mL) se agitó a temperatura ambiente bajo argón durante la noche, y después se secó sobre Na_2SO_4. La purificación por cromatografía instantánea por gel de sílice se eluye con EtOAc (gradiente con trietilamina desde 2% hasta 10%) dio el compuesto 783 (160 mg, 84%) como un sólido blanco. CLAR: 100% a 2.46 min (tiempo de retención) (Columna YMC S5 ODS-A de 4.6

x 50 mm se eluye con 10-90% metanol acuoso durante 4 min, contiene 0.2% ácido fosfórico, 4 mL/min, observando a 220 nm). EM (ES): m/z 378 $[M+H]^+$.

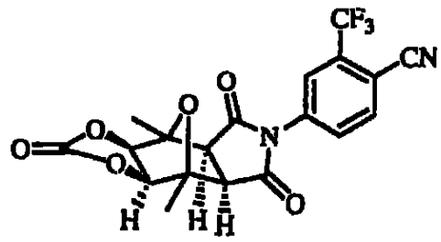
Ejemplo 784



A una solución transparente del compuesto 781 (20 mg, 0.055 mmol) y trietilamina (0.04 mL, 0.24 mmol) en cloruro de metileno anhidro (1 mL) enfriada a 0°C, se agregó cloruro de metanosulfonilo (0.01 mL, 0.13 mmol). Después de que la mezcla de reacción se agitó a 0°C por 30 min, se agregó una solución saturada de $NaHCO_3$ (0.1 mL). La mezcla se agitó por 10 min, se secó sobre Na_2CO_3, y se filtró a través de una almohadilla de SiO_2 que después se enjuagó con EtOAc. El filtrado se concentró bajo presión reducida. La cristalización en una mezcla de EtOAc y heptano dio el compuesto 784 (14 mg, 58%) como un sólido blanco. CLAR: 98% a 3.58 min (tiempo de retención) (Columna YMC S5 ODS-A de 4.6 x 50 mm se eluye con 10-90% metanol acuoso durante 4 min, contiene 0.2% ácido fosfórico, 4 mL/min, observando a 220 nm). EM (ES): m/z 440 $[M-H]^-$.

1213

Ejemplo 785



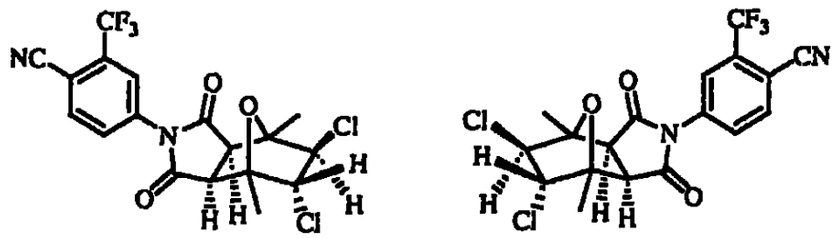
A una solución agitada del compuesto 230Bi (50 mg, 0.13 mmol) y trietilamina (0.09 mL, 0.65 mmol) en cloruro de metileno anhidro (5 mL) se agregó fosgeno (20% en tolueno, 0.25 mL, 0.48 mmol) gota a gota. Después de que la reacción se completó, se agregó una solución saturada de $NaHCO_3$. La mezcla se extrajo con EtOAc (3X). Los extractos combinados se secaron sobre Na_2SO_4, se filtraron a través de una almohadilla de SiO_2, y se concentraron bajo presión reducida. La cristalización en una mezcla de EtOH y H_2O dio el compuesto 785 (40 mg, 73%) como un sólido blanco. CLAR: 100% a 3.55 min (tiempo de retención) (Columna YMC S5 ODS-A de 4.6 x 50 mm se eluye con 10-90% metanol acuoso durante 4 min, contiene 0.2% ácido fosfórico, 4 mL/min, observando a 220 nm). EM (ES): m/z 377 $[M-CO2-H]^-$.

Ejemplos 786i y 786ii

[3aR-(3aα,4β,5β,6α,7β,7aα)]-4-(octahidro-5,6-dicloro-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo y [3aR-(3aα,4β,5β,6α,7β,7aα)]-4-

1214

(octahidro-5,6-dicloro-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo (786i y 786ii)



A una mezcla agitada del compuesto 230Bi (544 mg, 1.5 mmol), acetona (10 mL), ácido acético (2 mL), y salmuera (2 mL) enfriada a 0°C se agregó blanqueador (5 mL) gota a gota. La solución transparente obtenida se agitó a temperatura ambiente por 1 h, y después se concentró bajo presión reducida. La mezcla residual se extrajo con EtOAc (3X). Los extractos combinados se secaron sobre Na_2SO_4, y concentraron bajo presión reducida. La purificación por cromatografía instantánea por gel de sílice sobre SiO_2, se eluye con EtOAc/heptano (gradiente desde una relación de 1:9 hasta 1:2 ratio) dio un sólido blanco que se cristalizó en una mezcla de EtOAc y heptano para dar 301 mg (46%) de la mezcla racémica de los compuestos 786i y 786ii como un sólido blanco. CLAR: 100% a 4.11 min (tiempo de retención) (Columna YMC S5 ODS-A de 4.6 x 50 mm se eluye con 10-90% metanol acuoso durante 4 min, contiene 0.2% ácido fosfórico, 4 mL/min, observando a 220 nm). EM (ES): m/z 395 $[M-HCl-H]^-$.

La separación por CLAR quiral de la mezcla racémica dio dos enantiómeros: compuesto 786i y compuesto 786ii.

1215

Condiciones de CLAR quiral empleadas para la separación:

Condición de CLAR Quiral

Columna:	CHIRALPAK AD	
	50 x 500 mm, 20 µ	
Temperatura:	temperatura ambiente	
Volumen de inyección:	20 mL	
Fase Móvil:	A:	IPA con 0.1% dietilamina
	B:	Heptano con dietilamina
	Isocrática, 45% de A, 60 min.	
Relación de flujo:	50 mL/min.	
Detección UV:	245 nm	

Condiciones de CLAR quiral empleadas para el análisis:

Condición de CLAR quiral

Columna:	CHIRALPAK AD	
	4.6 x 250 mm, 10 µ,	
Temperatura:	25°C	
Volumen de inyección:	10 µL	
Fase Móvil:	A:	IPA con 0.1% dietilamina
	B:	Heptano con

1216

dietilamina

Isocrática, 45% de A, 15 min.

Relación de flujo: 1 mL/min.

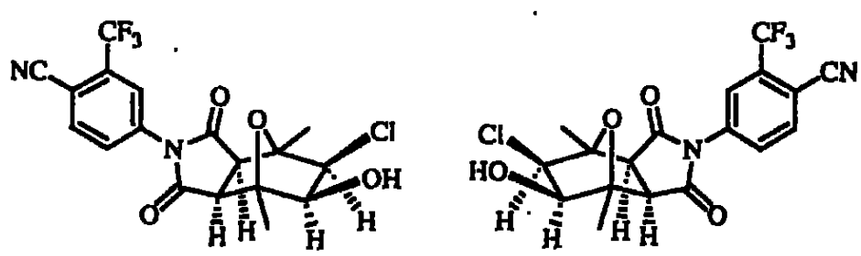
Detección UV: 245 nm

TR:	Compuesto 786i	10.6 min
	Compuesto 786ii	7.0 min

La estereoquímica absoluta de los compuestos 785i y 785ii no se ha establecido. Aunque cada compuesto representa un antípodo sencillo, la nomenclatura y estructura mostradas no reflejan la estereoquímica absoluta del compuesto.

Ejemplo 787i y 787ii

[3aR-(3aα,4β,5β,6β,7β,7aα)]-4-(octahidro-5-cloro-6-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo y [3aS-(3aα,4β,5β,6β,7β,7aα)]-4-(octahidro-5-cloro-6-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo (787i y 787ii)



1217

A una solución agitada del compuesto 230Bi (181 mg, 0.5 mmol) en cloruro de metileno anhidro (4 mL) enfriada a -78°C bajo argón se agregó cloruro de cromilo (0.048 mL, 0.6 mmol) gota a gota. Después de que la mezcla de reacción se agitó a -78°C por 1 h, la temperatura de reacción se elevó lentamente hasta la temperatura ambiente. La mezcla de reacción se agitó a temperatura ambiente por 2 h. Se agregó luego una solución saturada de $NaHCO_3$ (10 mL) a 0°C con agitación vigorosa. La mezcla se extrajo con EtOAc (3X). Los extractos combinados se secaron sobre Na_2SO_4, y se concentraron bajo presión reducida. La purificación por cromatografía instantánea por gel de sílice sobre SiO_2 se eluye con EtOAc/heptano (gradiente desde una relación de 1:4 hasta 1:0) dio 98 mg (47%) de mezcla racémica de los compuestos 787i y 787ii como un sólido blanco. CLAR: 100% a 3.32 min (tiempo de retención) (Columna YMC S5 ODS-A de 4.6 x 50 mm se eluye con 10-90% metanol acuoso durante 4 min, contiene 0.2% ácido fosfórico, 4 mL/min, observando a 220 nm). EM (ES): m/z 377 $[M-HCl-H]^-$.

La separación por CLAR quiral del racemato dio dos enantiómeros: compuesto 787i y compuesto 787ii.

Condiciones de CLAR quiral empleadas para la separación:

Condición de CLAR Quiral

Columna:	CHIRALCEL OD
	50 x 500 mm, 20μ

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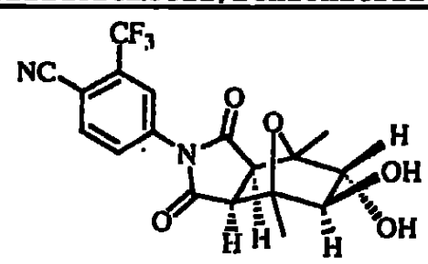
Temperatura:	temperatura ambiente
Volumen de Inyección:	20 mL
Fase Móvil:	A: IPA con 0.1% de dietilamina
	B: heptano con 0.1% de dietilamina
	Isocrática, 35% de A, 90 min.
Relación de flujo:	50 ml/min.
Detección UV:	245 nm

TR:	Compuesto 787i	41 min
	Compuesto 787ii	51 min

La estereoquímica absoluta de los compuestos 787i y 787ii no se ha establecido. Aunque cada compuesto representa un antípodo sencillo, la nomenclatura y estructura mostradas no reflejan la estereoquímica absoluta del compuesto.

Ejemplo 788

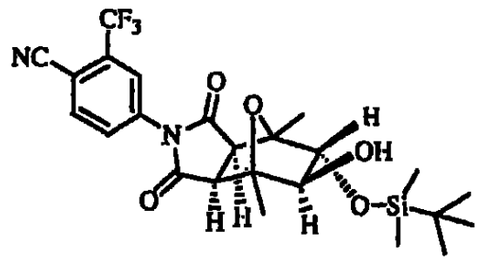
(3aα,4β,5β,6α,7β,7aα)-4-(Octahidro-5,6-dihidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo (788B)



A. **(3aα,4β,5α,6β,7β,7aα)-4-(Octahidro-5-[[(1,1-dimetiletil)dimetilsilil]oxi]-6-hidroxi-4,7-dimetil-1,3-**

1219

dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo (788A)



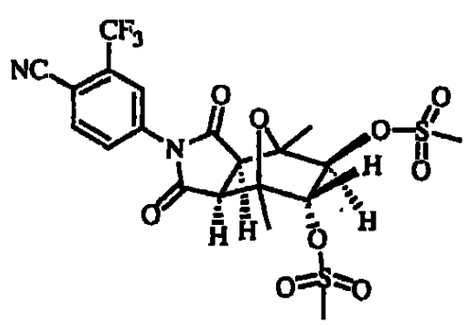
A una solución agitada del compuesto 222B (1.49 g, 3 mmol) en THF anhidro (31 mL) se agregó un complejo de borano-metil sulfuro (0.61 mL, 6.1 mmol) gota a gota a temperatura ambiente bajo argón. Después de que la mezcla de reacción se agitó a temperatura ambiente por 1.5 h, EtOH (20 mL) se agregó lentamente a 0°C, seguido por solución amortiguadora de fosfato (pH = 7.2, 39 mL), y H_2O_2 (30% acuoso, 12 mL). La mezcla se agitó vigorosamente a 0°C por 30 min, a temperatura ambiente por 21 h, y después se concentró bajo presión reducida a temperatura ambiente para eliminar el THF. El residuo se dividió entre EtOAc (160 mL) y salmuera (160 mL). La solución orgánica se separó, se lavó con 5% de solución de Na_2SO_3 (120 mL), se secó sobre Na_2SO_4, y se concentró bajo presión reducida. La purificación por cromatografía instantánea por gel de sílice sobre SiO_2 se eluye con EtOAc/heptano (gradiente desde una relación de 1:8 hasta 1:0) compuesto 788A (1.15 g, 75%) como una espuma sólida.

1220

B. [3aS-(3aα,4β,5β,6α,7β,7aα)]-4-(Octahidro-5,6-dihidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo (788B)

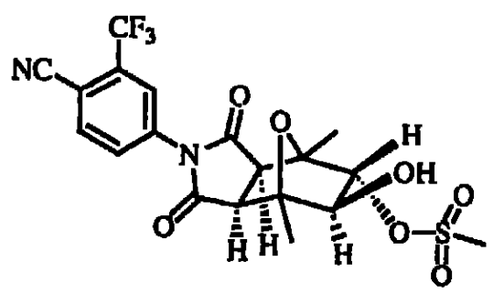
A una solución agitada del compuesto 788A (0.67 g, 1.3 mmol) en EtOH (100%, 19 mL) se agregó HCl concentrado (3.7 mL). La mezcla se agitó a temperatura ambiente por 21 h, a 40°C por 3 h, y después se concentró bajo presión reducida. La purificación por cromatografía instantánea por gel de sílice se eluye con EtOAc/heptano (gradiente desde una relación de 1:1 hasta 1:0) dio el compuesto 788B (0.47 mg, 92%) como un sólido vidrioso. CLAR: 98% a 3.07 min (tiempo de retención) (Columna YMC S5 ODS-A de 4.6 x 50 mm se eluye con 10-90% metanol acuoso durante 4 min, contiene 0.2% ácido fosfórico, 4 mL/min, observando a 220 nm). EM (ES): m/z 397 $[M+H]^+$. El compuesto 788B representa una mezcla racémica de antípodos. La nomenclatura y estructura mostradas no reflejan la estereoquímica absoluta del compuesto.

Ejemplo 789



A una solución agitada del compuesto 788B (40 mg, 0.1 mmol) y trietilamina (0.16 mL, 1.1 mmol) en cloruro de metileno anhidro (1 mL) se agregó cloruro de metanosulfonilo (0.042 mL, 0.54 mmol) a 0°C bajo argón. La mezcla de reacción se agitó a 0°C por 10 min, y a temperatura ambiente por 30 min. La purificación por cromatografía instantánea por gel de sílice que se eluye con EtOAc/heptano (gradiente desde una relación de 1:2 hasta 1:0) dio el compuesto 789 (50 mg, 90%) como un sólido vidrioso. CLAR: 100% a 3.66 min (tiempo de retención) (Columna YMC S5 ODS-A de 4.6 x 50 mm se eluye con 10-90% metanol acuoso durante 4 min, contiene 0.2% ácido fosfórico, 4 mL/min, observando a 220 nm). EM (ES): m/z 575 $[M+Na]^+$. El compuesto 789 representa una mezcla racémica de antípodos. La nomenclatura y estructura mostradas no reflejan la estereoquímica absoluta del compuesto.

Ejemplo 790

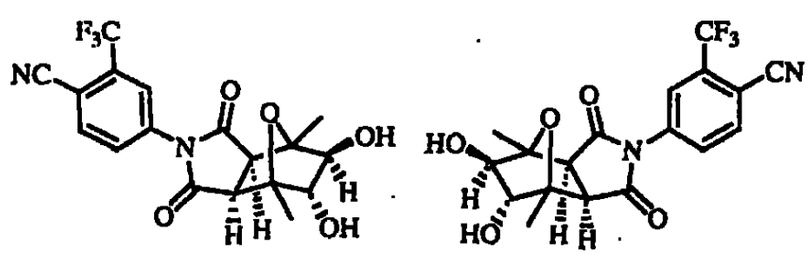


Una solución transparente del compuesto 788B (40 mg, 0.1 mmol), piridina (0.04 mL, 0.49 mmol), y cloruro de metansulfonilo (0.032 mL, 0.41 mmol) en cloruro de metileno

anhidro (1 mL) se agitó a temperatura ambiente por 1 día. La purificación por CLAR preparativa (Columna YMC S5 ODS 20 x 100 mm, 20 mL/min, observando a 245 nm, gradiente de elución con 10-100% de solvente B durante 10 mins. Solvente A: 10% MeOH-90% H2O-0.1% TFA. Solvente B: 90% MeOH-10% H_2O-0.1% TFA.) dio el compuesto 790 (23 mg, 48%) como un sólido vidrioso. CLAR: 98% a 3.46 min (tiempo de retención) (Columna YMC S5 ODS-A de 4.6 x 50 mm se eluye con 10-90% metanol acuoso durante 4 min, contiene 0.2% ácido fosfórico, 4 mL/min, observando a 220 nm). EM (ES): m/z 475 $[M+H]^+$. El compuesto 790 representa una mezcla racémica de antípodos. La nomenclatura y estructura mostradas no reflejan la estereoquímica absoluta del compuesto.

Ejemplo 791

[3aS-(3aα,4β,5β,6α,7β,7aα)]-4-(Octahidro-5,6-dihidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo y [3aR-(3aα,4β,5β,6α,7β,7aα)]-4-(Octahidro-5,6-dihidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo (791i y 791ii)



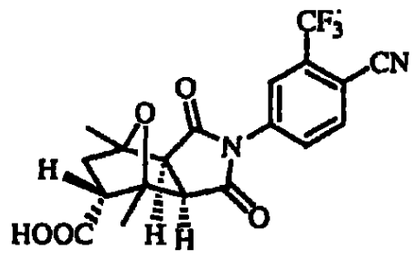
1223

El compuesto racémico 788B (1g) se separó en sus enantiómeros por CLAR quiral preparativa de fase normal (columna CHIRALPAK OJ 5 x 50 cm; se eluye con 20% MeOH/EtOH (1:1) en heptano (isocrático) + 0.1% dietilamina a 50 mL/min) para dar 296 mg del compuesto de elusión más rápida 791i (CLAR quiral: 8.92 min; columna CHIRALPAK OJ 4.6 x 250 mm; se eluye con 20% MeOH/EtOH (1:1) en heptano +0.1% dietilamina a 1 mL/min); CLAR: 95% a 1.25 min (tiempo de retención) (Columna Phenomenex S5 ODS de 4.6 x 50 mm se eluye con 10-90% metanol acuoso durante 2 min, contiene 0.1% TFA, 4 mL/min, observando a 254 nm); EM (ES): m/z 397.37 $[M+H]^+$ y 274 mg del 791ii de elusión más lenta (CLAR quiral: 11.25 min; columna CHIRALPAK OJ 4.6 x 250 mm; se eluye con 20% MeOH/EtOH (1:1) en heptano +0.1% dietilamina a 1 mL/min); CLAR: 95% a 1.25 min (tiempo de retención) (columna Phenomenex S5 ODS 4.6 x 50 mm se eluye con 10-90% metanol acuoso durante 2 min, contiene 0.1% TFA, 4 mL/min, observando a 254 nm); EM (ES): m/z 397.43 $[M+H]^+$. La estereoquímica absoluta de los compuestos 791i y 791ii no se ha establecido. Aunque cada compuesto representa un antípodo sencillo, la nomenclatura y estructura mostradas no reflejan la estereoquímica absoluta del compuesto.

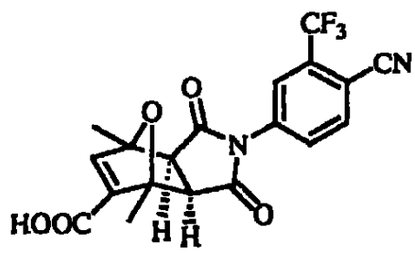
1224

Ejemplo 792

Ácido (3aα,4β,5α,7β,7aα)-2-(4-Ciano-3-(trifluorometil)fenil)hexahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-1H-isoindol-5-carboxílico (792B)



A. Ácido (3aα,4β,7β,7aα)-2-(4-Ciano-3-(trifluorometil)fenil)tetrahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-1H-isoindol-5-carboxílico (792A)



Una mezcla de ácido 2,5-dimetil-3-furoico (11.2 g; 80 mmol) y 4-(2,5-dihidro-2,5-2,5-dioxo-1H-pirrol-1-il)-2-trifluorometilbenzonitrilo (5.32 g; 20 mmol) en 20 mL de THF se calentó hasta 65°C. por 2 h. Después de enfriar a temperatura ambiente, el residuo sólido formó suspensión en EtOAc y se cargó sobre una columna de 5 x 30 cm de gel de sílice, empacada en hexanos. La columna se eluyó con 2 L de EtOAc, seguido por 1.5 L de 1% AcOH/EtOAc. Las fracciones que contienen el ácido acrílico deseado se concentraron y el

residuo se co-evaporó a partir de EtOAc/Heptano (3 x 100 mL). Después de disolver el residuo sólido en ~15 mL de EtOAc, se agregó heptano (~50 mL) y la mezcla se concentró hasta un volumen de ~25 mL. La suspensión se filtró y la torta filtro se lavó con hexano. La separación del solvente in vacuo produjo el compuesto 792A (1.5g, 16%) como un polvo blanco.

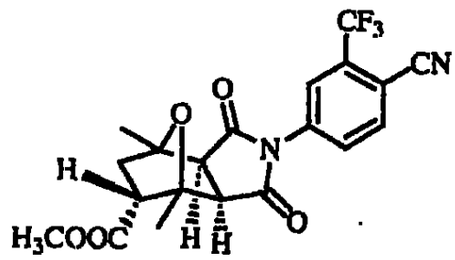
B. Ácido (3aα,4β,5α,7β,7aα)-2-(4-Ciano-3-(trifluorometil)fenil)hexahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-1H-isoindol-5-carboxílico (792B)

El compuesto 792A (220 mg; 0.54 mmol) se hidrogenó a 1 atm. en EtOAc (5 mL) sobre 10% Pd/C (20 mg) por 4 horas. Después de filtrar a través de Celite, el filtrado se concentró y el residuo se cromatografió sobre una columna de 2.5 x 15 cm de gel de sílice que se eluye con EtOAc: Heptano, 1:1 + 0.5% AcOH. Las fracciones puras se concentraron para resultar el compuesto 792B (173 mg, 79%) como un vidrio incoloro. CLAR: 95.7% a 1.64 min (tiempo de retención) (columna Phenomonex S5 ODS 4.6 x 50 mm se eluye con 10-90% metanol acuoso durante 2 min, contiene 0.1% TFA, 4 mL/min, observando a 254 nm); EM (ES): m/z 409.23 $[M+H]^+$.

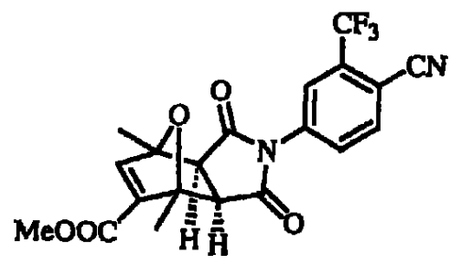
1216

Ejemplo 793

Éster de metilo del ácido (3aα,4β,5α,7β,7aα)-2-(4-Ciano-3-(trifluorometil)fenil)hexahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-1H-isoindol-5-carboxílico (793B)



A. Éster de metilo del ácido (3aα,4β,7β,7aα)-2-(4-Ciano-3-(trifluorometil)fenil)tetrahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-1H-isoindol-5-carboxílico (793A)



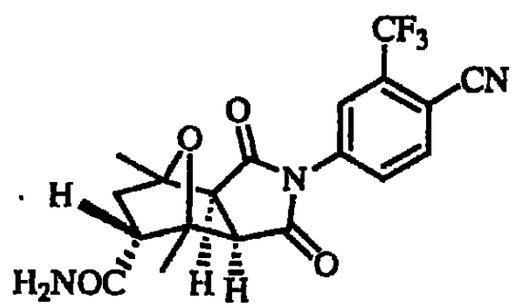
Una mezcla de metil-2,5-dimetil-3-furoato (30 mL; 200 mmol) y 4-(2,5-dihidro-2,5-2,5-dioxo-1H-pirrol-1-il)-2-trifluorometilbenzonitrilo (13.3 g; 50 mmol) se calentó hasta 120°C por 5 h. Después de enfriar lentamente hasta temperatura ambiente durante 18 h, se agregó éter de etilo (~150 mL) y la suspensión espesa resultante se filtró. Al enjuagar completamente con éter de etilo y secar, se produjo el compuesto 793A (11.3 g, 54%) como un polvo blanco.

1227

B. Éster de metilo del ácido (3aα,4β,5α,7β,7aα)-2-(4-Ciano-3-(trifluorometil)fenil)hexahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-1H-isoindol-5-carboxílico (793B)

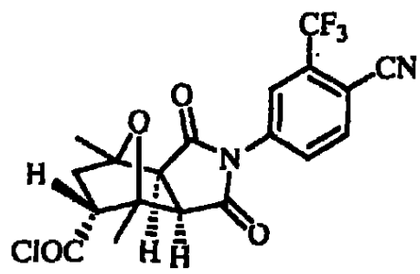
El compuesto 793A (1 g; 2.38 mmol) se hidrogenó a 1 atm. en EtOAc (25 mL) sobre 10% Pd/C (100 mg) por 2 h. Después de filtrar a través de Celite, el filtrado se concentró y el residuo se cromatografió en una columna de 2.5 x 15 cm de gel de sílice que se eluye con EtOAc:Hexano, 1:3. Las fracciones puras se concentraron para resultar el compuesto 793B (665 mg, 65%) como un polvo amarillo. CLAR: 99% a 1.67 min (tiempo de retención) (Columna Phenominex S5 ODS 4.6 x 50 mm se eluye con 10-90% metanol acuoso durante 2 min, contiene 0.1% TFA, 4 mL/min, observando a 254 nm); EM (ES): m/z 423.27 $[M+H]^+$. El compuesto 793B representa una mezcla racémica de antípodos. La nomenclatura y estructura mostradas no reflejan la estereoquímica absoluta del compuesto.

Ejemplo 794B



1228

A. (794A)



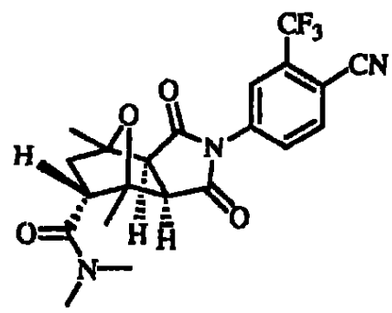
Una gota de DMF se agregó a una solución del compuesto 792B (160 mg; 0.4 mmol) y cloruro de oxalilo (0.09 mL; 1 mmol) en cloruro de metileno (4 mL) a temperatura ambiente. Después de agitar 1 h a temperatura ambiente, los compuestos volátiles se separaron in vacuo y el residuo se disolvió en 2 mL de THF para resultar una solución 0.2 M del compuesto 794A en THF.

C. (794B)

Una solución 0.2M del compuesto 794A en THF (1 mL; 0.2 mmol) se agregó a una solución 0.5 M de amoniaco en dioxano (5 mL; 2.5 mmol) a temperatura ambiente. Después de reposar 1 h a temperatura ambiente, la mezcla de reacción se dividió entre EtOAc (25 mL) y agua (25 mL). La capa orgánica se lavó con solución saturada de bisulfato de potasio (25 mL) y salmuera (25 mL). El secado sobre $MgSO_4$ seguido por la concentración in vacuo dio un residuo sólido que se trituró con éter de etilo para resultar el compuesto 794B (60 mg, 74%) como un sólido blanco. CLAR: 95.6% a 1.41 min (tiempo de

retención) (Columna Phenominex S5 ODS 4.6 x 50 mm se eluye con 10-90% metanol acuoso durante 2 min, contiene 0.1% TFA, 4 mL/min, observando a 254 nm); EM (ES): m/z 408.03 $[M+H]^+$. El compuesto 794B representa una mezcla racémica de antípodos. La nomenclatura y estructura mostradas no reflejan la estereoquímica absoluta del compuesto.

Ejemplo 795



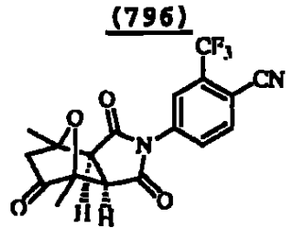
Una solución 0.2 M del compuesto 794A en THF (1 mL; 0.2 mmol) se agregó a una solución 2.0 M de dimetilamina en dioxano (2.5 mL; 5 mmol) a temperatura ambiente. Después de reposar 1 h a temperatura ambiente, la mezcla de reacción se dividió entre EtOAc (25 mL) y agua (25 mL). La capa orgánica se lavó con solución saturada de bisulfato de potasio (25 mL) y salmuera (25 mL). El secado sobre $MgSO_4$ seguido por la concentración in vacuo dio un residuo que se purificó por CCD preparativa (EtOAc:Hexano, 3:2) para resultar el compuesto 795 (45 mg, 52%) como un polvo blanco. CLAR: 99% a 1.52 min (tiempo de retención) (Columna Phenominex S5 ODS 4.6 x 50 mm se eluye con 10-90% metanol acuoso durante 2 min, contiene

0.1% TFA, 4 mL/min, observando a 254 nm); EM (ES): m/z 435.10 $[M+H]^+$. El compuesto 795 representa una mezcla racémica de antípodos. La nomenclatura y estructura mostradas no reflejan la estereoquímica absoluta del compuesto.

Ejemplo 796

[3aR-(3aα,4β,7β,7aα)]-4-(Octahidro-4,7-dimetil-1,3,5-trioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo

(796)



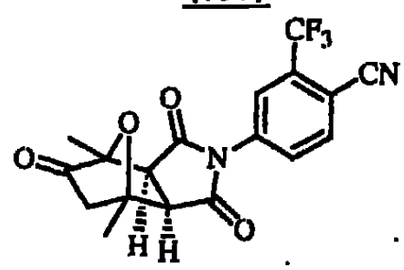
El compuesto 471Di (0.10 g, 0.263 mmol) se disolvió en una mezcla de CH_2Cl_2 (1.0 mL) y THF (2.0 mL) a 22°C. Se agregó peryodinano Dess-Martin (0.279 g, 0.658 mmol) con agitación. Después de 3 h, La reacción se apagó con una mezcla 1:1 de $NaHCO_3$ saturado acuoso y $NaHSO_3$ saturado acuoso (5 mL). Después de agitación por 15 min, la mezcla se extrajo con CH_2Cl_2 (3 x 10 mL) y los compuestos orgánicos combinados se secaron sobre Na_2SO_4. El material crudo se purificó por cromatografía instantánea por gel de sílice que se eluye con 5 - 10 - 20% de acetona en cloroformo para dar el compuesto 796 (0.090 g) como un sólido blanco. CLAR: 100% a 3.170 min. (tiempo de retención) (Columna YMC S5 ODS 4.6 x 50 mm se eluye con 10-90% metanol acuoso durante 4 min, contiene 0.2%

ácido fosfórico, 4 mL/min, observando a 220 nm), EM (ES): m/z 379.11 $[M+H]^+$. CLAR analítica quiral usando una columna Chiracel OD de 4.6 X 250 mm, se eluye con 20% (1:1) EtOH/MeOH en hexanos a 2.0 mL/min y observando a 220 nm dio un tiempo de retención de 9.097 minutos. La estereoquímica absoluta del compuesto 796 se establece por la estereoquímica conocida del compuesto intermediario 741Di y la retención de la configuración en ella. La estereoquímica absoluta es como se obtiene en la figura anterior y resulta de la nomenclatura.

Ejemplo 797

[3aS-(3aα,4β,7β,7aα)]-4-(octahidro-4,7-dimetil-1,3,5-trioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo

(797)

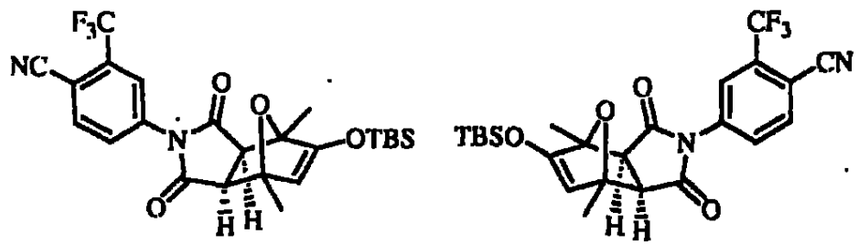


El compuesto 471Dii (0.10 g, 0.263 mmol) se disolvió en una mezcla de CH_2Cl_2 (1.0 mL) y THF (2.0 mL) a 22°C. Se agregó peryodinano Dess-Martin (0.279 g, 0.658 mmol) con agitación. Después de 3 h, la reacción se apagó con una mezcla 1:1 de $NaHCO_3$ acuoso saturado y $NaHSO_3$ acuoso saturado (5 mL). Después de agitación por 15 min, la mezcla se extrajo con CH_2Cl_2 (3 x 10 mL) y los compuestos orgánicos combinados se secaron sobre

Na_2SO_4. El material crudo se purificó por cromatografía instantánea por gel de sílice sobre SiO_2 que se eluye con 5 - 10 - 20% acetona en cloroformo para dar el compuesto 797 (0.094 g) como un sólido blanco. CLAR: 100% a 3.170 min (tiempo de retención) (Columna YMC S5 ODS 4.6 x 50 mm se eluye con 10-90% metanol acuoso durante 4 min, contiene 0.2% ácido fosfórico, 4 mL/min, observando a 220 nm), EM (ES): m/z 379.11 $[M+H]^+$. CLAR quiral analítica usando una columna de Chiracel OD, de 4.6 X 250 mm, que se eluye con 20% (1:1) EtOH/MeOH en hexanos a 2.0 mL/min y observando a 220 nm dio un tiempo de retención de 5.710 mins. La estereoquímica absoluta del compuesto 797 se establece por la estereoquímica conocida del compuesto intermediario 471Dii y la retención de la configuración en ella. La estereoquímica absoluta es como se obtiene en la figura anterior y resulta de la nomenclatura.

Ejemplo 798

[3aR-(3aα,4β,7β,7aα)]-4-[5-[[(1,1-dimetiletil)dimetilsilil]oxi]tetrahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2-(trifluorometil)benzonitrilo y [3aR-(3aα,4β,7β,7aα)]-4-[5-[[(1,1-dimetiletil)dimetilsilil]oxi]tetrahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2-(trifluorometil)benzonitrilo (798i y 798ii)

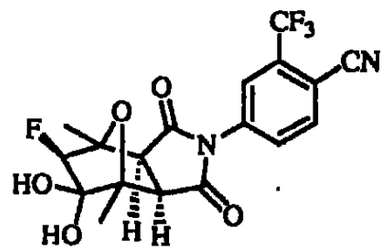


Los enantiómeros individuales del compuesto 222B se separaron por CLAR quiral preparativa usando una columna Chiracel OD, de 50 X 500 mm, que se eluye con 12% EtOH en hexanos a 50 mL/min y observando a 220 nm. El compuesto 798i tiene un tiempo de retención de 22 min (>99% ee por analítica) y el compuesto 798ii tuvo un tiempo de retención de 40 min (95% ee por analítica). La estereoquímica absoluta se confirmó por hidrólisis ácida del enol éter de sililo para la cetona correspondiente (compuestos 796 y 797). La comparación por CLAR quiral analítica demuestra claramente que el producto de cetona derivado del compuesto 798i tuvo un tiempo de retención idéntico a aquel observado por el compuesto 796 y el producto de cetona derivado del compuesto 798ii tuvo un tiempo de retención idéntico a aquel observado por el compuesto 797. En esta forma, la configuración absoluta de los compuestos 798i y 798ii se puede inferir por la configuración absoluta conocida de los compuestos 796 y 797. Compuesto 798i: CLAR: 100% a 4.211 min (tiempo de retención) (Columna YMC S5 ODS 4.6 x 50 mm se eluye con 10-90% metanol acuoso durante 4 min, contiene 0.2% ácido

fosfórico, 4 mL/min, observando a 220 nm). Compuesto 798ii: CLAR: 100% a 4.210 min (tiempo de retención) (Columna YMC S5 ODS 4.6 x 50 mm se eluye con 10-90% metanol acuoso durante 4 min, contiene 0.2% ácido fosfórico, 4 mL/min, observando a 220 nm).

Ejemplo 799

[3aS-(3aα,4β,6β,7β,7aα)]-4-(octahidro-6-fluoro-5,5-dihidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo (799)

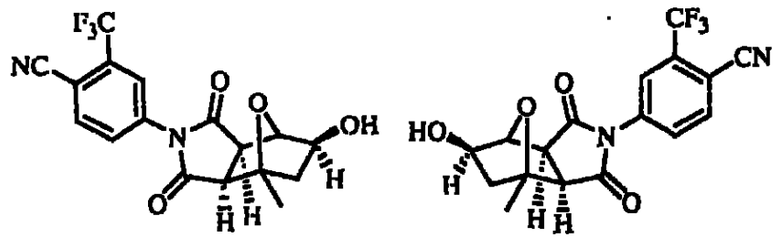


El compuesto 798i (2.20 g, 4.47 mmol) se disolvió en acetonitrilo (45 mL) y enfrió hasta 0°C. Se agregó después 1-Fluoro-4-hidroxi-1,4-diazoniabiciclo[2.2.2]octano bis-(tetrafluoro-borato) (50% p/p sobre alúmina, 5.75 g, 8.94 mmol) con agitación vigorosa. Después de 0.5 h, la reacción se apagó con $NaHCO_3$ acuoso saturado (20 mL) y salmuera (20 mL). La mezcla resultante se extrajo con EtOAc (3 x 50 mL). Los compuestos orgánicos combinados se secaron sobre $MgSO_4$ anhidro y se concentraron in vacuo. El material crudo se purificó por cromatografía instantánea por gel de sílice sobre SiO_2 que se eluye con 0-35% acetona en cloroformo para

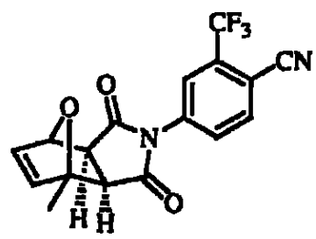
dar una mezcla de cetona e hidrato. La mezcla se disolvió en CH_3CN (50 mL) y se agregó agua (5.0 mL). La mezcla se agitó por 3 h y después se concentró in vacuo seguida por la formación de azeótropo con CH_3CN adicional tres veces y después se secó in vacuo a 50°C por 12 h para dar el compuesto 799 (1.09 g) como un sólido blanco. El compuesto 799 se mostró que era el hidrato solamente por ^1H y ^{19}F espectroscopia RMN. CLAR: 100% a 2.687 min (tiempo de retención) (Columna YMC S5 ODS 4.6 x 50 mm se eluye con 10-90% metanol acuoso durante 4 min, contiene 0.2% ácido fosfórico, 4 mL/min, observando a 220 nm), EM (ES): m/z 413.27 $[M-H]^+$. La estereoquímica absoluta del compuesto 799 se establece por la estereoquímica conocida del compuesto intermediario 798i y la retención de la configuración en ella. La estereoquímica absoluta es como se obtiene en la figura anterior y resulta de la nomenclatura.

Ejemplo 800

[3aS-(3aα,4β,6β,7β,7aα)]-4-(octahidro-6-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo y [3aR-(3aα,4β,6β,7β,7aα)]-4-(octahidro-6-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo (799Ci y 799Cii)



A. (800A)



2-Metil furano (5.33 mL, 59.1 mmol) se agregó a 4-(2,5-dioxo-2,5-dihidro-pirrol-1-il)-2-trifluorometil-benzonitrilo (1.50 g, 5.91 mmol) y la mezcla se calentó a 60°C por 3 h. Con el calentamiento, la reacción se hizo homogénea, seguido rápidamente por la trituración del producto a partir de la solución. La mezcla se enfrió hasta 22°C y se diluyó con heptano (25 mL) y se filtró, enjuagando con heptano frío. La concentración in vacuo dio el compuesto 800A (1.76 g) como un sólido blanco. Este compuesto se lleva más adelante sin purificación adicional. CLAR: 100% a 2.250 min (tiempo de retención) (Columna YMC S5 ODS 4.6 x 50 mm se eluye con 10-90% metanol acuoso durante 4 min, contiene 0.2% ácido fosfórico, 4 mL/min, observando a 220 nm).

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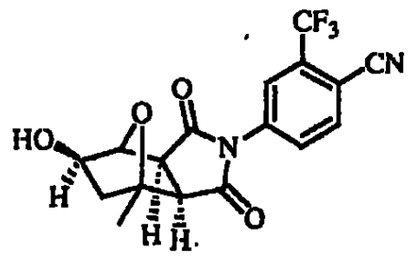
B. (3aα,4β,6β,7β,7aα)]-4-(octahidro-6-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo (800B)



El compuesto 800A (0.500 g, 1.49 mmol) se disolvió en THF seco (15 mL) y se agregó catalizador de Wilkinson (0.028 g, 0.029 mmol). Después de la agitación por 10 min, se agregó después catecolborano (solución 1.0 M en THF, 3.00 mL, 3.00 mmol) durante un periodo de 5 min. Después de 1 h, la reacción se enfrió hasta 0°C seguida por la adición secuencial de EtOH (7.0 mL), solución amortiguadora de fosfato de pH 7.4 (16.0 mL) y 30% de H_2O_2 acuoso (1.5 g). La mezcla se entibió lentamente hasta 22°C y después de 2 h, se extrajo con CH_2Cl_2 (3 x 50 mL). Los compuestos orgánicos combinados se lavaron una vez con una mezcla 1:1 de NaOH 1N/ $NaHSO_3$ saturado acuoso (50 mL), una vez con salmuera y se secaron sobre Na_2SO_3 anhidro. El material crudo se purificó por cromatografía instantánea por gel de sílice sobre SiO_2 que se eluye con 5 - 10 - 20 - 40% acetona en cloroformo para dar el compuesto 800B (0.344 g) como una espuma blanca. La espectroscopia por RMN confirmó la asignación y no estuvieron presentes otros isómeros. CLAR: 94% a 2.460 min (tiempo de

retención) (Columna YMC S5 ODS 4.6 x 50 mm se eluye con 10-90% metanol acuoso durante 4 min, contiene 0.2% ácido fosfórico, 4 mL/min, observando a 220 nm), EM (ES): m/z 367.22 $[M+H]^+$.

C. [3aS-(3aα,4β,6β,7β,7aα)]-4-(Octahidro-6-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo y [3aR-(3aα,4β,6β,7β,7aα)]-4-(Octahidro-6-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo (800Ci y 800Cii)

Los enantiómeros individuales del compuesto 800B se separaron por CLAR quiral preparativa usando una columna Chiralcel OD (50 x 500 mm) que se eluye con 17% EtOH/hexanos a 50 mL/min observando a 220 nm. El compuesto 800Ci tiene un tiempo de retención de 69.4 min y el compuesto 800Cii tiene un tiempo de retención de 84.1 min. La estereoquímica absoluta no se determinó. Compuesto 800Ci: CLAR: 100% a 2.460 min, (tiempo de retención) (Columna YMC S5 ODS 4.6 x 50 mm se eluye con 10-90% metanol acuoso durante 4 min, contiene 0.2% ácido fosfórico, 4 mL/min, observando a 220 nm). Compuesto 800Cii: CLAR: 100% a 2.460 min, (tiempo de retención) (Columna YMC S5 ODS 4.6 x 50 mm se eluye con 10-90% metanol acuoso durante 4 min, conteniendo 0.2% ácido fosfórico, 4 mL/min, observando a 220 nm). La estereoquímica absoluta de

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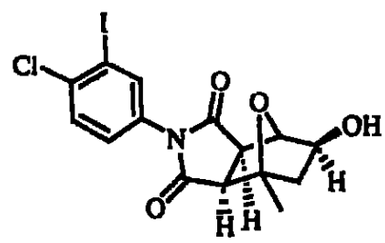
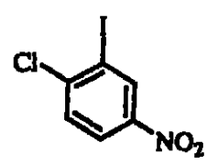
los compuestos 800Ci y 800Cii no se ha establecido. Aunque cada compuesto representa un antípodo sencillo, la nomenclatura y estructura mostradas no reflejan la estereoquímica absoluta del compuesto.

Ejemplo 801

[3aR-(3aα,4β,5β,7β,7aα)]-2-(4-Cloro-3-yodofenil)hexahidro-5-hidroxi-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3(2H)-diona (801C)



A. 1-Cloro-2-yodo-4-nitro-benceno (801A)



El 2-amino-5-nitro-yodobenceno (10.00 g, 37.9 mmol) se suspendió en HCl 12 N (25 mL) y agua (40 mL) y se agitó por 30 min a 22°C. La mezcla después se enfrió hasta 0°C y $NaNO_2$ (5.23 g, 75.8 mmol en 18 mL de H_2O) se agregó durante un periodo de 10 min. Después de 1 h, esta solución se transfirió a una solución de CuCl (3.75 g, 37.9 mmol) en agua (50 mL) a 60°C. Después de 2 h, la mezcla se enfrió hasta 22°C y se extrajo con EtOAc (3 x 150 mL) y los compuestos

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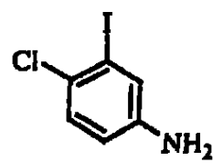
orgánicos se secaron sobre $MgSO_4$ anhidro. El producto crudo se purificó por cromatografía instantánea por gel de sílice que se eluye con 10 - 20% CH_2Cl_2 en hexanos para dar el compuesto 801A (4.20 g) como un sólido amarillo. CLAR: 100% a 3.447 min, (tiempo de retención) (Columna YMC S5 ODS 4.6 x 50 mm se eluye con 10-90% metanol acuoso durante 4 min, contiene 0.2% ácido fosfórico, 4 mL/min, observando a 220 nm).

B. 4-Cloro-3-yodo-fenilamina (801B)



El 1-Cloro-2-yodo-4-nitro-benceno (2.00 g, 7.09 mmol) se disolvió en THF (30 mL) a 60°C y EtOH (35 mL) se agregó seguido por NH_4Cl (0.569 g, 10.6 mmol en 30 mL de agua) y polvo de hierro (1.58 g, 28.4 mmol). Esta mezcla se agitó vigorosamente por 3 h y después se enfrió a 22°C y se filtró a través de celite enjuagando con EtOAc. La solución se concentró después hasta ~30 mL in vacuo y después se vació dentro de una solución 1:1 de NaOH 1N/salmuera (100 mL). Esta mezcla después se extrajo con EtOAc (3 x 50 mL) y los compuestos orgánicos se secaron sobre $MgSO_4$ anhidro. La filtración y la concentración dieron el compuesto 801B como un sólido amarillo. No fue necesaria purificación. CLAR: 100% a 2.310 min (tiempo de retención) (Columna YMC S5 ODS 4.6 x

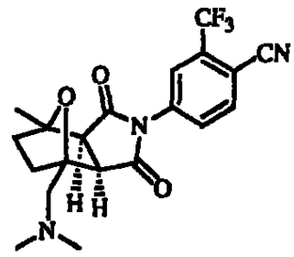
50 mm se eluye con 10-90% metanol acuoso durante 4 min, contiene 0.2% ácido fosfórico, 4 mL/min, observando a 220 nm), EM (ES): m/z 517.6 $[M+Na]^+$.

C. [3aR-(3aα,4β,5β,7β,7aα)]-2-(4-Cloro-3-yodofenil)hexahidro-5-hidroxi-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3(2H)-diona (801C)

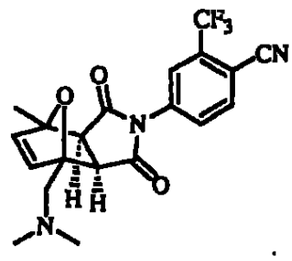
El compuesto 801B (0.300 g, 1.19 mmol) y el compuesto 752 (0.229 g, 1.08 mmol) se agregaron a DMA (1.2 mL) en un recipiente de reacción a alta presión. Se agregaron después mallas moleculares de 4Å (0.300 g) y se selló y calentó el recipiente hasta 190°C. Después de 45 min, la reacción se enfrió hasta temperatura ambiente y se vació en EtOAc (50 mL). La solución después se lavó una vez con agua (20 mL), tres veces con NH_4Cl acuosa saturada (20 mL) y se secó sobre $MgSO_4$ anhidro. El material crudo se purificó por cromatografía instantánea sobre sílice que se eluye con 10 - 20 - 30% acetona en cloroformo para dar el compuesto 801C (0.217 g) como un sólido color marrón. CLAR: 100% a 3.000 min, (tiempo de retención) (Columna YMC S5 ODS 4.6 x 50 mm se eluye con 10-90% metanol acuoso durante 4 min, contiene 0.2% ácido fosfórico, 4 mL/min, observando a 220 nm), EM (ES): m/z 448.18 $[M+H]^+$. La estereoquímica absoluta del compuesto 801C se establece por la estereoquímica conocida del compuesto intermediario 752 y la retención de la configuración en ella.

La estereoquímica absoluta es como se obtiene en la figura anterior y resulta de la nomenclatura.

Ejemplo 802



A. (802A)



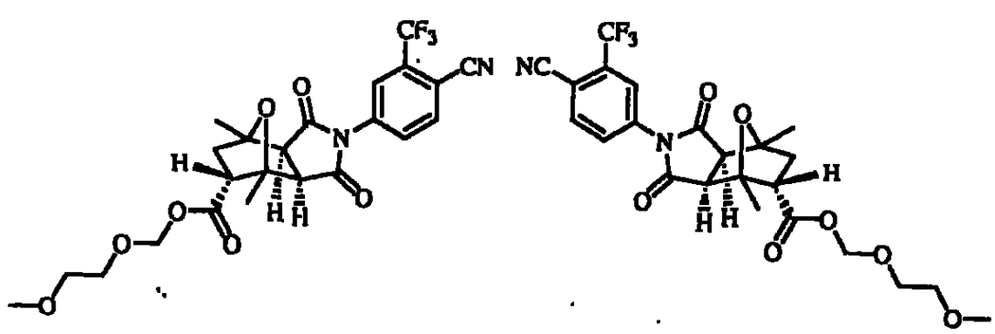
El 4-(2,5-Dioxo-2',5-dihidro-pirrol-1-il)-2-trifluorometil-benzonitrilo (0.200 g, 0.79 mmol) y 2-(N,N-dimetilaminometil)-5-metilfurano (0.548 g, 3.94 mmol) fueron disueltos en THF (0.5 mL) y se calentaron a 60°C por 3 h. La mezcla se concentró después in vacuo para dar el compuesto 802A como un aceite color café. El material crudo se usó sin purificación.

B. (802B)

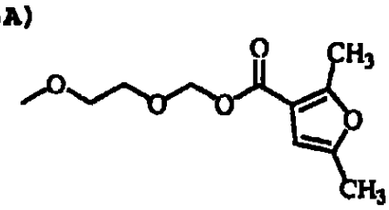
El compuesto 802A (~ 0.4 mmol) se disolvió en EtOAc (5.0 mL) y Pd/C (10% Pd, 0.020 g) se agregó, seguido por la

introducción de H_2 por medio de un globo. Después de 3 h, la reacción se purgó con N_2 y se filtró a través de celite, enjuagando con EtOAc. El material crudo se purificó por cromatografía instantánea por gel de sílice que se eluye con 10 - 20 - 30% acetona en cloroformo para dar el compuesto 802B (0.080 g) como un aceite color marrón. CLAR: 95% a 2.040 min (tiempo de retención) (Columna YMC S5 ODS 4.6 x 50 mm se eluye con 10-90% metanol acuoso durante 4 min, contiene 0.2% ácido fosfórico, 4 mL/min, observando a 220 nm), EM (ES): m/z 408.31 $[M+H]^+$. El compuesto 802B representa una mezcla racémica de antípodos. La nomenclatura y estructura mostradas no reflejan la estereoquímica absoluta del compuesto.

Ejemplo 803



A. Éster 2-metoxietoximetil del ácido 2,5-Dimetilfuran-3-carboxílico (803A)



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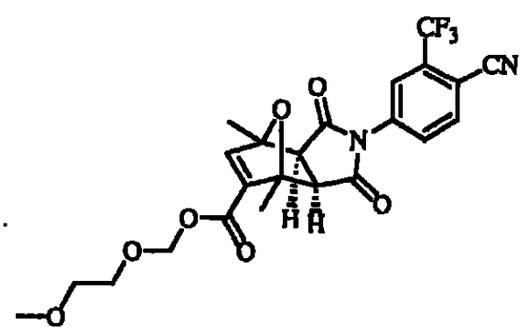
Un matraz de fondo redondo de 2 L equipado con un agitador mecánico se cargó con ácido 2,5-dimetil-3-furoico (81.0 g, 0.58 mol) y carbonato de potasio (95.9 g, 0.69 mol) en DMF (500 mL). Un baño de hielo se usó para enfriar la reacción cuando el cloruro de 2-metoxietoximetilo (72.2 g, 0.58 mol) se agregó en porciones. La reacción se agitó por 5 h a temperatura ambiente. La mezcla después se diluyó con agua (1.5 L) y se extrajo con EtOAc (2 x 600 mL). Los compuestos orgánicos combinados se lavaron con agua (2 x 900 mL) y solución saturada de cloruro de sodio (1 L), se secaron sobre $MgSO_4$, se filtraron y concentraron para resultar el compuesto 803A (103 g, 82%) como un aceite amarillo. ^1H RMN($CDCl_3$): δ = 6.23 (s, 1H), 5.47 (s, 1H), 3.84 (m, 2H), 3.56 (m, 2H), 3.38 (s, 3H), 2.51 (s, 3H) y 2.20 ppm (s, 3H).

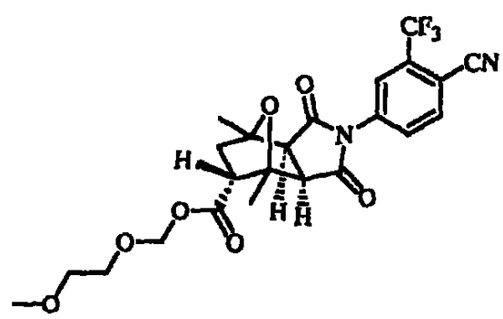
B. (803B)



Un matraz de fondo redondo de 250 mL se cargó con 4-(2,5-dioxo-2,5-dihidropirrol-1-il)-2-trifluorometilbenzonitrilo (15.0 g, 0.056 mol) y ácido 2,5-dimetilfuran-3-carboxílico, éster 2-metoxietoximetilo (22.8

g, 0.10 mol). La mezcla se calentó hasta 125°C por 1.5 h después se agitó a temperatura ambiente durante la noche. El producto crudo se disolvió en EtOAc y adsorbió sobre gel de sílice. La purificación por cromatografía de gel de sílice, se eluye con 30% EtOAc en hexanos, produjo el compuesto 803B (8.21 g, 30%) como un aceite viscoso. ^{1}H RMN ($CDCl_3$): δ = 7.95 (d, J = 8.3 Hz, 1H), 7.86 (d, J= 1.9 Hz, 1H), 7.75 (m, 1H), 7.13 (s, 1H), 5.44 (m, 2H), 3.83 (m, 2H), 3.57 (m, 2H), 3.39 (s, 3H), 3.19 (d, J= 6.5 Hz, 1H), 3.09 (d, J = 6.5 Hz, 1H), 2.04 (s, 3H) y 1.91 ppm (s, 3H).

C. (803C)



Una botella de hidrogenación de 250 mL Parr se cargó con el compuesto 803B (7.75 g, 0.015 mol), EtOAc (80 mL) y paladio sobre carbón (0.40 g, 10% Pd, 50% húmedo). La botella se colocó en un aparato de hidrogenación Parr, se presurizó con hidrógeno a 5 psi (0.35 kg/cm^2), y se agitó hasta que cesó la absorción de hidrógeno. La filtración de los contenidos sobre celite y la concentración produjo un aceite amarillo. La purificación por cromatografía de gel de sílice,

se eluye con 30% de EtOAc en hexanos, produjo el compuesto 803C (3.92 g, 50%) como un sólido blanco. CLAR: 100% a 14.5 min (tiempo de retención) (columna Hypersil C18 BDS, 250 x 4.6 mm, 5 µm, una longitud de onda de detección de 254 nm, y una relación de flujo de 1 mL/min. Un gradiente lineal de 90% de 0.1% ácido trifluoroacético en agua, 10% acetonitrilo (comienzo) hasta 100% acetonitrilo durante 15 min, después 100% acetonitrilo por 5 min se usó). R_f = 0.61 (SiO_2, 60% EtOAc en hexanos). P.f. >300°C. ^{1}H RMN ($CDCl_3$): δ = 7.94 (d, J = 8.3 Hz, 1H), 7.84 (d, J = 1.9 Hz, 1H), 7.74 (m, 1H), 5.46 (d, J = 6.1 Hz, 1H), 5.34 (d, J = 6.1 Hz, 2H), 3.85 (m, 2H), 3.57 (t, J = 4.5 Hz, 2H), 3.38 (s, 3H), 3.33 (d, J = 7.2 Hz, 1H), 3.19 (d, J = 7.2 Hz, 1H), 3.04 (m, 1H), 2.28 (m, 1H), 2.05 (t, J = 12.2 Hz, 1H), 1.78 (s, 3H) y 1.64 ppm (s, 3H). m/z = 496 $[M+H]^+$.

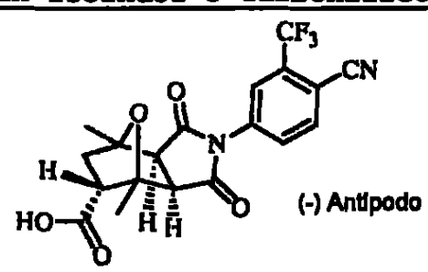
D. (803Di y 803Dii).

El compuesto racémico 803C se separó en sus dos enantiómeros por CLAR quiral preparativa usando una columna Chiracel OD (50 x 500 mm) se eluye con 50% EtOH en heptano a 100 mL/min y detección a 290 nm. El compuesto 803Di tuvo un tiempo de retención de 6.68 min y $[\alpha]_{25}^{D}$ = +28.7° (c = 1.0, MeOH). El compuesto 803Dii tuvo un tiempo de retención de 13.9 min y $[\alpha]_{25}^{D}$ = -29.2° (c = 1.0, MeOH). La estereoquímica

absoluta de los compuestos 803Di y 803Dii no se ha establecido. Aunque cada compuesto representa un antípodo sencillo, la nomenclatura y estructura mostradas no reflejan la estereoquímica absoluta del compuesto.

Ejemplo 804

Ácido [3aR-(3aα,4β,5α,7β,7aα)]-2-(4-Ciano-3-(trifluorometil)fenil)hexahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-1H-isoindol-5-carboxílico (804)

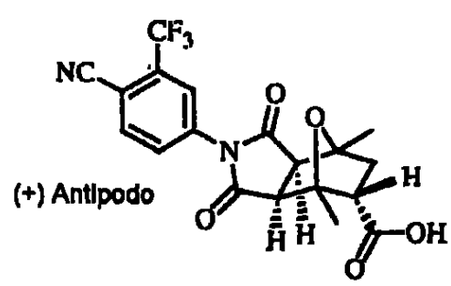


Un matraz de fondo redondo de 250 mL se cargó con el compuesto 803Di (9.85 g, 19.8 mmol) y THF (60 mL). Una solución de ácido clorhídrico 3N (50 mL) se agregó y la mezcla de reacción se agitó por 16 h a temperatura ambiente. Se agregó agua (60 mL) después y la capa acuosa se extrajo con EtOAc (3 x 120 mL). Los compuestos orgánicos combinados se secaron sobre sulfato de sodio, se filtraron y concentraron para resultar el compuesto 804 (8.00 g, 98%) que mostró ser idéntico al compuesto 791. CLAR: 100% a 13.3 min (tiempo de retención) (columna Hypersil C18 BDS, 250 x 4.6 mm, 5 µm, una longitud de onda de detección de 254 nm, y una

relación de flujo de 1 mL/min. Un gradiente lineal de 90% de 0.1% ácido trifluoroacético en agua, 10% acetonitrilo (comienzo) hasta 100% acetonitrilo durante 15 min, después 100% acetonitrilo por 5 min se usó), EM (ES): m/z 409 $[M+H]^+$. R_f = 0.41 (SiO_2, 10% MeOH en CH_2Cl_2). P.f. >300°C. $[\alpha]_{25}^{D}$ = -28.5° (c = 1.0, MeOH). ^1H RMN (CD_3OD): δ = 8.12 (d, J = 8.3 Hz, 1H), 7.92 (s, 1H), 7.82 (dd, J = 8.3 y 2.0 Hz, 1H), 3.39 (t, J = 6.7 Hz, 1H), 3.30 (d, J = 6.7 Hz, 1H), 3.00 (dd, J = 12.0 y 5.2 Hz, 1H), 2.23 (dd, J = 12.0 y 5.2 Hz, 1H), 2.01 (t, J = 12.0 Hz, 1H), 1.70 (s, 3H) y 1.57 ppm (s, 3H). La estereoquímica absoluta del compuesto 804 no se ha establecido. Aunque el compuesto representa un antípodo sencillo la nomenclatura y estructura mostradas no reflejan la estereoquímica absoluta del compuesto.

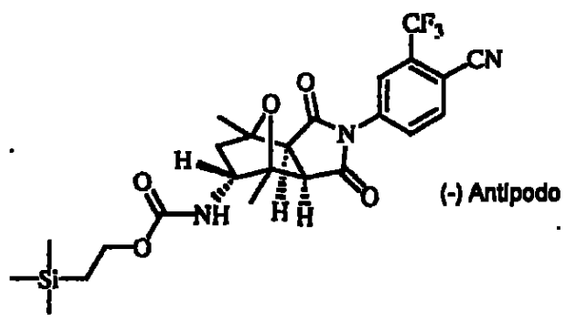
Ejemplo 805

Ácido [3S-(3aα,4β,5α,7β,7aα)]-2-(4-Ciano-3-(trifluorometil)fenil)hexahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-1H-isoindol-5-carboxílico (805)



El compuesto 805 se preparó en forma idéntica como se describe en el ejemplo 804 con la excepción de que el compuesto 803Dii fue el material de partida en lugar del compuesto 803Di. El compuesto 805 se obtuvo en 98% de rendimiento. $[\alpha]^{25}_{D}$ = +28.0° (c = 1.0, MeOH). La estereoquímica absoluta del compuesto 805 no se ha establecido. Aunque el compuesto representa un antípodo sencillo la nomenclatura y estructura mostradas no reflejan la estereoquímica absoluta del compuesto.

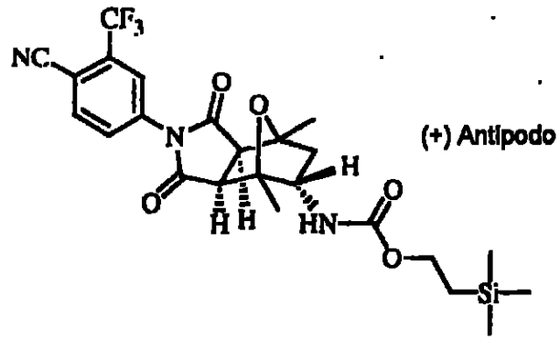
Ejemplo 806



Un matraz de fondo redondo de 50 mL se cargó con dioxano (6 mL), compuesto 804 (400 mg, 0.984 mmol), difenilfosforilo azida (334 mg, 1.21 mmol), trietilamina (123 mg, 1.22 mmol) y mallas moleculares pulverizadas de 4Å (400 mg). La suspensión resultante se calentó a 50°C por 1.5 h, la temperatura se elevó después hasta 75°C y 2-(trimetilsilil)etanol (590 mg, 5.02 mmol) se agregó. Se continuó el calentamiento por 1.5 h adicionales. La mezcla de reacción se enfrió después, se filtró a través de una almohadilla de celite y el filtrado se

concentró bajo presión reducida. La purificación del residuo por cromatografía de gel de sílice, que se eluye con 20% después 40% EtOAc en hexanos, produjo el compuesto 806 (400 mg, 78%) como un sólido blanco. CLAR: 100% a 15.3 min (tiempo de retención) (columna Hypersil C18 BDS, 250 x 4.6 mm, 5 µm, una longitud de onda de detección de 254 nm, y una relación de flujo de 1 mL/min. Un gradiente lineal de 90% de 0.1% de ácido trifluoroacético en agua, 10% acetonitrilo (comienzo) hasta 100% acetonitrilo durante 15 min, después 100% acetonitrilo por 5 min se usó), EM (ES): m/z 524 $[M+H]^+$. R_f = 0.79 (SiO_2, 50% EtOAc en hexanos). P.f. >300°C. $[\alpha]_{25}^{D}$ = -1.8° (c = 1.0, MeOH). ^1H RMN($CDCl_3$): δ = 7.96 (d, J = 8.3 Hz, 1H), 7.83 (s, 1H), 7.73 (dd, J = 8.3 y 2.0 Hz, 1H), 4.72 (bs, 1H), 4.19 (t, J = 12.0 Hz, 2H), 4.05 (m, 1H), 3.45 (d, J = 8.3 Hz, 1H), 3.12 (d, J = 8.3 Hz, 1H), 2.36 (t, J = 12.0 Hz, 1H), 1.61 (s, 6H), 1.04 (t, J = 12.0 Hz, 2H) y 0.05 ppm (s, 6H). La estereoquímica absoluta del compuesto 806 no se ha establecido. Aunque el compuesto representa un antípodo sencillo, la nomenclatura y estructura mostradas no reflejan la estereoquímica absoluta del compuesto.

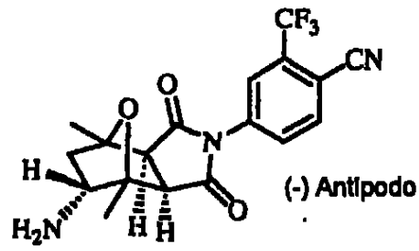
Ejemplo 807



El compuesto 807 se preparó en forma idéntica como se describe en el ejemplo 806 con la excepción de que el compuesto 805 fue el material de partida en lugar del compuesto 804. El compuesto 807 se obtuvo en 80% de rendimiento, $[\alpha]^{25}_{D}$ = +1.1° (c = 1.0, MeOH). La estereoquímica absoluta del compuesto 807 no se ha establecido. Aunque el compuesto representa un antípodo sencillo, la nomenclatura y estructura mostradas no reflejan la estereoquímica absoluta del compuesto.

Ejemplo 808

[3aR-(3aα,4β,5α,7β,7aα)]-4-(octahidro-5-amino-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo (808)

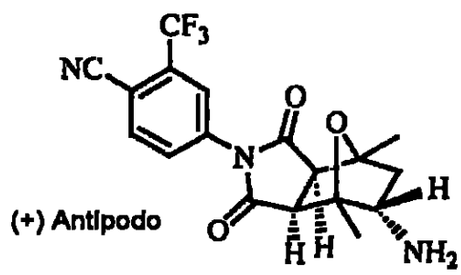


Una solución del compuesto 806 (400 mg, 0.76 mmol) en cloruro de metileno (10 mL) se trató con ácido trifluoroacético (2 mL) y la mezcla se agitó a temperatura ambiente por 2 h. Después de este tiempo, la reacción se hizo básica (pH = 9) por la adición de una solución de carbonato de sodio acuoso saturada (20 mL) y carbonato de potasio sólido. La fase orgánica después se separó y la capa acuosa se extrajo con cloruro de metileno (3 x 40 mL). Los compuestos orgánicos combinados se secaron sobre sulfato de sodio, se filtraron, y concentraron para resultar el compuesto 808 (283 mg, 99%) como un sólido blanco. CLAR: 100% a 10.5 min (tiempo de retención) (columna Hypersil C18 BDS, 250 x 4.6 mm, 5 µm, una longitud de onda de detección de 254 nm, y una relación de flujo de 1 mL/min. Un gradiente lineal de 90% de 0.1% ácido trifluoroacético en agua, 10% acetonitrilo (comienzo) hasta 100% acetonitrilo durante 15 min, después 100% acetonitrilo por 5 min se usó), EM (ES): m/z 380 $[M+H]^+$. R_f = 0.59 (SiO_2, 5% MeOH en CH_2Cl_2). $[\alpha]_{25}^{D}$ = -26.7° (c = 1.0, MeOH). P.f. = 150-152°C. ^1H RMN (CD_3OD): δ =

8.12 (d, J = 8.3 Hz, 1H), 7.94 (s, 1H), 7.83 (dd, J = 8.3 y 2.0 Hz, 1H), 3.66 (d, J = 7.2 Hz, 1H), 3.21 (m, 4H), 2.16 (t, 7= 12.0 Hz, 1H), 1.51 (s, 3H), 1.49 (s, 3H) y 1.42 ppm (dd, 7 = 12.0 y 5.0 Hz, 1H). La estereoquímica absoluta del compuesto 808 no se ha establecido. Aunque el compuesto representa un antípodo sencillo, la nomenclatura y estructura mostradas no reflejan la estereoquímica absoluta del compuesto.

Ejemplo 809

[3aS-(3aα,4β,5α,7β,7aα)]-4-(Octahidro-5-amino-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo (809)



El compuesto 809 se preparó en forma idéntica como se describe en el ejemplo 808 con la excepción de que el compuesto 807 fue el material de partida en lugar del compuesto 806. El compuesto 809 se aisló en 94% rendimiento global, $[\alpha]^{25}_{D}$ = +27.3° (c = 1.0, MeOH). La estereoquímica absoluta del compuesto 809 no se ha establecido. Aunque el

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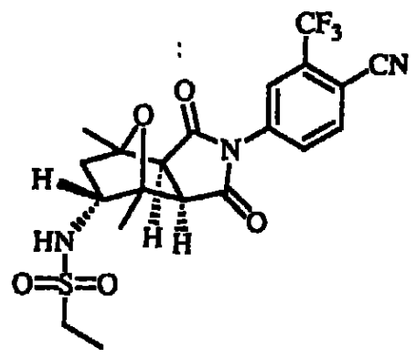
compuesto representa un antípodo sencillo, la nomenclatura y estructura mostradas no reflejan la estereoquímica absoluta del compuesto.

Ejemplo 810

(3aα,4β,5α,7β,7aα)-4-(octahidro-5-etilsulfonamido-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo (810)



Un matraz de fondo redondo de 25 mL se cargó con una mezcla racémica de los compuestos 808 y 809 (102 mg, 0.27 mmol) y cloruro de metileno (10 mL). Se agregaron cloruro de etansulfonilo (54.3 mg, 0.42 mmol) y trietilamina (43.6 mg, 0.43 mmol) y la mezcla resultante se agitó a temperatura ambiente durante la noche. El análisis de la mezcla de reacción por CCD (SiO_2, EtOAc) indicó la presencia del material de partida, entonces se agregó un equivalente adicional de cloruro de etansulfonilo (54.3 mg, 0.42 mmol) y la agitación continuó a temperatura ambiente por 4 h. La mezcla de reacción después se diluyó con CH_2Cl_2 (25 mL) y se

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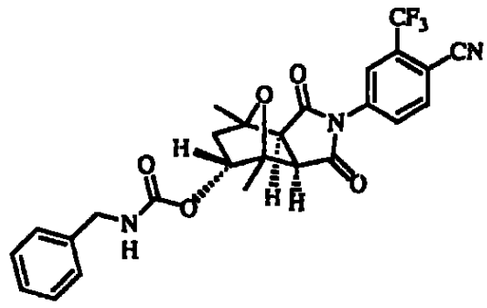
lavó con agua (10 mL). El secado sobre sulfato de magnesio, filtración, y la concentración produjo un aceite amarillo. La purificación de este aceite por cromatografía de gel de sílice, se eluye con 25% EtOAc en hexanos, después 50% EtOAc en hexanos y finalmente EtOAc, produjo el compuesto 810 (55.9 mg, 44%) como un sólido blanco. CLAR: 100% a 13.8 min (tiempo de retención) (columna Hypersil C18 BDS, 250 x 4.6 mm, 5 µm, una longitud de onda de detección de 254 nm, y una relación de flujo de 1 mL/min. Un gradiente lineal de 90% de 0.1% ácido trifluoroacético en agua, 10% acetonitrilo (comienzo) hasta 100% acetonitrilo durante 15 min, después 100% acetonitrilo por 5 min se usó), EM (ES): m/z 472 $[M+H]^+$. Rf = 0.72 (EtOAc). P.f. = 189-192°C. ^1H RMN ($CDCl_3$): δ = 7.94 (d, J = 8.3 Hz, 1H), 7.85 (s, 1H), 7.74 (dd, J = 8.3 y 2.0 Hz, 1H), 5.72 (d, J = 8.3 Hz, 1H), 3.71 (m, 1H), 3.51 (d, J = 7.2 Hz, 1H), 3.18 (d, J = 7.2 Hz, 1H), 3.11 (q, J = 7.2 Hz, 2H), 2.37 (t, J = 12.0 Hz, 1H), 1.67 (m, 1H), 1.62 (s, 3H), 1.61 (s, 3H) y 1.40 ppm (t, J = 7.2 Hz, 3H). La estereoquímica absoluta del compuesto 810 no se ha establecido. Aunque el compuesto representa un antípodo sencillo, la nomenclatura y estructura mostradas no reflejan la estereoquímica absoluta del compuesto.

Ejemplo 811

(3aα,4β,5α,7β,7aα)-4-(octahidro-5-[[((fenilmetil)amino)carbonil]oxi]-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo (811)



Un matraz de fondo redondo de 25 mL se cargó con el compuesto 222D (102 mg, 0.27 mmol) y THF (2 mL). Se agregó isocianato de bencilo (37.7 mg, 0.28 mmol) y la mezcla resultante se agitó a temperatura ambiente por 1.5 h, después se calentó a 60°C por 1.5 h. adicionales. Se agregó después hidruro de sodio (50 mg, 60% dispersión en aceite mineral) seguido por isocianato de bencilo adicional (37.7 mg, 0.28 mmol). El calentamiento continuó a 60°C durante la noche. Se agregó después isocianato de bencilo (75.4 mg, 0.56 mmol) y THF (2 mL) y la reacción se volvió a calentar hasta 60°C por 3 h adicionales. La mezcla de reacción después se enfrió hasta temperatura ambiente y se concentró bajo presión reducida para resultar un sólido blanco descolorido. Se agregó después éter (20 mL) y se formó un precipitado. La mezcla se filtró y el filtrado se concentró hasta un sólido blanco, que se purificó además por CLAR preparativa. Las

fracciones conteniendo el producto deseado se concentraron y se agregó una solución de bicarbonato de sodio saturado (15 mL). La capa acuosa se extrajo con cloruro de metileno (3 x 25 mL), se secó sobre sulfato de magnesio, se filtró, y concentró para resultar el compuesto 811 (119 mg, 80%) como un sólido blanco. CLAR: 100% a 15.3 min (tiempo de retención) (columna Hypersil C18 BDS, 250 x 4.6 mm, 5 µm, una longitud de onda de detección de 254 nm, y una relación de flujo de 1 mL/min. Un gradiente lineal de 90% de 0.1% ácido trifluoroacético en agua, 10% acetonitrilo (comienzo) hasta 100% acetonitrilo durante 15 min, después 100% acetonitrilo por 5 min se usó), EM (ES): m/z 514 $[M+H]^+$. R_f = 0.58 (SiO_2, 50% EtOAc en hexanos). P.f. >300°C. ^1H RMN ($CDCl_3$): δ = 7.94 (d, J = 8.1 Hz, 1H), 7.85 (s, 1H), 7.74 (m, 1H), 7.36-7.34 (m, 5H), 5.07 (bs, 1H), 4.92 (m, 1H), 4.39 (bs, 2H), 3.59 (m, 1H), 3.11 (m, 1H), 2.35 (t, J = 12.0 Hz, 1H) y 1.61 ppm (s, 6H). La estereoquímica absoluta del compuesto 811 no se ha establecido. Aunque el compuesto representa un antípodo sencillo, la nomenclatura y estructura mostradas no reflejan la estereoquímica absoluta del compuesto.

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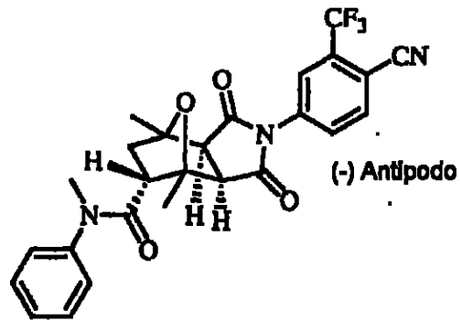
Ejemplo 812

[3aR-(3aα,4β,5α,7β,7aα)]-2-(4-Ciano-3-(trifluorometil)fenil)hexahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-N-metil-N-fenil-1H-isoindol-5-carboxamida (812)



A un matraz de fondo redondo seco, purgado con nitrógeno, de 100 mL, se agregó el compuesto 804 (100 mg, 0.245 mmol) y CH_2Cl_2 (10 mL). La solución se agitó a temperatura ambiente y se agregaron cloruro de oxalilo (311 mg, 2.45 mmol) y N,N-dimetilformamida (28.0 mg, 0.387 mmol). Se observó la evolución del gas y la reacción se agitó a temperatura ambiente por 1 h. La solución resultante se concentró después hasta sequedad bajo presión reducida y se agregó CH_2Cl_2 (10 mL). Se agregó N-metilanilina (262 mg, 2.45 mmol) y la reacción se agitó por 15 h a temperatura ambiente. Después de concentrar la solución resultante bajo presión reducida, el aceite resultante se cromatografió sobre gel de sílice, usando 50% EtOAc en hexanos como el eluyente, para dar un aceite color naranja que se contaminó con N-metilanilina. El material se volvió a procesar por cromatografía sobre gel de sílice, usando 40% EtOAc en

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hexanos como eluyente, para resultar el compuesto 812 (115 mg, 94%) como una espuma blanca. CLAR: 100% a 18.7 min (tiempo de retención) (columna Hypersil C18 BDS, 250 x 4.6 mm, 5 µm, una longitud de onda de detección de 254 nm, y una relación de flujo de 1 mL/min. Un gradiente lineal de 90% de 0.1% ácido trifluoroacético en agua, 10% acetonitrilo (comienzo) hasta 100% acetonitrilo durante 15 min, después 100% acetonitrilo por 5 min se usó), EM (ES): m/z 498 $[M+H]^+$. R_f = 0.37 (SiO_2, 40% EtOAc en hexanos). P.f. >300°C. $[\alpha]^{25}_D$ = -30.0° (c = 1.0, MeOH). ^1H RMN ($CDCl_3$): δ = 7.92 (d, J = 8.4 Hz, 1H), 7.84 (d, J = 1.5 Hz, 1H), 7.73 (dd, J = 8.3 y 2.0 Hz, 1H), 7.52-7.35 (m, 3H), 7.17 (d, J= 7.1 Hz, 2H), 4.24 (d, J = 7.3 Hz, 1H), 3.30 (s, 3H), 3.28 (d, J = 7.3 Hz, 1H), 3.09-2.96 (m, 1H), 2.10-1.99 (m, 1H), 1.81 (t, J = 12.0 Hz, 1H), 1.56 (s, 3H) y 1.41 ppm (s, 3H). La estereoquímica absoluta del compuesto 812 no se ha establecido. Aunque el compuesto representa un antípodo sencillo, la nomenclatura y estructura mostradas no reflejan la estereoquímica absoluta del compuesto.

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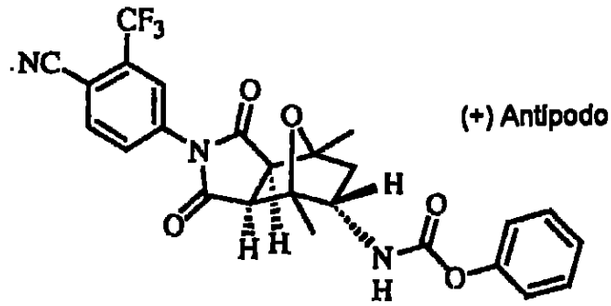
Ejemplo 813



Un matraz de fondo redondo de 25 mL se cargó con dioxano (3 mL), compuesto 805 (76.3 mg, 0.187 mmol), difenilfosforil azida (62.6 mg, 0.227 mmol), trietilamina (23.2 mg, 0.230 mmol) y mallas moleculares pulverizadas de 4A (200 mg) y la suspensión resultante se calentó a 50°C por 1.5 h. La temperatura después se elevó hasta 75°C y se agregó fenol (93.0 mg, 0.988 mmol). Se continuó el calentamiento por 1.5 h adicionales. La mezcla de reacción después se enfrió, se filtró a través de una almohadilla de celite y el filtrado se concentró bajo presión reducida. La purificación del residuo por cromatografía en gel de sílice, que se eluye con 10%-50% EtOAc en hexanos, produjo el compuesto 813 (71.5 mg, 77%) como un sólido blanco. CLAR: 100% a 15.9 min. (tiempo de retención) (columna Hypersil C18 BDS, 250 x 4.6 mm, 5 µm, una longitud de onda de detección de 254 nm, y una relación de flujo de 1 mL/min. Un gradiente lineal de 90% de 0.1% ácido trifluoroacético en agua, 10% acetonitrilo (comienzo) hasta 100% acetonitrilo durante 15 min., después 100% acetonitrilo por 5 min. se usó), R_f = 0.70 (SiO_2, 50% EtOAc en hexanos).

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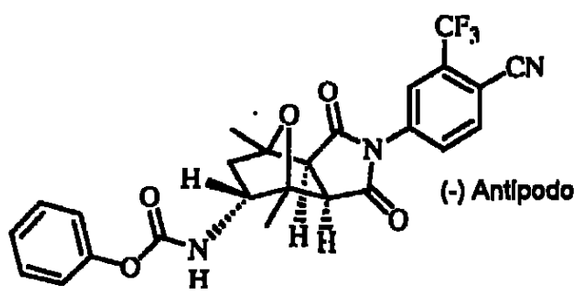
$[\alpha]_{25}^{D}$ = +13.0° (c = 1.0, MeOH). P.f. >300°C. CLAR: R_t = 15.9 min. ^{1}H RMN (CD_3OD): δ = 8.14 (d, J = 8.3 Hz, 1H), 7.95 (s, 1H), 7.85 (dd, J = 8.3 y 2.0 Hz, 1H), 7.41-7.12 (m, 5H), 4.06 (dd, J = 12.0 y 5.0 Hz, 1H), 3.55 (d, J = 7.2 Hz, 1H), 3.29 (d, J = 7.2 Hz, 1H), 2.29 (t, J = 12.0 Hz, 1H), 1.71 (dd, J = 12.0 y 5.0 Hz, 1H), 1.56 (s, 3H) y 1.54 ppm (s, 3H). La estereoquímica absoluta del compuesto 813 no se ha establecido. Aunque el compuesto representa un antípodo sencillo, la nomenclatura y estructura mostradas no reflejan la estereoquímica absoluta del compuesto.

Ejemplo 814



El compuesto 814 se preparó en forma idéntica como se describe en el ejemplo 813 con la excepción de que el compuesto 804 fue el material de partida en lugar del compuesto 805. El compuesto 814 se aisló en 62% rendimiento global, $[\alpha]^{25}_{D}$ = -11.7° (c = 1.0, MeOH). La estereoquímica absoluta del compuesto 814 no se ha establecido. Aunque el compuesto representa un antípodo sencillo, la nomenclatura y

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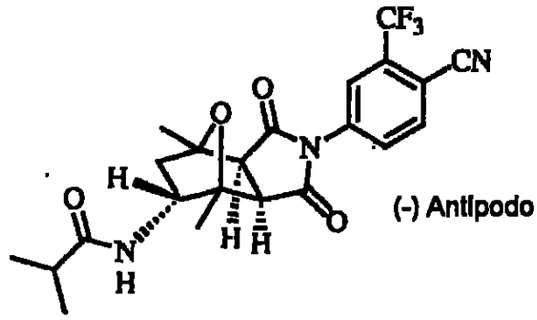
estructura mostradas no reflejan la estereoquímica absoluta del compuesto.

Ejemplo 815

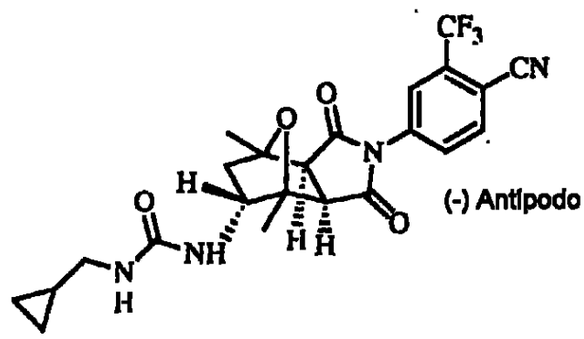


El compuesto 807 (0.060 g, 0.15 mmol) se disolvió en 2 mL de CH_2Cl_2 y trietilamina (0.020 g, 0.16 mmol) y se agregó una cantidad catalítica de DMAP, seguida por cloruro de isobutirilo (0.02g, 0.16 mmol). La reacción se agitó por 1 h a 23°C cuando la CLAR mostró un consumo completo del material de partida. La reacción se diluyó con CH_2Cl_2, se lavó sucesivamente con HCl 1N, bicarbonato de sodio saturado, salmuera, se secó ($MgSO_4$), se filtró y concentró in vacuo para dar el compuesto 815 (0.06 g, 83%), como un sólido blanco. No fue necesaria la purificación. CLAR: 100% a 3.12 min. (Columna YMC S5 ODS) se eluye con 10-90% metanol acuoso conteniendo 0.2% ácido fosfórico durante un gradiente de 4 min. observando a 220 nm. CL/EM - [M+H] = 450.12. La estereoquímica absoluta del compuesto 815 no se ha establecido. Aunque el compuesto representa un antípodo

sencillo, la nomenclatura y estructura mostradas no reflejan la estereoquímica absoluta del compuesto.

Ejemplo 816

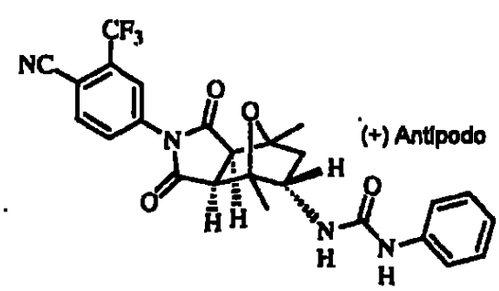
[3aR-(3aα,4β,5α,7β,7aα)]-4-(octahidro-5-[[[(ciclopropilmetil)amino]carbonil]amino]-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo (816)



Un matraz de fondo redondo de 50 mL se cargó con el compuesto 815 (0.052 g, 0.10 mmol), metil sulfóxido (2 mL) y aminometil ciclopropano (10 μL, 8.2 mg, 0.11 mmol). La reacción se agitó por 4 h tiempo después del cual la mezcla de reacción se diluyó con agua (9 mL) y una solución saturada de $NaHCO_3$ (1 mL). La extracción con CH_2Cl_2 (1 x 20 mL después 1 x 10 mL), secado sobre $MgSO_4$, filtración y la concentración produjo el producto crudo como un aceite amarillo. La purificación por cromatografía de gel de sílice, que se eluye con 20% hasta 50% EtOAc en hexanos produjo el compuesto 816

(33.6 mg, 67%). CLAR: 100% a 12.9 min. (tiempo de retención) (columna Hypersil C18 BDS, 250 x 4.6 mm, 5 µm, una longitud de onda de detección de 254 nm, y una relación de flujo de 1 mL/min. Un gradiente lineal de 90% de 0.1% ácido trifluoroacético en agua, 10% acetonitrilo (comienzo) hasta 100% acetonitrilo durante 15 min., después 100% acetonitrilo por 5 min. se usó), EM (ES): m/z 477 $[M+H]^+$. R_f = 0.42 (SiO_2, 50% EtOAc en hexanos). P.f. > 300°C. $[\alpha]^{25}_D$ = -31.5° (c =1.0, MeOH). ^1H RMN($CDCl_3$): δ = 8.12 (d, J = 8.3 Hz, 1H), 7.94 (s, 1H), 7.84 (d, J = 8.3 Hz, 1H) 4.12-4.06 (m, 1H), 3.46 (d, J = 8.3 Hz, 1H), 3.34 (bs, 1H), 3.22 (d, J = 8.3 Hz, 1H), 1.41 (t, J = 12.3 Hz, 1H), 1.54 (s, 3H), 1.50 (s, 3H), 1.01-0.92 (m, 1H), 0.51-0.45 (m, 2H) y 0.21-0.17 ppm (m, 2H). La estereoquímica absoluta del compuesto 816 no se ha establecido. Aunque el compuesto representa un antípodo sencillo, la nomenclatura y estructura mostradas no reflejan la estereoquímica absoluta del compuesto.

Ejemplo 817



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Un matraz de fondo redondo de 50 mL se cargó con el compuesto 809 (0.057 g, 0.15 mmol) y fenil isocianato (0.1 mL, 0.9 mmol). Después de calentar por 3 h a 65-70°C, el análisis de la reacción por CLAR indicó un consumo completo del material de partida. La dilución con EtOAc (0.5 mL) y la purificación por cromatografía de gel de sílice, que se eluye con 60% EtOAc en hexanos produjo el compuesto 817 (39 mg, 52%) como un sólido blanco. CLAR: 100% a 14.2 min. (tiempo de retención) (columna Hypersil C18 BDS, 250 x 4.6 mm, 5 µm, una longitud de onda de detección de 254 nm, y una relación de flujo de 1 mL/min. Un gradiente lineal de 90% de 0.1% ácido trifluoroacético en agua, 10% acetonitrilo (comienzo) hasta 100% acetonitrilo durante 15 min, después 100% acetonitrilo por 5 min. se usó), EM (ES): m/z 499 $[M+H]^+$. Rf = 0.17 (50% EtOAc en hexanos). P.f. > 300°C. $[\alpha]^{25}_D$ = +30.7° (c = 1.0, MeOH). ^{1}H RMN($CDCl_3$): δ = 8.12 (d, J = 8.3 Hz, 1H), 7.94 (s, 1H), 7.84 (d, J = 8.3 Hz, 1H), 7.35 (d, J = 7.8 Hz, 2H), 7.26 (t, J = 7.7 Hz, 2H), 6.99 (t, J = 7.1 Hz, 1H), 4.19-4.14 (m, 1H), 3.51 (d, J = 7.1 Hz, 1H), 3.27-3.25 (m, 2H), 2.31 (t, J= 12.3 Hz, 1H), 1.63-1.61 (m, 1H), 1.56 (s, 3H) y 1.55 ppm (s, 3H). La estereoquímica absoluta del compuesto 817 no se ha establecido. Aunque el compuesto representa un antípodo sencillo, la nomenclatura y estructura mostradas no reflejan la estereoquímica absoluta del compuesto.

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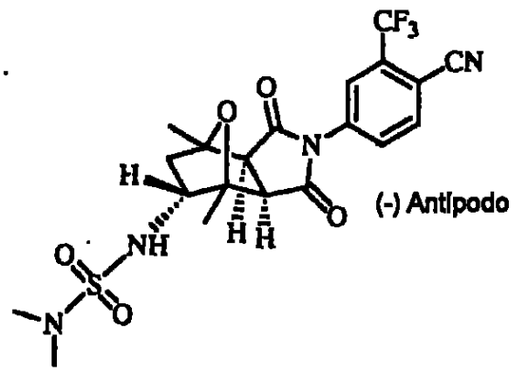
Ejemplo 818

[3aR-(3aα,4β,5α,7β,7aα)]-4-(octahidro-5-[[(dimetilamino)sulfonil]amino]-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo (817)



Un matraz de fondo redondo de 50 mL se cargó con el compuesto 808 (100 mg, 0.28 mmol), cloruro de metileno (2 mL), trietilamina (28.3 mg, 0.28 mmol) y cloruro de dimetilsulfamoilo (40.2 mg, 0.28 mmol). La reacción después se agitó a temperatura ambiente por 3 h, tiempo después del cual se apagó con agua (10 mL) y se extrajo con CH_2Cl_2 (2 x 20 mL). La capa orgánica se lavó una vez más con agua (10 mL), se secó sobre $MgSO_4$, se filtró y concentró hasta un aceite amarillo. La purificación por cromatografía de gel de sílice, se eluye con 20% EtOAc en hexanos hasta 100% EtOAc resultó en el compuesto 818 (64.2 mg, 47%). CLAR: 100% a 14.2 min. (tiempo de retención) (columna Hypersil C18 BDS, 250 x 4.6 mm, 5 corridas, una longitud de onda de detección de 254 nm, y una relación de flujo de 1 mL/min. Un gradiente lineal de 90% de 0.1% ácido trifluoroacético en agua, 10% acetonitrilo

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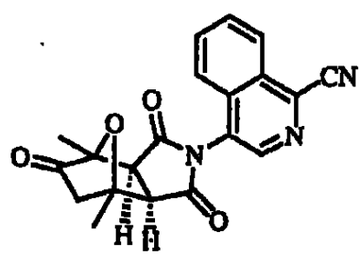
(comienzo) hasta 100% acetonitrilo durante 15 min., después 100% acetonitrilo por 5 min. se usó), EM (ES): m/z 487 $[M+H]^+$. R_f = 0.19 (SiO_2, 50% EtOAc en hexanos). $[\alpha]^{25}_D$ = -22.8° (c = 1.0, MeOH). P.f. = 262-269°C. ^1H RMN($CDCl_3$): δ = 8.12 (d, J = 8.3 Hz, 1H), 7.94 (s, 1H), 7.84 (d, J = 8.2 Hz, 1H), 3.61 (m, 1H), 3.54 (d, J = 7.2 Hz, 1H), 3.35 (s, 1H), 3.22 (d, J = 7.2 Hz, 1H), 2.79 (s, 6H), 2.27 (t, J = 12.4 Hz, 1H), 1.68 (m, 1H), 1.54 (s, 3H) y 1.53 ppm (s, 3H). La estereoquímica absoluta del compuesto 818 no se ha establecido. Aunque el compuesto representa un antípodo sencillo, la nomenclatura y estructura mostradas no reflejan la estereoquímica absoluta del compuesto.

Ejemplo 819



Una mezcla de 4-(2,5-dioxo-2,5-dihidro-pirrol-1-il)-isoquinolin-1-carbonitrilo (1 g, 4 mmol), 2,5-dimetil-2,3-dihidrofurano-3-ona (0.45 g, 4 mmol), DMAP (20 mg, 0.16 mmol), cloruro de metileno anhidro (10 mL), y THF (20mL) se agitó a 80°C durante la noche, y después se concentró bajo presión reducida. La purificación por cromatografía

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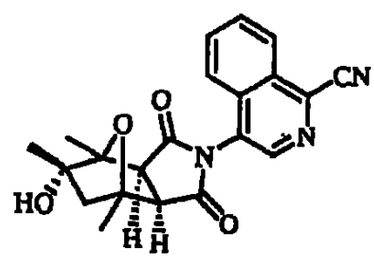
instantánea por gel de sílice sobre SiO_2 se eluye con EtOAc/heptano (gradiente desde una relación de 1:4 hasta 1:0) dio un sólido que se cristalizó en una mezcla de EtOAc y heptano para dar 0.4 g (28%) del compuesto 819 como a sólido amarillento. CLAR: 90% a 3.37 min. (tiempo de retención) (Columna YMC S5 ODS-A de 4.6 x 50 mm se eluye con 10-90% metanol acuoso durante 4 min., contiene 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 362 $[M+H]^+$. Compuesto 819 representa una mezcla racémica de antípodos. La nomenclatura y estructura mostradas no reflejan la estereoquímica absoluta del compuesto.

Ejemplo 820



A una solución agitada del compuesto 819 (36 mg, 0.1 mmol) en THF anhidro (1 mL) enfriada a 0°C bajo argón se agregó MeMgBr (solución de THF 1.4 M, 0.3 mL, 0.4 mmol) gota a gota. Después de que la mezcla se agitó a 0°C por 1 h y a temperatura ambiente por 10 min., se agregó una solución acuosa saturada de NH_4Cl con agitación. La mezcla se extrajo con EtOAc (3X). Los extractos combinados se secaron sobre Na_2SO_4, y concentraron bajo presión reducida. La purificación

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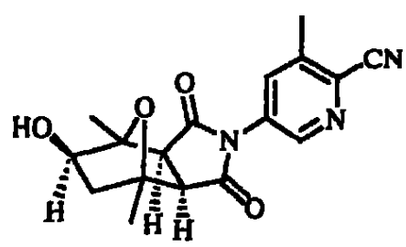
por cromatografía instantánea por gel de sílice se eluye con EtOAc/heptano (gradiente desde una relación de 1:2 hasta 1:0) dio un sólido que se cristalizó en una mezcla de EtOH y H_2O para dar el compuesto 820 (8 mg, 21%) como un sólido blanco. CLAR: 97% a 3.36 min. (tiempo de retención) (Columna YMC S5 ODS-A de 4.6 x 50 mm que se eluye con 10-90% metanol acuoso durante 4 min, contiene 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 378 $[M+H]^+$. El compuesto 820 representa una mezcla racémica de antípodos. La nomenclatura y estructura mostradas no reflejan la estereoquímica absoluta del compuesto.

Ejemplo 821

[3aS-(3aα,4β,5β,7β,7aα)]-5-(octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-3-metil-2-piridincarbonitrilo (821)



Una mezcla del compuesto 772B (20 mg, 0.14 mmol), compuesto 751 (48 mg, 0.20 mmol) y mallas moleculares de 4Å (100 mg) en DMA (0.2 mL) se calentó a 70°C en un tubo sellado por 5 h. La mezcla de reacción se filtró y el residuo se lavó con EtOAc. Los filtrados se combinaron y se lavaron con H_2O

(2 x 5 mL) y salmuera (1 x 5 mL). Las capas acuosas combinadas se extrajeron con EtOAc (2 x 5 mL) y las capas orgánicas combinadas se secaron sobre Na_2SO_4 y concentraron bajo presión reducida. La purificación por cromatografía instantánea por gel de sílice se eluye con 30% acetona/$CHCl_3$ dio 55 mg de producto contaminado con el compuesto 751. La purificación adicional por cromatografía instantánea por gel de sílice sobre SiO_2 que se eluye con 90% EtOAc/hexanos dio el compuesto 821 (46 mg, 62%) como un sólido blanco. CLAR: 100% a 2.27 min. (tiempo de retención) (Columna YMC S5 ODS 4.6 x 50 mm se eluye con 10-90% metanol acuoso durante 4 min., contiene 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 328.2 $[M+H]^+$. La estereoquímica absoluta del compuesto 821 se establece por la estereoquímica conocida del compuesto intermediario 751 y la retención de la configuración en ella. La estereoquímica absoluta es como se obtiene en la figura anterior y resulta de la nomenclatura.

Ejemplo 822

[3aR-(3aα,4β,4aα,5aα,6β,7aα)]-4-(Octahidro-4a-hidroxi-4,6-dimetil-1,3-dioxo-4,6-epoxiciclopropf[f]isoindol-2(1H)-il)-2-(trifluorometil)benzonitrilo (822)

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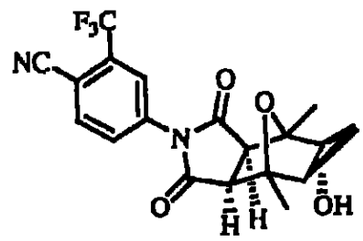
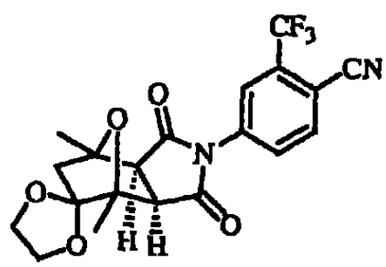


Una solución del compuesto 222B (114 mg, 0.231 mmol) en 1,2-dicloroetano (2.30 mL), en un matraz seco bajo argón, se enfrió hasta 0°C con un baño de hielo. A esta solución se agregó una solución de Et_2Zn (0.460 mL, 0.462 mmol, 1 M en hexanos), seguido por la adición gota a gota de cloroyodometano (70.0 µL, 0.926 mmol). La mezcla de reacción se agitó a 0°C por 1 h después a temperatura ambiente por 18 h. Después de juzgar la reacción por estar solamente terminada en un 50% por los métodos de CCD y CLAR, se agregaron más Et_2Zn (0.469 mL) y cloroyodometano (70.0 µL) y la mezcla se agitó a temperatura ambiente por 2.5 h. La mezcla de reacción se apagó con NH_4Cl saturado, se extrajo con t-butil metil éter (2 X 10 mL) y las capas orgánicas combinadas se secaron sobre $MgSO_4$ e in vacuo. El material crudo (174 mg) se disolvió en una mezcla de EtOH (5 mL) y HCl concentrado (2 mL) y se agitó a temperatura ambiente por 1 h. La mezcla después se diluyó con H_2O y se extrajo con EtOAc (1 X 25 mL). La capa orgánica se lavó con salmuera (1 X 25 mL), se secó y concentró bajo presión reducida. La purificación por CCD preparativa (SiO_2) que se eluye con 30% acetona/$CHCl_3$

dio el compuesto 822 (9.1 mg, 10%) como un sólido color marrón. CLAR: 90% a 3.15 min. (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, se eluye con 10-90% metanol acuoso durante 4 min conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 393.03 $[M+H]^+$. El compuesto 822 representa una mezcla racémica de antípodos. La nomenclatura y estructura mostradas no reflejan la estereoquímica absoluta del compuesto.

Ejemplo 823

[3'aR(3'aα,4'β,7'β,7'aα)]-Tetrahidro-4',7'-dimetil-2'-[4-ciano-3(trifluorometil)fenil]-espiro[1,3-dioxolan-2,5'-4,7-epoxi(5H)isoindol]-1',3'(2'H,4'H)-diona (823)

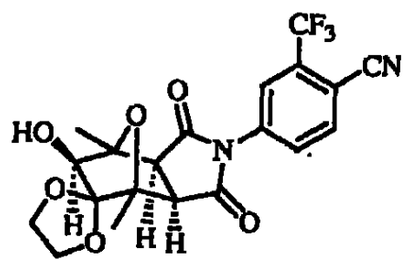


Una mezcla del compuesto 796 (44.3 mg, 0.117 mmol), etilen glicol (0.065 mL, 1.17 mmol) y ácido p-toluensulfónico (2.2 mg, 0.012 mmol) en benceno (3 mL) se puso a reflujo por 18 h. La mezcla de reacción después se diluyó con benceno, se lavó con 5% Na_2CO_3 (1 X 10 mL), H_2O (1 X 10 mL), se secó (Na_2SO_4) y concentró in vacuo. La purificación por cromatografía instantánea por gel de sílice sobre gel de sílice que se eluye con 10% acetona/$CHCl_3$ dio el compuesto

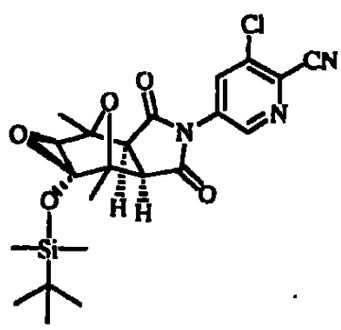
823 (44.5 mg, 90%) como un sólido blanco. CLAR: 99% a 3.11 min. (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, 10-90% metanol acuoso durante 4 min. conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ESI): m/z 423.01 $[M+H]^+$. El compuesto 823 representa una mezcla racémica de antípodos. La nomenclatura y estructura mostradas no reflejan la estereoquímica absoluta del compuesto.

Ejemplo 824

[3'aR-(3'aα,4'β,6'β,7'β,7'aα)]-Tetrahidro-6'-hidroxi-4',7'-dimetil-2'-[4-ciano-3(trifluorometil)fenil]-espiro[1,3-dioxolan-2,5'-4,7-epoxi(5H)isoindol]1',3'(2'H,4'H)-diona (824B)



A. (824A)



Una solución de dimetildioxirano (32 mL, 1.588 mmol, 0.05 M) se agregó a una solución del compuesto 222B (521.6

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mg, 1.059 mmol) en acetona (1 mL) a temperatura ambiente. Después de 2.5 h la reacción mostró estar completa por CLAR y se concentró bajo presión reducida para dar 559 mg (cuant.) de compuesto crudo 824A como un sólido amarillo.

B. [3'aR(3'aα,4'β,6'β,7'β,7'aα)]-Tetrahidro-6'-hidroxi-4',7'-dimetil-2'-[4-ciano-3(trifluorometil)fenil]-espiro[1,3-dioxolano-2,5'-4,7-epoxi(5H)isoindol]-1',3'(2'H,4'H)-diona (824B)

Una mezcla del compuesto 824A (57.5 mg, 0.113 mmol), etilen glicol (0.100 mL, 1.13 mmol) y ácido p-toluenosulfónico (11.0 mg, 0.057 mmol) en benceno (5 mL) se puso a reflujo por 18 h. La mezcla de reacción se concentró in vacuo. La purificación por cromatografía instantánea por gel de sílice que se eluye con 30% acetona/$CHCl_3$ dio el compuesto 824B (43 mg, 88%) como un sólido blanco. CLAR: 98% a 2.87 min. (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, 10-90% metanol acuoso durante 4 min conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ESI): m/z 439.07 $[M+H]^+$. El compuesto 824B representa una mezcla racémica de antípodos. La nomenclatura y estructura mostradas no reflejan la estereoquímica absoluta del compuesto.

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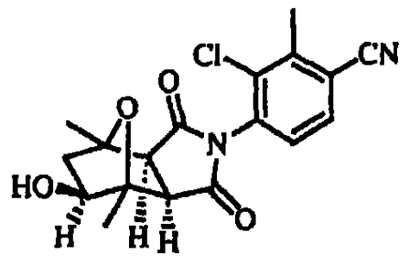
Ejemplo 825

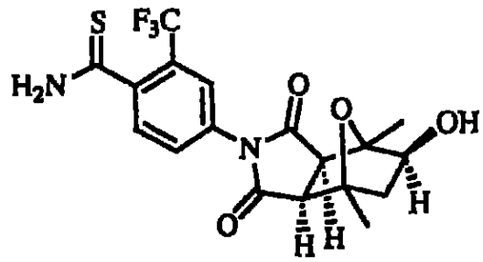
[3aR-(3aα,4β,5β,7β,7aα)]-4-[Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-3-cloro-2-metilbenzonitrilo (825)



Una mezcla de 4-amino-3-cloro-2-metil-benzonitrilo (23 mg, 0.14 mmol), compuesto 752 (44 mg, 0.21 mmol) y mallas moleculares de 4Å (100 mg) en DMA (0.2 mL) se calentó a 135°C en un tubo sellado por 18 h. Purificación por CCD preparativa (SiO_2) se eluye con 30% acetona/$CHCl_3$ dio el compuesto 825 (5.0 mg, 10%) como una película amarilla. CLAR: 90% a 2.37 min (tiempo de retención) (Columna YMC S5 ODS 4.6 x 50 mm se eluye con 10-90% metanol acuoso durante 4 min., contiene 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 360.97 $[M+H]^+$. La estereoquímica absoluta del compuesto 825 se establece por la estereoquímica conocida del compuesto intermediario 752 y la retención de la configuración en ella. La estereoquímica absoluta es como se obtiene en la figura anterior y resulta de la nomenclatura.

Ejemplo 826

[3aR-(3aα,4β,5β,7β,7aα)]-4-[Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2-(trifluorometil)bencencarbotioamida (826)

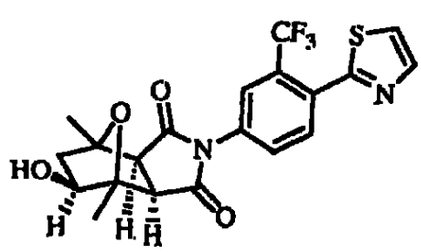


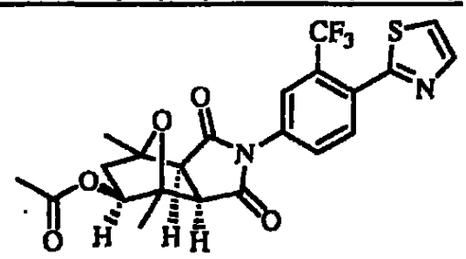
Se condensó el gas de H_2S en un tubo pyrex a -78°C hasta que hubieron 5 mL de líquido. Se agregaron el compuesto 471Di (108 mg, 0.284 mmol), Et_3N (50.0 µL, 0.341 mmol) y DMF (1 mL) a -78°C y se selló el tubo. La mezcla de reacción se dejó entibiar hasta temperatura ambiente con agitación, detrás de un blindaje contra explosiones y después se calentó a 90°C por 50 min., tiempo en el cual el color cambió a verde. La mezcla de reacción se re-enfrió hasta -78°C para verificar el avance por CLAR. Todo el material de partida se consumió, de manera que la mezcla se dejara entibiar a temperatura ambiente para eliminar el H_2S, se diluyó con EtOAc y se lavó con H_2O (4 X 10 mL). La purificación por cromatografía instantánea por gel de sílice que se eluye con 50% acetona/$CHCl_3$ dio el compuesto 826 (116 mg, 98%) como un sólido blanco. CLAR: 98% a 1.90 min. (tiempo de retención) (Columna YMC S5 ODS 4.6 x 50 mm se eluye con 10-90% metanol

acuoso durante 4 min., contiene 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 415.23 $[M+H]^+$. La estereoquímica absoluta del compuesto 826 se establece por la estereoquímica conocida del compuesto intermediario 471Di y la retención de la configuración en ella. La estereoquímica absoluta es como se obtiene en la figura anterior y resulta de la nomenclatura.

Ejemplo 827

[3aR(3aα,4β,5β,7β,7aα)]-2-[3-(trifluorometil)-4-(2-tiazolil)fenil]-5-(acetoxi)hexahidro-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3(2H)-diona (827i) y [3R-(3aα,4β,5β,7β,7aα)]-2-[3-trifluorometil)-4-(2-tiazolil)fenil]hexahidro-5-hidroxi-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3(2H)-diona (827ii)





Una solución del compuesto 826 (61.6 mg, 0.149 mmol), bromoacetaldehido dietil acetal (30.0 µL, 0.186 mmol) y ácido p-toluensulfónico (1 mg, cat.) en AcOH (1 mL) se calentó a 100°C por 1 h. La mezcla de reacción se enfrió hasta temperatura ambiente y se diluyó con H_2O. La mezcla se extrajo con EtOAc (1 X 10 mL) y la capa orgánica resultante

se lavó con H_2O (1 X 10 mL), $NaHCO_3$ saturado (1 X 10 mL) y salmuera (1 X 10 mL), después se secó sobre $MgSO_4$ y se concentró in vacuo. La purificación por CCD preparativa (SiO_2) se eluye con 30% acetona/$CHCl_3$ dio dos productos, los cuales ambos se sometieron a purificación adicional. El producto menos polar se purificó además por cromatografía instantánea por gel de sílice que se eluye con 50% EtOAc/hexanos para dar el compuesto 827i (30.0 mg, 42%) como un sólido blanco. El producto más polar producto se purificó además por cromatografía instantánea por gel de sílice que se eluye con 10% acetona/$CHCl_3$ para dar el compuesto 827ii (4.6 mg, 7%) como un sólido blanco. Compuesto 827i: CLAR: 99% a 3.12 min. (tiempo de retención) (Columna YMC S5 ODS 4.6 x 50 mm que se eluye con 10-90% metanol acuoso durante 4 min., contiene 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 481.04 $[M+H]^+$. Compuesto 827ii: CLAR: 99% a 2.62 min. (tiempo de retención) (Columna YMC S5 ODS 4.6 x 50 mm se eluye con 10-90% metanol acuoso durante 4 min., contiene 0.2% ácido fosfórico, 4 mL/min, observando a 220 nm). EM (ES): m/z 439.02 $[M+H]^+$. La estereoquímica absoluta de los compuestos 827i y 827ii se establece por la estereoquímica conocida del compuesto intermediario 471Di y la retención de la configuración en ella. La estereoquímica absoluta es como se obtiene en la figura anterior y resulta de la nomenclatura.

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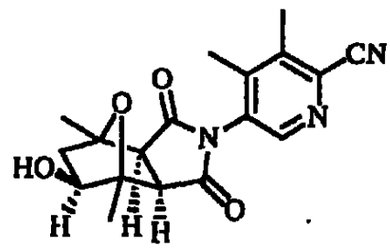
Ejemplo 828

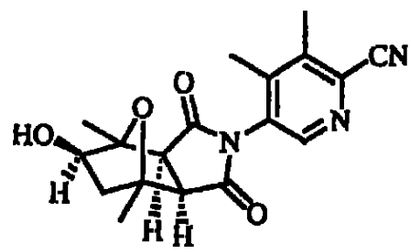
[3aR-(3aα,4β,5β,7β,7aα)]-5-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-3,4-dimetil-2-piridincarbonitrilo (828)



Una mezcla de 5-amino-3,4-dimetilpiridina-2-carbonitrilo (30 mg, 0.20 mmol), compuesto 752 (65 mg, 0.31 mmol) y mallas moleculares de 4Å (200 mg) en DMA (1 mL) se calentó a 160°C en un tubo sellado por 18 h. La mezcla de reacción se filtró, el residuo se lavó con EtOAc y los filtrados combinados se concentraron bajo presión reducida. La purificación por CCD preparativa (SiO_2) que se eluye con 90% EtOAc/hexanos dio el compuesto 828 (42 mg, 40%) como un sólido color rosa claro. CLAR: 94% a 1.92 y 2.00 min. (tiempo de retención-atropisómeros) (Columna YMC S5 ODS 4.6 x 50 mm se eluye con 10-90% metanol acuoso durante 4 min, contiene 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 342.21 $[M+H]^+$. La estereoquímica absoluta del compuesto 828 se establece por la estereoquímica conocida del compuesto intermediario 752 y la retención de la configuración en ella. La estereoquímica absoluta es como se obtiene en la figura anterior y resulta de la nomenclatura.

Ejemplo 829

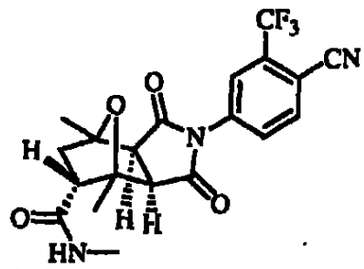
[3aS-(3aα,4β,5β,7β,7aα)]-5-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-3,4-dimetil-2-piridincarbonitrilo (829)



Una mezcla de 5-amino-3,4-dimetilpiridina-2-carbonitrilo (30 mg, 0.20 mmol), compuesto 751 (65 mg, 0.31 mmol) y mallas moleculares de 4Å (200 mg) en DMA (0.25 mL) se calentó a 160°C en un tubo sellado por 18 h. La mezcla de reacción se filtró, el residuo se lavó con EtOAc y los filtrados combinados se lavaron con H_2O (2 X 10 mL), salmuera (1 X 10 mL), se secaron (Na_2SO_4) y concentraron bajo presión reducida. La purificación por cromatografía instantánea por gel de sílice sobre gel de sílice se eluye con 90% EtOAc/hexanos seguida por CCD preparativa (SiO2) que se eluye con 90% EtOAc/hexanos dio el compuesto 829 (35 mg, 33%) como un sólido color de rosa claro. CLAR: 98% a 1.92 y 2.00 min. (tiempo de retención-atropisómeros) (Columna YMC S5 ODS 4.6 x 50 mm se eluye con 10-90% metanol acuoso durante 4 min., contiene 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ES): m/z 342.21 [M+H]+. La estereoquímica absoluta del compuesto 829 se establece por la estereoquímica conocida

del compuesto intermediario 751 y la retención de la configuración en ella. La estereoquímica absoluta es como se obtiene en la figura anterior y resulta de la nomenclatura.

Ejemplo 830

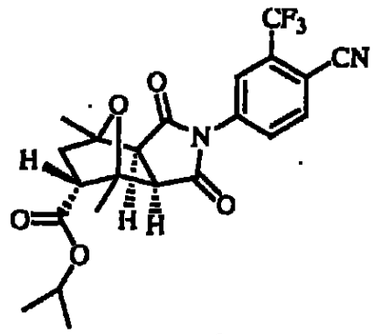


Una solución del compuesto 791B (41 mg; 0.1 mmol), metilamina 2.0 M en THF (0.2 mL; 0.4 mmol), 1-hidroxi-7-azabenzotriazol (17 mg; 0.12 mmol), EDCI (40 mg; 0.2 mmol) y diisopropiletilamina (0.075 mL; 0.4 mmol) en 0.5 mL de DMF se calentó hasta 55°C por 3 horas. Después de dividir la mezcla de reacción entre EtOAc (20 mL) y agua (20 mL), la capa orgánica se lavó con NaOH 1N (2 x 20 mL), solución saturada de bisulfato de potasio (2 x 20 mL) y salmuera (20 mL). El secado ($MgSO_4$) y la concentración in vacuo dio un residuo que se cristalizó a partir de éter de etilo para resultar el compuesto 830 (30 mg, 71%) como un sólido blanco. CLAR: 97.5% a 1.48 min. (tiempo de retención) (Columna Phenominex S5 ODS 4.6 x 50 mm se eluye con 10-90% metanol acuoso durante 2 min., contiene 0.1% TFA, 4 mL/min., observando a 254 nm); EM (ES): m/z 422.30 $[M+H]^+$. El compuesto 830 representa una mezcla racémica de antípodos. La nomenclatura y estructura

mostradas no reflejan la estereoquímica absoluta del compuesto.

Ejemplo 831

Nombre 831



Una gota de DMF se agregó a una solución del compuesto 792B (60 mg; 0.15 mmol) y cloruro de oxalilo (0.026 mL; 0.3 mmol) en cloruro de metileno (1 mL) a temperatura ambiente. Después de agitación por 2 h a temperatura ambiente, los compuestos volátiles se separaron in vacuo. El residuo se disolvió en ~2 mL de isopropanol. Después de reposar 30 min. a temperatura ambiente, los compuestos volátiles se separaron in vacuo y el residuo se disolvió en EtOAc:isopropanol, 9:1 (20 mL). La solución se dejó reposar 15 min. sobre carbón decolorante. La filtración a través de celite y la concentración del filtrado produjo el compuesto 831 (56 mg, 83%) como una espuma amarillo claro. CLAR: 96.9% a 1.52 min. (tiempo de retención) (Columna Phenominex S5 ODS 4.6 x 50 mm se eluye con 10-90% metanol acuoso durante 2 min, contiene 0.1% TFA, 4 mL/min, observando a 254 nm); EM (ES): m/z 451.08

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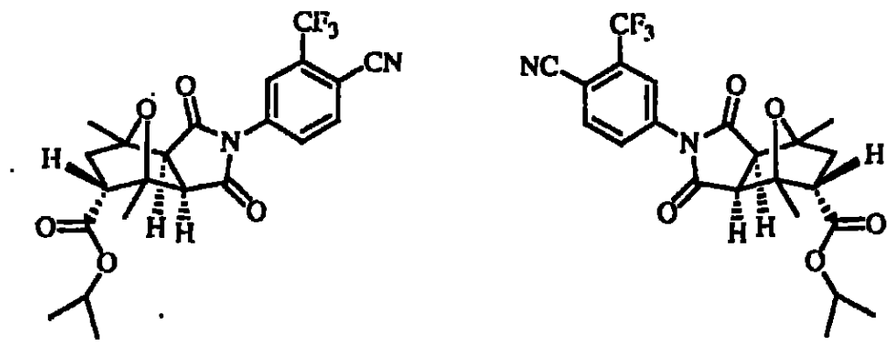
$[M+H]^+$. El compuesto 831 representa una mezcla racémica de antípodos. La nomenclatura y estructura mostradas no reflejan la estereoquímica absoluta del compuesto.

Ejemplo 832

Nombre 832i y 832ii



El compuesto racémico 831 (0.4 g) se separó en sus enantiómeros por CLAR quiral preparativa de fase normal (columna CHIRALPAK OJ 5 x 50 cm; se eluye con 25% MeOH/EtOH (1:1) en hexano (isocrática) a 50 mL/min.) para dar 170 mg de enantiómero de elución más rápida, compuesto 832i (CLAR quiral: 8.97 min.; columna CHIRALPAK OJ 4.6 x 250 mm; se eluye con 20% MeOH/EtOH (1:1) en hexano a 1 mL/min.); CLAR: 99% a 1.84 min. (tiempo de retención) (Columna Phenominex S5 ODS 4.6 x 50 mm se eluye con 10-90% metanol acuoso durante 2 min., contiene 0.1% TFA, 4 mL/min., observando a 254 nm); EM (ES): m/z 451.06 $[M+H]^+$ y 190 mg del enantiómero de elución más lenta, compuesto 832ii (CLAR quiral: 14.79 min.; columna CHIRALPAK OJ 4.6 x 250 mm; se eluye con 20% MeOH/EtOH (1:1)

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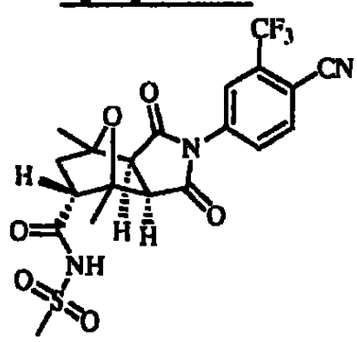
en hexano a 1 mL/min.); CLAR: 99% a 1.85 min. (tiempo de retención) (Columna Phenominex S5 ODS 4.6 x 50 mm se eluye con 10-90% metanol acuoso durante 2 min., contiene 0.1% TFA, 4 mL/min, observando a 254 nm); EM (ES): m/z 451.03 $[M+H]^+$. La estereoquímica absoluta de los compuestos 832i y 832ii no se ha establecido. Aunque cada compuesto representa un antípodo sencillo, la nomenclatura y estructura mostradas no reflejan la estereoquímica absoluta del compuesto.

Ejemplo 833

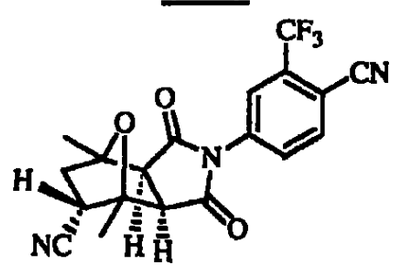


Una solución del compuesto 792B (45 mg; 0.11 mmol), metan sulfonamida (27 mg; 0.28 mmol), 4-dimetilaminopiridina (34 mg; 0.28 mmol) y EDCI (24 mg; 0.12 mmol) en 1 mL de diclorometano se agitó a temperatura ambiente por 18 hs. Después de dividir la mezcla de reacción entre EtOAc (25 mL) y agua (25 mL), la capa orgánica se lavó con solución saturada de bisulfato de potasio (25 mL), agua (25 mL) y salmuera (25 mL). El secado ($MgSO_4$) y la concentración dio un residuo que se trituró con éter de etilo para resultar el compuesto 833 (29 mg, 55%) como un polvo blanco descolorido.

CLAR: 98% a 1.44 min. (tiempo de retención) (Columna Phenominex S5 ODS 4.6 x 50 mm se eluye con 10-90% metanol acuoso durante 2 min,. contiene 0.1% TFA, 4 mL/min., observando a 254 nm); EM (ES): m/z 485.94 $[M+H]^+$. El compuesto 833 representa una mezcla racémica de antípodos. La nomenclatura y estructura mostradas no reflejan la estereoquímica absoluta del compuesto.

Ejemplo 834

3aα,4β,5α,7β,7aα)-2-(4-Ciano-3-(trifluorometil)fenil)-hexahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-1H-isoindol-5-carb (834)



Una mezcla del compuesto 792B (100 mg; 0.24 mmol), hidróxido de (metoxicarbonilsulfamoil)trietilamonio, sal interna (125 mg; 0.5 mmol) y trietilamina (0.15 mL; 1 mmol) en 2.5 mL de THF se agitó a temperatura ambiente por 2 hs. Después de dividir la mezcla de reacción entre éter de etilo (30 mL) y agua (30 mL), la capa orgánica se lavó con solución saturada de bisulfato de potasio (30 mL), solución de bicarbonato de sodio saturado (30 mL) y salmuera (30 mL). El secado ($MgSO_4$) y la concentración in vacuo produjo el compuesto 834 (80 mg, 97%)

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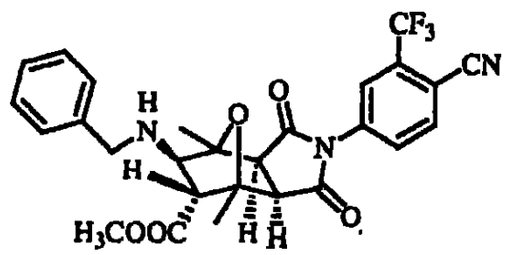
como un polvo blanco. CLAR: 99% a 1.51 min. (tiempo de retención) (Columna Phenominex S5 ODS 4.6 x 50 mm se eluye con 10-90% metanol acuoso durante 2 min., contiene 0.1% TFA, 4 mL/min., observando a 254 nm); EM (ES): m/z 390.03 $[M+H]^+$. El compuesto 834 representa una mezcla racémica de antípodos. La nomenclatura y estructura mostradas no reflejan la estereoquímica absoluta del compuesto.

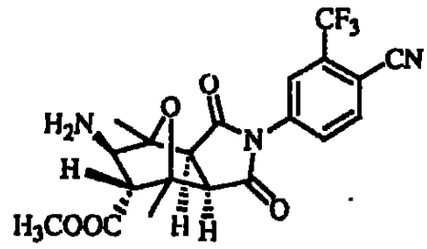
Ejemplo 835



Una mezcla del compuesto 793A (121 mg; 0.29 mmol) y bencilamina (0.032 mL; 0.29 mmol) en 0.6 mL de THF se agitó a temperatura ambiente por 18 hs. Después de agregar ~5 mL de hexano, la suspensión resultante se filtró y se secó para resultar el compuesto 835 (135 mg, 89%) como un polvo blanco. CLAR: 99% a 1.42 min. (tiempo de retención) (Columna Phenominex S5 ODS 4.6 x 50 mm se eluye con 10-90% metanol acuoso durante 2 min., contiene 0.1% TFA, 4 mL/min., observando a 254 nm); EM (ES): m/z 528.39 $[M+H]^+$. El compuesto 835 representa una mezcla racémica de antípodos. La nomenclatura y estructura mostradas no reflejan la estereoquímica absoluta del compuesto.

1287

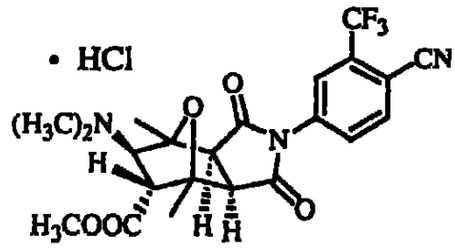
Ejemplo 836



Una mezcla del compuesto 793A (190 mg; 0.45 mmol) y amoniaco 2.0 M en THF (0.3 mL; 0.6 mmol) en 0.7 mL de THF se agitó a temperatura ambiente. Después de 1 h, se agregó una cantidad adicional de amoniaco 2.0 M en THF (0.7mL; 1.4 mmol) y la mezcla de reacción se agitó a temperatura ambiente por 18 hs. Los compuestos volátiles se separaron in vacuo y el residuo se trituró a partir de hexano para resultar el compuesto 835 (145 mg; 74%) como un polvo blanco descolorido. CLAR: 95.1% a 1.28 min. (tiempo de retención) (Columna Phenominex S5 ODS 4.6 x 50 mm se eluye con 10-90% metanol acuoso durante 2 min., contiene 0.1% TFA, 4 mL/min., observando a 254 nm); EM (ES): m/z 438.26 $[M+H]^+$. El compuesto 836 representa una mezcla racémica de antípodos. La nomenclatura y estructura mostradas no reflejan la estereoquímica absoluta del compuesto.

1288

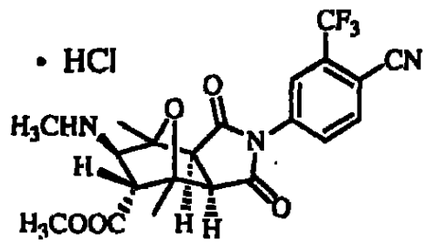
Ejemplo 837



Una mezcla del compuesto 793A (42 mg; 0.1 mmol) y dimetilamina 2.0 M en MeOH (0.1 mL; 0.1 mmol) en 0.5 mL de THF se agitó a temperatura ambiente por 18 h. Los compuestos volátiles se separaron in vacuo y el residuo se filtró a través de un tapón de 0.5 x 5 cm de gel de sílice, se eluyó con ~50 mL de EtOAc. Después de la concentración del filtrado, el residuo amarillo claro se disolvió en éter de etilo y se agregaron 0.3 mL de HCl 1M en éter de etilo. Los compuestos volátiles se separaron in vacuo y el residuo sólido se trituró a partir del éter de etilo para resultar el compuesto 837 (25 mg, 50%) como un polvo color crema. CLAR: 99% a 1.31 min. (tiempo de retención) (Columna Phenominex S5 ODS 4.6 x 50 mm se eluye con 10-90% metanol acuoso durante 2 min., contiene 0.1% TFA, 4 mL/min., observando a 254 nm); EM (ES): m/z 466.33 $[M+H]^+$. El compuesto 837 representa una mezcla racémica de antípodos. La nomenclatura y estructura mostradas no reflejan la estereoquímica absoluta del compuesto.

1289

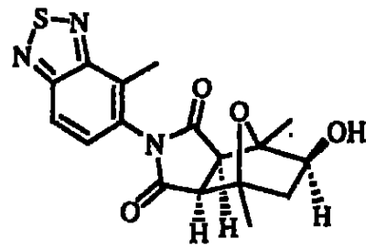
Ejemplo 838



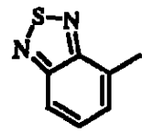
Una mezcla del compuesto 793A (42 mg; 0.1 mmol) y dimetilamina 2.0 M en THF (0.1 mL; 0.1 mmol) en 0.5 mL de THF se agitó a temperatura ambiente por 18 h. Los compuestos volátiles se separaron in vacuo y el residuo se filtró a través de un tapón de 0.5 x 5 cm de gel de sílice, eluido con ~50 mL de EtOAc. Después de la concentración del filtrado, el residuo amarillo se disolvió en éter de etilo y se agregó 0.3 mL de HCl 1M en éter de etilo. Los compuestos volátiles se separaron in vacuo y el residuo sólido se trituró a partir del éter de etilo para resultar el compuesto 838 (22 mg, 46%) como un polvo amarillo. CLAR: 99% a 1.28 min. (tiempo de retención) (Columna Phenominex S5 ODS 4.6 x 50 mm se eluye con 10-90% metanol acuoso durante 2 min, contiene 0.1% TFA, 4 mL/min., observando a 254 nm); EM (ES): m/z 452.31 $[M+H]^+$. El compuesto 838 representa una mezcla racémica de antípodos. La nomenclatura y estructura mostradas no reflejan la estereoquímica absoluta del compuesto.

1290

Ejemplo 839

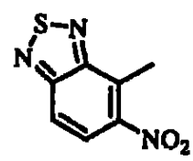


A. 4-Metil-benzo[1,2,5]tiadiazol (839A)



A una solución de 2,3-diaminotolueno (5.0g, 40.9 mmol) en piridina (40 mL) a 0°C se agregó cloruro de tionilo (7.0 mL, 98.2 mmol) gota a gota. La mezcla de reacción se agitó a 0°C por 30 min., después se agregó agua (200 mL). La solución se extrajo con diclorometano (2 x 250 mL). Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre Na_2SO_4 y concentraron in vacuo para dar el compuesto 839A (5.57g) como un líquido café obscuro.

B. 4-Metil-5-nitro-benzo[1,2,5]tiadiazol (839B)



A una solución de 4-metil-benzo[1,2,5]tiadiazol (5.57 g, 37.1 mmol) en H_2SO_4 concentrado (14.5 mL) a 0°C se agregó lentamente HNO_3/H_2SO_4 (3.25 mL/4.25 mL). La mezcla de reacción se agitó a 0°C por 20 min. y después a temperatura ambiente

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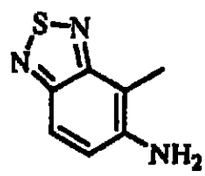
por 30 min. y después se vació en agua helada (200 mL). El precipitado resultante se aisló por filtración, se enjuagó con agua y se purificó por cromatografía instantánea por gel de sílice, se eluye con $CHCl_3$ para dar el compuesto 839B (1.5 g) como un sólido amarillo y 4-metil-7-nitro-benzo[1,2,5]tiadiazol (2.0 g) como un sólido amarillo.

C. 4-Metil-benzo[1,2,5]tiadiazol-5-ilamina (839C)



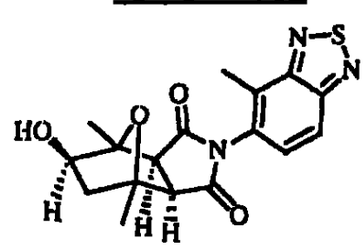
El 4-Metil-5-nitro-benzo[1,2,5]tiadiazol (1.4 g, 7.18 mmol) se disolvió en THF (10 mL), ácido acético (1 mL) y agua (21 mL) y polvo de hierro (1.4 g, 25.0 mmol, malla 325) se agregó. La mezcla de reacción se calentó a 80°C por 1.5 h, enfrió hasta temperatura ambiente y se filtró a través de celite para separar el polvo de hierro. La solución se extrajo con $CHCl_3$ (2 x 250 mL). Las capas orgánicas combinadas se lavaron con salmuera, se secaron sobre Na_2SO_4 y concentraron in vacuo para dar el compuesto 839C (1.1 g) como un sólido café claro.

D. (839D)

4-Metil-benzo[1,2,5]tiadiazol-5-ilamina (0.10 g, 0.610 mmol), mallas moleculares de 4Å (0.46 g) y el compuesto 752

(0.128 g, 0.610 mmol) fueron disueltos en DMA (0.60 mL) en un tubo sellado. La mezcla de reacción se calentó a 190°C por 1 h y después se enfrió hasta temperatura ambiente. La solución se filtró a través de celite para separar las mallas y después el filtrado se lavó con NH_4Cl saturado (10 mL) seguido por salmuera (10 mL). La capa orgánica después se secó sobre Na_2SO_4 y se concentró in vacuo para resultar un aceite amarillo. El material resultante se purificó por CCD preparativa (SiO_2), se eluye con 20% acetona en $CHCl_3$ para dar el compuesto 839D (70 mg) como un sólido amarillo claro. CLAR: 98% a 2.87 min. (tiempo de retención) (columna YMC S-5 ODS-A, 4.6 x 50 mm, se eluye con 10-90% metanol acuoso durante 4 min. conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ESI): m/z 360.19 [M+H]. La estereoquímica absoluta del compuesto 752 se establece por la estereoquímica conocida del compuesto intermediario 839D y la retención de la configuración en ella. La estereoquímica absoluta es como se obtiene en la figura anterior y resulta de la nomenclatura.

Ejemplo 840



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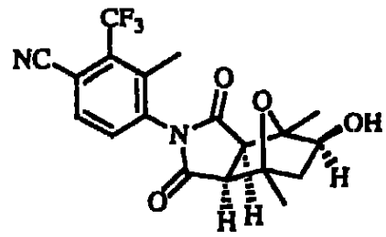
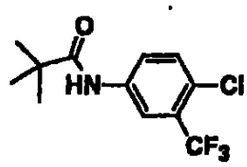
4-Metil-benzo[1,2,5]tiadiazol-5-ilamina (0.078g, 0.47 mmol), mallas moleculares de 4Å (0.46 g) y el compuesto 751 (0.100 g, 0.47 mmol) fueron disueltos en DMA (0.50 mL) en un tubo sellado. La mezcla de reacción se calentó a 190°C por 1 h y después se enfrió hasta temperatura ambiente. La solución se filtró a través de celite para separar las mallas y después el filtrado se lavó con saturated NH_4Cl saturado (10 mL), seguido por salmuera (10 mL). La capa orgánica después se secó sobre Na_2SO_4 y se concentró in vacuo para resultar un aceite amarillo. El material resultante se purificó por CCD preparativa (SiO_2), se eluye con 20% acetona en $CHCl_3$ para dar el compuesto 840 (20 mg) como un sólido amarillo claro. CLAR: 97% a 2.87 min. (tiempo de retención) (columna YMC S-5 ODS-A, 4.6 x 50 mm, se eluye con 10-90% metanol acuoso durante 4 min. conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ESI): m/z 360.30 [M+H]. La estereoquímica absoluta del compuesto 840 se establece por la estereoquímica conocida del compuesto intermediario 751 y la retención de la configuración en ella. La estereoquímica absoluta es como se obtiene en la figura anterior y resulta de la nomenclatura.

Ejemplo 841

[3aR-(3aα,4β,5β,7β,7aα)]-4-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-3-metil-2-(trifluorometil)benzonitrilo (841E)

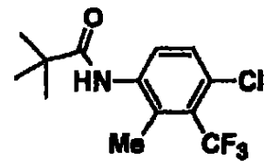


A. N-(4-Cloro-3-trifluorometilfenil)-2,2-dimetilpropionamida (841A)



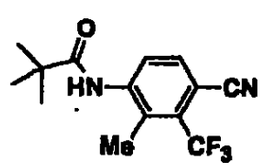
A una solución de 4-cloro-3-(trifluorometil)anilina comercialmente disponible(15.0 g, 76.7 mmol) en THF anhidro (200 mL) enfriada hasta 0-5°C, se agregó trietilamina (11.7 mL, 84.4 mmol) seguida por cloruro de pivaloilo (10.4 mL, 84.4 mmol) durante 30 min. El baño de hielo se separó y la mezcla se agitó a temperatura ambiente por 1 h. La mezcla se diluyó con éter y se filtró. El filtrado se lavó con agua (2X) y salmuera, se secó sobre $MgSO_4$, se filtró y concentró. El residuo se trituró con hexanos y el sólido se filtró y se secó in vacuo para resultar el compuesto 841A (20.4 g, 95%). EM (ES): m/z = 280 $[M+1]^+$.

B. N-(4-Cloro-2-metil-3-trifluorometilfenil)-2,2-dimetil-propionamida (841B)



A una solución de N-(4-cloro-3-trifluorometilfenil)-2,2-dimetilpropionamida (2.29 g, 8.19 mmol) en THF anhidro (25 mL) enfriada hasta 0-5°C se agregó una solución de 1.6 M n-butillitio en hexanos (12.3 mL, 19.7 mmol), se agregó lentamente de manera que la temperatura de reacción se mantuvo debajo de 5°C. La solución se agitó a 0-5°C por 1.5 h. Una solución de yodometano (0.56 mL, 9.01 mmol) en éter de petróleo (2 mL) se agregó durante 20 min. mientras se mantenía la temperatura debajo de 5°C. La suspensión se agitó a 0-5°C por 1 h y se diluyó con agua y éter. La capa acuosa se extrajo con éter y las capas orgánicas combinadas se lavaron con salmuera, se secó sobre $MgSO_4$, se filtró y concentró in vacuo. El residuo se cromatografió (gel de sílice), se eluye con CH_2Cl_2 para resultar el compuesto 841B (1.60 g, 67%). EM (ES): m/z = 294 $[M+1]^+$.

C. N-(4-Ciano-2-metil-3-trifluorometilfenil)-2,2-dimetil-propionamida (841C)



1296

Una suspensión de N-(4-cloro-2-metil-3-trifluorometilfenil)-2,2-dimetil-propionamida (8.36 g, 28.5 mmol) y CuCN (4.33 g, 65.5 mmol) en N-metilpirrolidinona anhidra (85 mL) se puso a reflujo por 38 h. Después de enfriar a temperatura ambiente, la suspensión se vació en agua con hielo con agitación. El sólido resultante se filtró, se lavó con agua y se secó para resultar una mezcla 85:15 (7.55 g) del compuesto 841C y 841D. La mezcla resultante se usó en la siguiente etapa.

D. 4-Amino-3-metil-2-trifluorometilbenzonitrilo (841D)

Una solución del producto mezclado del 841C (7.53 g, 26.5 mmol) se disolvió en 120 mL de HCl concentrado /EtOH (1:1) y se puso a reflujo por 14 h. Después de enfriar a temperatura ambiente, la solución se concentró in vacuo. El residuo resultante se disolvió en EtOAc, se lavó con $NaHCO_3$ acuoso saturado (2X) y salmuera (IX), se secó sobre $MgSO_4$, se filtró y concentró in vacuo. El residuo se cromatografió (gel de sílice), se eluye con cloroformo/metanol (98:2) para ensamblar el compuesto 841D (4.62 g, 87%). EM (ES): m/z = 201 $[M+1]^+$.

1297

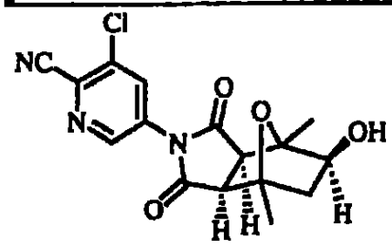
E. [3aR-(3aα,4β,5β,7β,7aα)]-4-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-3-metil-2-(trifluorometil)benzonitrilo (841E)

4-Amino-3-metil-2-trifluorometilbenzonitrilo (0.051 g, 0.25 mmol), malla molecular de 4Å (0.20 g) y el compuesto 752 (0.059 g, 0.28 mmol) fueron disueltos en DMA (0.30 mL) en un tubo sellado. La mezcla de reacción se calentó a 175°C por 30 min y después se enfrió hasta temperatura ambiente. La solución se filtró a través de celite para separar las mallas y después el filtrado se lavó con NH_4Cl saturado (10 mL), seguido por salmuera (10 mL). La capa orgánica después se secó sobre Na_2SO_4 y se concentró in vacuo para resultar un aceite amarillo. El material resultante se purificó por CCD preparativa (SiO_2), se eluye con 25% acetona en $CHCl_3$ para dar el compuesto 841E (40 mg) como un sólido café claro. CLAR: 97% a 3.18 min. (tiempo de retención) (columna YMC S-5 ODS-A, 4.6 x 50 mm, se eluye con 10-90% metanol acuoso durante 4 min. conteniendo 0.2% ácido fosfórico, 4 mL/min., observando a 220 nm). EM (ESI): m/z 393.18 $[M-H]^-$. La estereoquímica absoluta del compuesto 841E se establece por la estereoquímica conocida del compuesto intermediario 752 y la retención de la configuración en ella. La estereoquímica absoluta es como se obtiene en la figura anterior y resulta de la nomenclatura.

1298

Ejemplo 842

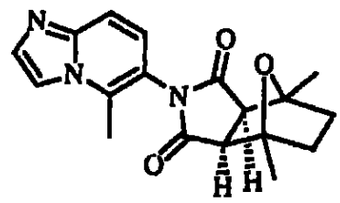
[3aS-(3aα,4β,5β,7β,7aα)]-5-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-3-cloro-2-piridincarbonitrilo (842)



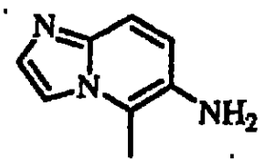
El compuesto 752 (500 mg, 2.36 mmol), mallas moleculares de 4 Å (1.5 g), 5-amino-3-cloro-2-cianopiridina (357 mg, 2.34 mmol) y DMA (2 mL) se combinaron en un tubo sellado. La mezcla se calentó en un baño de aceite precalentado a 170°C por 25 min., se enfrió y la malla se separó por filtración, se eluye con EtOAc. Los compuestos orgánicos se lavaron 3x con agua, seguido por salmuera. Los compuestos orgánicos resultantes se secaron sobre $MgSO_4$ y se concentró in vacuo. El residuo se pre-adsorbió sobre Celite y se purificó por cromatografía instantánea por gel de sílice con 0 hasta 40% de acetona en CH_2Cl_2 para dar el compuesto 842 (480 mg, 63%) como un sólido color marrón. CLAR: 97% a 2.66 min. (tiempo de retención) (Columna YMC S5 ODS-A de 4.6 x 50 mm Ballistic, 10-90% metanol acuoso durante 4 min., contiene 0.2% H_3PO_4, 4 mL/min., observando a 220 nm). EM (ES): m/z 348.30 $[M+H]^+$. La estereoquímica absoluta del compuesto 842 se establece por la estereoquímica conocida del compuesto intermediario 752 y la

retención de la configuración en ella. La estereoquímica absoluta es como se obtiene en la figura anterior y resulta de la nomenclatura.

Ejemplo 843



A. 5-Metil-imidazo[1,2-a]piridin-6-ilamina (843A)



2-Metil-3-nitro-6-amino piridina (63 mg, 0.41 mmol) se suspendió en 1.3 mL de EtOH conteniendo 0.3 mL de HCl concentrado. Se agregó 2-Bromo-1,1-dimetoxi-etano (73 µL, 0.62 mmol) y la mezcla resultante se puso a reflujo por 8 h, punto en el cual se agregó 2-bromo-1,1-dimetoxi-etano adicional (0.1 mL, 0.85 mmol). La mezcla se agitó a reflujo durante la noche, se enfrió y diluyó con CH_2Cl_2. Los compuestos orgánicos se lavaron con una solución saturada de $NaHCO_3$, se secaron sobre $MgSO_4$ y se concentraron in vacuo. El residuo se disolvió en 4 mL AcOH/EtOAc (1:1) y la solución resultante se calentó hasta 75°C. Polvo de hierro (46 mg, 0.82 mmol, malla 325) se agregó y la mezcla se agitó por 20

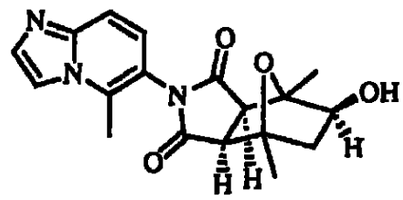
min. Se agregó polvo de hierro adicional (46 mg, 0.82 mmol, malla 325) y la agitación continuó por 30 min. La mezcla se enfrió hasta temperatura ambiente y se concentró. El residuo resultante se purificó por cromatografía instantánea por gel de sílice con 20% de MeOH en CH_2Cl_2 para dar el compuesto 843A (51 mg, 85%) como un sólido amarillo-café. CLAR: 72% a 0.18 min y 28% a 0.27 min (tiempo de retención) (Columna YMC S5 ODS-A de 4.6 x 50 mm Ballistic, 10-90% metanol acuoso durante 4 min, contiene 0.2% H_3PO_4, 4 mL/min, observando a 220 nm). EM (ES): m/z 147.85 $[M+H]^+$.

C. (843B)

En un tubo sellado se colocó 5-metil-imidazo[1,2-a]piridin-6-ilamina (46 mg, 0.31 mmol), compuesto 20A (92 mg, 0.47 mmol), 250 mg de mallas moleculares de 4Å y 0.3 mL de DMA. El tubo se selló y calentó en un baño de aceite precalentado a 170°C por 30 min. La mezcla se enfrió y se filtró, se eluye con EtOAc. El filtrado se lavó 3x con agua seguido por salmuera. La capa orgánica se secó sobre $MgSO_4$, se concentró in vacuo y se purificó por CCD preparativa (SiO_2) con 50% acetona en $CHCl_3$ para dar el compuesto 843B (32 mg, 32%) como un sólido amarillo pálido. CLAR: 99% a 1.47 min (tiempo de retención) (Columna YMC S5 ODS-A de 4.6 x 50 mm Ballistic, 10-90% metanol acuoso durante 4 min, contiene 0.2%

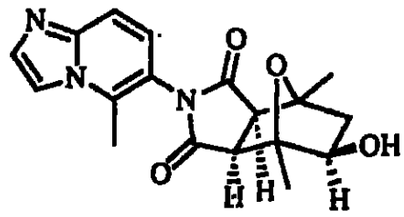
H_3PO_4, 4 mL/min, observando a 220 nm). EM (ES): m/z 326.39 $[M+H]^+$.

Ejemplo 844



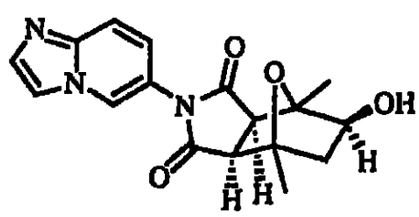
En un tubo sellado se combinaron 5-metil-imidazo[1,2-a]piridin-6-ilamina (50 mg, 0.34 mmol), compuesto 752 (108 mg, 0.51 mmol), $MgSO_4$ (102 mg, 0.85 mmol), Et_3N (0.24 mL, 1.7 mmol) y 0.3 mL de 1,2-dimetoxi-etano. El tubo se selló y se calentó a 135°C por 14 h. La mezcla se enfrió hasta temperatura ambiente, se filtró para separar la malla, se eluye con MeOH, y se concentró in vacuo. La purificación del residuo resultante por cromatografía instantánea por gel de sílice con 0 hasta 10% MeOH en CH_2Cl_2 produjo el compuesto 844 (86 mg, 74%) como un sólido color marrón. CLAR: 100% a 0.85 min (tiempo de retención) (Columna YMC S5 ODS-A de 4.6 x 50 mm Ballistic, 10-90% metanol acuoso durante 4 min, contiene 0.2% H_3PO_4, 4 mL/min, observando a 220 nm). EM (ES): m/z 342.20 $[M+H]^+$. La estereoquímica absoluta del compuesto 844 se establece por la estereoquímica conocida del compuesto intermediario 752 y la retención de la configuración en ella. La estereoquímica absoluta es como se obtiene en la figura anterior y resulta de la nomenclatura.

Ejemplo 845

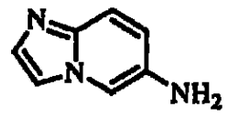


Según el procedimiento de Ejemplo 843, 5-metil-imidazo[1,2-a]piridin-6-ilamina (50 mg, 0.34 mmol), el compuesto 751 (108 mg, 0.51 mmol), $MgSO_4$ (102 mg, 0.85 mmol), Et_3N (0.24 mL, 1.7 mmol) reaccionaron en 0.3 mL de 1,2-dimetoxi-etano. La purificación dio el compuesto 845 (79 mg, 68%) como un sólido color marrón. CLAR: 100% a 0.85 min (tiempo de retención) (Columna YMC S5 ODS-A de 4.6 x 50 mm Ballistic, 10-90% metanol acuoso durante 4 min, contiene 0.2% H_3PO_4, 4 mL/min, observando a 220 nm). EM (ES): m/z 342.20 $[M+H]^+$. La estereoquímica absoluta del compuesto 845 se establece por la estereoquímica conocida del compuesto intermediario 751 y la retención de la configuración en ella. La estereoquímica absoluta es como se obtiene en la figura anterior y resulta de la nomenclatura.

Ejemplo 846



A. Imidazo[1,2-a]piridin-6-ilamina (846A)



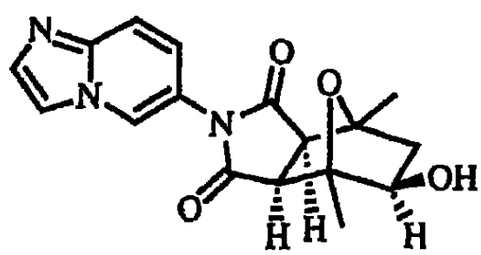
2-Amino-5-nitro piridina se suspendió en 40 mL de una solución de EtOH/HCl concentrado (3:1). A esta suspensión se agregó 2-bromo-1,1-dimetoxi-etano (6.37 mL, 53.91 mmol) y la mezcla resultante se calentó hasta reflujo por 8 h, después de lo cual se agregó 2-bromo-1,1-dimetoxi-etano adicional (6.37 mL, 53.91 mmol). La mezcla se calentó a reflujo durante la noche, se enfrió hasta temperatura ambiente y se colocó en un refrigerador por 24 h. Los precipitados se colectaron, se lavaron con EtOH enfriado con hielo, se secaron con aire y convirtieron a la base libre usando procedimientos estándar para resultar un sólido amarillo. El sólido amarillo crudo resultante, (404 mg) se disolvió en 150 mL THF/MeOH (1:1) y la solución resultante se hidrogenó por 4 h sobre Pd/C (250 mg, 10%) usando un globo de hidrógeno. La mezcla se filtró a través de Celite se eluye con THF/MeOH (1:1) y se concentró el filtrado. La purificación se alcanzó usando cromatografía instantánea por gel de sílice con 20% MeOH en CH_2Cl_2 para dar el compuesto 846A (241 mg, 75%) como un aceite incoloro que se obscurece con el reposo.

1304

B. (846B)

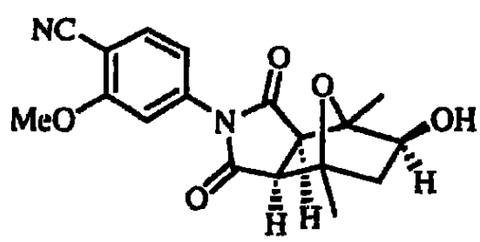
En un tubo sellado se combinaron imidazo[1,2-a]piridin-6-ilamina (64 mg, 0.48 mmol), compuesto 752 (148 mg, 0.71 mmol), $MgSO_4$ (146 mg, 1.21 mmol), Et_3N (0.34 mL, 2.40 mmol) y 0.4 mL de 1,2-dimetoxi-etano. El tubo se selló y se calentó hasta 135°C por 14 h. La mezcla se enfrió, se filtró a través de Celite se eluye con MeOH y se concentró. La purificación se alcanzó por cromatografía instantánea por gel de sílice con 10% MeOH en CH_2Cl_2 para dar el compuesto 846B (107 mg, 64%) como un sólido amarillo pálido. CLAR: 40% a 0.19 min y 60% a 0.38 min (tiempo de retención) (Columna YMC S5 ODS-A de 4.6 x 50 mm Ballistic, 10-90% metanol acuoso durante 4 minutos y contiene 0.2% H_3PO_4, 4 mL/min, observando a 220 nm). EM (ES): m/z 328.16 $[M+H]^+$. La estereoquímica absoluta del compuesto 846B se establece por la estereoquímica conocida del compuesto intermediario 752 y la retención de la configuración en ella. La estereoquímica absoluta es como se obtiene en la figura anterior y resulta de la nomenclatura.

Ejemplo 847

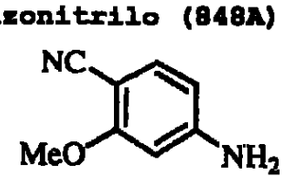


Según el procedimiento dado en el Ejemplo 846, imidazo[1,2-a]piridin-6-ilamina (50 mg, 0.38 mmol), compuesto 751 (119 mg, 0.56 mmol), $MgSO_4$ (114 mg, 0.95 mmol), Et_3N (0.26 mL, 1.9 mmol) reaccionaron en 0.35 mL de 1,2-dimetoxi-etano. La purificación dio el compuesto 847 (87 mg, 70%) como un sólido blanco. CLAR: 32% a 0.20 min y 68% a 0.37 min (tiempo de retención) (Columna YMC S5 ODS-A de 4.6 x 50 mm Ballistic, 10-90% metanol acuoso durante 4 min, contiene 0.2% H_3PO_4, 4 mL/min, observando a 220 nm). EM (ES): m/z 328.12 $[M+H]^+$. La estereoquímica absoluta del compuesto 847 se establece por la estereoquímica conocida del compuesto intermediario 751 y la retención de la configuración en ella. La estereoquímica absoluta es como se obtiene en la figura anterior y resulta de la nomenclatura.

Ejemplo 848



A. 4-amino-2-metoxi-benzonitrilo (848A)



1306

El 2-Metoxi-4-nitro-benzonitrilo (500 mg, 2.81 mmol) se suspendió en 4 mL de AcOH/EtOAc (1:1) y la mezcla resultante se calentó hasta 75°C para dar una solución transparente. Se agregó polvo de Fe (313 mg, 5.61 mmol, malla 325) y la mezcla se agitó por 30 min, después de lo cual se introdujo polvo de Fe adicional (313 mg, 5.61 mmol, malla 325). La mezcla se agitó a 75°C por 30 min adicionales, y después enfrió hasta temperatura ambiente y se filtró, se eluye con EtOAc. Se concentró el filtrado in vacuo, re-disuelto en EtOAc, se filtró (se eluye con EtOAc) y concentró. La purificación se alcanzó por cromatografía instantánea por gel de sílice con 0 a 10% de MeOH en CH_2Cl_2 para dar el compuesto 848A como un sólido color marrón.

B. (848B)

En un tubo sellado se combinaron 4-amino-2-metoxi-benzonitrilo (40 mg, 0.27 mmol), compuesto 752 (86 mg, 0.41 mmol), $MgSO_4$ (81 mg, 0.68 mmol), Et_3N (0.19 mL, 1.4 mmol) y 0.25 mL de 1,2-dimetoxi-etano. El tubo se cerró y calentó a 135°C por 14 h. La mezcla se enfrió hasta temperatura ambiente, se filtró (se eluye con MeOH) y se concentró in vacuo. La purificación del residuo resultante por cromatografía instantánea por gel de sílice usando 0 hasta 100% EtOAc en CH_2Cl_2 para resultar el compuesto 848B (36 mg, 39%) como un sólido blanco descolorido. CLAR: 100% a 2.36 min

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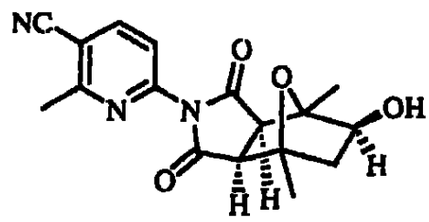
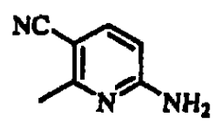
(tiempo de retención) (Columna YMC S5 ODS-A de 4.6 x 50 mm Ballistic, 10-90% metanol acuoso durante 4 min, contiene 0.2% H_3PO_4, 4 mL/min, observando a 220 nm). EM (ES): m/z 341.23 $[M-H]^-$. La estereoquímica absoluta del compuesto 848B se establece por la estereoquímica conocida del compuesto intermediario 752 y la retención de la configuración en ella. La estereoquímica absoluta es como se obtiene en la figura anterior y resulta de la nomenclatura.

Ejemplo 849



A. 6-amino-2-metil-nicotinonitrilo (849A)



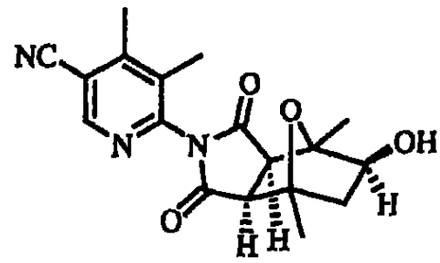
Una mezcla de 6-amino-2-metil-nicotinonitrilo (500 mg, 2.67 mmol), CuCN (478 mg, 5.34 mmol) y DMA (2 mL) se agitó bajo nitrógeno por 20 h a 170°C. La mezcla de reacción se enfrió y se agregó a 50 mL de una solución acuosa al 20% de etan-1,2-diamina. Las capas se separaron y la capa acuosa se extrajo 3x con EtOAc. Los compuestos orgánicos combinados se lavaron con agua seguida por salmuera, se secaron sobre $MgSO_4$ y se concentraron in vacuo. La purificación por cromatografía

instantánea por gel de sílice con 0 hasta 100% EtOAc en CH_2Cl_2 dio el compuesto 849A (199 mg, 56%) como un sólido blanco.

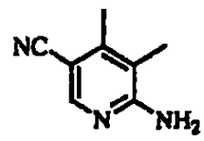
B. (849B)

En un tubo sellado se colocó 6-amino-2-metil-nicotinonitrilo (50 mg, 0.38 mmol), compuesto 752 (119 mg, 0.56 mmol), $MgSO_4$ (114 mg, 0.95 mmol), Et_3N (0.26 mL, 1.9 mmol) y 0.3 mL de 1,2-dimetoxi-etano. El tubo se selló y calentó a 135°C por 14 h. La mezcla se enfrió hasta temperatura ambiente, se filtró (se eluye con MeOH) y se concentró in vacuo. Se concentró el filtrado y se purificó por cromatografía instantánea por gel de sílice con 0 hasta 100% EtOAc en CH_2Cl_2 para dar el compuesto 849B (36 mg, 29%) como un sólido blanco. CLAR: 100% a 1.99 min (tiempo de retención) (Columna YMC S5 ODS-A de 4.6 x 50 mm Ballistic, 10-90% metanol acuoso durante 4 min conteniendo 0.2% H_3PO_4, 4 mL/min, observando a 220 nm). EM (ES): m/z 328.04 $[M+H]^+$. La estereoquímica absoluta del compuesto 849B se establece por la estereoquímica conocida del compuesto intermediario 752 y la retención de la configuración en ella. La estereoquímica absoluta es como se obtiene en la figura anterior y resulta de la nomenclatura.

Ejemplo 850



A. 6-amino-4,5-dimetil-nicotinonitrilo (850A)



Una mezcla de 5-bromo-3,4-dimetil-piridin-2-ilamina (500 mg, 2.49 mmol), CuCN (445 mg, 4.97 mmol) y DMA (3.5 mL) se agitó bajo nitrógeno por 20 h a 170°C. La mezcla de reacción se enfrió y se agregó a 50 mL de una solución acuosa al 20% de etano-1,2-diamina. Las capas se separaron y la capa acuosa se extrajo 3x con EtOAc. Los compuestos orgánicos combinados se lavaron con agua, seguido por salmuera y se secaron sobre $MgSO_4$. La concentración in vacuo produjo el compuesto 850A (362 mg, 99%) como un sólido blanco.

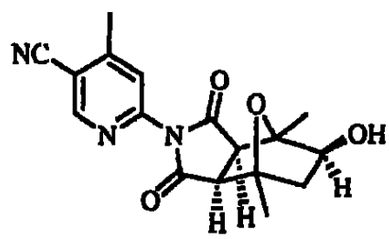
B. (850B)

En un tubo sellado se combinaron 6-amino-4,5-dimetil-nicotinonitrilo (50 mg, 0.34 mmol), compuesto 752 (108 mg, 0.50 mmol), $MgSO_4$ (102 mg, 0.85 mmol), Et_3N (0.24 mL, 1.7 mmol) y 0.3 mL de 1,2-dimetoxi-etano. El tubo se cerró y se calentó hasta 135°C por 14 h. La mezcla se enfrió hasta temperatura ambiente, se filtró (se eluye con MeOH) y se

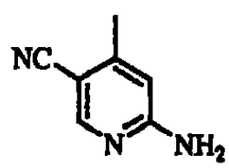
1310

concentró in vacuo. La purificación del residuo resultante por cromatografía instantánea por gel de sílice con 0 hasta 100% EtOAc en CH_2Cl_2 produjo el compuesto 850B (68 mg, 59%) como un sólido blanco descolorido. CLAR: 10% a 2.15 min y 82% a 2.31 min (tiempo de retención) (Columna YMC S5 ODS-A de 4.6 x 50 mm Ballistic, 10-90% metanol acuoso durante 4 min, contiene 0.2% H_3PO_4, 4 mL/min, observando a 220 nm). EM (ES): m/z 342.06 $[M+H]^+$. La estereoquímica absoluta del compuesto 850B se establece por la estereoquímica conocida del compuesto intermediario 752 y la retención de la configuración en ella. La estereoquímica absoluta es como se obtiene en la figura anterior y resulta de la nomenclatura.

Ejemplo 851



A. 6-amino-4-metil-nicotinonitrilo (851A)



Una mezcla de 5-bromo-4-metil-piridin-2-ilamina (500 mg, 2.67 mmol), CuCN (478 mg, 5.34 mmol) y DMA (2 mL) se agitó bajo nitrógeno por 20 h a 170°C. La mezcla de reacción se

1311

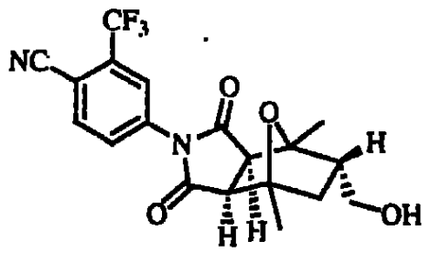
enfrió y se agregó a 50 mL de una solución acuosa al 20% de etano-1,2-diamina. Las capas se separaron y la capa acuosa se extrajo 3x con EtOAc. Los compuestos orgánicos combinados se lavaron con agua seguida por salmuera y se secaron sobre $MgSO_4$. La concentración in vacuo produjo el compuesto 851A (309 mg, 87%) como un sólido blanco.

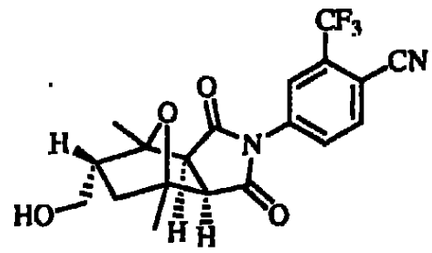
B. (851B)

En un tubo sellado se colocó 6-amino-4-metil-nicotinonitrilo (50 mg, 0.38 mmol), compuesto 752 (119 mg, 0.56 mmol), $MgSO_4$ (114 mg, 0.95 mmol), Et_3N (0.26 mL, 1.9 mmol) y 0.3 mL de 1,2-dimetoxi-etano. El tubo se selló y se calentó hasta 135°C por 14 h. La mezcla se permitió enfriar a temperatura ambiente y se filtró, se eluye con MeOH. Se filtró el concentrado in vacuo y se purificó por cromatografía instantánea por gel de sílice con 0 hasta 100% de EtOAc en CH_2Cl_2 para dar el compuesto 851B (67 mg, 54%) como un sólido blanco. CLAR: 100% a 1.95 min (tiempo de retención) (Columna YMC S5 ODS-A de 4.6 x 50 mm Ballistic, 10-90% metanol acuoso durante 4 min, contiene 0.2% H_3PO_4, 4 mL/min, observando a 220 nm). EM (ES): m/z 328.04 $[M+H]^+$. La estereoquímica absoluta del compuesto 851B se establece por la estereoquímica conocida del compuesto intermediario 752 y la retención de la configuración en ella. La estereoquímica

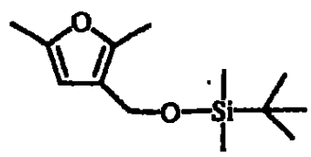
absoluta es como se obtiene en la figura anterior y resulta de la nomenclatura.

Ejemplo 852





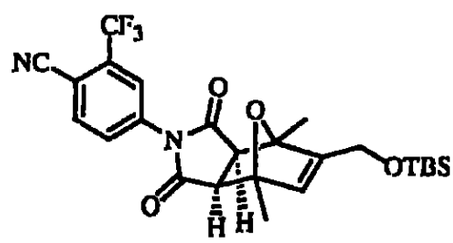
A. tert-Butil-(2,5-dimetil-furan-3-ilmetoxi)-dimetil-silano (852A)



En un matraz de fondo redondo seco de 100 mL, se preparó una solución de metil 2,5-dimetil-3-furoato (2.00 g, 13.0 mmol) en Et_2O anhidro (10 mL) bajo una atmósfera inerte. A esta solución se agregó gota a gota una solución 1.0 M de $LiAlH_4$ en Et_2O (13 mL, 13 mmol) a 0°C. La suspensión resultante se agitó a 0°C por 30 min y se dejó después entibiar a temperatura ambiente, en donde se mantuvo por 4 h. La reacción se apagó por la adición cuidadosa de $Na_2SO_4 \cdot 10 H_2O$ sólido (exceso) y Celite (exceso). Para facilitar la agitación, se agregó Et_2O como fue necesario. La mezcla resultante se agitó durante la noche, se filtró y se concentró cuidadosamente in vacuo para resultar el alcohol

volátil que se disolvió en DMF anhidro (5 mL) bajo una atmósfera inerte. A esta solución se le agregó imidazol (1.32 g, 19.5 mmol) y TBSCl (2.05 g, 13.6 mmol) y la mezcla se agitó por 6 h. La mezcla de reacción se diluyó con EtOAc y se agregó agua. Las capas se separaron y la capa orgánica se lavó varias veces con agua. Los compuestos orgánicos se secaron sobre $MgSO_4$, se concentraron in vacuo y se purificaron por cromatografía instantánea por gel de sílice con 0 hasta 50% de EtOAc en hexanos, resultando el compuesto 852A (3.08 g, 99%) como un aceite incoloro.

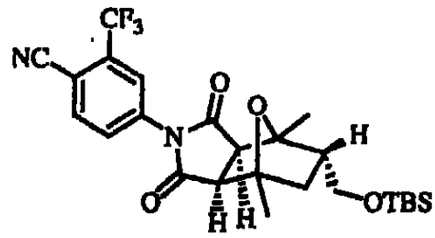
B. (852B)



En un tubo sellado se combinaron tert-butil-(2,5-dimetil-furan-3-ilmetoxi)-dimetil-silano (2.60 g, 10.8 mmol), 4-(2,5-dihidro-2,5-2,5-dioxo-H-pirrol-1-il)-2-trifluorometilbenzonitrilo (1.44 g, 5.41 g) y THF (1 mL). El tubo se selló y se calentó rápidamente hasta 95°C para resultar una solución casi transparente. La mezcla después se dejó enfriar a temperatura ambiente y se agitó a temperatura ambiente durante la noche. La purificación se logró por cromatografía instantánea por gel de sílice con 0 hasta 100%

de EtOAc en hexanos para dar el compuesto 852B (2.37 g, 86%) como un sólido blanco.

C. (852C)



Una solución del compuesto 852B de (1.4 g, 2.8 mmol) en EtOAc (50 mL) se hidrogenó sobre Pd/C (10%, 800 mg) por 6 h usando un globo de hidrógeno. La mezcla se filtró, se eluye con EtOAc, y se concentró in vacuo. La purificación se logró usando cromatografía instantánea por gel de sílice con 0 hasta 100% de EtOAc en hexanos para resultar el compuesto 852C (0.9 g, 64%) como una espuma blanca.

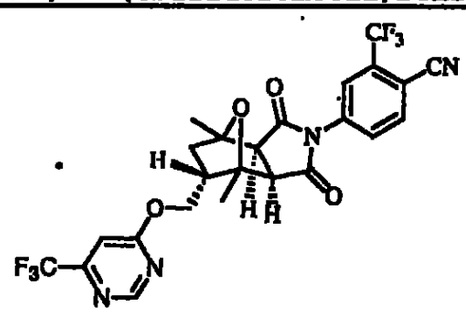
D.

El compuesto 852C (0.9 g, 1.8 mmol) se disolvió en 7 mL de EtOH conteniendo 2% de HCl concentrado a temperatura ambiente y la mezcla resultante se agitó por 2 h. La mezcla de reacción se vació cuidadosamente en solución saturada de $NaHCO_3$ y la capa acuosa se extrajo dos veces con EtOAc. Los compuestos orgánicos combinados se secaron sobre $MgSO_4$, se concentraron in vacuo y se purificaron por cromatografía instantánea por gel de sílice con 0 hasta 100 % de EtOAc en CH_2Cl_2 para resultar una mezcla racémica del compuesto 852Di y

852Dii (0.7 g, 100%) como un sólido blanco. El material racémico se separó en sus enantiómeros por CLAR quiral preparativa de fase normal (columna CHIRALPAK OJ 5 x 50 cm; se eluye con 30% MeOH/EtOH (1:1) en heptano (isocrático) a 50 mL/min) para dar el enantiómero de elución más rápida compuesto 852Di (CLAR quiral: 5.56 min; columna CHIRALPAK OJ 4.6 x 250 mm; se eluye con 30% MeOH/EtOH (1:1) en heptano conteniendo 0.1% DBA a 1 mL/min) y el enantiómero de elución más lenta compuesto 852Dii (CLAR quiral: 7.01 min; columna CHIRALPAK OJ 4.6 x 250 mm; se eluye con 30% MeOH/EtOH (1:1) en heptano conteniendo a 1 mL/min). La estereoquímica absoluta de los compuestos 852Di y 852Dii no se ha establecido. Aunque cada compuesto representa un antípodo sencillo, la nomenclatura y estructura mostradas no reflejan la estereoquímica absoluta del compuesto.

Ejemplo 853

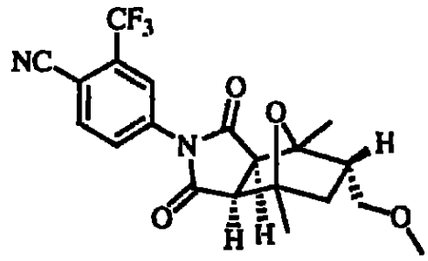
(3aα,4β,5α,7β,7aα)-4-(Octahidro-5-[[[6-(trifluorometil)-4-pirimidinil]oxi]metil]-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo (853)



1316

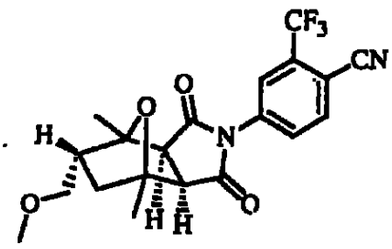
Trifenilfosfina (0.066g, 0.254 mmol) y di-ter-butil-azodicarboxilato (0.058g, 0.254 mmol) en THF (0.5 mL) se agitaron a temperatura ambiente bajo N_2 por 10 min, se agregó después 6-trifluorometil-4-pirimidinol (0.042g, 0.254 mmol). La mezcla de reacción se agitó bajo N_2 por otros 15 min, seguido por la adición de una mezcla racémica de los compuestos 852Di y 852Dii (0.050g, 0.127 mmol). La reacción se dejó proceder por 2 h, punto en el cual se agregó el CH_2Cl_2 (15 mL). La capa orgánica se aisló y después se lavó consecutivamente con NaOH 1N (15 mL), salmuera (15 mL) y se secó sobre $MgSO_4$ y se concentró in vacuo. El sólido resultante se purificó por cromatografía en gel de sílice, se eluye con EtOAc en hexano desde 0% hasta 100%, para dar el compuesto 853 (60 mg) como un sólido blanco. CLAR: 99% a 4.083 min (tiempo de retención) (columna YMC S-5 ODS-A, 4.6 x 50 mm, se eluye con 10-90% metanol acuoso durante 4 min conteniendo 0.2% ácido fosfórico, 4 mL/min, observando a 220 nm). EM (ESI): m/z 541.06 [M+H]. El compuesto 853 representa una mezcla racémica de antípodos. La nomenclatura y estructura mostradas no reflejan la estereoquímica absoluta del compuesto.

Ejemplo 854



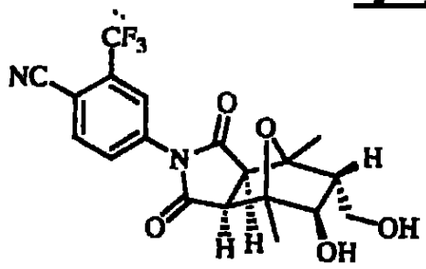
En un tubo sellado se preparó una mezcla del compuesto 852Di (150 mg, 0.38 mmol), MeI (0.24 mL, 3.8 mmol) y Ag_2O (881 mg, 3.8 mmol) en 2 mL de CH_3CN. El tubo se selló y calentó hasta 80°C durante la noche. La mezcla se enfrió hasta temperatura ambiente, se filtró, se eluye con EtOAc, y concentra. La purificación se logró por cromatografía instantánea por gel de sílice con 0 hasta 100% de EtOAc en hexanos para dar el compuesto 854 (49 mg, 32%) como un aceite incoloro. CLAR: 97% a 3.58 min (tiempo de retención) (Columna YMC S5 ODS-A de 4.6 x 50 mm Ballistic, 10-90% metanol acuoso durante 4 min, contiene 0.2% H_3PO_4, 4 mL/min, observando a 220 nm). EM (ES): m/z 407.20 $[M+H]^+$. La estereoquímica absoluta del compuesto 854 no se ha establecido. Aunque el compuesto representa un antípodo sencillo, la nomenclatura y estructura no reflejan la estereoquímica absoluta del compuesto.

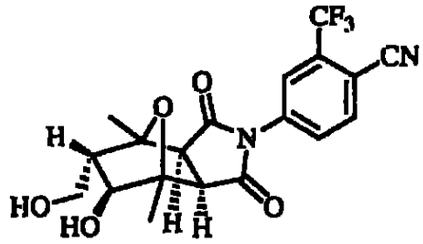
Ejemplo 855



El compuesto 852Dii (150 mg, 0.38 mmol), MeI (0.24 mL, 3.8 mmol) y Ag_2O (881 mg, 3.8 mmol) reaccionaron en 2 mL de CH_3CN y la mezcla de reacción se purificó como se describe por el Ejemplo 854 para resultar el compuesto 855 (45 mg, 29%) como un aceite incoloro. CLAR: 98% a 3.58 min (tiempo de retención) (Columna YMC S5 ODS-A de 4.6 x 50 mm Ballistic, 10-90% metanol acuoso durante 4 min, contiene 0.2% H_3PO_4, 4 mL/min, observando a 220 nm). EM (ES): m/z 407.19 $[M-H]^-$. La estereoquímica absoluta del compuesto 855 no se ha establecido. Aunque el compuesto representa un antípodo sencillo, la nomenclatura y estructura mostradas no reflejan la estereoquímica absoluta del compuesto.

Ejemplo 856





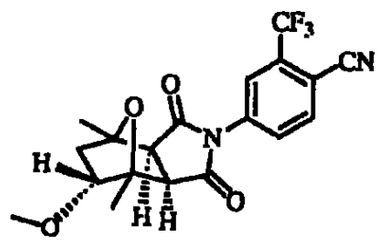
A una solución del compuesto 852B (835 mg, 1.65 mmol) en 10 mL de THF se agregó una solución 1.0 M de BH_3•THF (3.3 mL,

3.30 mmol) gota a gota a 0°C. La mezcla resultante se agitó a 0°C por 2 h, después de lo cual se agregaron 15 mL de EtOH, 5 mL de THF, 30 mL de una solución amortiguadora de fosfato de pH 7 y 2.1 mL de 30% de H_2O_2. La mezcla resultante se agitó por 2 h a 0°C, después de lo cual se agregaron agua y EtOAc. Las capas se separaron y la capa acuosa se extrajo nuevamente con EtOAc. Las fases orgánicas combinadas se lavaron con una solución al 10% de $Na_2S_2O_3$ seguida por salmuera. Los compuestos orgánicos se secaron sobre $MgSO_4$, se concentraron y purificaron por cromatografía instantánea con 0 hasta 25% de EtOAc en CH_2Cl_2. El material se disolvió en 8 mL de EtOH conteniendo 2% de HCl concentrado y la mezcla resultante se agitó por 2 h. La mezcla de reacción se diluyó con EtOAc y se vació cuidadosamente en una solución saturada de $NaHCO_3$. Las capas se separaron y la capa acuosa se extrajo nuevamente con EtOAc. Las capas orgánicas combinadas se secaron sobre $MgSO_4$ y se concentraron in vacuo. El material racémico resultante se separó en sus enantiómeros por CLAR quiral preparativa de fase normal (columna CHIRALPAK OD 5 x 50 cm; se eluye con 15% MeOH/EtOH (1:1) en heptano (isocrática) a 50 mL/min) para dar el compuesto de elución más rápida 856i (128 mg) (CLAR quiral: 13.64 min; columna CHIRALPAK OD 4.6 x 250 mm; se eluye con 15% MeOH/EtOH (1:1) en heptano conteniendo a 1 mL/min) y el compuesto de elución más lenta 856ii (137 mg, 39% rendimiento combinado) (CLAR quiral: 16.31 min; columna

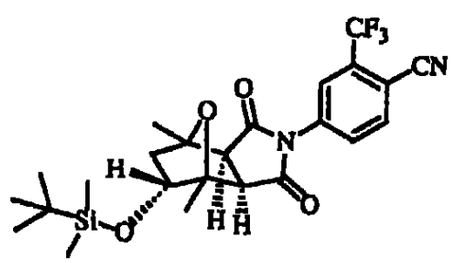
1320

CHIRALPAK OD 4.6 x 250 mm; se eluye con 15% MeOH/EtOH (1:1) en heptano a 1 mL/min).). EM (ES): m/z 411.01 $[M+H]^+$. La estereoquímica absoluta de los compuestos 856i y 856ii no se ha establecido. Aunque cada compuesto representa un antípodo sencillo, la nomenclatura y estructura mostradas no reflejan la estereoquímica absoluta del compuesto.

Ejemplo 857

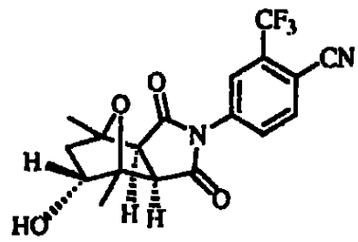


A. (857A)



El compuesto 798i se convirtió al compuesto 857A por el procedimiento descrito en el Ejemplo 774. CLAR: 95% a 4.307 min, (tiempo de retención) (Columna YMC S5 ODS-A de 4.6 x 50 mm se eluye con 10-90% metanol acuoso durante 4 min, contiene 0.2% ácido fosfórico, 4 mL/min, observando a 220 nm).

B. (857B)



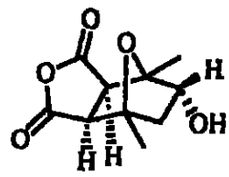
El compuesto 857A se convirtió al compuesto 857B por el procedimiento descrito en el ejemplo 774. CLAR: 100% a 2.89 min, (tiempo de retención) (columna YMC S5 ODS-A 4.6 x 50 mm se eluye con 10-90% metanol acuoso durante 4 min, contiene 0.2% ácido fosfórico, 4 mL/min, observando a 220 nm). EM (ES): m/z 381.16 $[M+H]^+$.

C. (857C)

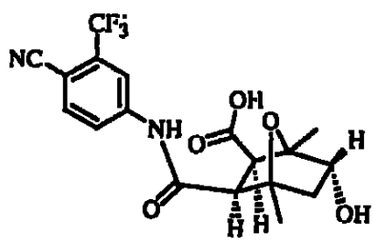
El compuesto 857B (0.100 g, 0.26 mmol), MeI (0.163 mL, 2.6 mmol), Ag_2O (0.603 g, 2.60 mmol) y acetonitrilo (2.5 mL) se agregaron a un recipiente de reacción de alta presión. El recipiente se selló y calentó hasta 75°C. Después de 16 h, la reacción se enfrió hasta temperatura ambiente, se diluyó con EtOAc y se filtró a través de celite, enjuagando con EtOAc. El material crudo se purificó por cromatografía instantánea sobre sílice, que se eluye con 0-5-8% acetona en cloroformo para dar el compuesto 857C como un sólido blanco. CLAR: 90% a 2.887 min (tiempo de retención) (Columna YMC S5 ODS-A de 4.6 x 50 mm se eluye con 10-90% metanol acuoso durante 4 min, contiene 0.2% ácido fosfórico, 4 mL/min, observando a 220

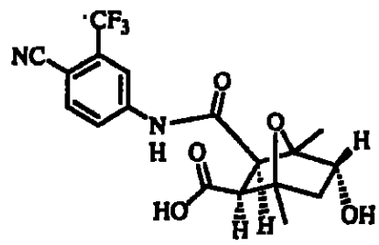
nm). EM (ES): m/z 395.07 $[M+H]^+$. La estereoquímica absoluta del compuesto 857C no se ha establecido. Aunque el compuesto representa un antípodo sencillo, la nomenclatura y estructura mostradas no reflejan la estereoquímica absoluta del compuesto.

Ejemplo 858



A. (858Ai y 858Aii)





El compuesto 857B (2.50 g, 6.57 mmol) se disolvió en THF (10.0 mL) a 22°C y se agregó NaOH 1N (10.0 mL). Después de 1 h, se agregaron THF (10.0 mL), HCl 1N (1.10 mL) y salmuera (10.0 mL). La mezcla después se extrajo una vez con EtOAc (20.0 mL) y dos veces con 1:1 THF/EtOAc (20.0 mL). Los compuestos orgánicos combinados se secaron sobre $MgSO_4$ anhidro, se filtraron y concentraron in vacuo para dar los compuestos 858Ai y 858Aii (1:1 por CLAR) como un sólido blanco. No fue necesaria la purificación. CLAR: 100% a 2.383 y 2.573 min (tiempo de retención) (Columna YMC S5 ODS-A de

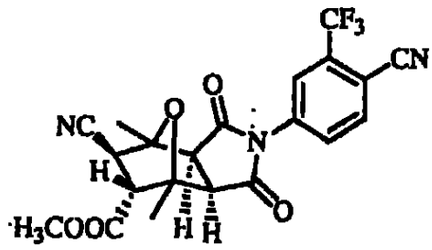
4.6 x 50 mm se eluye con 10-90% metanol acuoso durante 4 min, contiene 0.2% ácido fosfórico, 4 mL/min, observando a 220 nm).

B. (858B)

Los compuestos 858Ai y 858Aii se suspendieron en una mezcla de THF (50.0 mL) y AcOH (20.0 mL) y se calentaron hasta 60°C por 16 h. La reacción se hizo homogénea después de 4 h. La reacción se enfrió hasta 22°C y se concentró in vacuo. Se agregó después tolueno (20.0 mL) y la mezcla se calentó hasta 90°C por 4 h hasta que todo el producto fue disuelto. La mezcla después se enfrió hasta 22°C y se dejó reposar por 20 h. El compuesto 858B se precipita de la solución durante el periodo de 20 h. El producto se filtró y se enjuagó con tolueno seguido por secado in vacuo. El compuesto 858B (1.10 g) se aisló como un sólido blanco descolorido y se usó sin purificación adicional. ^{1}H RMN(DMSO-d_6): δ = 4.91 (d, 1H, J = 6.2 Hz), 3.97 (dd, 1H, J = 3.9, 6.2 Hz), 3.82 (d, 1H, J = 7.6 Hz), 3.31 (d, 1H, J = 7.6 Hz), 2.27 (dd, 1H, J = 10.2, 12.8 Hz), 1.77 (s, 3H), 1.49 (m, 1H) y 1.47 ppm (s, 3H). La estereoquímica absoluta del compuesto 858B no se ha establecido. Aunque el compuesto representa un antípodo sencillo, la nomenclatura y estructura mostradas no reflejan la estereoquímica absoluta del compuesto.

Ejemplo 859

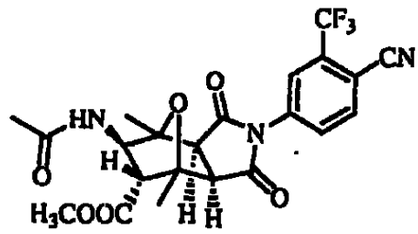
Ester de metilo del ácido (3aα,4β,5α,6β,7β,7aα)-2-(4-Ciano-3-(trifluorometil)fenil)hexahidro-6-ciano-4,7-dimetil-1,3-dioxo-4,7-epoxi-1H-isoindol-5-carboxílico (859)



Una mezcla del compuesto 792A (84 mg; 0.2 mmol), KCN (15 mg; 0.22 mmol) y cloruro de amonio (12 mg; 0.22 mmol) en 1 ml de DMF y 0.25 ml de agua se agitó a temperatura ambiente por 18 hr. Se formó un precipitado al reposar durante la noche. Después de agregar 10 ml adicionales de agua, la suspensión se filtró y la torta filtro se lavó con agua. El secado y trituración con hexano produjo el compuesto 859 (25 mg, 28%) como a un polvo color marrón. CLAR: 95% a 1.67 min (tiempo de retención) (Columna Phenominex S5 ODS 4.6 x 50 mm se eluye con 10-90% metanol acuoso durante 2 min, contiene 0.1% TFA, 4 mL/min, observando a 254 nm); EM (ES): m/z 448.29 $[M+H]^+$. El compuesto 859 representa una mezcla racémica de antípodos. La nomenclatura y estructura mostradas no reflejan la estereoquímica absoluta del compuesto.

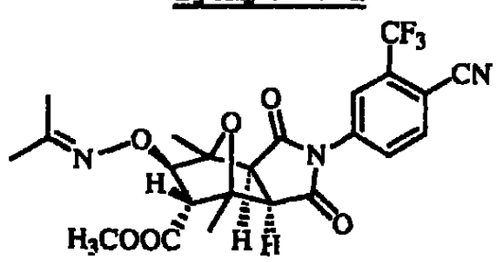
1345

Ejemplo 860



Una mezcla del compuesto 792A (44 mg; 0.1 mmol) y anhidrido acético (0.25 ml) se calentó hasta 60°C por 2 hr. Los compuestos volátiles se separaron in vacuo y el residuo se co-evaporó del heptano (3 x 2 ml) para resultar el compuesto 860 (47 mg, 99%) como un polvo blanco. CLAR: 95.8% a 1.49 min (tiempo de retención) (Columna Phenominex S5 ODS 4.6 x 50 mm se eluye con 10-90% metanol acuoso durante 2 min, contiene 0.1% TFA, 4 mL/min, observando a 254 nm); EM (ES): m/z 480.35 $[M+H]^+$. El compuesto 860 representa una mezcla racémica de antípodos. La nomenclatura y estructura mostradas no reflejan la estereoquímica absoluta del compuesto.

Ejemplo 861

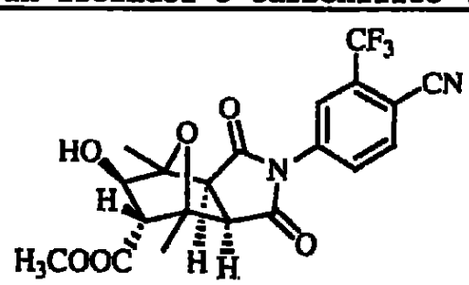


Se agregó hidruro de sodio, 60% en aceite mineral (120 mg; 3 mmol) en porciones durante 10 min a una solución del compuesto 792A (1.9 g; 4.5 mmol) y acetona oxima (667 mg; 9

mmol) en THF a temperatura ambiente. Después de agitación por 45 min, la mezcla de reacción se dividió entre salmuera (100 ml) y EtOAc (150 ml). La capa orgánica se lavó con salmuera (50 ml), se secó ($MgSO_4$) y se concentró in vacuo. El residuo se cromatografió sobre una columna de 5 x 20 cm de gel de sílice, se eluye con 1000 ml de 25% EtOAc/hexano y 500 ml de 40% EtOAc/hexano. La concentración de las fracciones puras in vacuo produjo el compuesto 861 (1.75 g, 80%) como un polvo blanco. CLAR: 98% a 1.82 min (tiempo de retención) (Columna Phenominex S5 ODS 4.6 x 50 mm se eluye con 10-90% metanol acuoso durante 2 min, contiene 0.1% TEA, 4 mL/min, observando a 254 nm); EM (ES): m/z 494.05 $[M+H]^+$. El compuesto 861 representa una mezcla racémica de antípodos. La nomenclatura y estructura mostradas no reflejan la estereoquímica absoluta del compuesto.

Ejemplo 862

Ester de metilo del ácido (3aα,4β,5α,6β,7β,7aα)]-2-(4-Ciano-3-(trifluorometil)fenil)-hexahidro-6-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-1H-isoindol-5-carboxílico (862)

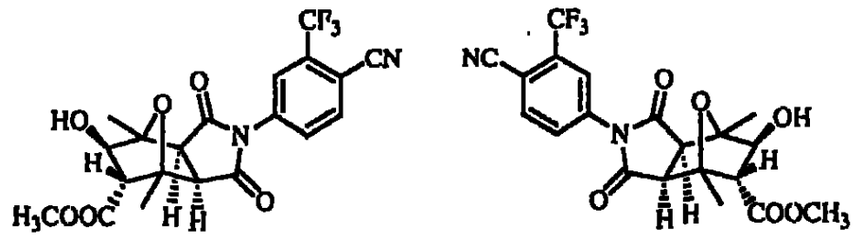


Una mezcla del compuesto 861 (1.75 g; 3.5 mmol) y polvo de zinc (6.07 g, 87.50 mA) en 19 ml de ácido fórmico se puso a reflujo por 20 min. Después de enfriar a temperatura ambiente, la mezcla de reacción se diluyó con ~50 ml de EtOAc y se filtró a través de celite. El filtrado se diluyó con ~200 ml de EtOAc y la capa orgánica se lavó con agua (200 ml), NaOH 0.5 M (2 x 200 ml), agua (200 ml) y salmuera (100 ml). El secado sobre $MgSO_4$ y la concentración in vacuo dio un residuo que se cromatografió en una columna de 2.5 x 20 cm de gel de sílice, se eluye con 1000 ml de 40% EtOAc/hexano y 500 ml de 50% EtOAc/hexano. La concentración de las fracciones puras in vacuo produjo el compuesto 862 (820 g, 54%) como una espuma incolora. CLAR: 99% a 1.47 min (tiempo de retención) (Columna Phenominex S5 ODS 4.6 x 50 mm se eluye con 10-90% metanol acuoso durante 2 min, contiene 0.1% TFA, 4 mL/min, observando a 254 nm); EM (ES): m/z 438.99 $[M+H]^+$. Compuesto 862 representa una mezcla racémica de antípodos. La nomenclatura y estructura mostradas no reflejan la estereoquímica absoluta del compuesto.

Ejemplo 863

Ester de metilo del ácido [3aS-(3aα,4β,5α,6β,7β,7aα)]-2-(4-Ciano-3-trifluorometil)fenil)-hexahidro-6-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-1H-isoindol-5-carboxílico (863i)

y éster de metilo del ácido [3aS-(3aα,4β,5α,6β,7β,7aα)]-2-(4-Ciano-3-trifluorometil)fenil)-hexahidro-6-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-1H-isoindol-5-carboxílico (863ii)



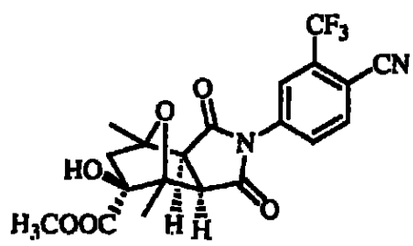
El compuesto racémico 862 (0.8 g) se separó en sus enantiómeros por CLAR quiral preparativa de fase normal (columna CHIRALPAK OD 5 x 50 cm; se eluye con 15% EtOH en hexanos (isocrática) a 50 mL/min) para dar 355 mg del compuesto de elución más rápida 863i (CLAR quiral: 8.89 min; columna CHIRALPAK OD 4.6 x 250 mm; se eluye con 15% EtOH en hexanos a 2 mL/min); CLAR: 99% a 2.91 min (tiempo de retención) (Columna YMC S5 ODS 4.6 x 50 mm se eluye con 10-90% metanol acuoso durante 2 min, contiene 0.2% ácido fosfórico, 4 mL/min, observando a 220 nm); EM (ES): m/z 471.00 $[M+MeOH]^+$ y 330 mg de el compuesto de elución más lenta 863ii (CLAR quiral: 12.30 min; columna CHIRALPAK OD 4.6 x 250 mm; se eluye con 15% EtOH en hexanos a 2 mL/min); CLAR: 99% a 2.89 min (tiempo de retención) (Columna YMC S5 ODS 4.6 x 50 mm se eluye con 10-90% metanol acuoso durante 2 min, contiene 0.2% ácido fosfórico, 4 mL/min, observando a 220 nm); EM (ES): m/z 471.99 $[M+MeOH]^+$. La estereoquímica absoluta de los compuestos 863i y 863ii no se ha establecido.

1329

Aunque cada compuesto representa un antípodo sencillo, la nomenclatura y estructura mostradas no reflejan la estereoquímica absoluta del compuesto.

Ejemplo 864

Ester de metilo del ácido (3aα,4β,5α,7β,7aα)-2-(4-Ciano-3-(trifluorometil)fenil)-hexahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-1H-isoindol-5-carboxílico (864)

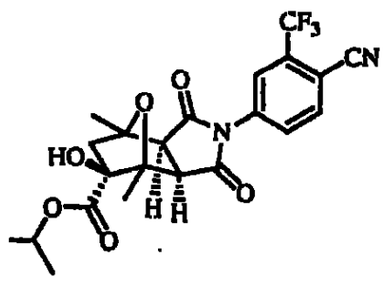


Una mezcla del compuesto 792A (210 mg; 0.5 mmol), fenilsilano (0.13 ml, 1 mmol) y $Mn(acac)_2$ (5mg; 0.01 mmol) en 2.5 ml de isopropanol y 0.25 ml de THF se agitó 3 días a temperatura ambiente en aire abierto. Después de agregar 5% de bisulfito de sodio (5 ml) y agitación por 30 min, la mezcla de reacción se dividió entre EtOAc (30 ml) y agua (30 ml). El lavado de la capa orgánica con salmuera (20 ml), seguido por el secado sobre $MgSO_4$ y la concentración in vacuo, produjo un residuo que se cromatografió sobre una columna de 2.5 x 15 cm de gel de sílice, se eluye con 50%EtOAc/hexano. La concentración de las fracciones puras in vacuo, produjo el compuesto 864 (109 mg, 50%) como un polvo blanco. CLAR: 98.6% a 1.18 min (tiempo de retención) (Columna

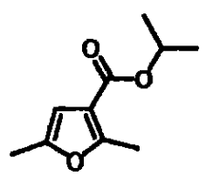
Phenominex S5 ODS 4.6 x 50 mm se eluye con 10-90% metanol acuoso durante 2 min, contiene 0.1% TFA, 4 mL/min, observando a 254 nm); EM (ES): m/z 438.98 $[M+H]^+$. El compuesto 864 representa una mezcla racémica de antípodos. La nomenclatura y estructura mostradas no reflejan la estereoquímica absoluta del compuesto.

Ejemplo 865

Ester de (1-metiletilo) del ácido (3aα,4β,5α,7β,7aα)-2-(4-Ciano-3-(trifluorometil)fenil)hexahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-1H-isoindol-5-carboxílico (865C)



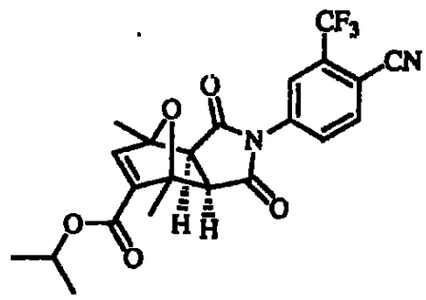
A. éster de isopropilo del ácido 2,5-Dimetil-furan-3-carboxílico (865A)



Se agregó isopropanol (5 ml) a una solución de cloruro de 2,5-dimetilfuran-3-carbonilo (1.64 g; 10.3 mmol) en 15 ml de cloruro de metileno a temperatura ambiente. Después de permitir que la mezcla de reacción reposara a temperatura ambiente por 30 minutos, los compuestos volátiles se

separaron in vacuo y el residuo se co-evaporó del isopropanol para resultar el compuesto 865A (1.8 g, 96%) como un líquido color ámbar claro. ^{1}HRMN ($CDCl_3$): δ 1.30 (d, j= 6.5 Hz, 6H), 2.23 (s, 3H), 2.52 (s, 3H), 5.14 (m, 1H), 6.21 (s, 1H).

B. éster de (1-metiletilo) del ácido (3aα,4β,7β,7aα)-2-(4-Ciano-3-(trifluorometil)fenil)tetrahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-1H-isoindol-5-carboxílico (865B)



Una mezcla de 4-(2,5-dihidro-2,5-2,5-dioxo-1H-pirrol-1-il)-2-trifluorometil-benzonitrilo (851 mg; 3.2 mmol) y compuesto 865A (1.7 g; 9.4 mmol) se calentó hasta 140°C por 4 h. Después de permitir a la mezcla enfriar a temperatura ambiente y reposar 4 días, la mezcla de reacción se cromatografió sobre una columna de 5 x 25 cm de gel de sílice, que se eluye con 25% EtOAc/hexano. La concentración de las fracciones puras in vacuo produjo el compuesto 865B (869 mg, 60%) como un aceite amarillo espeso. Debido a la inestabilidad de este compuesto, se almacenó a -20C y se usó rápidamente.

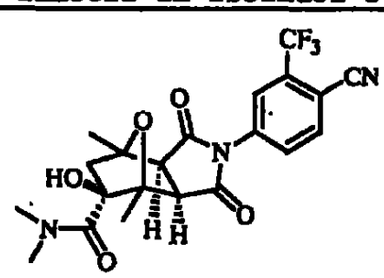
C. éster de (1-metiletilo) del ácido (3aα,4β,5α,7β,7aα)-2-(4-Ciano-3-(trifluorometil)fenil)hexahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-1H-isoindol-5-carboxílico (865C)

El compuesto 865B (224; 0.5 mmol) se convirtió al compuesto 865C usando el procedimiento descrito en el ejemplo 791B para resultar el compuesto 865C (82 mg, 35%) como un polvo blanco. CLAR: 98.4% a 1.18 min (tiempo de retención) (Columna Phenominex S5 ODS 4.6 x 50 mm se eluye con 10-90% metanol acuoso durante 2 min, contiene 0.1% TFA, 4 mL/min, observando a 254 nm); EM (ES): m/z 466.98 $[M+H]^+$.

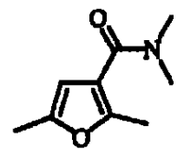
El compuesto 865 C representa una mezcla racémica de antípodos. La nomenclatura y estructura mostradas no reflejan la estereoquímica absoluta del compuesto.

Ejemplo 866

(3aα,4β,5α,7β,7aα)-2-[4-Ciano-3-(trifluorometil)fenil)hexahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-N,N-dimetil-1H-isoindol-5-carboxamida (866C)

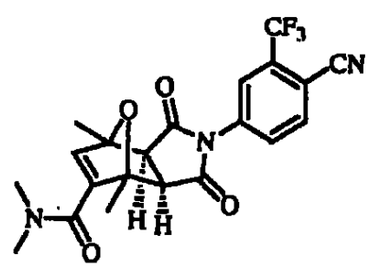


A. dimetilamida del ácido 2,5-Dimetil-furan-3-carboxílico (866A)



Una solución de cloruro de 2,5-dimetilfuran-3-carbonilo (2.19 g; 13.8 mmol) en 10 ml de THF se agregó a una solución 2M de dimetilamina en dioxano (21 ml; 42 mmol) en 80 ml de THF a temperatura ambiente. Después de agitación por 1 hr, los compuestos volátiles se separaron in vacuo y el residuo se dividió entre EtOAc (100 ml) y agua (100 ml). La capa orgánica se lavó con solución saturada de bisulfato de potasio (100 ml), NaOH 1N (50 ml) y salmuera (50 ml). El secado sobre $MgSO_4$ y la concentración in vacuo produjo el compuesto 866A (1.84 g, 80%) como un líquido color ámbar. ^{1}HRMN ($CDCl_3$): δ 2.23 (s, 3H), 2.33 (s, 3H), 3.04 (s, 6H), 5.96 (s, 1H).

B. (866B)



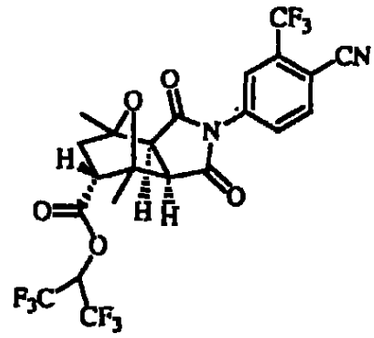
Una mezcla de 4-(2,5-dihidro-2,5-2,5-dioxo-1H-pirrol-1-il)-2-trifluorometil-benzonitrilo (1.45 mg; 5.4 mmol) y compuesto 866A (1.82 g; 10.9 mmol) se calentó puro hasta 125°C por 1 hr. Después de dejar a la mezcla enfriar a

temperatura ambiente durante la noche, la mezcla de reacción se disolvió en ~75 ml de EtOAc. El tratamiento con carbón decolorante, filtración a través de celite y la concentración in vacuo del filtrado dio un residuo que se disolvió en ~20 ml de éter de etilo. La adición de ~30 ml de hexano, seguida por filtración y secado produjo el compuesto 866B (1.89 g, 81%) como un sólido color rosa claro.

C. (3aα,4β,5α,7β,7aα)-2-(4-Ciano-3-(trifluorometil)fenil)hexahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-N,N-dimetil-1H-isoindol-5-carboxamida (866C)

El compuesto 866B (433; 1 mmol) se convirtió al compuesto 866C usando el procedimiento descrito en el ejemplo 792B para resultar el compuesto 866C (85 mg, 18%) como un polvo blanco. CLAR: 97.9% a 1.39 min (tiempo de retención) (Columna Phenominex S5 ODS 4.6 x 50 mm se eluye con 10-90% metanol acuoso durante 2 min, contiene 0.1% TFA, 4 mL/min, observando a 254 nm); EM (ES): m/z 452.00 $[M+H]^+$. El compuesto 866C representa una mezcla racémica de antípodos. La nomenclatura y estructura mostradas no reflejan la estereoquímica absoluta del compuesto.

Ejemplo 867

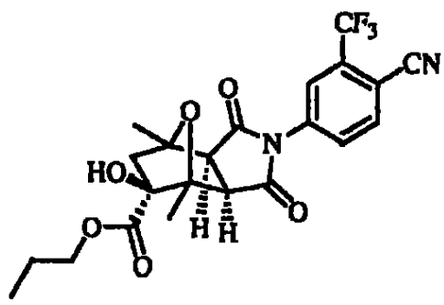


Una gota de DMF se agregó a una solución del compuesto 792B (50 mg; 0.125 mmol) y cloruro de oxalilo (0.03 ml; 0.36 mmol) en cloruro de metileno (1 ml) a temperatura ambiente. Después de agitación 1.5 h a temperatura ambiente, los compuestos volátiles se separaron in vacuo. El residuo se trató con 1 ml de 1,3-hexafluoro-2-propanol, seguido por 0.04 ml de piridina y 2 mg de 4-dimetilpiridina. Después de agitación por 18 h a temperatura ambiente la mezcla de reacción se dividió entre EtOAc (20 ml) y solución de bicarbonato de sodio saturado (20 ml). La capa orgánica se lavó con solución saturada de bisulfato de potasio (20 ml) y salmuera (20 ml). El secado sobre $MgSO_4$ y la concentración in vacuo produjo un residuo que se cromatografió sobre una columna de 2.5 x 15 cm de gel de sílice, que se eluye con 25%EtOAc/hexano. La concentración de las fracciones puras in vacuo produjo el compuesto 867 (36 mg, 52%) como un sólido blanco. CLAR: 99% a 1.96 min (tiempo de retención) (Columna Phenominex S5 ODS 4.6 x 50 mm se eluye con 10-90% metanol

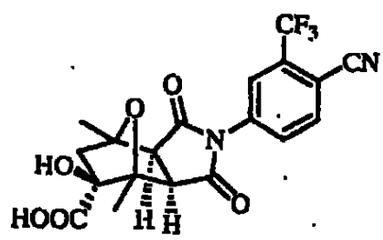
acuoso durante 2 min, contiene 0.1% TFA, 4 mL/min, observando a 254 nm); EM (ES): m/z 558.00 $[M+H]^+$. El compuesto 867 representa una mezcla racémica de antípodos. La nomenclatura y estructura mostradas no reflejan la estereoquímica absoluta del compuesto.

Ejemplo 868

Éster de propilo del ácido (3aα,4β,5α,7β,7aα)-2-(4-Ciano-3-(trifluorometil)fenil)hexahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-1H-isoindol-5-carboxílico (868B)



A ácido (3aα,4β,5α,7β,7aα)-2-(4-Ciano-3-(trifluorometil)fenil)hexahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-1H-isoindol-5-carboxílico (868A)



Se agregó NaOH 1N (2.2 ml; 2.2 mmol) a una solución del compuesto 867 (238 mg; 0.54 mmol) en 5 ml de metanol a

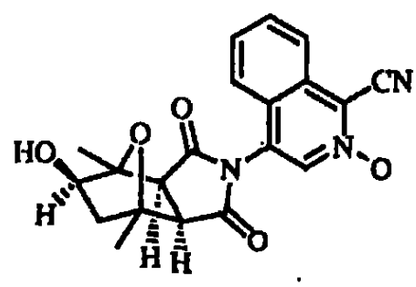
temperatura ambiente. Después de agitación por 5 h a temperatura ambiente, los compuestos volátiles se separaron in vacuo y el residuo se trató con 2 ml de ácido trifluoroacético por 18 hr. La concentración de la mezcla de reacción in vacuo, seguida por co-evaporación del tolueno (3 x 8 ml) dio un residuo que se dividió entre EtOAc (40 ml) y salmuera (20 ml). El secado sobre $MgSO_4$ y la concentración in vacuo produjo el sólido que se trituró con hexano para resultar el compuesto 868A (120 mg, 53%) como un sólido de color crema. CLAR: 93% a 1.35 min (tiempo de retención) (Columna Phenominex S5 ODS 4.6 x 50 mm se eluye con 10-90% metanol acuoso durante 2 min, contiene 0.1% TFA, 4 mL/min, observando a 254 nm); EM (ES): m/z 425.08 $[M+H]^+$.

B. éster de propilo del ácido (3aα,4β,5α,7β,7aα)-2-(4-Ciano-3-(trifluorometil)fenil)hexahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-1H-isoindol-5-carboxílico (868B)

Se agregó cloruro de oxalilo (0.18 ml, 2 mmol) a una solución del compuesto 868A (135 mg; 0.32 mmol) en 4 ml de THF a temperatura ambiente. Se observó inmediatamente el burbujeo. Se agregó una gota de DMF y la mezcla de reacción se agitó 4 hrs. Después de agregar 2 ml de n-propanol y agitación por 18 h a temperatura ambiente, la mezcla de reacción se dividió entre EtOAc (30 ml) y agua (30 ml). La capa orgánica se lavó con solución de bicarbonato de sodio

saturado (30 ml), se secó sobre $MgSO_4$ y se concentró in vacuo. El residuo se cromatografió sobre una columna de 2.5 x 15 cm de gel de sílice, se eluye con 25% EtOAc/hexano. Las fracciones puras se concentraron in vacuo para resultar el compuesto 868B (78 mg, 52%) como un polvo blanco. CLAR: 95.4% a 1.63 min (tiempo de retención) (Columna Phenominex S5 ODS 4.6 x 50 mm se eluye con 10-90% metanol acuoso durante 2 min, contiene 0.1% TFA, 4 mL/min, observando a 254 nm); EM (ES): m/z 467.10 $[M+H]^+$. El compuesto 868B representa una mezcla racémica de antípodos. La nomenclatura y estructura mostradas no reflejan la estereoquímica absoluta del compuesto.

Ejemplo 869

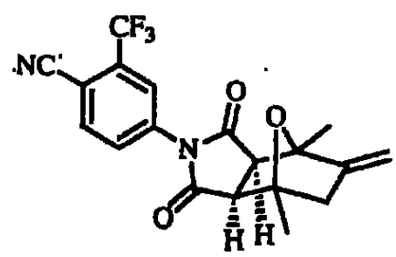


Se agregó peróxido de hidrógeno al 30% (0.1 ml) a una solución del compuesto 748 (36 mg; 0.1 mmol) en 1 ml de AcOH a 100 C. Se agregaron cuatro alícuotas adicionales de 0.1 ml de peróxido de hidrógeno al 30% en intervalos de 30 min a la mezcla de reacción. Se agregó agua (8 ml) a la mezcla de reacción 30 minutos después de la última adición de peróxido de hidrógeno al 30%. Después de enfriar a temperatura

ambiente y reposar 2 días, la suspensión resultante se filtró y la torta filtro se lavó con agua. Después de secar, el sólido se disolvió en ~2 ml de acetona y la solución se aplicó a una placa de cromatografía preparativa de capa delgada en SiO_2. La elución con 30% acetona/cloroformo, la extracción de la banda más polar, filtración y la concentración produjeron el compuesto 869 (6 mg, 16%) como un sólido blanco descolorido. CLAR: 99% a 1.06 min (tiempo de retención) (Columna Phenominex S5 ODS 4.6 x 50 mm se eluye con 10-90% metanol acuoso durante 2 min, contiene 0.1% TFA, 4 mL/min, observando a 254 nm); EM (ES): m/z 380.43 $[M+H]^+$.

El compuesto 869 representa una mezcla racémica de antípodos. La nomenclatura y estructura mostradas no reflejan la estereoquímica absoluta del compuesto.

Ejemplo 870

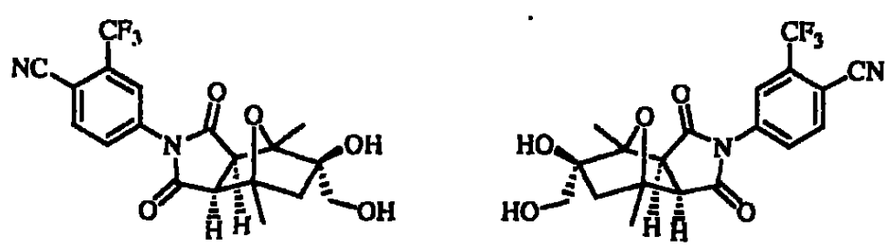


Una mezcla racémica del compuesto 852Di y 852Dii (150 mg, 0.38 mmol) se disolvió en THF (2 mL) bajo nitrógeno y se agregó 2-nitrofenil selenocianato (202 mg, 0.89 mmol) seguido por PBu_3 (0.22 mL, 0.89 mmol). La mezcla resultante se agitó por 20 h, concentró y se purificó por cromatografía

instantánea con 0 hasta 100% de EtOAc en hexanos. El producto resultante se disolvió en THF (11 mL) y se trató con 2 mL de 30% H_2O_2 a 0°C. La mezcla de reacción se agitó por 10 min, después se entibió a temperatura ambiente y se agitó durante la noche. La reacción se apagó por la adición de una solución al 5% de $Na_2S_2O_3$ y salmuera. Las capas se separaron y la capa acuosa se extrajo 2X con CH_2Cl_2. Las capas orgánicas combinadas se secaron sobre $MgSO_4$, se concentraron in vacuo y se purificaron por cromatografía instantánea con 0 hasta 100% de EtOAc en hexanos para dar el compuesto 870 (114 mg, 80%) como un sólido amarillo. CLAR: 100% a 3.67 min (tiempo de retención) (Columna YMC S5 ODS-A de 4.6 x 50 mm Ballistic, 10-90% metanol acuoso durante 4 min, contiene 0.2% H_3PO_4, 4 mL/min, observando a 220 nm). EM (ES): m/z 375.23 $[M-H]^-$. El compuesto 870 representa una mezcla racémica de antípodos. La nomenclatura y estructura mostradas no reflejan la estereoquímica absoluta del compuesto.

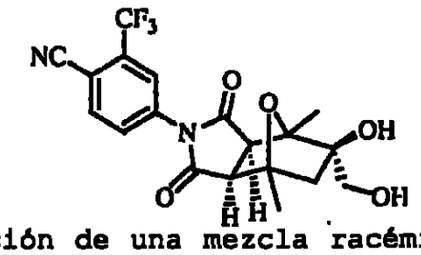
Ejemplo 871

(871Bi y 871Bii)



1341

A. (871A)



A una solución de una mezcla racémica de los compuestos 852Di y 852Dii (33 mg, 0.09 mmol) en 0.5 mL acetona/0.4 mL agua, se agregó una solución al 50% en peso de NMO en agua (22 µL, 0.11 mmol) seguido por una solución al 4% en peso de OsO_4 en agua (54 µL, 8.7 µmol). La mezcla resultante se agitó por 12 h y la reacción se apagó por la adición de una solución al 5% de $Na_2S_2O_3$. Se agregó CH_2Cl_2, las capas se separaron y la capa acuosa se extrajo con CH_2Cl_2. Las capas orgánicas combinadas se secaron sobre $MgSO_4$, concentraron in vacuo y se purificaron por CCD preparativa de SiO_2 con 40% de acetona en CH_2Cl_2 para dar el compuesto racémico 871A (30 mg, 83%) como un sólido blanco. CLAR: 100% a 2.91 min (tiempo de retención) (Columna YMC S5 ODS-A de 4.6 x 50 mm Ballistic, 10-90% metanol acuoso durante 4 min, contiene 0.2% H_3PO_4, 4 mL/min, observando a 220 nm). EM (ES): m/z 469.26 [M+OAc]. El compuesto 871A representa una mezcla racémica de antípodos. La nomenclatura y estructura mostradas no reflejan la estereoquímica absoluta del compuesto.

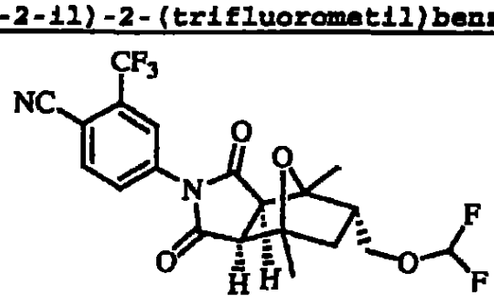
1342

B. (871Bi y 871Bii)

El compuesto racémico 871A se separó en sus enantiómeros por CLAR quiral preparativa de fase normal (columna CHIRALPAK OJ 5 x 50 cm; se eluye con 30% MeOH/EtOH (1:1) en heptano (isocrático) a 50 mL/min) para dar el compuesto antípodo de elución más rápida 871Bi (CLAR quiral: 7.35 min; columna CHIRALPAK OJ 4.6 x 250 mm; se eluye con 30% MeOH/EtOH (1:1) en heptano a 1 mL/min) y el compuesto antípodo de elución más lenta 871Bii (CLAR quiral: 11.49 min; columna CHIRALPAK OJ 4.6 x 250 mm, se eluye con 30% MeOH/EtOH (1:1) en heptano a 1 mL/min). La estereoquímica absoluta de los compuestos 871Bi y 871Bii no se ha establecido. Aunque cada compuesto representa un antípodo sencillo, La nomenclatura y estructura mostradas no reflejan la estereoquímica absoluta del compuesto.

Ejemplo 872

(3aα,4β,5α,7β,7aα)-4-(Octahidro-5-[[[difluorometil]oxi]metil]-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo(872)

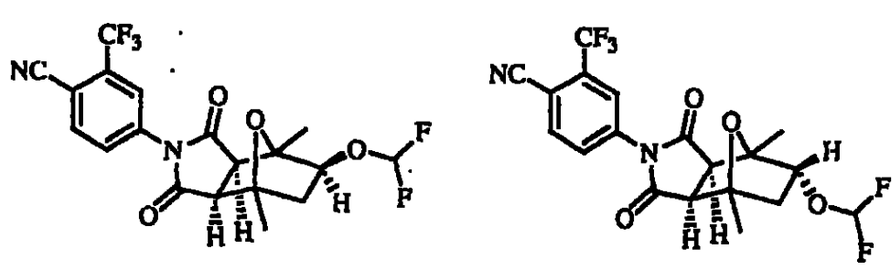


Una mezcla racémica de los compuestos 852Di y 852Dii (50 mg, 0.13 mmol) fue disuelta bajo nitrógeno en 1 mL de CH_3CN y

se agregó CuI (2 mg, 8.9 μmol). Esta mezcla se calentó hasta 45°C y se agregó ácido 2-(fluorosulfonil)difluoroacético (27 mg, 0.15 mmol) por medio de una jeringa. La mezcla de reacción se agitó por 1.5 h a 45°C y después se dejó enfriar a temperatura ambiente. La reacción se apagó por la adición de agua y CH_2Cl_2. Las capas se separaron y la capa acuosa se extrajo con CH_2Cl_2. Las fases orgánicas combinadas se secaron sobre $MgSO_4$, se concentraron in vacuo y purificaron dos veces por cromatografía instantánea sobre SiO_2 con 0 hasta 100% de EtOAc en hexanos para resultar el compuesto 872 (10 mg, 18%) como una espuma blanca. CLAR: 92% a 3.72 min (tiempo de retención) (Columna YMC S5 ODS-A de 4.6 x 50 mm Ballistic, 10-90% metanol acuoso durante 4 min, contiene 0.2% H_3PO_4, 4 mL/min, observando a 220 nm). EM (ES): m/z 443.22 $[M-H]^-$. El compuesto 872 representa una mezcla racémica de antípodos. La nomenclatura y estructura mostradas no reflejan la estereoquímica absoluta del compuesto.

Ejemplo 873

(873i y 873ii)

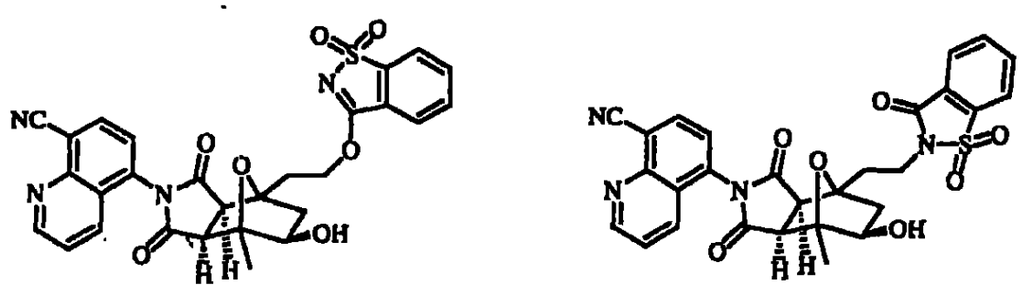


1342

El compuesto 471Di (50 mg, 0.13 mmol), CuI (2 mg, 8.9 μmol) y ácido 2-(fluorosulfonil)difluoroacético (28 mg, 0.16 mmol) reaccionaron en 1 mL de CH_3CN y se purificaron como se describe en el ejemplo 872. Los compuestos 873i y 873ii (15 mg, 0.03 mmol) se obtuvieron como una mezcla inseparable 6:1 como se determina por ^{1}H-RMN. CLAR: 91% a 3.64 min (tiempo de retención) (Columna YMC S5 ODS-A de 4.6 x 50 mm Ballistic, 10-90% metanol acuoso durante 4 min, contiene 0.2% H_3PO_4, 4 mL/min, observando a 220 nm). EM (ES): m/z 489.22 $[M+OAc]^-$. Los compuestos 873i y 873ii representan cada uno, una mezcla racémica de antípodos. La nomenclatura y estructura mostradas no reflejan la estereoquímica absoluta del compuesto.

Ejemplo 874

(874i y 874ii)



Trifenilfosfina (0.067g, 0.254 mmol) y di-tert-butil-azodicarboxilato (0.059g, 0.254 mmol) en THF (1 mL) se agitaron a temperatura ambiente bajo N_2 por 10 min, después se agregó sacarina (0.047g, 0.254 mmol). La mezcla de reacción se agitó bajo N_2 por otros 15 min, seguido por la

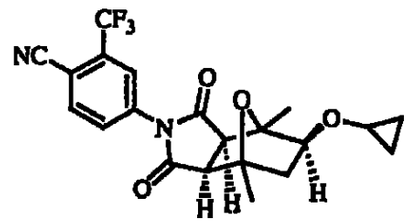
1345

adición del compuesto 429i (0.050g, 0.127 mmol). La reacción se dejó avanzar por 24 h, punto en el cual se agregó CH_2Cl_2 (15 mL). La capa orgánica se aisló y después se lavó consecutivamente con NaOH 1N (15 mL), salmuera (15 mL) y se secó sobre $MgSO_4$ y se concentró in vacuo. El sólido resultante se purificó por CCD preparativa de SiO_2, que se eluye con 25% de acetona en $CHCl_3$, para dar el compuesto 874i (18 mg, 25%) como un sólido blanco (CLAR: 91% a 2.96 min (tiempo de retención) (columna YMC S-5 ODS-A, 4.6 x 50 mm, se eluye con 10-90% metanol acuoso durante 4 min conteniendo 0.2% ácido fosfórico, 4 mL/min, observando a 220 nm). EM (ESI): m/z 559.42 $[M+H]^+$) y compuesto 874ii (18 mg, 25%) como un sólido blanco (CLAR: 93% a 2.85 min (tiempo de retención) (columna YMC S-5 ODS-A, 4.6 x 50 mm, se eluye con 10-90% metanol acuoso durante 4 min conteniendo 0.2% ácido fosfórico, 4 mL/min, observando a 220 nm). EM (ESI): m/z 557.12 $[M-H]^-$). La estereoquímica absoluta de los compuestos 874i y 874ii no se ha establecido. Aunque cada compuesto representa un antípodo sencillo, la nomenclatura y estructura mostradas no reflejan la estereoquímica absoluta del compuesto.

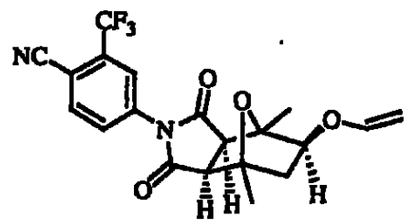
1346

Ejemplo 875

[3aR-(3aα,4β,5β,7β,7aα)]-4-(Octahidro-5-ciclopropiloxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo (875A)



A. (875A)

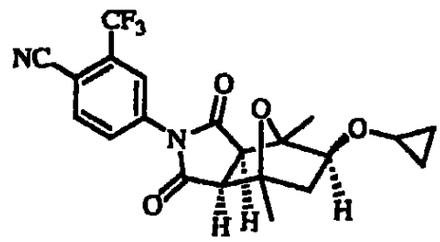


Una solución del compuesto 471Di (300 mg, 0.79 mmol), trifluoroacetato mercúrico (17 mg, 0.04 mmol) en tetrahidrofurano (THF, 1.5 mL) y éter de etil vinilo (3 mL) en un tubo sellado de pared gruesa, se calentó hasta 45°C por 48 h. El tubo se enfrió y la mezcla de reacción se concentró in vacuo para dar un aceite. El material crudo se purificó por cromatografía instantánea por gel de sílice que se eluye con 1:4:4 EtOAc/cloruro de metileno/heptano para dar el compuesto 875A (115 mg, 36%) como un sólido blanco. CLAR: 99% a 3.80 min (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, se eluye con 10-90% metanol acuoso durante 4 min conteniendo 0.2% ácido fosfórico, 4 mL/min, observando a 220

1347

nm). EM (ES): m/z 407.09 $[M+H]^+$. La estereoquímica absoluta del compuesto 875A se establece por la estereoquímica conocida del compuesto intermediario 471Di y la retención de la configuración en ella. La estereoquímica absoluta es como se obtiene en la figura anterior y resulta de la nomenclatura.

B. [3aR-(3aα,4β,5β,7β,7aα)]-4-(Octahidro-5-ciclopropiloxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo(875B)

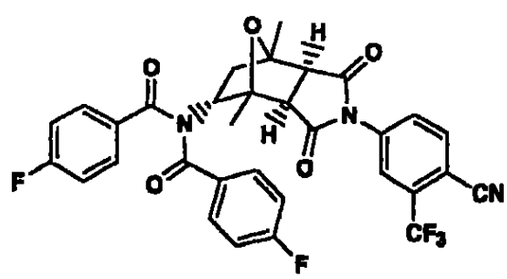


A una solución del compuesto 875A (100 mg, 0.25 mmol) en cloruro de metileno seco (5 mL) enfriado a 5°C, se agregó, gota a gota, una solución de dietilzinc (1.0 M en hexanos, 1.4 mL, 1.4 mmol). La mezcla de reacción se entibió hasta temperatura ambiente, después se introdujo diyodometano (80 mL, 1.0 mmol). Después de 3 h, la CLAR indicó que la reacción estaba 2/3 completa. Se agregaron sucesivamente dos porciones adicionales de dietilzinc y diyodometano, después la mezcla de reacción se enfrió en un baño de hielo, se apagó con agua, y se dividió entre una solución de HCl 1M (20 mL) y EtOAc (20 mL). La fase orgánica se separó, se secó sobre sulfato de

sodio, se concentró in vacuo y se purificó por cromatografía instantánea por gel de sílice que se eluye con 2:3 EtOAc/heptano para dar el compuesto 875B como un sólido blanco. CLAR: 100% a 3.72 min (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, se eluye con 10-90% metanol acuoso durante 4 min conteniendo 0.2% ácido fosfórico, 4 mL/min, observando a 220 nm). EM (ES): m/z 421.08 $[M+H]^+$. La estereoquímica absoluta del compuesto 875B se establece por la estereoquímica conocida del compuesto intermediario 471Di y la retención de la configuración en ella. La estereoquímica absoluta es como se obtiene en la figura anterior y resulta de la nomenclatura.

Ejemplo 876

(876)

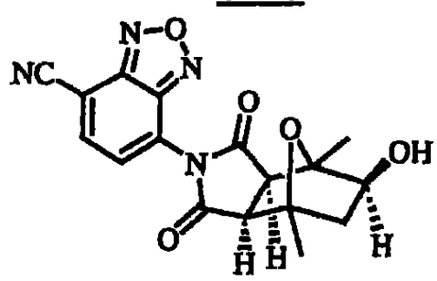


Una mezcla racémica de los compuestos 808 y 809 (0.057g, 0.15 mmol) se disolvió en 2 mL de CH_2Cl_2. Se agregaron trietilamina (0.018g, 0.18 mmol), una cantidad catalítica de DMAP, y cloruro de 4-fluorobenzoilo (0.075g, 0.48 mmol) y la reacción se agitó por 6 h. La mezcla de reacción se diluyó

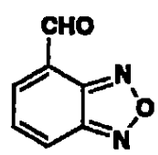
con CH_2Cl_2 y se lavó secuencialmente con HCl 1N, 10% K_2CO_3, y salmuera, se secaron sobre $MgSO_4$, se filtraron y concentraron in vacuo. El residuo se purificó por CCD preparativa sobre gel de sílice usando 2:1 EtOAc/hexanos como eluyente. La separación del solvente dio el compuesto 876 (0.066g, 70%) como un sólido blanco. CLAR: 100% a 3.94 min (Columna YMC S5 ODS) se eluye con 10-90% metanol acuoso conteniendo 0.2% ácido fosfórico durante un gradiente de 4 min observando a 220 nm. EM (ES): m/z 552.11 $[M+H]^+$.

Ejemplo 877

(877)



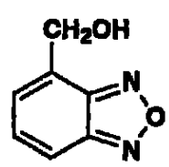
A. (877A)



Una solución 1.6 M de n-BuLi (54.6 mL, 87.4 mL) se agregó gota a gota a una solución de diisopropilamina (12.8 mL, 91.6 mmol) en THF (40 mL) a -20 °C. La mezcla de reacción se enfrió a -78 °C y se agregó una solución de benzofurazano (10.0 g, 83.3 mmol) en THF (34 mL) gota a gota. Después de agitación por 35 minutos, la mezcla se vació en una solución

de DMF (10.3 mL, 133.2 mmol) en THF (34 mL) a -78 °C y se agregó una solución de 3:1 H_2O:AcOH (80 mL). Después de agitación a temperatura ambiente por 12 h, se agregó tolueno (150 mL) y las capas se separaron. La capa orgánica se concentró hasta ~30 mL y se trituró con hexanos (150 mL). El sólido resultante se filtró y se enjuagó con hexanos. La purificación por cromatografía instantánea sobre gel de sílice que se eluye con 50% EtOAc/hexanos dio el compuesto 877A (7.77 g, 63%) como un sólido color marrón. CLAR: 99% a 1.22 min (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, se eluye con 10-90% metanol acuoso durante 4 min conteniendo 0.2% ácido fosfórico, 4 mL/min, observando a 220 nm). EM (ES): m/z 149.08 $[M+H]^+$.

B. (877B)



Se agregó $NaBH_4$ (2.00 g, 52.5 mmol) en porciones a una solución del compuesto 877A (7.77 g, 52.5 mmol) en MeOH (100 mL) a 0 °C. Después de 5 minutos, la mezcla se dividió entre H_2O (100 mL) y CH_2Cl_2 (100 mL). La capa acuosa se extrajo con EtOAc (2 X 100 mL) y las capas orgánicas combinadas se secaron ($MgSO_4$) y concentraron bajo presión reducida para dar el compuesto crudo 877B (7.55 g, 96%) que se tomó sin

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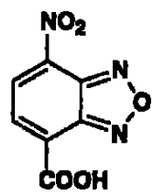
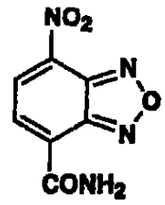
purificación. CLAR: 99% a 1.63 min (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, se eluye con 10-90% metanol acuoso durante 4 min conteniendo 0.2% ácido fosfórico, 4 mL/min, observando a 220 nm). EM (ES): m/z 133.05 $[M+H-H_2O]^+$.

C. (877C)



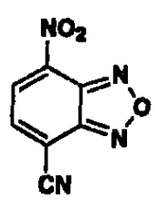
Se agregó HNO_3 fumante(4.25 mL, 100.58 mmol) gota a gota a una solución de compuesto crudo 877B (7.55 g, 50.29 mmol) en H_2SO_4 (50 mL) a 0 °C. La mezcla se agitó a temperatura ambiente por 20 minutos, se vació sobre hielo (1 L), se entibió a temperatura ambiente y después se extrajo con EtOAc (3 X 250 mL). Las capas orgánicas combinadas se secaron ($MgSO_4$) y concentraron bajo presión reducida. El sólido resultante se lavó con H_2O y se secó con aire para dar el compuesto 877C (6.0 g) como un sólido color naranja. Se recuperaron 2.7 g adicionales del lavado acuoso por extracción con EtOAc para un rendimiento total de 8.7 g (83%). CLAR: 99% a 1.63 min (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, se eluye con 10-90% metanol acuoso durante 4 min conteniendo 0.2% ácido fosfórico, 4 mL/min, observando a 220 nm). EM (ES): m/z 210.18 $[M+H]^+$.

D. (877D)



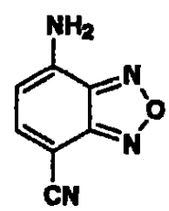
Se agregó urea (29.3 mg, 0.488 mmol) en porciones a una solución del compuesto 877C (100 mg, 0.488 mmol) en H_2SO_4 fumante (2 mL) a 50 °C con agitación vigorosa. La mezcla después se calentó hasta 100 °C por 30 minutos, se enfrió a temperatura ambiente y se vació sobre hielo (100 mL). La mezcla acuosa resultante se extrajo con EtOAc (3 X 50 mL) y las capas orgánicas combinadas se lavaron con H_2O (1 X 100 mL), se secaron ($MgSO_4$) y concentraron bajo presión reducida. La purificación por cromatografía instantánea sobre gel de sílice que se eluye con 50% EtOAc/hexanos dio el compuesto 877D (76.3 mg, 77%) como un sólido amarillo-naranja. CLAR: 96% a 1.39 min (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, se eluye con 10-90% metanol acuoso durante 4 min conteniendo 0.2% ácido fosfórico, 4 mL/min, observando a 220 nm). EM (ES): m/z 209.17 $[M+H]^+$.

E. (877E)



Una mezcla del compuesto 877D (1.01 mg, 4.85 mmol) y P_2O_5 (2.75 g, 9.70 mmol) en tolueno (24 mL) se puso a reflujo por 30 minutos. Se agregó H_2O (50 mL) y la mezcla resultante se extrajo con EtOAc (3 X 100 mL). Las capas orgánicas combinadas se secaron ($MgSO_4$) y concentraron bajo presión reducida para dar el compuesto 877E (0.90 g, 98%) como un sólido café que se llevó sin purificación. CLAR: 90% a 1.78 min (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, se eluye con 10-90% metanol acuoso durante 4 min conteniendo 0.2% ácido fosfórico, 4 mL/min, observando a 220 nm).

F. (877F)



Se agregó polvo de hierro (0.53 g, 9.47 mmol, malla 325) en una porción a una solución del compuesto 877E (0.90 g, 4.73 mmol) en AcOH (24 mL) a 70 °C. La reacción estuvo completa después de 30 minutos, como se calificó por CLAR. La mezcla se concentró bajo presión reducida, fue disuelta en EtOAC (50 mL) y se lavó con $NaHCO_3$ saturado (2 X 50 mL). La capa acuosa se extrajo con EtOAc (4 X 20 mL) y las capas orgánicas combinadas se secaron (Na_2SO_4) y concentraron bajo presión reducida. La purificación por cromatografía instantánea sobre gel de sílice que se eluye con 50%

EtOAc/hexanos dio el compuesto 877F (0.62 g, 82%) como un sólido color naranja obscuro. CLAR: 94% a 1.94 min (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, se eluye con 10-90% metanol acuoso durante 4 min conteniendo 0.2% ácido fosfórico, 4 mL/min, observando a 220 nm). EM (ES): m/z 161.00 $[M+H]^+$.

G. (877G)

Se cargó un pequeño vial con el compuesto 752 (22.1 mg, 0.104 mmol) compuesto 877F (11.1 mg, 0.069 mmol) y $MgSO_4$ (21 mg, 0.173 mmol). Se agregó DME (0.07 mL), después Et_3N (0.05 mL) y se selló el vial con cinta de teflón y se calentó a 135 °C por 18 h. La purificación por CCD preparativa (SiO_2) que se eluye con 30% acetona/$CHCl_3$ dio el compuesto 877G (6.3 mg, 17%) como un sólido café. CLAR: 98% a 2.15 min (tiempo de retención) (Columna YMC S5 ODS, 4.6 x 50 mm, se eluye con 10-90% metanol acuoso durante 4 min conteniendo 0.2% ácido fosfórico, 4 mL/min, observando a 220 nm). EM (ES): m/z 337.16 $[M+H-H_2O]^+$. La estereoquímica absoluta del compuesto 877G se establece por la estereoquímica conocida del compuesto intermediario 752 y la retención de la configuración en ella. La estereoquímica absoluta es como se obtiene en la figura anterior y resulta de la nomenclatura.

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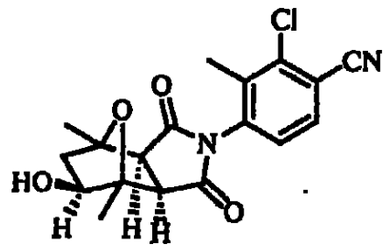
Ejemplo 878

[3aR-(3aα,4β,5β,7β,7aα)]-4-[Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2-cloro-3-metilbenzonitrilo (878)



Una mezcla de 4-amino-2-cloro-3-metil-benzonitrilo (54.5 mg, 0.327 mmol), compuesto 752 (104 mg, 0.491 mmol), $MgSO_4$ (98 mg, 0.818 mmol) y diisopropiletil amina (0.28 mL, 1.64 mmol) en DME (0.33 mL) se calentó a 150 °C en un tubo sellado por 18 h. La purificación por CCD preparativa (SiO_2) que se eluye con 30% acetona/$CHCl_3$ dio 53.0 mg (45%) del compuesto 878 como un sólido color marrón. CLAR: 95% a 2.63 min (tiempo de retención) (Columna YMC S5 ODS 4.6 x 50 mm se eluye con 10-90% metanol acuoso durante 4 minutos y contiene 0.2% ácido fosfórico, 4 mL/min, observando a 220 nm). EM (ES): m/z 361.03 $[M+H]^+$. La estereoquímica absoluta del compuesto 878 se establece por la estereoquímica conocida del compuesto intermediario 752 y la retención de la configuración en ella. La estereoquímica absoluta es como se obtiene en la figura anterior y resulta de la nomenclatura.

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Ejemplos 879 al 1020

Los compuestos adicionales de la presente invención se prepararon por procedimientos análogos a aquellos antes descritos. Los compuestos de los Ejemplos 879 al 1020 tienen la siguiente estructura (L es un enlace):

en donde la estructura, el nombre del compuesto, tiempo de retención, masa molecular, y el procedimiento empleado se establecen en la Tabla 18. No se determinó la configuración absoluta para los compuestos designados. Los compuestos que tienen uno o más centros ópticos, se designan por ser racémicos o quirales. Los compuestos racémicos representan una mezcla de ambos antípodos posibles. Quiral se refiere a un compuesto que representa un antípodo sencillo de un par posible. Para los compuestos que son quirales pero que no se conoce la estereoquímica absoluta, la estructura no refleja la estereoquímica absoluta. Para los compuestos que son quirales y que se conoce la estereoquímica absoluta con referencia al material de partida, entonces la estructura refleja la estereoquímica absoluta del compuesto.

Las técnicas de cromatografía usadas para determinar los tiempos de retención de los compuestos de la Tabla 18 son como sigue: CLEM = Columna YMC S5 ODS, 4.6 X 50 mm que se eluye con 10-90% MeOH/H_2O durante 4 minutos y contiene 0.1% TFA; 4 mL/min, observando a 220 nm. CLEM* = Columna YMC S5 ODS, 4.6 X 50 mm que se eluye con 10-90% MeOH/H_2O durante 2

minutos y contiene 0.1% TFA; 4 mL/min, observando a 220 nm. CL* = columna Hypersil C18 BDS, 250 x 4.6 mm, 5 m, una longitud de onda de detección de 254 nm, y una relación de flujo de 1 mL/min. Un gradiente lineal de 90% de 0.1% ácido trifluoroacético en agua, 10% acetonitrilo (comienzo) to 100% acetonitrilo durante 15 min, después 100% acetonitrilo por 5 min se usó. CL = Columna YMC S5 ODS 4.6 x 50 mm eluyendo con 10-90% de MeOH/H_2O durante 4 minutos conteniendo ácido fosfórico al 0.2%, 4 mL/min, observado a 220 nm.

La masa molecular de los compuestos enlistados en la Tabla 18 se determinaron por EM(ES) por la fórmula m/z.

UHTHOFF, GOMEZ VEGA & UHTHOFF, S.C.

Presentaciones de Casos en el IMPI por Responsable
(Área de Patentes - JLM)
de fecha: 10 de Junio del 2004

1353

Orden No.: 155749 PATENTE **Sts.** Orden Programada **Cliente:** Merck KGaA [Patents]
Solicitud: 0
Titular(es): MERCK PATENT GESELLSCHAFT MIT BESCHRANKTER HAFTUNG
Título: "INHIBICION DE TRISTETRAPROLINA PARA PROTEGER AL CORAZON CONTRA LESIONES CARDIACAS"
Referencia(s): Ref. 101D154-RW/JL
Prioridade(s): Alemana PCT/EP02/13545 30/11/2002 PCT CAPITULO II
Alemana 01129564.9 12/12/2001 EUROPEA
Inventor(es): FRANZ-WERNER KLUXEN, BERND HENTSCH, THOMAS EHRING, MARIAN BRÄNDLE, JÖRG DIETRICH HOHEISEL, MARCUS FROHME y DIMITRI ZUBAKOV
Documentos PCT: DIB PET ISR PUB IPER

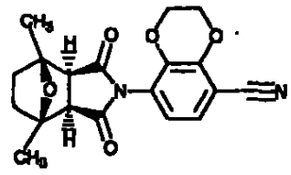
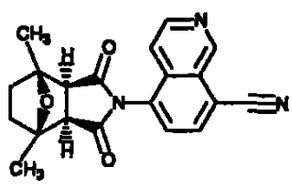
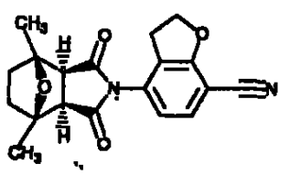
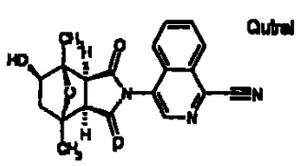
Orden No.: 156081 PATENTE **Sts.** Orden Programada **Cliente:** 3M Innovative Properties Company
Solicitud: 0
Titular(es): 3M INNOVATIVE PROPERTIES COMPANY
Título: "INDICADOR DE PARAMETROS AMBIENTALES PARA ARTICULOS PERECEDEROS"
Referencia(s): Ref. 57127MX0112 - EP 01129831.2
Prioridade(s): Norteamericana PCT/US02/33741 22/10/2002 PCT CAPITULO II
Alemana 01129831.2 14/12/2001 EUROPEA
Inventor(es): ANTON KUEPPER y KARL-HEINZ ROMANN
Documentos PCT: DIB PET ISR PUB WO RWO IPER

Orden No.: 156464 PATENTE **Sts.** Orden Programada **Cliente:** F. Hoffmann-La Roche AG
Solicitud: 0
Titular(es): F. HOFFMANN-LA ROCHE AG
Título: "BENZOTIOFENOS COMO MODULADORES DE RECEPTORES DE ADENOSINA"
Referencia(s): Case 21016
Prioridade(s): Suiza PCT/EP02/13704 04/12/2002 PCT CAPITULO II
Suiza 01129269.5 12/12/2001 EUROPEA
Inventor(es): ALEXANDER ALANINE y ALEXANDER FLOHR
Documentos PCT: PET ISR PUB IPER

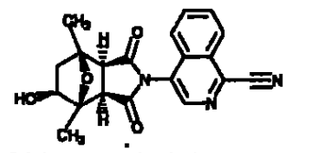
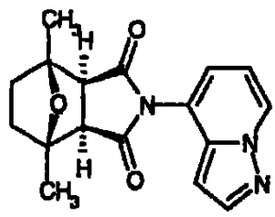
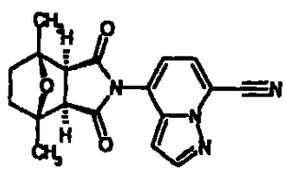
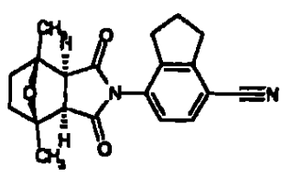
Total: 3

1359

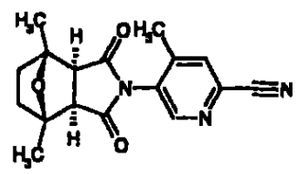
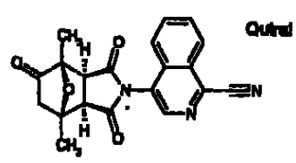
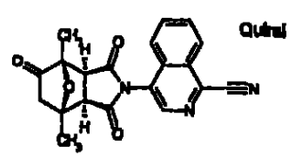
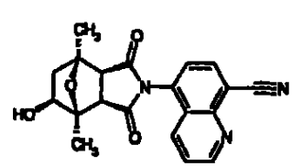
Tabla 18

Ej. No.	Estructura	Compuesto Nombre/Comentarios	Tiempo de retención Min./Masa molecular	Proc. Del Ej.
879			2.34 CLEM $[M+H]^+$= 355.23	470E
880			2.44 CLEM $[M+H]^+$= 348.24	470E
881			3.21 CLEM $[M+H]^+$= 339.24	470E
882		Quiral, estereoquímica absoluta no se conoce	1.2 CLEM $[M+H]^+$= 364.15	754

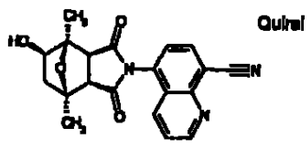
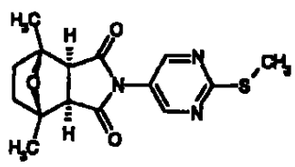
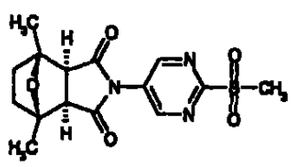
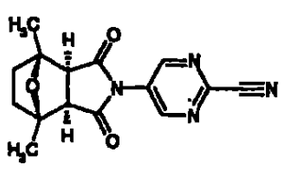
1360

Ej. No.	Estructura	Compuesto Nombre/Comentarios	Tiempo de retención Min./Masa molecular	Proc. Del Ej.
883	 Quiral, estereoquímica absoluta no se conoce	Quiral, estereoquímica absoluta no se conoce	1.20 CLEM $[M+H]^+$= 364.15	761
884			2.72 CLEM $[M+H]^+$= 312.18	470E
885			2.95 CLEM $[M+H]^+$= 337.09	470E, 777F
886			2.93 CLEM $[M+H]^+$= 337.23	470E

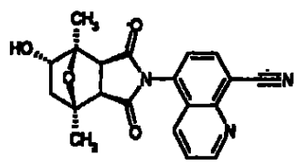
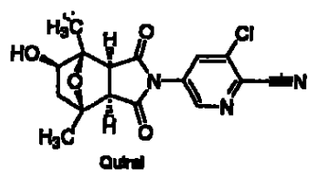
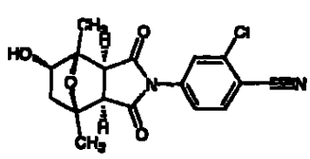
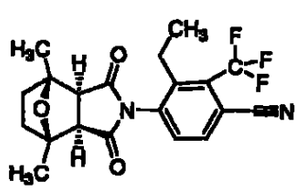
1361

Ej. No.	Estructura	Compuesto Nombre/Comentarios	Tiempo de retención Min./Masa molecular	Proc. Del Ej.
887			2.69 CLEM $[M+H]^+$= 312.06	470E
888		Quiral, estereoquímica absoluta no se conoce	1.46 CLEM $[M+H]^+$= 362.15	795, 818
889		Quiral, estereoquímica absoluta no se conoce	1.48 CLEM $[M+H]^+$= 362.15	795, 818
890		Quiral, estereoquímica absoluta como se muestra	1.833 CLEM $[M+H]^+$= 364.16	761

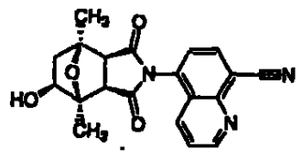
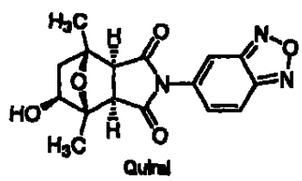
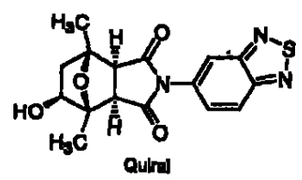
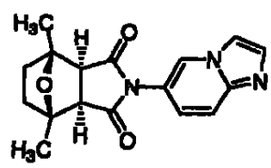
1362

Ej. No.	Estructura	Compuesto Nombre/Comentarios	Tiempo de retención Min./Masa molecular	Proc. Del Ej.
891		Quiral, estereoquímica absoluta como se muestra	1.827 CLEM $[M+H]^+$= 364.17	754
892			3.09 CLEM $[M+H]^+$= 319.93	470E
893			2.30 CLEM $[M+H]^+$= 351.96	470E
894			2.88 CLEM $[M+H]^+$= 299.02	470E

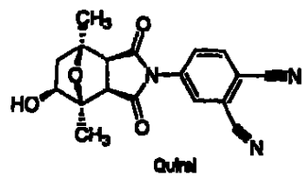
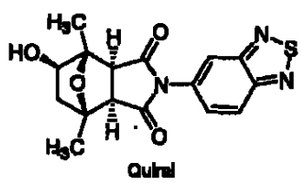
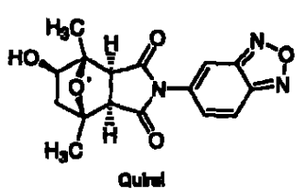
1363

Ej. No.	Estructura	Compuesto Nombre/Comentarios	Tiempo de retención Min./Masa molecular	Proc. Del Ej.
895		Quiral, estereoquímica absoluta como se muestra	2.16 CLEM $[M+H]^+$= 364.20	799
896		Quiral, estereoquímica absoluta como se muestra	2.66 CLEM $[M+H]^+$= 348.30	754
897		Quiral, estereoquímica absoluta como se muestra	2.32 CLEM $[M+H]^+$= 347.18	754
898			3.47 CLEM $[M+H]^+$= 393.19	470E

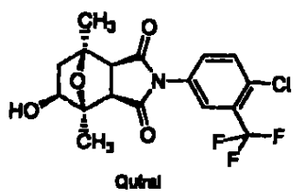
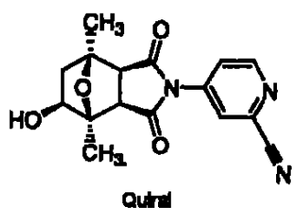
1364

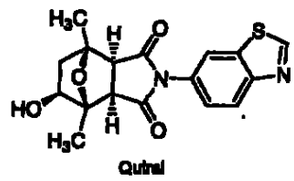
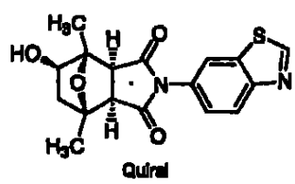
Ej. No.	Estructura	Compuesto Nombre/Comentarios	Tiempo de retención Min./Masa molecular	Proc. Del Ej.
899		Quiral, estereoquímica absoluta como se muestra	1.83 CLEM $[M+H]^+$= 364.17	761
900		Quiral, estereoquímica absoluta como se muestra	2.56 CLEM $[M+H]^+$= 330.20	480A, 761
901		Quiral, estereoquímica absoluta como se muestra	2.54 CLEM $[M+H]^+$= 346.12	424A, 761
902			1.48 CLEM $[M+H]^+$= 312.14	470E, 844A

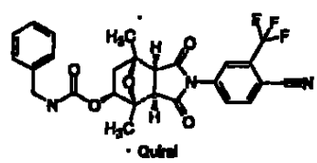
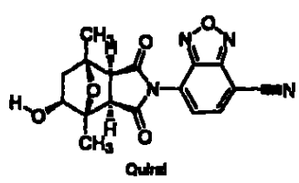
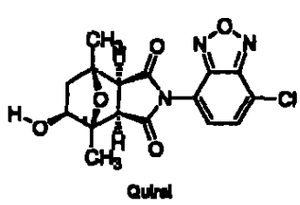
1365

Ej. No.	Estructura	Compuesto Nombre/Comentarios	Tiempo de retención Min./Masa molecular	Proc. Del Ej.
903		Quiral, estereoquímica absoluta como se muestra	1.89 CLEM $[M+H]^+$= 336.17	761
904		Quiral, estereoquímica absoluta como se muestra	2.52 CLEM $[M+H]^+$= 346.06	424A, 754
905		Quiral, estereoquímica absoluta como se muestra [3aS-(3aα,4β,5β,7β,7aα)]-2-(2,1,3-Benzoxadiazol-5-il)hexahidro-5-hidroxi-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3(2H)-diona	2.55 CLEM $[M-H]^-$ =328.10	480A, 754

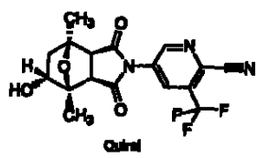
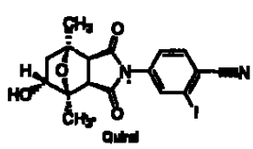
1366

Ej. No.	Estructura	Compuesto Nombre/Comentarios	Tiempo de retención Min./Masa molecular	Proc. Del Ej.
906		Quiral, estereoquímica absoluta como se muestra [3aR-(3aα,4β,5β,7β,7aα)]-2-(4-Cloro-3-(trifluorometil)fenil)hexahidro-5-hidroxi-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3(2H)-diona	3.06 CLEM $[M+H]^+$= 390.20	761
907		Quiral, estereoquímica absoluta como se muestra	1.567 CLEM $[M+H]^+$= 314.16	761

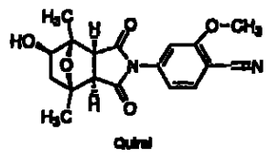
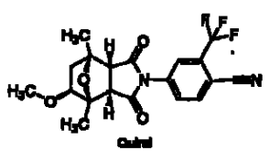
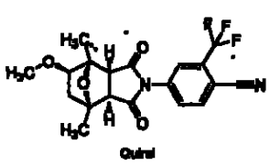
Ej. No.	Estructura	Compuesto Nombre/Comentarios	Tiempo de retención Min./Masa molecular	Proc. Del Ej.
908		Quiral, estereoquímica absoluta como se muestra	2.10 CLEM $[M+H]^+$= 345.14	761
909		Quiral, estereoquímica absoluta como se muestra [3aS-(3aα,4β,5β,7β,7aα)]-2-(6-Benzotiazolil)hexahidro-5-hidroxi-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3(2H)-diona	2.10 CLEM $[M+H]^+$= 345.14	754

Ej. No.	Estructura	Compuesto Nombre/Comentarios	Tiempo de retención Min./Masa molecular	Proc. Del Ej.
910		Quiral, estereoquímica absoluta como se muestra	3.90 CLEM $[M+H]^+$= 514.36	756
911		Quiral, estereoquímica absoluta como se muestra	2.15 CLEM $[M+H]^+$= 337.16	761
912		Quiral, estereoquímica absoluta como se muestra [3aR-(3aα,4β,5β,7β,7aα)]-2-(7-Cloro-2,1,3-benzoxadiazol-4-il)hexahidro-5-hidroxi-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3(2H)-diona	2.55 CLEM $[M+H]^+$= 364.18	761

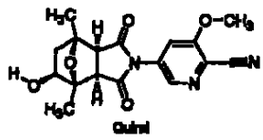
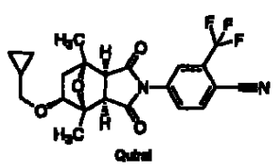
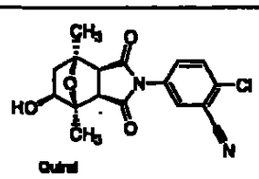
1369

Ej. No.	Estructura	Compuesto Nombre/Comentarios	Tiempo de retención Min./Masa molecular	Proc. Del Ej.
913		Quiral, estereoquímica absoluta no se conoce [3aR-(3aα,4β,5α,7β,7aα)]-2-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-3-(trifluorometil)-2-piridincarbonitrilo	2.933 CLEM $[M+H]^+$= 382.26	763E, 799
914		Quiral, estereoquímica absoluta no se conoce [3aR-(3aα,4β,5α,7β,7aα)]-4-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-yodobenzonitrilo	2.73 CLEM $[M+H]^+$= 439.30	753F, 799

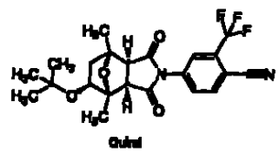
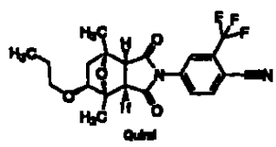
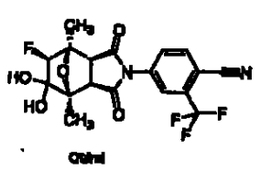
1370

Ej. No.	Estructura	Compuesto Nombre/Comentarios	Tiempo de retención Min./Masa molecular	Proc. Del Ej.
915		Quiral, estereoquímica absoluta como se muestra	2.34 CLEM $[M+H]^+$= 341.26	846
916		Quiral, estereoquímica absoluta como se muestra [3aR-(3aα,4β,5β,7β,7aα)]-4-(Octahidro-5-metoxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo	3.44 CLEM $[M+H]^+$= 395.43	757A
917		Quiral, estereoquímica absoluta como se muestra [3aS-(3aα,4β,5β,7β,7aα)]-4-(Octahidro-5-metoxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo	$[M+H]^+$= 395.07	757A

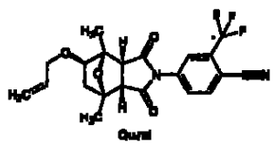
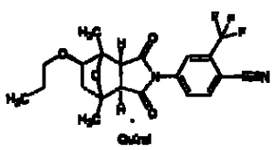
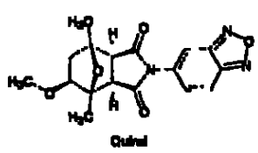
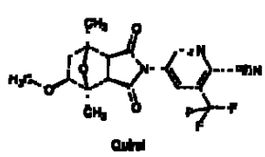
1371

Ej. No.	Estructura	Compuesto Nombre/Comentarios	Tiempo de retención Min./Masa molecular	Proc. Del Ej.
918		Quiral, estereoquímica absoluta como se muestra	1.83 CLEM $[M+H]^+$= 344.03	761
919		Quiral, estereoquímica absoluta como se muestra [3aR-(3aα,4β,5β,7β,7aα)]-4-(Octahidro-5-ciclopropilmetoxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo	3.84 CLEM $[M+H]^+$= 435.10	757A
920		Quiral, estereoquímica absoluta como se muestra	2.373 CLEM $[M+H]^+$= 347.01	761

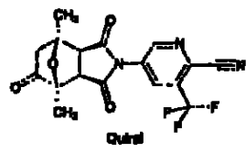
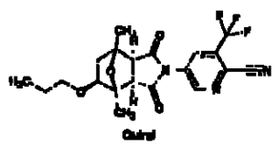
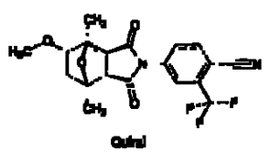
1372

Ej. No.	Estructura	Compuesto Nombre/Comentarios	Tiempo de retención Min./Masa molecular	Proc. Del Ej.
921		Quiral, estereoquímica absoluta como se muestra	3.91 CLEM $[M+H]^+$= 436	757A
922		Quiral, estereoquímica absoluta como se muestra	3.88 CLEM $[M+H]^+$= 422.99	757A
923		Quiral, estereoquímica absoluta como se muestra [3aR-(3aα,4β,6β,7β,7aα)]-4-(Octahidro-6-fluoro-5,5-dihidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo	2.663 CLEM $[M+H]^+$= 413.19	798

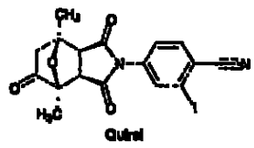
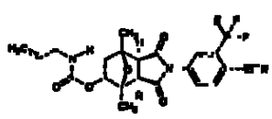
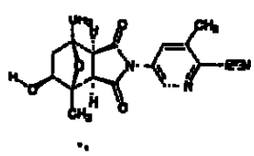
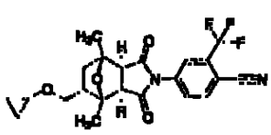
1373

Ej. No.	Estructura	Compuesto Nombre/Comentarios	Tiempo de retención Min./Masa molecular	Proc. Del Ej.
924		Quiral, estereoquímica absoluta como se muestra	3.74 CLEM $[M+H]^+$= 421.06	757A
925		Quiral, estereoquímica absoluta como se muestra	3.89 CLEM $[M+H]^+$= 423.07	757A
926		Quiral, estereoquímica absoluta como se muestra	3.027 CLEM $[M+H]^+$= 344.01	480A, 757A, 761
927		Quiral, estereoquímica absoluta como se muestra	2.993 CLEM $[M+H]^+$= 396.00	757A, 763F

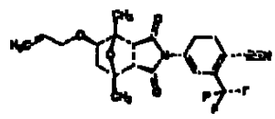
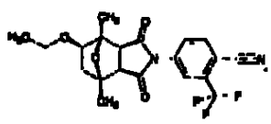
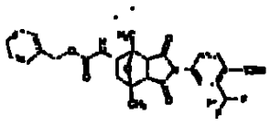
1374

Ej. No.	Estructura	Compuesto Nombre/Comentarios	Tiempo de retención Min./Masa molecular	Proc. Del Ej.
928		Quiral, estereoquímica absoluta como se muestra [3aR-(3aα,4β,7β,7aα)]-5-(Octahidro-4,7-dimetil-1,3,5-trioxo-4,7-epoxi-2H-isoindol-2-il)-3-(trifluorometil)-2-piridincarbonitrilo	3.153 CLEM $[M+H]^+$= 411.04	763E, 795
929		Quiral, estereoquímica absoluta como se muestra	3.50 CLEM $[M+H]^+$= 424.07	757A
930		Quiral, estereoquímica absoluta como se muestra	2.887 CLEM $[M+H]^+$= 395.07	757A

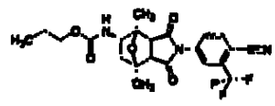
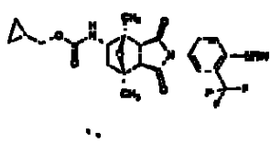
1375

Ej. No.	Estructura	Compuesto Nombre/Comentarios	Tiempo de retención Min./Masa molecular	Proc. Del Ej.
931		Quiral, estereoquímica absoluta como se muestra (3aα,4β,7β,7aα)-4-(Octahidro-4,7-dimetil-1,3,5-trioxo-4,7-epoxi-2H-isoindol-2-il)-2-yodonitrilo	2.963 CLEM $[M+H]^+$= 469.0	753F, 795
932		Quiral, estereoquímica absoluta no se conoce	14.30 CL** $[M+H]^+$= 464	810
933		Quiral, estereoquímica absoluta como se muestra	1.83 CLEM $[M+H]^+$= 328.37	761
934		Quiral, estereoquímica absoluta no se conoce	3.85 CLEM $[M+H]^+$= 433.27	852

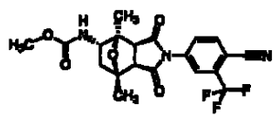
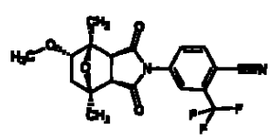
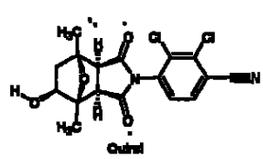
1376

Ej. No.	Estructura	Compuesto Nombre/Comentarios	Tiempo de retención Min./Masa molecular	Proc. Del Ej.
935		Quiral, estereoquímica absoluta como se muestra	16.070 CL* $[M+H]^+$= 421	757A
936		Quiral, estereoquímica absoluta como se muestra	15.812 CL* $[M+H]^+$= 409	
937		Quiral, estereoquímica absoluta no se conoce (3aα,4β,5α,7β,7aα)-4-(Octahidro-5-[[fenilmetoxicarbonil]amino]-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo	15.627 CL* $[M+H]^+$= 514	812

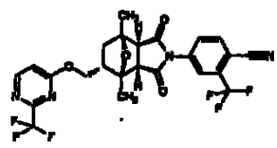
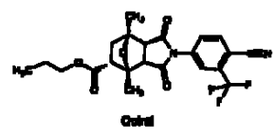
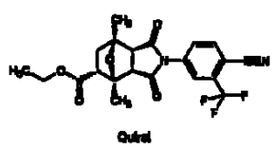
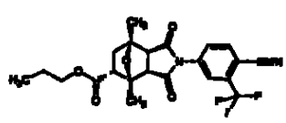
1377

Ej. No.	Estructura	Compuesto Nombre/Comentarios	Tiempo de retención Min./Masa molecular	Proc. Del Ej.
938		Quiral, estereoquímica absoluta no se conoce (3aα,4β,5α,7β,7aα)-4-(Octahidro-5-[[propiloxicarbonil]amino]-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo	14.842 CL* $[M+H]^+$= 416	812
939		Quiral, estereoquímica absoluta no se conoce (3aα,4β,5α,7β,7aα)-4-(Octahidro-5-[[[ciclopropilmetiloxi]carbonil]amino]-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo	14.852 CL* $[M+H]^+$= 478	812

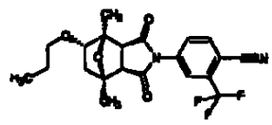
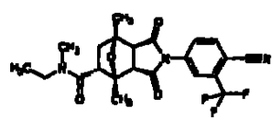
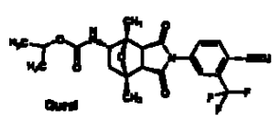
1378

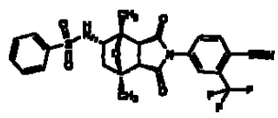
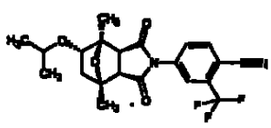
Ej. No.	Estructura	Compuesto Nombre/Comentarios	Tiempo de retención Min./Masa molecular	Proc. Del Ej.
940		Quiral, estereoquímica absoluta no se conoce (3aα,4β,5α,7β,7aα)-4-(Octahidro-5-[[metoxicarbonil]amino]-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo	13.241 CL* $[M+H^+]$= 438	812
941		Quiral, estereoquímica absoluta no se conoce	14.671 CL* $[M+H]^+$= 395.3	855
942		Quiral, estereoquímica absoluta como se muestra [3aR-(3aα,4β,5α,7β,7aα)-4-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2,3-diclorobenzonitrilo	2.63 CLEM [M+H]+= 382.95	761

1379

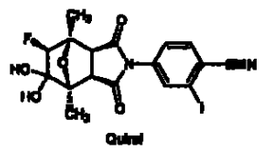
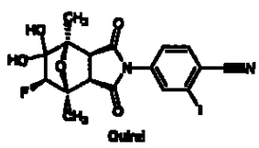
Ej. No.	Estructura	Compuesto Nombre/Comentarios	Tiempo de retención Min./Masa molecular	Proc. Del Ej.
943		Quiral, estereoquímica absoluta no se conoce	3.987 CLEM $[M+H]^+$=	851
944		Quiral, estereoquímica absoluta no se conoce	16.595 CL* $[M+H]^+$= 451.3	830
945		Quiral, estereoquímica absoluta no se conoce	16.294 CL* $[M+H]^+$= 437.3	830
946		Quiral, estereoquímica absoluta no se conoce	17.077 CL* $[M+H]^+$= 451.2	830

1330

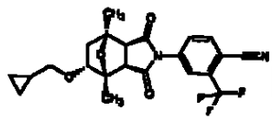
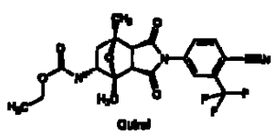
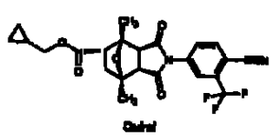
Ej. No.	Estructura	Compuesto Nombre/Comentarios	Tiempo de retención Min./Masa molecular	Proc. Del Ej.
947		Quiral, estereoquímica absoluta no se conoce	16.970 CL* $[M+H]^+$= 423.7	757A
948		Quiral, estereoquímica absoluta no se conoce	14.750 CL* $[M+H]^+$= 450.4	811
949		Quiral, estereoquímica absoluta no se conoce [3aS-(3aα,4β,5α,7β,7aα)]-4-(Octahidro-5-[[(1-metiletoxi)carbonil]amino]-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo	15.314 CL* $[M+H]^+$= 465	812

Ej. No.	Estructura	Compuesto Nombre/Comentarios	Tiempo de retención Min./Masa molecular	Proc. Del Ej.
950		Quiral, estereoquímica absoluta no se conoce (3aα,4β,5α,7β,7aα)-4-(Octahidro-5-bencensulfonamido-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo	15.394 CL* $[M+H]^+$= 519	809
951		Quiral, estereoquímica absoluta no se conoce	16.902 CL* $[M+H]^+$= 423	757A

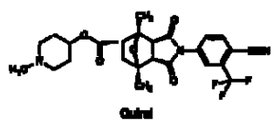
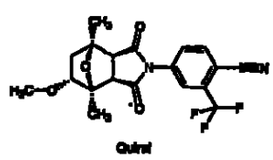
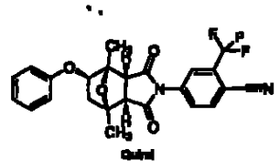
1382

Ej. No.	Estructura	Compuesto Nombre/Comentarios	Tiempo de retención Min./Masa molecular	Proc. Del Ej.
952		Quiral, estereoquímica absoluta como se muestra [3aR-(3aα,4β,6α,7β,7aα)]-4-(Octahidro-6-fluoro-5,5-dihidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-yodobenzonitrilo	2.497 CLEM $[M+H]^+$= 471.07	753F, 798
953		Quiral, estereoquímica absoluta como se muestra [3aS-(3aα,4β,6α,7β,7aα)]-4-(Octahidro-6-fluoro-5,5-dihidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-yodobenzonitrilo	2.497 CLEM $[M-H]^+$= 471.07	

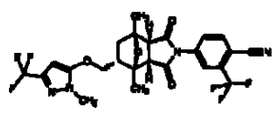
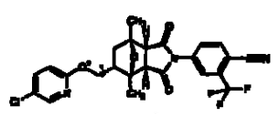
1383

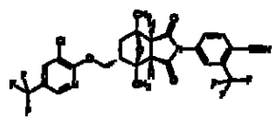
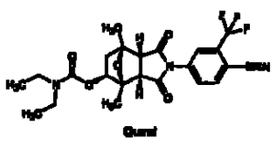
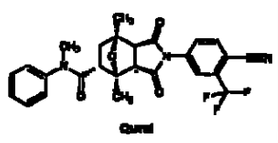
Ej. No.	Estructura	Compuesto Nombre/Comentarios	Tiempo de retención Min./Masa molecular	Proc. Del Ej.
954		Quiral, estereoquímica absoluta no se conoce	17.119** EM $[M+H]^+$= 435	A. 757A
955		Quiral, estereoquímica absoluta no se conoce [3aR-(3aα,4β,5α,7β,7aα)]-4-(Octahidro-5-[[etoxicarbonil]amino]-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo	14.536 CL* $[M+H]^+$= 452	812
956		Quiral, estereoquímica absoluta no se conoce	18.043 CL* $[M+H]^+$= 436.2	830

1384

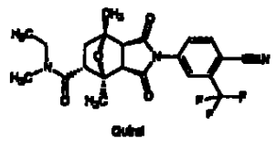
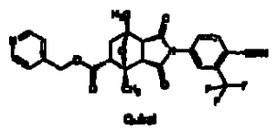
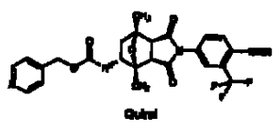
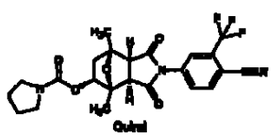
Ej. No.	Estructura	Compuesto Nombre/Comentarios	Tiempo de retención Min./Masa molecular	Proc. Del Ej.
957		Quiral, estereoquímica absoluta no se conoce	13.764 CL* $[M+H]^+$= 506.2	830
958		Quiral, estereoquímica absoluta no se conoce [3aR-(3aα,4β,5α,7β,7aα)]-4-(Octahidro-5-metoxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo	3.243 CLEM $[M+H]^+$= 395.07	855
959		Quiral, estereoquímica absoluta como se muestra	4.15 CLEM $[M+H]^+$= 455.00	757

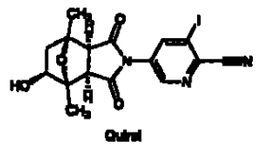
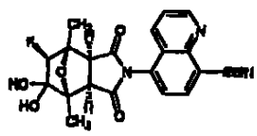
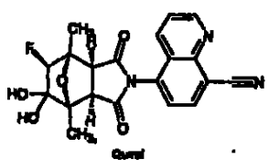
1385

Ej. No.	Estructura	Compuesto Nombre/Comentarios	Tiempo de retención Min./Masa molecular	Proc. Del Ej.
960		Quiral, estereoquímica absoluta como se muestra (3aα,4β,5α,7β,7aα)]-4-(Octahidro-5-[[[2-metil-5-(trifluorometil)-2H-pirazol-3-il]oxi]metil]-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo	3.933 CLEM $[M+H]^+$= 543.00	851
961		Quiral, estereoquímica absoluta como se muestra (3aα,4β,5α,7β,7aα)-4-(Octahidro-5-[[[5-cloro-2-piridinil]oxi]metil]-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo	4.46 CLEM $[M+H]^+$= 505.92	851

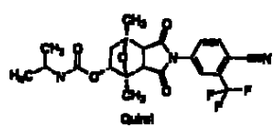
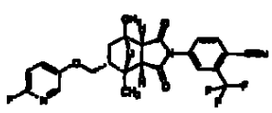
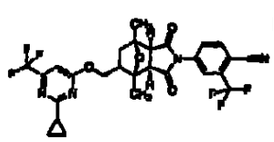
Ej. No.	Estructura	Compuesto Nombre/Comentarios	Tiempo de retención Min./Masa molecular	Proc. Del Ej.
962		Quiral, estereoquímica absoluta como se muestra	4.46 CLEM $[M+H]^+$= 573.93	851
963		Quiral, estereoquímica absoluta como se muestra	4.00 CLEM $[M+H]^+$= 480.03	756
964		Quiral, estereoquímica absoluta no se conoce [3aR-(3aα,4β,5α,7β,7aα)]-2-(4-Ciano-3-(trifluorometil)fenil)hexa hidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-N-metil-N-fenil-1H-isoindol-5-carboxamida	18.695 CL* $[M+H]^+$= 498.0	811

1387

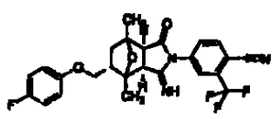
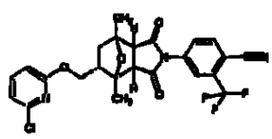
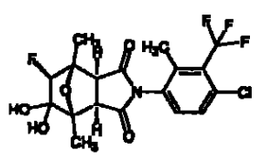
Ej. No.	Estructura	Compuesto Nombre/Comentarios	Tiempo de retención Min./Masa molecular	Proc. Del Ej.
965		Quiral, estereoquímica absoluta no se conoce	17.025 CL* $[M+H]^+$= 450.2	811
966		Quiral, estereoquímica absoluta no se conoce	15.425 CL* $[M+H]^+$= 500.2	830
967		Quiral, estereoquímica absoluta no se conoce	14.375 CL* $[M+H]^+$= 498	812
968		Quiral, estereoquímica absoluta como se muestra	3.90 CLEM $[M+H]^+$= 478.09	756

Ej. No.	Estructura	Compuesto Nombre/Comentarios	Tiempo de retención Min./Masa molecular	Proc. Del Ej.
969		Quiral, estereoquímica absoluta como se muestra	2.32 CLEM $[M+H]^+$= 439.92	761
970		Quiral, estereoquímica absoluta como se muestra	1.95 CLEM $[M+H]^+$= 398.25	798
971		Quiral, estereoquímica absoluta como se muestra [3aR-(3aα,4β,5α,7β,7aα)]-4-(Octahidro-5-[[(4-fluorofenilamino)carbonil]oxi]-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo	3.757 CLEM $[M+H]^+$= 516.31	798

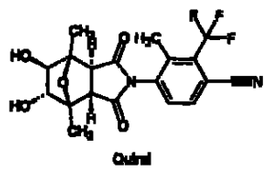
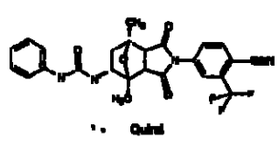
1339

Ej. No.	Estructura	Compuesto Nombre/Comentarios	Tiempo de retención Min./Masa molecular	Proc. Del Ej.
972		Quiral, estereoquímica absoluta no se conoce [3aR-(3aα,4β,5α,7β,7aα)]-4-(Octahidro-5-[[(1-metiletilamino)carbonil]oxi]-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo	3.367 CLEM $[M+H]^+$= 464.32	810
973		Quiral, estereoquímica absoluta no se conoce	3.80 CLEM $[M+H]^+$= 490.04	851
974		Quiral, estereoquímica absoluta no se conoce	4.383 CLEM $[M+H]^+$= 581.10	851

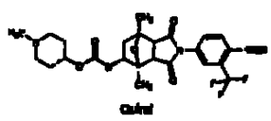
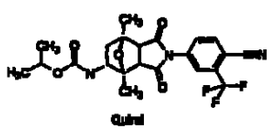
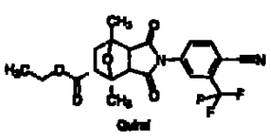
1390

Ej. No.	Estructura	Compuesto Nombre/Comentarios	Tiempo de retención Min./Masa molecular	Proc. Del Ej.
975		Quiral, estereoquímica absoluta no se conoce	4.147 CLEM $[M+H]^+$= 489.01	851
976		Quiral, estereoquímica absoluta no se conoce	4.173 CLEM $[M+H]^+$= 507.99	851
977		Quiral, estereoquímica absoluta como se muestra	3.34 CLEM $[M+H]^+$= 436.26	798

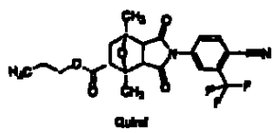
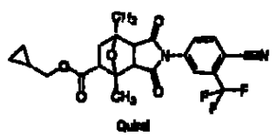
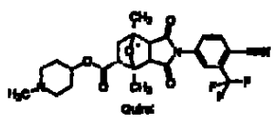
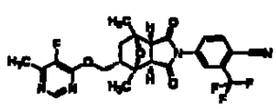
1391

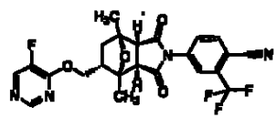
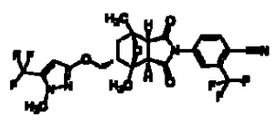
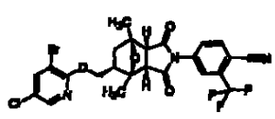
Ej. No.	Estructura	Compuesto Nombre/Comentarios	Tiempo de retención Min./Masa molecular	Proc. Del Ej.
978		Quiral, estereoquímica absoluta no se conoce [3aR-(3aα,4β,5β,6α,7β,7aα)]-4-(Octahidro-5,6-dihidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-3-metil-2-(trifluorometil)benzonitrilo	3.28 CLEM $[M+H]^+$= 411.10	787
979		Quiral, estereoquímica absoluta no se conoce [3aR-(3aα,4β,5α,7β,7aα)]-4-(Octahidro-5-[[[fenilamino]carbonil]amino]-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo	14.736 CL* $[M+H]^+$= 499.3	815

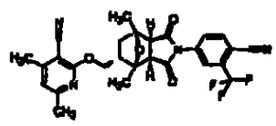
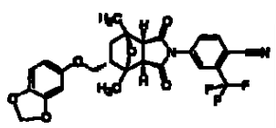
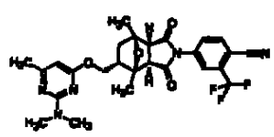
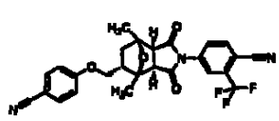
1392

Ej. No.	Estructura	Compuesto Nombre/Comentarios	Tiempo de retención Min./Masa molecular	Proc. Del Ej.
980		Quiral, estereoquímica absoluta no se conoce	15.370 CL* $[M+H]^+$= 521.4	812
981		Quiral, estereoquímica absoluta no se conoce [3aR-(3aα,4β,5α,7β,7aα)]-4-(Octahidro-5-[[(1-metiletiloxi)carbonil]amino]-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo	15.108 CL* $[M+H]^+$= 466	812
982		Quiral, estereoquímica absoluta no se conoce	16.235 CL* $[M+H]^+$= 437.0	830

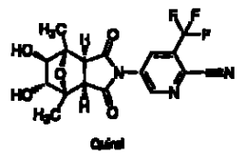
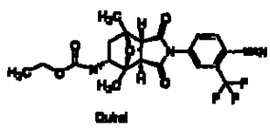
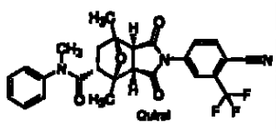
1393

Ej. No.	Estructura	Compuesto Nombre/Comentarios	Tiempo de retención Min./Masa molecular	Proc. Del Ej.
983		Quiral, estereoquímica absoluta no se conoce	17.195 CL* $[M+H]^+$= 451.20	830
984		Quiral, estereoquímica absoluta no se conoce	16.851 CL* $[M+H]^+$= 463.25	830
985		Quiral, estereoquímica absoluta no se conoce	12.530 CL* $[M+H]^+$= 506.30	830
986		Quiral, estereoquímica absoluta no se conoce	3.947 CLEM $[M+H]^+$= 505.27	851

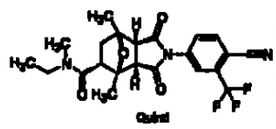
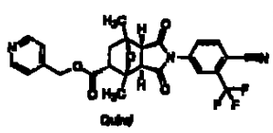
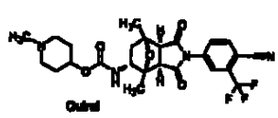
Ej. No.	Estructura	Compuesto Nombre/Comentarios	Tiempo de retención Min./Masa molecular	Proc. Del Ej.
987		Quiral, estereoquímica absoluta no se conoce (3aα,4β,5α,7β,7aα)-4-(Octahidro-5-[[[5-fluoro-4-pirimidinil]oxi]metil-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo	3.80 CLEM $[M+H]^+$= 491.08	851
988		Quiral, estereoquímica absoluta no se conoce	3.80 CLEM $[M+H]^+$= 543.07	851
989		Quiral, estereoquímica absoluta no se conoce	4.50 CLEM $[M+H]^+$= 585.96	851

Ej. No.	Estructura	Compuesto Nombre/Comentarios	Tiempo de retención Min./Masa molecular	Proc. Del Ej.
990		Quiral, estereoquímica absoluta no se conoce	4.09 CLEM $[M+H]^+$= 525.12	851
991		Quiral, estereoquímica absoluta no se conoce	4.12 CLEM $[M+H]^+$= 515.05	851
992		Quiral, estereoquímica absoluta no se conoce	3.10 CLEM $[M+H]^+$= 530.13	851
993		Quiral, estereoquímica absoluta no se conoce	3.95 CLEM $[M+H]^+$= 496.05	851

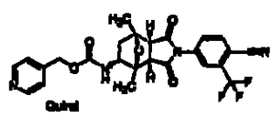
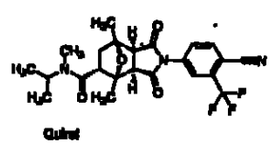
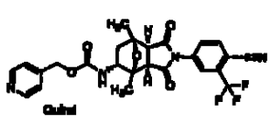
1396

Ej. No.	Estructura	Compuesto Nombre/Comentarios	Tiempo de retención Min./Masa molecular	Proc. Del Ej.
994		Quiral, estereoquímica absoluta no se conoce	XXX CLEM $[M+H]^+$= XXX	797
995		Quiral, estereoquímica absoluta no se conoce [3aR-(3aα,4β,5α,7β,7aα)]-4-(Octahidro-5-[[etiloxicarbonil]amino]-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo	14.522 CL* $[M+H]^+$= 452	812
996		Quiral, estereoquímica absoluta no se conoce	16.068 CL* $[M+H]^+$= 498.25	811

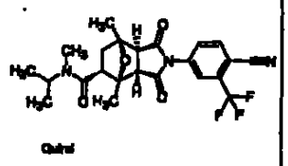
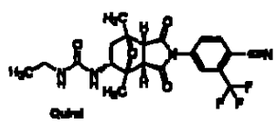
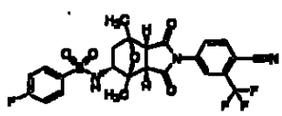
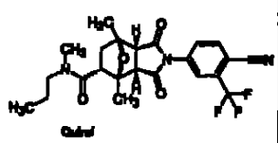
1397

Ej. No.	Estructura	Compuesto Nombre/Comentarios	Tiempo de retención Min./Masa molecular	Proc. Del Ej.
997		Quiral, estereoquímica absoluta no se conoce	14.076 CL* $[M+H]^+$= 450.20	811
998		Quiral, estereoquímica absoluta no se conoce Éster de 4-piridinilmetilo del ácido [3aR-(3aα,4β,5α,7β,7aα)]-2-(4-Ciano-3-(trifluorometil)fenil)-hexahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-1H-isoindol-5-carboxílico	12.008 CL* $[M+H]^+$= 500.2	830
999		Quiral, estereoquímica absoluta no se conoce	11.196 CL* $[M+H]^+$= 521.3	812

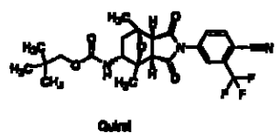
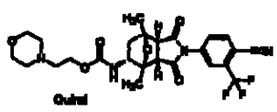
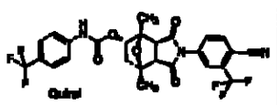
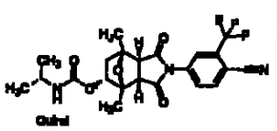
1398

Ej. No.	Estructura	Compuesto Nombre/Comentarios	Tiempo de retención Min./Masa molecular	Proc. Del Ej.
1000		Quiral, estereoquímica absoluta no se conoce [3aR-(3aα,4β,5α,7β,7aα)]-4-(Octahidro-5-[[4-piridinilmetoxicarbonil]amino] -4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo	11.342 CL* $[M+H]^+$= 515.4	812
1001		Quiral, estereoquímica absoluta no se conoce	14.897 CL* $[M+H]^+$= 464.25	811
1002		Quiral, estereoquímica absoluta no se conoce	14.905 CL* $[M+H]^+$= 464.25	811

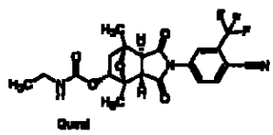
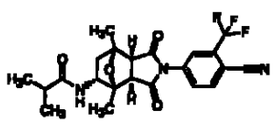
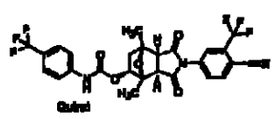
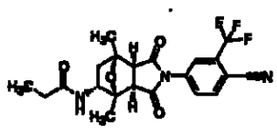
1399

Ej. No.	Estructura	Compuesto Nombre/Comentarios	Tiempo de retención Min./Masa molecular	Proc. Del Ej.
1003		Quiral, estereoquímica absoluta no se conoce	14.692 CL* $[M+H]^+$= 464.25	815
1004		Quiral, estereoquímica absoluta no se conoce	11.93 CL* $[M+H]^+$= 451.50	809
1005		Quiral, estereoquímica absoluta no se conoce	15.325 CL* $[M+H]^+$= 538.40	811
1006		Quiral, estereoquímica absoluta no se conoce	14.724 CL* $[M+H]^+$= 464.25	812

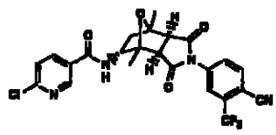
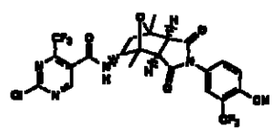
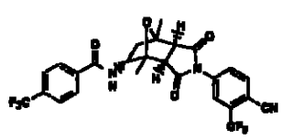
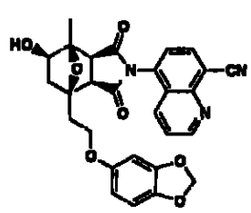
1400

Ej. No.	Estructura	Compuesto Nombre/Comentarios	Tiempo de retención Min./Masa molecular	Proc. Del Ej.
1007		Quiral, estereoquímica absoluta no se conoce	16.123 CL* $[M+H]^+$= 494.0	812
1008		Quiral, estereoquímica absoluta no se conoce	11.187 CL* $[M+H]^+$= 537.3	812
1009		Quiral, estereoquímica absoluta no se conoce	4.02 CLEM $[M-H]^-$= 566.18	812
1010		Quiral, estereoquímica absoluta no se conoce	3.35 CLEM $[M-H]^-$= 464.19	810

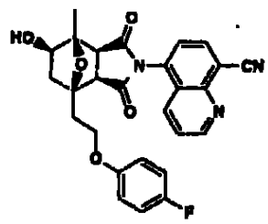
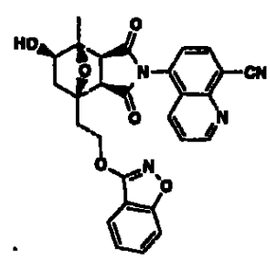
1401

Ej. No.	Estructura	Compuesto Nombre/Comentarios	Tiempo de retención Min./Masa molecular	Proc. Del Ej.
1011		Quiral, estereoquímica absoluta no se conoce	3.23 CLEM	814
1012		Quiral, estereoquímica absoluta no se conoce	3.12 CLEM $[M+H]^+$= 450.12	812
1013		Quiral, estereoquímica absoluta no se conoce	4.04 CLEM	810
1014		Quiral, estereoquímica absoluta no se conoce	3.02 CLEM $[M-H]^-$= 436.1	814

1402

Ej. No.	Estructura	Compuesto Nombre/Comentarios	Tiempo de retención Min./Masa molecular	Proc. Del Ej.
1015		Racémico	3.32 CLEM $[M+H]^+$= 519.05	812
1016		Racémico	3.56 CLEM $[M+H]^+$= 587.97	812
1017		Racémico	3.65 CLEM $[M-H]^-$= 552.11	812
1018		[3aS-(3aα,4β,5β,7β,7aα)]-5-[7-[2-(1,3-Benzodioxol-5-iloxi)etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-8-quinolincarbonitrilo	2.86 CLEM $[M+H]^+$= 514.16	485, 486, 487 & 488

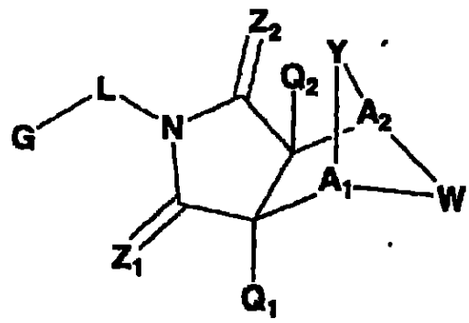
1403

Ej. No.	Estructura	Compuesto Nombre/Comentarios	Tiempo de retención Min./Masa molecular	Proc. Del Ej.
1019		[3aS-(3aα,4β,5β,7β,7aα)]-5-[7-[2-(4-fluorofenoxi)etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-8-quinolincarbonitrilo	3.02 CLEM $[M+H]^+$= 488.2	485, 486, 487 & 488
1020		[3aS-(3aα,4β,5β,7β,7aα)]-5-[7-[2-(1,2-Benzisoxazol-3-iloxi)etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-8-quinolincarbonitrilo	2.94 CLEM $[M+H]^+$= 511.2	485, 486, 487 & 488

1404

Reivindicaciones

1. Un compuesto de la siguiente fórmula:



(Ia)

caracterizado porque los símbolos tienen los siguientes significados y son, cada que se presentan, seleccionados independientemente:

G es un grupo arilo o heterociclo donde el grupo es mono- o policíclico, y el cual está opcionalmente substituido en una o más posiciones;

Z_1 es O, S, NH, o NR^6;

Z_2 es O, S, NH, o NR^6;

A_1 es CR^7 o N;

A_2 es CR^7 o N;

Y es J-J'-J" donde J es $(CR^7R^{7'})n$ y n = 0-3, J' es un enlace u O, S, S=O, SO_2, NH, NR^7, $CR^7R^{7'}$, $R^2P=O$, $R^2P=S$, $R^2OP=O$, $R^2NHP=O$, $OP=OOR^2$, $OP=ONHR^2$, OSO_2, NHNH, $NHNR^6$, NR^6NH, N=N, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, o heterociclo o heterociclo substituido, y J" es $(CR^7R^{7'})n$ y n = 0-3, donde Y no es un enlace; y

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W' es $CR^7CR^{7'}-CR^7R^{7'}$, $CR^7CR^{7'}-C=O$, $C=O-C=O$, $CR^7R^{7'}-C=CH_2$, $C=CH_2-C=CH_2$, $CR^7R^{7'}-C=NR^1$, $C=NR^1-C=NR^1$, $NR^9-CR^7R^{7'}$, $N=CR^8$, $N=N$, $NR^9-NR^{9'}$, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, o arilo o arilo substituido, en donde cuando W' no es $NR^9-CR^7R^{7'}$, $N=CR^8$, $N=N$, $NR^9-NR^{9'}$, o heterociclo o heterociclo substituido, entonces J' deberá ser O, S, S=O, SO_2, NH, NR^7, $OP=OOR^2$, $OP=ONHR^2$, OSO_2, NHNH, $NHNR^6$, NR^6NH, o N=N;

cuando W es $CR^7R^{7'}-CR^7R^{7'}$, los substituyentes R^7 y $R^{7'}$ cada que se presentan, pueden tomarse juntos para formar un sistema de anillo heterocíclico substituido o no substituido o carbocíclico substituido o no substituido que puede formarse por cualquier combinación de R^7 y $R^{7'}$ enlazado al mismo átomo de carbono;

Q_1 es H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilalquilo o arilalquilo substituido, alquinilo o alquinilo substituido, arilo o arilo substituido, heterociclo (por ejemplo heteroarilo) o heterociclo substituido (por ejemplo heteroarilo), halo, CN, $R^1OC=O$, $R^4C=O$, $R^5R^6NC=O$, $HOCR^7R^{7'}$, nitro, R^1OCH_2, R^1O, NH_2, $C=OSR^1$,

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SO_2R^1 o NR^4R^5;

Q_2 es H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilalquilo o arilalquilo substituido, alquinilo o alquinilo substituido, arilo o arilo substituido, heterociclo (por ejemplo heteroarilo) o heterociclo substituido (por ejemplo heteroarilo substituido), halo, CN, $R^1OC{=}O$, $R^4C{=}O$, $R^5R^6NC{=}O$, $HOCR^7R^{7'}$, nitro, R^1OCH_2, R^1O, NH_2, $C{=}OSR^1$, SO_2R^1, o NR^4R^5;

L es un enlace, $(CR^7R^{7'})n$, NH, NR^5, $NH(CR^7R^{7'})n$, o $NR^5(CR^7R^{7'})n$, donde n = 0-3;

R^1 y $R^{1'}$ son cada uno independientemente H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido;

R^2 es alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido,

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cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido;

R^3 y $R^{3'}$ son cada uno independientemente H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido, halo, CN, hidroxilamina, hidroxamida, alcoxi o alcoxi substituido, amino, NR^1R^2, tiol, alquiltio o alquiltio substituido;

R^4 es H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo

substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido, $R^1C{=}O$, $R^1OC{=}O$, $R^1NHC{=}O$, SO_2OR^1, o $SO_2NR^1R^{1'}$;

R^5 es alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido, $R^1C{=}O$, $R^1NHC{=}O$, SO_2R^1, SO_2OR^1, o $SO_2NR^1R^{1'}$;

R^6 es alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido, CN, OH, OR^1, $R^1C{=}O$, $R^1NHC{=}O$, SO_2R^1, SO_2OR^1, o $SO_2NR^1R^{1'}$;

R^7 y $R^{7'}$ son cada uno independientemente H, alquilo o alquilo

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substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido, halo, CN, OR^4, nitro, hidroxilamina, hidroxilamida, amino, NHR^4, NR^2R^5, NOR^1, tiol, alquiltio o alquiltio substituido, HOC=O, R^1C=O, R^1(C=O)O, R^1OC=O, R^1NHC=O, NH_2C=O, SO_2R^1, SOR^1, $PO_3R^1R^{1'}$, $R^1R^{1'}NC$=O, C=OSR^1, SO_2R^1, SO_2OR^1, o $SO_2NR^1R^{1'}$, o, en donde A_1 o A_2 contiene un grupo R^7 y W contiene un grupo R^7, los grupos R^7 de A_1 o A_2 y W forman juntos un anillo heterocíclico;

R^8 y $R^{8'}$ son cada uno independientemente H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido, nitro, halo, CN, OR^1, amino,

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NHR^4, NR^2R^5, NOR^1, alquiltio o alquiltio substituido, $C{=}OSR^1$, $R^1OC{=}O$, $R^1C{=}O$, $R^1NHC{=}O$, $R^1R^{1'}NC{=}O$, SO_2OR^1, $S{=}OR^1$, SO_2R^1, $PO_3R^1R^{1'}$, o $SO_2NR^1R^{1'}$; y

R^9 y $R^{9'}$ son cada uno independientemente H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido, CN, OH, OR^1, $R^1C{=}O$, $R^1OC{=}O$, $R^1NHC{=}O$, SO_2R^1, SO_2OR^1, o $SO_2NR^1R^{1'}$;

con la condición de que:

(1) cuando Y' es -O-, Q_1 y Q_2 son hidrógeno, Z_1 y Z_2 son O, W' es $-CH_2-CH_2-$, y A_1 y A_2 son CH, entonces G-L no es fenilo, fenilo monosubstituido o fenilo que está substituido con dos o más de los siguientes grupos: metoxi, halo, NO_2, metilo, CH_3-S-, OH, CO_2H, trifluorometilo, $-C(O)-C_6H_5$, NH_2, 4-7-epoxi, hexahidro-1H-isoindol-1,3(2H)diona, o $-C(O)-CH_3$;

(2) cuando Y' es -O-, Q_1 y Q_2 son hidrógeno, Z_1 y Z_2 son O, W' es CH_2-CH_2, y uno de A_1 y A_2 es CH y el otro es CR^7, entonces G-L no es fenilo insubstituido;

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(3) cuando Y' es -O-, Q_1 y Q_2 son hidrógeno, Z_1 y Z_2 son O, W' es CH_2-CH_2, y uno de A_1 y A_2 es CH y el otro es C-CH_3, entonces G-L no es fenilo substituido con cloro y/o metilo;

(4) cuando Y' es -O- o -S-, Q_1 y Q_2 son hidrógeno, Z_1 y Z_2 son O, W' es CH_2-CH_2, y uno de A_1 y A_2 es CH y el otro es CH o C-alquilo, entonces G-L no es piperazin-alquilo N-substituido o imidazolidin-alquilo N-substituido;

(5) cuando Y' es -O-; Q_1 y Q_2 son hidrógeno, Z_1 y Z_2 son O, W' es CH_2-CH_2, y A_1 y A_2 son CH, entonces G-L no es oxazol o triazol;

(6) cuando Y' es -O-; Q_1 y Q_2 son hidrógeno o metilo, Z_1 y Z_2 son O, W' es CH_2-CH_2, y A_1 y A_2 son CH o C-CH_3, entonces G-L no es tiazol o tiazol substituido;

(7) cuando Y' contiene un grupo J' seleccionado de S, S=O, SO_2, NH, NR^7, R^2P=O, R^2P=S, R^2OP=O, R^2NHP=O, OP=OOR^2, OP=$ONHR^2$, OSO_2, NHNH, NHR^6, NR^6NH o N=N, W' es $CR^7R^{7'}$-$CR^7R^{7'}$, y Z_1 y Z_2 son O, entonces G-L no es fenilo insubstituido;

(8) cuando Y es NR^7, W' es fenilo insubstituido o substituido, y Q_1 y Q_2 son hidrógeno, entonces Z_1 y Z_2 no son O;

(9) cuando Y' es -O-, Q_1 y Q_2 son hidrógeno, Z_1 y Z_2 son O, W' es dihidroisoxazol que porta un grupo fenilo opcionalmente substituido, y A_1 y A_2 son CH, entonces G-L

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no es fenilo insubstituido o diclorofenilo;

(10) cuando Y' es O, Q_1 y Q_2 son hidrógeno, Z_1 y Z_2 son O, W' es óxido de etileno, y A_1 y A_2 son CH, entonces G-L no es metilfenilo o clorofenilo;

(11) cuando Y' es NR^7—$CR^7R^{7'}$, W' es CR^8=$CR^{8'}$, Q_1 y Q_2 son hidrógeno, A_1 y A_2 son CH, C-CH_3, C-CH_2-C_6H_5 o C-CH_2-CH_3, y Z_1 y Z_2 son O, entonces G-L no es fenilo insubstituido, fenilo monosubstituido o metilpiridinilo;

(12) cuando Y' es $CR^7R^{7'}$—C=O, W' es NR^9—$CR^7R^{7'}$, Q_1 y Q_2 son hidrógeno, A_1 y A_2 son CH, y Z_1 y Z_2 son O, entonces G-L no es fenilo insubstituido;

(13) cuando Y' es $CHR^{7'}$—NR^7 donde $R^{7'}$ es fenilo insubstituido, metoxi o etoxi y R^7 es fenilo insubstituido, metilo o -C(O)-C_6H_5, W' es dimetoxifenileno o fenileno insubstituido, Z_1 y Z_2 son O, Q_1 y Q_2 son hidrógeno, A_1 y A_2 son CH, C-CN, C-C(O)-C_6H_5, o -C(O)-dimetoxifenilo, entonces G-L no es fenilo insubstituido;

(14) el compuesto de la fórmula Ia no es 6,10-epitio-4H-tieno-[3',4':5,6]ciclooct[1,2-f]isoindol-7,9(5H,8H)-diona, 8-(3,5-diclorofenil)-6,6a,9a,10,11,12,-hexahidro-1,3,6,10-tetrametil-2,2,13-trióxido, (6R,6aR,9aS,10S);

(15) cuando Y' es O, W' es -CH_2-CH_2-, Q_1 y Q_2 son metilo, Z_1 y Z_2 son O, y A_1 y A_2 son CH, entonces G-L no es

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fenilo insubstituido, fenilo substituido con metoxi, fenil-alquilo, o morfolin-alquilo, ni es el compuesto conectado a sí mismo a través de un grupo L que es alquileno para formar un compuesto bis;

(16) cuando Y' es -O-, Q_1 y Q_2 son hidrógeno, Z_1 y Z_2 son O, W' es $CR^7R^{7'}$—$CR^7R^{7'}$, y A_1 y A_2 son CH, entonces G-L no es un grupo fenilo insubstituido; y

(17) cuando Y' es -O-, Q_1 y Q_2 son hidrógeno, Z_1 y Z_2 son O, W' es ciclopentilo, ciclohexilo, 3-fenil-2-isoxazolina o $CR^7R^{7'}$—$CR^7R^{7'}$ donde R^7 y $R^{7'}$ son cada uno independientemente definidos como Cl, Br, H y 4-butirolactona y R^7 y $R^{7'}$ no son todos simultáneamente H, y A_1 y A_2 son CH, entonces G-L no es un anillo naftilo insubstituido o un anillo fenilo monosubstituido, donde el substituyente es metoxi, Br, Cl, NO_2, metilo, etilo, CH_2-fenilo, S-fenilo, u O-fenilo;

o una sal, solvato, profármaco o estereisómero farmacéuticamente aceptable del mismo.

2. El compuesto de conformidad con la reivindicación 1, caracterizado porque

G es un grupo arilo o heterociclo donde el grupo es mono- o policíclico, y el cual está opcionalmente substituido en una o más posiciones;

Z_1 es O, S, NH, o NR^6;

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Z_2 es O, S, NH, o NR^6;

A_1 es CR^7 o N;

A_2 es CR^7 o N;

Y' es J-J'-J" donde J es $(CR^7R^{7'})n$ y n = 0-3, J' es un enlace u O, S, S=O, SO_2, NH, NR^7, $CR^7R^{7'}$, $R^2P=O$, $R^2P=S$, $R^2OP=O$, $R^2NHP=O$, $OP=OOR^2$, $OP=ONHR^2$, OSO_2, NHNH, $NHNR^6$, NR^6NH, N=N, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, o heterociclo o heterociclo substituido, y J" es $(CR^7R^{7'})n$ y n = 0-3, donde Y' no es un enlace;

W' es $CR^7CR^{7'}$—$CR^7R^{7'}$, $CR^7R^{7'}$—C=O, C=O—C=O, $CR^7R^{7'}$—$C=CH_2$, $C=CH_2$—$C=CH_2$, $CR^7R^{7'}$—$C=NR^1$, $C=NR^1$—$C=NR^1$, NR^9—$CR^7R^{7'}$, $N=CR^8$, N=N, NR^9—$NR^{9'}$, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, o arilo o arilo substituido, en donde, cuando W' no es NR^9—$CR^7R^{7'}$, $N=CR^8$, N=N, NR^9—$NR^{9'}$, o heterociclo o heterociclo substituido, entonces J' deberá ser O, S, S=O, SO_2, NH, NR^7, $OP=OOR^2$, $OP=ONHR^2$, OSO_2, NHNH, $NHNR^6$, NR^6NH, o N=N; o

cuando W es $CR^7R^{7'}$—$CR^7R^{7'}$, los substituyentes R^7 y $R^{7'}$ cada que se presentan, pueden tomarse juntos para formar un sistema de anillo heterocíclico substituido o no substituido o carbocíclico substituido o no substituido que puede formarse por cualquier combinación de R^7 y $R^{7'}$ enlazado

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al mismo átomo de carbono;

Q_1 es H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilalquilo o arilalquilo substituido, alquinilo o alquinilo substituido, arilo o arilo substituido, heterociclo o heterociclo substituido, halo, CN, $R^1OC{=}O$, $R^4C{=}O$, $R^5R^6NC{=}O$, $HOCR^7R^{7'}$, nitro, R^1OCH_2, R^1O, NH_2, o NR^4R^5;

Q_2 es H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilalquilo o arilalquilo substituido, alquinilo o alquinilo substituido, arilo o arilo substituido, heterociclo o heterociclo substituido, halo, CN, $R^1OC{=}O$, $R^4C{=}O$, $R^5R^6NC{=}O$, $HOCR^7R^{7'}$, nitro, R^1OCH_2, R^1O, NH_2, o NR^4R^5;

L es un enlace, $(CR^7R^{7'})n$, NH, NR^5 o $NR^5(CR^7R^{7'})n$, donde n = 0-3;

R^1 y $R^{1'}$ son cada uno independientemente H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo

substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido;

R^2 es alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido;

R^3 y $R^{3'}$ son cada uno independientemente H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido, halo, CN, hidroxilamina, hidroxamida, alcoxi o alcoxi substituido, amino, NR^1R^2, tiol, alquiltio o alquiltio substituido;

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R^4 es H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido, $R^1C{=}O$, $R^1NHC{=}O$, o $SO_2NR^1R^{1'}$;

R^5 es alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido, $R^1C{=}O$, $R^1NHC{=}O$, SO_2R^1, o $SO_2NR^1R^{1'}$;

R^6 es alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo

substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido, CN, OH, OR^1, $R^1C{=}O$, $R^1NHC{=}O$, SO_2R^1, o $SO_2NR^1R^{1'}$;

R^7 y $R^{7'}$ son cada uno independientemente H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido, halo, CN, OR^4, nitro, hidroxilamina, hidroxilamida, amino, NHR^4, NR^2R^5, NOR^1, tiol, alquiltio o alquiltio substituido, $R^1C{=}O$, $R^1(C{=}O)O$, $R^1OC{=}O$, $R^1NHC{=}O$, SOR^1, $PO_3R^1R^{1'}$, $R^1R^{1'}NC{=}O$, $C{=}OSR^1$, SO_2R^1, o $SO_2NR^1R^{1'}$;

R^8 y $R^{8'}$ son cada uno independientemente H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo

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substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido, nitro, halo, CN, OR^1, amino, NHR^4, NR^2R^5, NOR^1, alquiltio o alquiltio substituido, $C{=}OSR^1$, $R^1OC{=}O$, $R^1C{=}O$, $R^1NHC{=}O$, $R^1R^{1'}NC{=}O$, $S{=}OR^1$, SO_2R^1, $PO_3R^1R^{1'}$, o $SO_2NR^1R^{1'}$;

R^9 y $R^{9'}$ son cada uno independientemente H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido; cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido, CN, OH, OR^1, $R^1C{=}O$, $R^1OC{=}O$, $R^1NHC{=}O$, o $SO_2NR^1R^{1'}$;

con las condiciones (1) hasta (17) de tal fórmula Ia donde (i) cuando Y' es -O- y W' es $CR^7R^{7'}$—$CR^7R^{7'}$, A_1 y A_2 no son simultáneamente CH; y (ii) cuando L es un enlace, G no es un grupo fenilo insubstituido;

o una sal, solvato, profármaco o estereisómero farmacéuticamente aceptable del mismo.

3. El compuesto de conformidad con la reivindicación 1, caracterizado porque

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G es un grupo arilo o heterociclo donde el grupo es mono- o policíclico, y el cual está opcionalmente substituido en una o más posiciones,

Z_1 es O;

Z_2 es O;

A_1 es CR^7;

A_2 es CR^7;

Y' es J-J'-J" donde J es $(CR^7R^{7'})n$ y n = 0-3, J' es un enlace u O, S, S=O, SO_2, NH, NR^7, $CR^7R^{7'}$, $R^2P=O$, $R^2P=S$, $R^2OP=O$, $R^2NHP=O$, $OP=OOR^2$, $OP=ONHR^2$, OSO_2, NHNH, $NHNR^6$, NR^6NH, N=N, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, o heterociclo o heterociclo substituido, y J" es $(CR^7R^{7'})n$ y n = 0-3, donde Y' no es un enlace;

W' es $CR^7R^{7'}$—$CR^7R^{7'}$, $CR^7R^{7'}$—C=O, C=O—C=O, $CR^7R^{7'}$—$C=CH_2$, $C=CH_2$—$C=CH_2$, $CR^7R^{7'}$—$C=NR^1$, $C=NR^1$—$C=NR^1$, NR^9—$CR^7R^{7'}$, $N=CR^8$, N=N, NR^9—$NR^{9'}$, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterocicl o heterociclo substituido, o arilo o arilo substituido, en donde, cuando W' no es NR^9—$CR^7R^{7'}$, $N=CR^8$, N=N, NR^9—$NR^{9'}$, o heterociclo o heterociclo substituido, entonces J' deberá ser O, S, S=O, SO_2, NH, NR^7, $OP=OOR^2$, $OP=ONHR^2$, OSO_2, NHNH, $NHNR^6$, NR^6NH, o N=N; o

cuando W es $CR^7R^{7'}$—$CR^7R^{7'}$, los substituyentes R^7 y $R^{7'}$ cada que

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se presentan, pueden tomarse juntos para formar un sistema de anillo heterocíclico substituido o no substituido o carbocíclico substituido o no substituido que puede formarse por cualquier combinación de R^7 y $R^{7'}$ enlazado al mismo átomo de carbono;

Q_1 es H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilalquilo o arilalquilo substituido, alquinilo o alquinilo substituido, arilo o arilo substituido, heterociclo o heterociclo substituido, halo, CN, $R^4C{=}O$, $R^5R^6NC{=}O$, $HOCR^7R^{7'}$, nitro, R^1OCH_2, R^1O, NH_2, o NR^4R^5;

Q_2 es H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilalquilo o arilalquilo substituido, alquinilo o alquinilo substituido, arilo o arilo substituido, heterociclo o heterociclo substituido, halo, CN, $R^4C{=}O$, $R^5R^6NC{=}O$, $HOCR^7R^{7'}$, nitro, R^1OCH_2, R^1O, NH_2, o NR^4R^5;

L es un enlace;

R^1 y $R^{1'}$ son cada uno independientemente H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o

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cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido;

R^2 es alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido;

R^3 y $R^{3'}$ son cada uno independientemente H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o

arilalquilo substituido, halo, CN, alcoxi o alcoxi substituido, amino, NR^1R^2, alquiltio o alquiltio substituido;

R^4 es H, alquilo o alquilo substituido, alquenilo o alquenil substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido, $R^1C{=}O$, $R^1NHC{=}O$, o $SO_2NR^1R^{1'}$;

R^5 es alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido, $R^1C{=}O$, $R^1NHC{=}O$, SO_2R^1, o $SO_2NR^1R^{1'}$;

R^6 es alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo

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o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido, CN, OH, OR^1, $R^1C{=}O$, $R^1NHC{=}O$, SO_2R^1, o $SO_2NR^1R^{1'}$;

R^7 y $R^{7'}$ son cada uno independientemente H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido, halo, CN, OR^4, nitro, amino, NHR^4, NR^2R^5, alquiltio o alquiltio substituido, $R^1C{=}O$, $R^1(C{=}O)O$, $R^1NHC{=}O$, SO_2R^1, $R^1R^{1'}NC{=}O$, o $SO_2NR^1R^{1'}$;

R^8 y $R^{8'}$ son cada uno independientemente H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo

substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido, nitro, halo, CN, OR^1, amino, NHR^4, NR^2R^5, alquiltio o alquiltio substituido, $R^1C{=}O$, $R^1NHC{=}O$, $R^1R^{1'}NC{=}O$, SO_2R^1, o $SO_2NR^1R^{1'}$; y

R^9 y $R^{9'}$ son cada uno independientemente H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido, CN, OH, OR^1, $R^1C{=}O$, $R^1NHC{=}O$, o $SO_2NR^1R^{1'}$;

con las condiciones (1) hasta (17) de tal fórmula Ia donde (i) cuando Y' es -O- y W' es $CR^7R^{7'}$—$CR^7R^{7'}$, A_1 y A_2 no son simultáneamente CH; y (ii) cuando L es un enlace, G no es un grupo fenilo insubstituido;

o una sal, solvato, profármaco o estereoisómero farmacéuticamente aceptable del mismo.

4. Un compuesto, caracterizado porque es seleccionado del grupo que consiste de:

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(3aα,4β,5β,7β,7aα)-4-[Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-1-isoquinolincarbonitrilo (748D);

[3aS-(3aα,4β,5β,7β,7aα)]-4-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo (471Di) o [3aR-(3aα,4β,5β,7β,7aα)]-4-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo (471Dii);

[3aS-(3aα,4β,5β,7β,7aα)]-5-[7-[2[[3-Cloro-5-(trifluorometil)-2-piridinil]oxi]etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-8-quinolincarbonitrilo (744);

[3aS-(3aα,4β,5β,7β,7aα)]-5-[7-[2-(3-Fluorofenoxi)etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-8-quinolincarbonitrilo (745);

[3aS-(3aα,4β,5β,7β,7aα)]-5-[7-[2-(1,3-Benzodioxol-5-iloxi)etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-8-quinolincarbonitrilo;

[3aS-(3aα,4β,5β,7β,7aα)]-5-[7-[2-(4-Fluorofenoxi)etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-8-quinolincarbonitrilo;

[3aS-(3aα,4β,5β,7β,7aα)]-5-[7-[2-(1,2-Bencisoxazol-3-iloxi)etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-

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2H-isoindol-2-il]-8-quinolincarbonitrilo;

[3aS-(3aα,4β,5β,7β,7aα)]-5-[7-[2-[(5-cloro-1,2-bencisoxazol-3-il)oxi]etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-8-quinolincarbonitrilo (737);

[3aS-(3aα,4β,7β,7aα)]-5-[4-[2-[(5-cloro-2-piridinil)oxi]etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-8-quinolincarbonitrilo (577);

[3aS-(3aα,4β,7β,7aα)]-5-[Octahidro-4-metil-1,3-dioxo-7-[2-[[6-(trifluorometil)-4-pirimidinil]oxi]etil]-4,7-epoxi-2H-isoindol-2-il]-8-quinolincarbonitrilo (579);

[3aS-(3aα,4β,7β,7aα)]-5-[4-[2-[(5-cloro-1,2-bencisoxazol-3-il)oxi]etil]octahidro-7-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-8-quinolincarbonitrilo (581);

[3aS-(3aα,4β,7β,7aα)]-5-[Octahidro-4-metil-7-[2-(5-metil-2H-1,2,3-benzotriazol-2-il)etil]-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-8-quinolincarbonitrilo (589);

[3aS-(3aβ,4β,5β,7β,7aα)]-5-[Octahidro-5-hidroxi-4-metil-1,3-dioxo-7-[2-[[6-(trifluorometil)-4-pirimidinil]oxi]etil]-4,7-epoxi-2H-isoindol-2-il]-8-quinolincarbonitrilo (689);

[3aR-(3aα,4β,7β,7aα)]-5-[7-[2-[(5-cloro-2-piridinil)oxi]etil]octahidro-5-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-8-quinolincarbonitrilo (487);

[3aR-(3aα,4β,5β,7β,7aα)]-4-(Octahidro-5-hidroxi-4,7-

dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-yodobenzonitrilo (489Gi);

[3aS-(3aα,4β,5β,7β,7aα)]-4-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-yodobenzonitrilo (489Gii);

(3aα,4β,7β,7aα)-4-(Octahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-1,2-bencencarbonitrilo (313);

(3aα,4β,7β,7aα)-2-Metoxi-4-(Octahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)benzonitrilo (328);

(3aα,4β,7β,7aα)-5-(Octahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-8-quinolincarbonitrilo (345);

(3aα,4β,7β,7aα)-2-(Metiltio)-4-(octahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)benzonitrilo (224);

(3aα,4β,7β,7aα)-2-(6-Benzotiazolil)hexahidro-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3(2H)-diona (368);

(3aα,4β,7β,7aα)-7-[Octahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il]-2,1,3-benzoxadiazol-4-carbonitrilo (423); y

(3aα,4β,7β,7aα)-2-(2,1,3-Benzoxadiazol-5-il)hexahidro-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3(2H)-diona (480B);

o una sal, solvato o profármaco farmacéuticamente aceptable del mismo.

5. Un compuesto caracterizado porque es seleccionado del grupo que consiste de:

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[3aS-(3aα,4β,6β,7β,7aα)]-4-(Octahidro-6-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

[3aR(3aα,4β,6β,7β,7aα)]-4-(Octahidro-6-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

[3aS-(3aα,4β,5β,6α,7β,7aα)]-4-(Octahidro-5,6-dihidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

[3aS-(3aα,4β,5β,7β,7aα)]-5-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-3metil-2-piridincarbonitrilo;

[3aS-(3aα,4β,5β,7β,7aα)]-2-(2,1,3-Benzoxadiazol-5-il)hexahidro-5-hidroxi-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3(2H)-diona;

[3aS-(3aα,4β,5β,7β,7aα)]-5-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-3,4-dimetil-2-piridincarbonitrilo;

[3aR-(3aα,4β,5β,7β,7aα)]-5-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-3,4-dimetil-2-piridincarbonitrilo;

[3aS-(3aα,4β,5β,7β,7aα)]-2-(6-Benzotiazolil)hexahidro-5-hidroxi-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3(2H)-diona;

[3aR-(3aα,4β,5β,7β,7aα)]-2-(7-Cloro-2,1,3-benzoxadiazol-

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4-il)hexahidro-5-hidroxi-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3(2H)-diona;

[3aR-(3aα,4β,5α,7β,7aα)]-5-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-3-(trifluorometil)-2-piridincarbonitrilo;

[3aR-(3aα,4β,5α,7β,7aα)]-4-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-yodobenzonitrilo;

éster de metilo del ácido (3aα,4β,5α,6β,7β,7aα)-2-(4-Ciano-3-(trifluorometil)fenil)hexahidro-6-ciano-4,7-dimetil-1,3-dioxo-4,7-epoxi-1H-isoindol-5-carboxílico;

(3aα,4β,7β,7aα)-4-(Octahidro-4,7,8-trimetil-1,3-dioxo-4,7-imino-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

[3aR-(3aα,4β,5β,6α,7β,7aα)]-4-(Octahidro-5,6-dicloro-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

[3aS-(3aα,4β,5β,6α,7β,7aα)]-4-(Octahidro-5,6-dicloro-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

(3aα,4β,7β,7aα)-4-(Octahidro-4,7-dimetil-1,3,5-trioxo-4,7-epoxi-2H-isoindol-2-il)-2-yodobenzonitrilo;

(3aα,4β,5α,7β,7aα)-4-(Octahidro-5-[[[difluorometil]oxi]metil]-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

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(3aα,4β,5α,7β,7aα)-4-(Octahidro-5-[[fenilmetoxicarbonil]amino]-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

(3aα,4β,5α,7β,7aα)-4-(Octahidro-5-[[propiloxicarbonil]amino]-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

(3aα,4β,5α,7β,7aα)-4-(Octahidro-5-[[[ciclopropilmetiloxi]carbonil]amino]-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

(3aα,4β,5α,7β,7aα)-4-(Octahidro-5-[[metoxicarbonil]amino]-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

[3aR-(3aα,4β,5β,7β,7aα)]-4-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2,3-diclorobenzonitrilo;

[3aR-(3aα,4β,4aα,5aα,6β,7aα)]-4-(Octahidro-4a-hidroxi-4,6-dimetil-1,3-dioxo-dimetil-1,3-dioxo-4,6-epoxiciclopropf[f]isoindol-2(1H)-il)-2-(trifluorometil)benzonitrilo;

(3aα,4β,5α,7β,7aα)-2-(4-Ciano-3-(trifluorometil)fenil)hexahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-N,N-dimetil-1H-isoindol-5-carboxamida;

[3aR-(3aα,4β,5β,6β,7β,7aα)]-4-(Octahidro-5-cloro-6-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-

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(trifluorometil)benzonitrilo;

[3aS-(3aα,4β,5β,6β,7β,7aα)]-4-(Octahidro-5-cloro-6-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

(3aα,4β,5α,7β,7aα)-4-(Octahidro-5-[[[6-(trifluorometil)-4-pirimidinil]oxi]metil]-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

(3aα,4β,5α,7β,7aα)-4-(Octahidro-5-[[[5-cloro-2-piridinil]oxi]metil]-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

[3aR-(3aα,4β,5α,7β,7aα)]-4-(Octahidro-5-[[[fenilamino]carbonil]amino]-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

[3aR-(3aα,4β,5α,7β,7aα)]-4-(Octahidro-5-[[(1-metiletiloxi)carbonil]amino]-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

(3aα,4β,5α,7β,7aα)-4-(Octahidro-5-[[[5-fluoro-4-pirimidinil]oxi]metil]-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

[3aR-(3aα,4β,5α,7β,7aα)]-4-(Octahidro-5-[[etiloxicarbonil]amino]-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

éster de 4-piridinilmetilo del ácido [3aR-(3aα,4β,5α,7β,7aα)]-2-(4-Ciano-3-(trifluorometil)fenil)-

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hexahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-1H-isoindol-5-carboxílico;

[3aR-(3aα,4β,5α,7β,7aα)]-4-(Octahidro-5-[[4-piridinilmetoxicarbonil]amino]-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

3aα,4β,5β,7β,7aα)-4-(Octahidro-5-[[[2-metil-5-(trifluorometil)-2H-pirazol-3-il]oxi]metil]-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

éster de metilo del ácido (3aα,4β,5α,7β,7aα)-2-(4-Ciano-3-(trifluorometil)fenil)hexahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-1H-isoindol-5-carboxílico;

[3aR-(3aα,4β,5β,7β,7aα)]-4-(Octahidro-5-ciclopropilmetoxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

(3aα,4β,5α,7β,7aα)-4-(Octahidro-5-[[((fenilmetil)amino)carbonil]oxi]-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo; y

[3aR-(3aα,4β,5β,7β,7aα)]-4-(Octahidro-5-ciclopropiloxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

o una sal, solvato o profármaco farmacéuticamente aceptable del mismo.

6. Un compuesto caracterizado porque es seleccionado del

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grupo que consiste de:

[3aR-(3aα,4β,5β,7β,7aα)]-5-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-3-(trifluorometil)-2-piridincarbonitrilo;

[3aS-(3aα,4β,5β,7β,7aα)]-5-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-3-(trifluorometil)-2-piridincarbonitrilo;

[3aR-(3aα,4β,5β,7β,7aα)]-2-(4-Cloro-3-yodofenil)hexahidro-5-hidroxi-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3(2H)-diona;

[3aS-(3aα,4β,5β,6α,7β,7aα)]-4-(Octahidro-5,6-dihidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

[3aR-(3aα,4β,7β,7aα)]-4-(Octahidro-4,7-dimetil-1,3,5-trioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

[3aR-(3aα,4β,5α,7β,7aα)]-4-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

[3aS-(3aα,4β,5α,7β,7aα)]-4-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

[3aS-(3aα,4β,6β,7β,7aα)]-4-(Octahidro-6-hidroxi-4-metil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-

(trifluorometil)benzonitrilo;

[3aR-(3aα,4β,5β,7β,7aα)]-2-(4-Cloro-3-(trifluorometil)fenil)hexahidro-5-hidroxi-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3(2H)-diona;

[3aS-(3aα,4β,5β,7β,7aα)]-4-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-yodobenzonitrilo;

[3aR-(3aα,4β,5β,7β,7aα)]-4-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-yodobenzonitrilo;

[3aS-(3aα,4β,5β,7β,7aα)]-2-(4-Cloro-3-(trifluorometil)piridinil)hexahidro-5-hidroxi-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3(2H)-diona;

[3aR-(3aα,4β,5β,7β,7aα)]-4-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-3-metil-2-(trifluorometil)benzonitrilo;

[3aR-(3aα;4β,5β,7β,7aα)]-4-(Octahidro-5-metoxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

[3aR-(3aα,4β,5α,7β,7aα)]-5-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-3-(trifluorometil)-2-piridincarbonitrilo;

[3aS-(3aα,4β,5β,7β,7aα)]-4-(Octahidro-5-metoxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-

(trifluorometil)benzonitrilo;

[3aS-(3aα,4β,6β,7β,7aα)]-4-(Octahidro-6-fluoro-5,5-dihidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

[3aR-(3aα,4β,7β,7aα)]-5-(Octahidro-4,7-dimetil-1,3,5-trioxo-4,7-epoxi-2H-isoindol-2-il)-3-(trifluorometil)-2-piridincarbonitrilo;

[3aS-(3aα,4β,5β,7β,7aα)]-2-(4-Cloro-2-metil-3-(trifluorometil)fenil)hexahidro-5-hidroxi-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3(2H)-diona;

[3aR-(3aα,4β,5β,7β,7aα)]-2-(4-Cloro-2-metil-3-(trifluorometil)fenil)hexahidro-5-hidroxi-4,7-dimetil-4,7-epoxi-1H-isoindol-1,3(2H)-diona;

(3aα,4β,6β,7β,7aα)-4-(Octahidro-6-fluoro-5,5-dihidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-yodobenzonitrilo;

éster de metilo del ácido (3aα,4β,5α,7β,7aα)-2-(4-Ciano-3-(trifluorometil)fenil)-hexahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-1H-isoindol-5-carboxílico;

[3aS-(3aα,4β,6β,7β,7aα)]-4-(Octahidro-6-fluoro-5,5-dihidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-yodobenzonitrilo;

(3aα,4β,5α,7β,7aα)-4-(Octahidro-5-etilsulfonamido-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-

(trifluorometil)benzonitrilo;

[3aR-(3aα,4β,5α,7β,7aα)]-4-(Octahidro-5-[[(4-fluorofenilamino)carbonil]oxi]-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

[3aR-(3aα,4β,5α,7β,7aα)]-4-(Octahidro-5-[[(1-metiletilamino)carbonil]oxi]-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

[3aS-(3aα,4β,5α,7β,7aα)]-4-(Octahidro-5-[[(1-metiletoxi)carbonil]amino]-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

[3aR-(3aα,4β,6β,7β,7aα)]-4-(Octahidro-6-fluoro-5,5-dihidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-yodobenzonitrilo;

[3aR-(3aα,4β,5α,7β,7aα)]-2-(4-Ciano-3-(trifluorometil)fenil)hexahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-N-metil-N-fenil-1H-isoindol-5-carboxamida;

[3R-(3aα,4β,5β,7β,7aα)]-4-(Octahidro-5-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-cloro-3-metilbenzonitrilo;

[3aR-(3aα,4β,5α,7β,7aα)]-4-(Octahidro-5-[[etoxicarbonil]amino]-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

(3aα,4β,5α,7β,7aα)-4-(Octahidro-5-[[[2-metil-5-(trifluorometil)-2H-pirazol-3-il]oxi]metil]-4,7-dimetil-1,3-

dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

éster de metilo del ácido [3aS-(3aα,4β,5α,6β,7β,7aα)]-2-(4-Ciano-3-(trifluorometil)fenil)-hexahidro-6-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-1H-isoindol-5-carboxílico;

(3aα,4β,5α,7β,7aα)-4-(Octahidro-5-[[[6-(trifluorometil)-4-pirimidinil]oxi]metil]-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

[3aR-(3aα,4β,5α,7β,7aα)]-4-(Octahidro-5-metoxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

(3aα,4β,5α,7β,7aα)-2-(4-Ciano-3-(trifluorometil)fenil)-hexahidro-4,7-dimetil-1,3-dioxo-4,7-epoxi-1H-isoindol-5-carbonitrilo;

[3aR-(3aα,4β,5β,6α,7β,7aα)]-4-(Octahidro-5,6-dihidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-3-metil-2-(trifluorometil)benzonitrilo;

[3aR-(3aα,4β,5α,7β,7aα)]-4-(Octahidro-5-[[[(ciclopropilmetil)amino]carbonil]amino]-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

[3aR-(3aα,4β,5α,7β,7aα)]-4-(Octahidro-5-[[(dimetilamino)sulfonil]amino]-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

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(3aα,4β,5α,7β,7aα)-4-(Octahidro-5-benzenesulfonamido-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

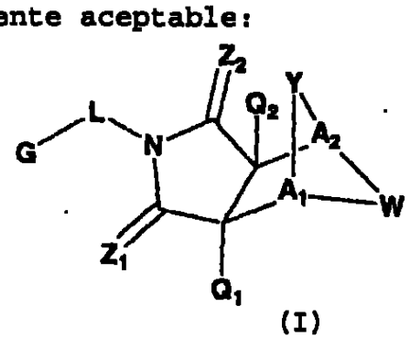
[3aR-(3aα,4β,6β,7β,7aα)]-4-(Octahidro-6-fluoro-5,5-dihidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

éster de metilo del ácido [3aR-(3aα,4β,5α,6β,7β,7aα)]-2-(4-Ciano-3-(trifluorometil)fenil)-hexahidro-6-hidroxi-4,7-dimetil-1,3-dioxo-4,7-epoxi-1H-isoindol-5-carboxílico; y

[3aR-(3aα,4β,5α,7β,7aα)]-4-(Octahidro-5-[[(dimetilamino)sulfonil]amino]-4,7-dimetil-1,3-dioxo-4,7-epoxi-2H-isoindol-2-il)-2-(trifluorometil)benzonitrilo;

o una sal, solvato, profármaco farmacéuticamente aceptable del mismo.

7. Una composición farmacéutica capaz de tratar una condición asociada a NHR, caracterizada porque comprende un compuesto de la siguiente fórmula I o una sal farmacéuticamente aceptable del mismo y un portador farmacéuticamente aceptable:



(I)

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en donde los símbolos tienen los siguientes significados y son, cada que se presentan, seleccionados independientemente:

G es un grupo arilo o heterociclo donde el grupo es mono- o policíclico, y el cual está opcionalmente substituido en una o más posiciones;

Z_1 es O, S, NH, o NR^6;

Z_2 es O, S, NH, o NR^6;

A_1 es CR^7 o N;

A_2 es CR^7 o N;

Y es J-J'-J" donde J es $(CR^7R^{7'})n$ y n = 0-3, J' es un enlace u O, S, S=O, SO_2, NH, NR^7, C=O, OC=O, $NR^1C=O$, $CR^7R^{7'}$, $C=CR^8R^{8'}$, $R^2P=O$, $R^2P=S$, $R^2OP=O$, $R^2NHP=O$, $OP=OOR^2$, $OP=ONHR^2$, $OP=OR^2$, OSO_2, $C=NR^7$, NHNH, $NHNR^6$, NR^6NH, N=N, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, o arilo o arilo substituido y J" es $(CR^7R^{7'})n$ y n = 0-3, donde Y no es un enlace;

W es $CR^7CR^{7'}$—$CR^7R^{7'}$, $CR^8=CR^{8'}$, $CR^7R^{7'}$—C=O, C=O—C=O, $CR^7R^{7'}$—$C=CH_2$, $C=CH_2$—$C=CH_2$, $CR^7R^{7'}$—$C=NR^1$, $C=NR^1$—$C=NR^1$, NR^9—$CR^7R^{7'}$, $N=CR^8$, N=N, NR^9—$NR^{9'}$, S-$CR^7R^{7'}$, SO-$CR^7R^{7'}$, SO_2-$CR^7R^{7'}$, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, o arilo o arilo substituido, en donde, cuando W no es NR^9—$CR^7R^{7'}$, $N=CR^8$, N=N, NR^9—$NR^{9'}$, S-$CR^7R^{7'}$,

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$SO-CR^7R^{7'}$, $SO_2-CR^7R^{7'}$, o heterociclo o heterociclo substituido, entonces J' deberá ser O, S, S=O, SO_2, NH, NR^7, OC=O, $NR^1C=O$, $OP=OOR^2$, $OP=ONHR^2$, OSO_2, NHNH, $NHNR^6$, NR^6NH, o N=N; o

cuando W es $CR^7R^{7'}-CR^7R^{7'}$, los substituyentes cada que se presentan, pueden tomarse juntos para formar un sistema de anillo heterocíclico substituido o no substituido o carbocíclico substituido o no substituido que puede formarse por cualquier combinación de R^7 y $R^{7'}$ enlazado al mismo átomo de carbono;

Q_1 es H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilalquilo o arilalquilo substituido, alquinilo o alquinilo substituido, arilo o arilo substituido, heterociclo (por ejemplo, heteroarilo) o heterociclo substituido (por ejemplo, heteroarilo substituido), halo, CN, $R^1OC=O$, $R^4C=O$, $R^5R^6NC=O$, $HOCR^7R^{7'}$, nitro, R^1OCH_2, R^1O, NH_2, $C=OSR^1$, SO_2R^1 o NR^4R^5;

Q_2 es H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilalquilo o arilalquilo substituido, alquinilo o

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alquinilo substituido, arilo o arilo substituido, heterociclo o heterociclo substituido, halo, CN, $R^1OC{=}O$, $R^4C{=}O$, $R^5R^6NC{=}O$, $HOCR^7R^{7'}$, nitro, R^1OCH_2, R^1O, NH_2, $C{=}OSR^1$, SO_2R^1 o NR^4R^5;

L es un enlace, $(CR^7R^{7'})n$, NH, NR^5, $NH(CR^7R^{7'})n$ o $NR^5(CR^7R^{7'})n$, donde n = 0-3;

R^1 y $R^{1'}$ son cada uno independientemente H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido;

R^2 es alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido;

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R^3 y $R^{3'}$ son cada uno independientemente H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido, halo, CN, hidroxilamina, hidroxamida, alcoxi o alcoxi substituido, amino, NR^1R^2, tiol, alquiltio o alquiltio substituido;

R^4 es H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido, $R^1C{=}O$, $R^1OC{=}O$, $R^1NHC{=}O$, SO_2OR^1, o $SO_2NR^1R^{1'}$;

R^5 es alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo

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o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido, $R^1C{=}O$, $R^1NHC{=}O$, SO_2R^1, SO_2OR^1, o $SO_2NR^1R^{1'}$;

R^6 es alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido, CN, OH, OR^1, $R^1C{=}O$, $R^1NHC{=}O$, SO_2R^1, SO_2OR^1, o $SO_2NR^1R^{1'}$;

R^7 y $R^{7'}$ son cada uno independientemente H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo

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substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido, halo, CN, OR^4, nitro, hidroxilamina, hidroxilamida, amino, NHR^4, NR^2R^5, NR^5R^5, NOR^1, tiol, alquiltio o alquiltio substituido, HOC=O, $R^1C{=}O$, $R^1(C{=}O)O$, $R^1OC{=}O$, $R^1NHC{=}O$, $NH_2C{=}O$, SO_2R^1, SOR^1, $PO_3R^1R^{1'}$, $R^1R^{1'}NC{=}O$, $C{=}OSR^1$, SO_2R^1, SO_2OR^1, o $SO_2NR^1R^{1'}$, o en donde A_1, A_2 contiene un grupo R^7 y W contiene un grupo R^7, los grupos R^7 de A_1 o A_2 y W forman juntos un anillo heterociclico;

R^8 y $R^{8'}$ son cada uno independientemente H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido, nitro, halo, CN, OR^1, amino, NHR^4, NR^2R^5, NOR^1, alquiltio o alquiltio substituido, $C{=}OSR^1$, $R^1OC{=}O$, $R^1C{=}O$, $R^1NHC{=}O$, $R^1R^{1'}NC{=}O$, SO_2OR^1, $S{=}OR^1$, SO_2R^1, $PO_3R^1R^{1'}$, o $SO_2NR^1R^{1'}$; y

R^9 y $R^{9'}$ son cada uno independientemente H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido; cicloalquilo o

cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido, CN, OH, OR^1, $R^1C{=}O$, $R^1OC{=}O$, $R^1NHC{=}O$, SO_2R^1, SO_2OR^1o $SO_2NR^1R^{1'}$;

8. Una composición farmacéutica de conformidad con la reivindicación 7, caracterizada porque además comprende otro agente anti-cáncer.

9. Una composición farmacéutica capaz de tratar una condición asociada con NHR, caracterizada porque comprende al menos un compuesto como se define en la reivindicación 2 o una sal farmacéuticamente aceptable del mismo, y un portador farmacéuticamente aceptable.

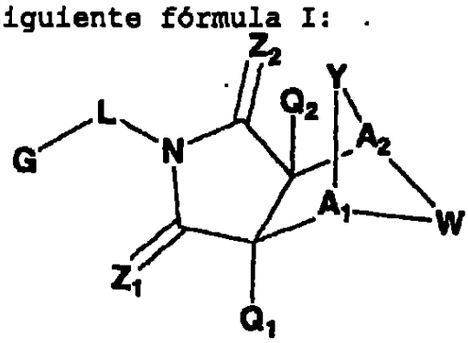
10. La composición farmacéutica de conformidad con la reivindicación 9, caracterizada porque comprende además otro agente anti-cáncer.

11. Una composición farmacéutica capaz de tratar una condición asociada con NHR, caracterizada porque comprende al menos un compuesto como se define en la reivindicación 3 o una sal farmacéuticamente aceptable del mismo, y un portador farmacéuticamente aceptable.

12. La composición farmacéutica de conformidad con la

reivindicación 11, caracterizada porque comprende además otro agente anti-cáncer.

13. Un método de modulación de la función del receptor de hormona nuclear, caracterizada porque comprende administrar a una especie de mamífero que necesite del mismo una cantidad efectiva moduladora del receptor de hormona nuclear de la siguiente fórmula I:



(I)

en donde los símbolos tienen los siguientes significados y son, cada que se presentan, seleccionados independientemente:

G es un grupo arilo o heterociclo donde el grupo es mono- o policíclico, y el cual está opcionalmente substituido en una o más posiciones;

Z_1 es O, S, NH, o NR^6;

Z_2 es O, S, NH, o NR^6;

A_1 es CR^7 o N;

A_2 es CR^7 o N;

Y es J-J'-J" donde J es $(CR^7R^{7'})n$ y n = 0-3, J' es un enlace u O, S, S=O, SO_2, NH, NR^7, C=O, OC=O, NR^1C=O, $CR^7R^{7'}$, $C=CR^8R^{8'}$, R^2P=O, R^2P=S, R^2OP=O, R^2NHP=O, OP=OOR^2, OP=$ONHR^2$,

$OP{=}OR^2$, OSO_2, $C{=}NR^7$, NHNH, $NHNR^6$, NR^6NH, N=N, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, o heterociclo o heterociclo substituido, o arilo o arilo substituido, y J" es $(CR^7R^{7'})n$ y n = 0-3, donde Y no es un enlace;

W es $CR^7CR^{7'}{-}CR^7R^{7'}$, $CR^8{=}CR^{8'}$, $CR^7CR^{7'}{-}C{=}O$, $C{=}O{-}C{=}O$, $CR^7R^{7'}{-}C{=}CH_2$, $C{=}CH_2{-}C{=}CH_2$, $CR^7R^{7'}{-}C{=}NR^1$, $C{=}NR^1{-}C{=}NR^1$, $NR^9{-}CR^7R^{7'}$, $N{=}CR^8$, N=N, $NR^9{-}NR^{9'}$, $S{-}CR^7R^{7'}$, $SO{-}CR^7R^{7'}$, $SO_2{-}CR^7R^{7'}$, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, o arilo o arilo substituido, en donde cuando W no es $NR^9{-}CR^7R^{7'}$, $N{=}CR^8$, N=N, $NR^9{-}NR^{9'}$, $S{-}CR^7R^{7'}$, $SO{-}CR^7R^{7'}$, $SO_2{-}CR^7R^{7'}$, o heterociclo o heterociclo substituido, entonces J' deberá ser O, S, S=O, SO_2, NH, NR^7, OC=O, $NR^1C{=}O$, $OP{=}OOR^2$, $OP{=}ONHR^2$, OSO_2, NHNH, $NHNR^6$, NR^6NH, o N=N; o

cuando W es $CR^7R^{7'}{-}CR^7R^{7'}$, los substituyentes cada que se presentan, pueden tomarse juntos para formar un sistema de anillo heterocíclico substituido o no substituido o carbocíclico substituido o no substituido que puede formarse por cualquier combinación de R^7 y $R^{7'}$ enlazado al mismo átomo de carbono;

Q_1 es H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, cicloalquilo o cicloalquilo substituido,

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cicloalquenilo o cicloalquenilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilalquilo o arilalquilo substituido, alquinilo o alquinilo substituido, arilo o arilo substituido, heterociclo o heterociclo substituido, halo, CN, $R^1OC{=}O$, $R^4C{=}O$, $R^5R^6NC{=}O$, $HOCR^7R^{7'}$, nitro, R^1OCH_2, R^1O, NH_2, $C{=}OSR^1$, SO_2R^1 o NR^4R^5;

Q_2 es H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilalquilo o arilalquilo substituido, alquinilo o alquinilo substituido, arilo o arilo substituido, heterociclo (por ejemplo, heteroarilo) o heterociclo substituido (por ejemplo, heteroarilo substituido), halo, CN, $R^1OC{=}O$, $R^4C{=}O$, $R^5R^6NC{=}O$, $HOCR^7R^{7'}$, nitro, R^1OCH_2, R^1O, NH_2, $C{=}OSR^1$, SO_2R^1, o NR^4R^5;

L es un enlace, $(CR^7R^{7'})n$, NH, NR^5, $NH(CR^7R^{7'})n$, o $NR^5(CR^7R^{7'})n$, donde n = 0-3;

R^1 y $R^{1'}$ son cada uno independientemente H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo

substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido;

R^2 es alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido;

R^3 y $R^{3'}$ son cada uno independientemente H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido, halo, CN, hidroxilamina, hidroxamida, alcoxi o alcoxi substituido, amino, NR^1R^2, tiol, alquiltio o alquiltio substituido;

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R^4 es H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido, $R^1C{=}O$, $R^1OC{=}O$, $R^1NHC{=}O$, SO_2OR^1, SO_2R^1 o $SO_2NR^1R^{1'}$;

R^5 es alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido, $R^1C{=}O$, $R^1NHC{=}O$, SO_2R^1, SO_2OR^1, o $SO_2NR^1R^{1'}$;

R^6 es alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo

substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido, CN, OH, OR^1, $R^1C{=}O$, $R^1NHC{=}O$, SO_2R^1, SO_2OR^1, o $SO_2NR^1R^{1'}$;

R^7 y $R^{7'}$ son cada uno independientemente H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido, halo, CN, OR^4, nitro, hidroxilamina, hidroxilamida, amino, NHR^4, NR^2R^5, NR^5R^5, NOR^1, tiol, alquiltio o alquiltio substituido, $HOC{=}O$, $R^1C{=}O$, $R^1(C{=}O)O$, $R^1OC{=}O$, $R^1NHC{=}O$, $NH_2C{=}O$, SO_2R^1, SOR^1, $PO_3R^1R^{1'}$, $R^1R^{1'}NC{=}O$, $C{=}OSR^1$, SO_2R^1, SO_2OR^1, o $SO_2NR^1R^{1'}$, o, en donde A_1 o A_2 contiene un grupo R^7 y W contiene un grupo R^7, los grupos R^7 de A_1 o A_2 y W forman juntos un anillo heterocíclico;

R^8 y $R^{8'}$ son cada uno independientemente H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o

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cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido, nitro, halo, CN, OR^1, amino, NHR^4, NR^2R^5, NOR^1, alquiltio o alquiltio substituido, $C{=}OSR^1$, $R^1OC{=}O$, $R^1C{=}O$, $R^1NHC{=}O$, $R^1R^{1'}NC{=}O$, SO_2OR^1, $S{=}OR^1$, SO_2R^1, $PO_3R^1R^{1'}$, o $SO_2NR^1R^{1'}$; y

R^9 y $R^{9'}$ son cada uno independientemente H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido CN, OH, OR^1, $R^1C{=}O$, $R^1OC{=}O$, $R^1NHC{=}O$, SO_2R^1, SO_2OR^1, o $SO_2NR^1R^{1'}$;

o una sal, solvato, profármaco farmacéuticamente aceptable del mismo.

14. El método de conformidad con la reivindicación 13, caracterizado porque el receptor de hormona nuclear es un

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receptor de hormona nuclear de enlace esteroide.

15. El método de conformidad con la reivindicación 13, caracterizado porque el receptor de hormona nuclear es el receptor andrógeno.

16. El método de conformidad con la reivindicación 13, caracterizado porque el receptor de hormona nuclear es el receptor estrógeno.

17. El método de conformidad con la reivindicación 13, caracterizado porque el receptor de hormona nuclear es el receptor de progesterona.

18. El método de conformidad con la reivindicación 13, caracterizado porque el receptor de hormona nuclear es el receptor glucocorticoide.

19. El método de conformidad con la reivindicación 13, caracterizado porque el receptor de hormona nuclear es el receptor mineralocorticoide.

20. El método de conformidad con la reivindicación 13, caracterizado porque el receptor de hormona nuclear es el receptor de aldosterona.

21. El método de conformidad con la reivindicación 13, caracterizado porque el receptor de hormona nuclear es el receptor RORbeta.

22. El método de conformidad con la reivindicación 13, caracterizado porque el receptor de hormona nuclear es el receptor COUP-TF2.

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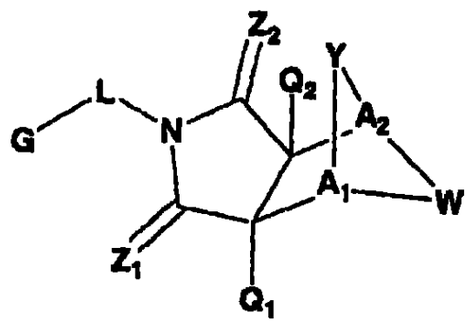
23. Un método para el tratamiento de una condición o trastorno, caracterizado porque comprende administrar a una especie de mamíferos en necesidad del mismo una cantidad terapéuticamente efectiva de un compuesto de la siguiente fórmula:



(I)

o una sal, solvato, profármaco farmacéuticamente aceptable del mismo,

en donde los símbolos tienen los siguientes significados y son, cada que se presentan, seleccionados independientemente:

G es un grupo arilo o heterociclo, donde el grupo es mono- o policíclico, y el cual está opcionalmente substituido en una o más posiciones;

Z_1 es O, S, NH, o NR^6;

Z_2 es O, S, NH, o NR^6;

A_1 es CR^7 o N;

A_2 es CR^7 o N;

Y es J-J'-J" donde J es $(CR^7R^{7'})n$ y n = 0-3, J' es un enlace u O, S, S=O, SO_2, NH, NR^7, C=O, OC=O, NR^1C=O, $CR^7R^{7'}$,

$C=CR^8R^{8'}$, $R^2P=O$, $R^2P=S$, $R^2OP=O$, $R^2NHP=O$, $OP=OOR^2$, $OP=ONHR^2$, $OP=OR^2$, OSO_2, $C=NR^7$, NHNH, $NHNR^6$, NR^6NH, N=N, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, o heterociclo o heterociclo substituido, o arilo o arilo substituido, y J" es $(CR^7R^{7'})n$ y n = 0-3, donde Y no es un enlace;

W es $CR^7CR^{7'}-CR^7R^{7'}$, $CR^8=CR^{8'}$, $CR^7CR^{7'}-C=O$, $C=O-C=O$, $CR^7R^{7'}-C=CH_2$, $C=CH_2-C=CH_2$, $CR^7R^{7'}-C=NR^1$, $C=NR^1-C=NR^1$, $NR^9-CR^7R^{7'}$, $N=CR^8$, N=N, $NR^9-NR^{9'}$, $S-CR^7R^{7'}$, $SO-CR^7R^{7'}$, $SO_2-CR^7R^{7'}$, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, o arilo o arilo substituido, en donde cuando W no es $NR^9-CR^7R^{7'}$, $N=CR^8$, N=N, $NR^9-NR^{9'}$, $S-CR^7R^{7'}$, $SO-CR^7R^{7'}$, $SO_2-CR^7R^{7'}$, o heterociclo o heterociclo substituido, entonces J' deberá ser O, S, S=O, SO_2, NH, NR^7, OC=O, $NR^1C=O$, $OP=OOR^2$, $OP=ONHR^2$, OSO_2, NHNH, $NHNR^6$, NR^6NH, o N=N; o

cuando W es $CR^7R^{7'}-CR^7R^{7'}$, los substituyentes cada que se presentan, pueden tomarse juntos para formar un sistema de anillo heterocíclico substituido o no substituido o carbocíclico substituido o no substituido que puede formarse por cualquier combinación de R^7 y $R^{7'}$ enlazado al mismo átomo de carbono;

Q_1 es H, alquilo o alquilo substituido, alquenilo o alquenilo

substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilalquilo o arilalquilo substituido, alquinilo o alquinilo substituido, arilo o arilo substituido, heterociclo (por ejemplo, heteroarilo) o heterociclo substituido (por ejemplo, heteroarilo substituido), halo, CN, $R^1OC{=}O$, $R^4C{=}O$, $R^5R^6NC{=}O$, $HOCR^7R^{7'}$, nitro, R^1OCH_2, R^1O, NH_2, $C{=}OSR^1$, SO_2R^1 o NR^4R^5;

Q_2 es H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilalquilo o arilalquilo substituido, alquinilo o alquinilo substituido, arilo o arilo substituido, heterociclo (por ejemplo, heteroarilo) o heterociclo substituido (por ejemplo, heteroarilo substituido), halo, CN, $R^1OC{=}O$, $R^4C{=}O$, $R^5R^6NC{=}O$, $HOCR^7R^{7'}$, nitro, R^1OCH_2, R^1O, NH_2, $C{=}OSR^1$, SO_2R^1, o NR^4R^5;

L es un enlace, $(CR^7R^{7'})n$, NH, NR^5, $NH(CR^7R^{7'})n$, o $NR^5(CR^7R^{7'})n$, donde n = 0-3;

R^1 y $R^{1'}$ son cada uno independientemente H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o

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cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido;

R^2 es alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido;

R^3 y $R^{3'}$ son cada uno independientemente H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido, halo, CN, hidroxilamina,

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hidroxamida, alcoxi o alcoxi substituido, amino, NR^1R^2, tiol, alquiltio o alquiltio substituido;

R^4 es H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido, $R^1C{=}O$, $R^1OC{=}O$, $R^1NHC{=}O$, SO_2OR^1, SO_2R^1 o $SO_2NR^1R^{1'}$;

R^5 es alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido, $R^1C{=}O$, $R^1NHC{=}O$, SO_2R^1, SO_2OR^1, o $SO_2NR^1R^{1'}$;

R^6 es alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo

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o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido, CN, OH, OR^1, $R^1C{=}O$, $R^1NHC{=}O$, SO_2R^1, SO_2OR^1, o $SO_2NR^1R^{1'}$;

R^7 y $R^{7'}$ son cada uno independientemente H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido, halo, CN, OR^4, nitro, hidroxilamina, hidroxilamida, amino, NHR^4, NR^2R^5, NR^5R^5, NOR^i, tiol, alquiltio o alquiltio substituido, $HOC{=}O$, $R^1C{=}O$, $R^1(C{=}O)O$, $R^1OC{=}O$, $R^1NHC{=}O$, $NH_2C{=}O$, SO_2R^1, SOR^1, $PO_3R^1R^{1'}$, $R^1R^{1'}NC{=}O$, $C{=}OSR^1$, SO_2R^1, SO_2OR^1, o $SO_2NR^1R^{1'}$, o, en donde A_1 o A_2 contiene un grupo R^7 y W contiene un grupo R^7, los grupos R^7 de A_1 o A_2 y W forman juntos un anillo heterocíclico;

R^8 y $R^{8'}$ son cada uno independientemente H, alquilo o alquilo

substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido, nitro, halo, CN, OR^1, amino, NHR^4, NR^2R^5, NOR^1, alquiltio o alquiltio substituido, $C{=}OSR^1$, $R^1OC{=}O$, $R^1C{=}O$, $R^1NHC{=}O$, $R^1R^{1'}NC{=}O$, SO_2OR^1, $S{=}OR^1$, SO_2R^1, $PO_3R^1R^{1'}$, o $SO_2NR^1R^{1'}$; y

R^9 y $R^{9'}$ son cada uno independientemente H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido CN, OH, OR^1, $R^1C{=}O$, $R^1OC{=}O$, $R^1NHC{=}O$, SO_2R^1, SO_2OR^1, o $SO_2NR^1R^{1'}$;

en donde la condición o trastorno se seleccionado del grupo que consiste de enfermedades proliferativas, cánceres,

hipertrofia benigna de la próstata, adenomas y neoplasias de la próstata, células de tumores malignos o benignos que contienen al receptor andrógeno, enfermedad del corazón, condiciones o trastornos angiogénicos, hirsutismo, acné, hiperpilosidad, inflamación, modulación inmune, seborrea, endometriosis, síndrome de los ovarios poliquístico, alopecia androgénica, hipogonadismo, osteoporosis, espermatogénesis supresora, líbido, caquexia, anorexia, inhibición de la atrofia muscular en pacientes ambulatorios, complementación de andrógenos en niveles de testosterona en hombres disminuidos con la edad, cánceres que expresan el receptor estrógeno, cáncer de próstata, cáncer de pecho, cáncer de endometrio, bochornos, sequedad vaginal, menopausia, amenorrea, dismenorrea, anticoncepción, terminación del embarazo, cánceres que contienen al receptor de la progesterona, endometriosi, caquexia, menopausia, sincronía de ciclos, meniginoma, fibroides, inducción del parto, enfermedades autoinmunes, enfermedad de Alzheimer, trastornos psicóticos, dependencia de fármacos, diabetes mellitus no dependiente de la insulina, trastornos mediados por el receptor de la dopamina, insuficiencia cardiaca congestiva, desregulación de la homeostasis de colesterol, y atenuación del metabolismo de un agente

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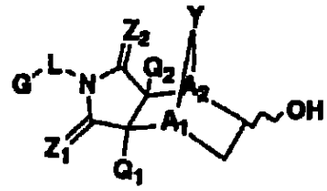
farmacéutico.

24. Un método para la preparación de un compuesto de la fórmula siguiente XVI, o una sal del mismo:



XVI

caracterizado porque

G es un grupo arilo o heterociclo, donde el grupo es mono- o policíclico, y el cual está opcionalmente substituido en una o más posiciones

Z_1 es O, S, NH, o NR^6;

Z_2 es O, S, NH, o NR^6;

A_1 es CR^7 o N;

A_2 es CR^7 o N;

Y' es J-J'-J" donde J es $(CR^7R^{7'})n$ y n = 0-3, J' es un enlace u O, S, S=O, SO_2, NH, NR^7, $OP{=}OOR^2$, OC=O, $NR^1C{=}O$, $OP{=}ONHR^2$, OSO_2, NHNH, $NHNR^6$, NR^6NH, o N=N, y J" es $(CR^7R^{7'})n$ y n = 0-3,

Q_1 es H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilalquilo o arilalquilo substituido, alquinilo o alquinilo substituido, arilo o arilo substituido,

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heterociclo o heterociclo substituido, halo, CN, $R^1OC{=}O$, $R^4C{=}O$, $R^5R^6NC{=}O$, $HOCR^7R^{7'}$, nitro, R^1OCH_2, R^1O, NH_2, $C{=}OSR^1$, SO_2R^1 o NR^4R^5;

Q_2 es H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilalquilo o arilalquilo substituido, alquinilo o alquinilo substituido, arilo o arilo substituido, heterociclo o heterociclo substituido, halo, CN, $R^1OC{=}O$, $R^4C{=}O$, $R^5R^6NC{=}O$, $HOCR^7R^{7'}$, nitro, R^1OCH_2, R^1O, NH_2, $C{=}OSR^1$, SO_2R^1 o NR^4R^5;

L es un enlace, $(CR^7R^{7'})n$, NH, NR^5, o $NR^5(CR^7R^{7'})n$, donde n = 0-3;

R^1 y $R^{1'}$ son cada uno independientemente H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido;

R^2 es alquilo o alquilo substituido, alquenilo o alquenilo

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substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido;

R^4 es H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o $R^1OC{=}O$, $R^1NHC{=}O$, SO_2OR^1, SO_2R^1 o $SO_2NR^1R^{1'}$;

R^5 es alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o

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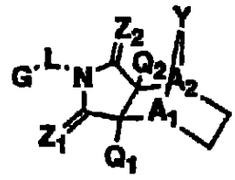
arilalquilo substituido, $R^1C{=}O$, $R^1NHC{=}O$, SO_2R^1, SO_2OR^1 o $SO_2NR^1R^{1'}$;

R^6 es alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido, CN, OH, OR^1, $R^1C{=}O$, $R^1NHC{=}O$, SO_2R^1, SO_2OR^1, o $SO_2NR^1R^{1'}$; y

R^7 y $R^{7'}$ son cada uno independientemente H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido, halo, CN, OR^4, nitro, hidroxilamina, hidroxilamida, amino, NHR^4, NR^2R^5, NOR^1, tiol, alquiltio o alquiltio substituido, $R^1C{=}O$, $R^1(C{=}O)O$, $R^1OC{=}O$, $R^1NHC{=}O$, SO_2R^1, SOR^1, $PO_3R^1R^{1'}$, $R^1R^{1'}NC{=}O$, $C{=}OSR^1$,

SO_2R^1, SO_2OR^1, o $SO_2NR^1R^{1'}$;

que comprende las etapas de hacer contacto de un compuesto de la siguiente fórmula XV, o una sal del mismo:

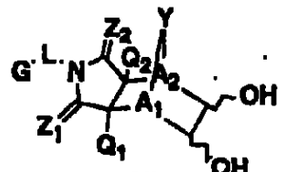


XV

en donde los símbolos son como se definieron arriba;

con una enzima o microorganismo capaz de catalizar la hidroxilación del compuesto XV al compuesto XVI y efectuar la hidroxilación.

25. Un método de preparación de un compuesto de la fórmula siguiente XVIII, o una sal del mismo:



XVIII

caracterizado porque

G es un grupo arilo o heterociclo, donde el grupo es mono- o policíclico, y el cual está opcionalmente substituido en una o más posiciones

Z_1 es O, S, NH, o NR^6;

Z_2 es O, S, NH, o NR^6;

A_1 es CR^7 o N;

A_2 es CR^7 o N;

Y' es J-J'-J" donde J es $(CR^7R^{7'})n$ y n = 0-3, J' es un enlace u O, S, S=O, SO_2, NH, NR^7, $OP{=}OOR^2$, OC=O, $NR^1C{=}O$, $OP{=}ONHR^2$, OSO_2, NHNH, $NHNR^6$, NR^6NH, o N=N, y J" es $(CR^7R^{7'})n$ y n = 0-3,

Q_1 es H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilalquilo o arilalquilo substituido, alquinilo o alquinilo substituido, arilo o arilo substituido, heterociclo o heterociclo substituido, halo, CN, $R^1OC{=}O$, $R^4C{=}O$, $R^5R^6NC{=}O$, $HOCR^7R^{7'}$, nitro, R^1OCH_2, R^1O, NH_2, $C{=}OSR^1$, SO_2R^1 o NR^4R^5;

Q_2 es H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilalquilo o arilalquilo substituido, alquinilo o alquinilo substituido, arilo o arilo substituido, heterociclo o heterociclo substituido, halo, CN, $R^1OC{=}O$, $R^4C{=}O$, $R^5R^6NC{=}O$, $HOCR^7R^{7'}$, nitro, R^1OCH_2, R^1O, NH_2, $C{=}OSR^1$, SO_2R^1 o NR^4R^5;

L es un enlace, $(CR^7R^{7'})n$, NH, NR^5, o $NR^5(CR^7R^{7'})n$, donde n = 0-3;

R^1 y $R^{1'}$ son cada uno independientemente H, alquilo o alquilo

substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido;

R^3 es alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido;

R^4 es H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo

substituido, arilo o arilo substituido, arilalquilo, $R^1C{=}O$, $R^1NHC{=}O$, SO_2OR^1, SO_2R^1 o $SO_2NR^1R^{1'}$;

R^5 es alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido, $R^1C{=}O$, $R^1NHC{=}O$, SO_2R^1, SO_2OR^1 o $SO_2NR^1R^{1'}$;

R^6 es alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido, CN, OH, OR^1, $R^1C{=}O$, $R^1NHC{=}O$, SO_2R^1, SO_2OR^1, o $SO_2NR^1R^{1'}$; y

R^7 y $R^{7'}$ son cada uno independientemente H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido,

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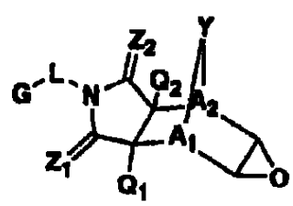
cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido, halo, CN, OR^4, nitro, hidroxilamina, hidroxilamida, amino, NHR^4, NR^2R^5, NOR^1, tiol, alquiltio o alquiltio substituido, $R^1C{=}O$, $R^1(C{=}O)O$, $R^1OC{=}O$, $R^1NHC{=}O$, SO_2R^1, SOR^1, $PO_3R^1R^{1'}$, $R^1R^{1'}NC{=}O$, $C{=}OSR^1$, SO_2R^1, SO_2OR^1, o $SO_2NR^1R^{1'}$;

que comprende las etapas de poner en contacto un compuesto de la siguiente fórmula XVII, o una sal del mismo:



XVII

en donde los símbolos son como se definieron arriba;

con una enzima o microorganismo capaz de catalizar la abertura del anillo epóxido del compuesto XVII para formar el diol del compuesto XVIII, y efectuar la abertura del anillo y la formación del diol.

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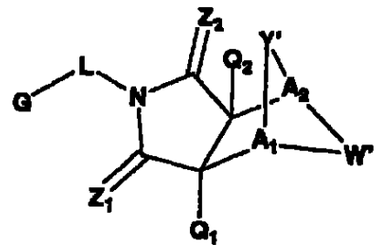
26. El compuesto de la siguiente fórmula Ib:



Ib

caracterizado porque G, Z_1, Z_2, Q_1 y Q_2 son como se definen en la reivindicación 1;

Y' es J-J'-J" donde J es $(CR^7R^{7'})n$ y n = 0-3, J' es un enlace u O, S, S=O, SO_2, NH, NR^7, $CR^7R^{7'}$, $R^2OP{=}O$, $R^2P{=}S$, $R^2OP{=}O$, $R^2NHP{=}O$, $OP{=}OOR^2$, $OP{=}ONHR^2$, OSO_2, NHNH, $NHNR^6$, NR^6NH, N=N, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, o heterociclo o heterociclo substituido, y J" es $(CR^7R^{7'})n$ y n = 0-3, donde Y no es un enlace; y

W' es $CR^7CR^{7'}$—$CR^7R^{7'}$, $CR^7R^{7'}$—C=O, NR^9—$CR^7R^{7'}$, $N{=}CR^8$, N=N, NR^9—$NR^{9'}$, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, o arilo o arilo substituido, en donde, cuando W' no es NR^9—$CR^7R^{7'}$, $N{=}CR^8$, N=N, NR^9—$NR^{9'}$, o heterociclo o heterociclo substituido, entonces J' debe ser O, S, S=O, SO_2, NH, NR^7, $OP{=}OOR^2$, $OP{=}ONHR^2$, OSO_2, NHNH, $NHNR^6$, NR^6NH, o N=N; o alternativamente,

Y' es $CR^7R^{7'}$-C=O y W' es NR^9-$CR^7R^{7'}$;

L es un enlace; y

A_1 y A_2 son como se definen arriba con la condición de que, cuando Y'=O y W'=-CH_2-CH_2-, entonces al menos uno de A_1 o A_2 no es CH;

con las condiciones adicionales (2), (3), (6), (7) y (8) de la reivindicación 1;

o una sal, solvato, profármaco farmacéuticamente aceptable del mismo.

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Resumen de la Invención.

Se describen compuestos cíclicos fusionados, métodos de uso de tales compuestos en el tratamiento de condiciones asociadas con el receptor de la hormona nuclear tal como el cáncer y padecimientos inmunes, y composiciones farmacéuticas que contienen tales compuestos.

LD0192A-NO TCI M

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:
KENNETH FEIST
BRISTIOL-MYERS SQUIBB COMPANY
P.O. BOX 4000
PRINCESTON, NJ 08543-4000

PCT

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of Mailing (*day/month/year*)	26 NOV 2003
Applicant's or agent's file reference LD0192A	IMPORTANT NOTIFICATION

International application No.	International filing date (*day/month/year*)	Priority date (*day/month/year*)
PCT/US02/40598	18 December 2002 (18.12.2002)	19 December 2001 (19.12.2001)

Applicant

BRISTOL-MYERS SQUIBB COMPANY

1. The applicant is hereby notified that this International Preliminary Examining Authority transmits herewith the international preliminary examination report and its annexes, if any, established on the international application.

2. A copy of the report and its annexes, if any, is being transmitted to the International Bureau for communication to all the elected Offices.

3. Where required by any of the elected Offices, the International Bureau will prepare an English translation of the report (but not of any annexes) and will transmit such translation to those Offices.

4. REMINDER

The applicant must enter the national phase before each elected Office by performing certain acts (filing translations and paying national fees) within 30 months from the priority date (or later in some Offices)(Article 39(1))(see also the reminder sent by the International Bureau with Form PCT/IB/301).

Where a translation of the international application must be furnished to an elected Office, that translation must contain a translation of any annexes to the international preliminary examination report. It is the applicant's responsibility to prepare and furnish such translation directly to each elected Office concerned.

For further details on the applicable time limits and requirements of the elected Offices, see Volume II of the PCT Applicant's Guide.

Name and mailing address of the IPEA/US Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703)305-3230	Authorized officer Robert Gerstl Telephone No. (703)308-9410

Form PCT/IPEA/416 (July 1992)

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DEC 01 2003

Docketed Item NO SIPE
Due Date
Attorney SB

PATENT COOPERATION TREATY

PCT

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

Applicant's or agent's file reference LD0192A	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
International application No. PCT/US02/40598	International filing date *(day/month/year)* 18 December 2002 (18.12.2002)	Priority date *(day/month/year)* 19 December 2001 (19.12.2001)
International Patent Classification (IPC) or national classification and IPC IPC(7): C07D 491/00; A61K 31/40 and US Cl.: 548/430, 432; 514/411		
Applicant BRISTOL-MYERS SQUIBB COMPANY		

1. This international preliminary examination report has been prepared by this International Preliminary Examining Authority and is transmitted to the applicant according to Article 36.

2. This REPORT consists of a total of 2 sheets, including this cover sheet.

   ☐ This report is also accompanied by ANNEXES, i.e., sheets of the description, claims and/or drawings which have been amended and are the basis for this report and/or sheets containing rectifications made before this Authority (see Rule 70.16 and Section 607 of the Administrative Instructions under the PCT).

   These annexes consist of a total of — sheets.

3. This report contains indications relating to the following items:

   - I ☒ Basis of the report
   - II ☐ Priority
   - III ☐ Non-establishment of report with regard to novelty, inventive step and industrial applicability
   - IV ☐ Lack of unity of invention
   - V ☒ Reasoned statement under Article 35(2) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement
   - VI ☐ Certain documents cited
   - VII ☐ Certain defects in the international application
   - VIII ☐ Certain observations on the international application

Date of submission of the demand	Date of completion of this report
09 July 2003 (09.07.2003)	30 October 2003 (30.10.2003)
Name and mailing address of the IPEA/US Mail Stop PCT, Attn: IPEA/US Commissioner for Patents P.O. Box 1450 Alexandria, Virginia 22313-1450 Facsimile No. (703)305-3230	Authorized officer Robert Gerdt Telephone No. 703-308-0196

Form PCT/IPEA/409 (cover sheet)(July 1998)

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US02/40598

I. Basis of the report

1. With regard to the elements of the international application:*

   ☒ the international application as originally filed.

   ☒ the description:
   pages 1-718 as originally filed
   pages NONE, filed with the demand
   pages NONE, filed with the letter of _____.

   ☒ the claims:
   pages 719-761, as originally filed
   pages NONE, as amended (together with any statement) under Article 19
   pages NONE, filed with the demand
   pages NONE, filed with the letter of _____.

   ☐ the drawings:
   pages NONE, as originally filed
   pages NONE, filed with the demand
   pages NONE, filed with the letter of _____.

   ☐ the sequence listing part of the description:
   pages NONE, as originally filed
   pages NONE, filed with the demand
   pages NONE, filed with the letter of _____.

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item.
   These elements were available or furnished to this Authority in the following language _____ which is:

   ☐ the language of a translation furnished for the purposes of international search (under Rule23.1(b)).

   ☐ the language of publication of the international application (under Rule 48.3(b)).

   ☐ the language of the translation furnished for the purposes of international preliminary examination(under Rules 55.2 and/or 55.3).

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

   ☐ contained in the international application in printed 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.

4. ☐ The amendments have resulted in the cancellation of:

   ☐ the description, pages NONE

   ☐ the claims, Nos. NONE

   ☐ the drawings, sheets/fig NONE

5. ☐ This report has been established as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).**

* *Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this report as "originally filed" and are not annexed to this report since they do not contain amendments (Rules 70.16 and 70.17).*
** *Any replacement sheet containing such amendments must be referred to under item 1 and annexed to this report.*

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INTERNATIONAL PRELIMINARY EXAMINATION REPORT

International application No.
PCT/US02/40598

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims	1-26	YES
	Claims	NONE	NO
Inventive Step (IS)	Claims	1-26	YES
	Claims	NONE	NO
Industrial Applicability (IA)	Claims	1-26	YES
	Claims	NONE	NO

2. CITATIONS AND EXPLANATIONS

Claims 1-26 meet the criteria set out in PCT Article 33(2)-(3), because the prior art does not teach or fairly suggest the compounds or their activity.

Claims 1-26 meet the criteria set out in PCT Article 33(4), and thus have industrial applicability because the subject matter claimed can be made or used in industry.

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TRATADO DE COOPERACION EN MATERIA DE PATENTES
P C T
REPORTE DE EXAMEN PRELIMINAR INTERNACIONAL
(Artículo 36 y Regla 70 del PCT)

Archivo de referencia del solicitante o agente LD0192A	PARA TOMAR ACCION ADICIONAL	Véase la Notificación de la Transmisión del Reporte de Examen Preliminar Internacional (Forma PCT/IPEA/416)
Solicitud Internacional No. PCT/US 02/40598	Fecha de Presentación Internacional 18 diciembre 2002 (18/12/2002)	Fecha de Prioridad 19 Diciembre 2001 (19.12.2001)

Clasificación de Patente Internacional (IPC) o Clasificación nacional e IPC
IPC(7): C07D 491/00; A61K 31/40 y US Cl.: 548/430, 432; 514/411

Solicitante
BRISTOL-MYERS SQUIBB COMPANY

1. Este reporte de examen preliminar internacional ha sido preparado por esta Autoridad de Examinación Preliminar Internacional y es transmitido al solicitante de acuerdo con el Artículo 36.

2. Este reporte consiste de 3 hojas.

☐ Este reporte también está acompañado por ANEXOS, es decir, hojas de la descripción, las reivindicaciones y/o los dibujos, los cuales han sido enmendados y son la base para este reporte y/o las hojas que contienen las rectificaciones hechas antes de esta Autoridad. (Véase la Regla 70.16 y la Sección 607 de las Instrucciones Administrativa bajo el PCT).

Estos anexos consisten de un total de _____ Hojas.

3. Este reporte contiene las indicaciones que están relacionadas con los siguientes puntos:

- I ☒ Base del reporte
- II ☐ Prioridad
- III ☐ Ningún establecimiento del reporte con respecto a la novedad, paso de la invención, o aplicabilidad industrial
- IV ☐ Carencia de unidad de la invención
- V ☒ Establecimiento razonado bajo el Artículo 35(2) con respecto a la novedad, paso de la invención o Aplicabilidad industrial; las citas y explicaciones que soportan tal establecimiento o fundamento.
- VI ☐ Ciertos documentos citados
- VII ☐ Ciertos defectos en la solicitud internacional
- VIII ☐ Ciertas observaciones en la solicitud internacional.

Fecha de presentación de la solicitud 09 Julio 2003 (09.07.2003)	Fecha en la que se completa este reporte 30 Octubre 2003 (30.10.2003)
Nombre y dirección para el envío por correo de la IPEA/US Mail Stop PCT, Attn: IPEA/US Comisionado de Patentes P.O. Box 1450 Alexandria, Virginia 22313-1450 Fax No.: (703) 305-3230	Oficial Autorizado (rúbrica) Robert Gerstl Teléfono No. 703-308-0198

Forma PCT/IPEA/409 (hoja de cubierta) (Julio de 1998)

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REPORTE DE EXAMEN PRELIMINAR INTERNACIONAL

Solicitud Internacional No.
PCT/US02/40598

I. Bases del Reporte

1. Con respecto a los elementos de la solicitud internacional:

[X] la solicitud internacional como se presentó originalmente.

[X] la descripción, páginas 1-718, como se presentó originalmente.

páginas NINGUNA, presentadas con la solicitud.

páginas NINGUNA, presentadas con la carta de _____.

[X] las reivindicaciones, páginas 719-761, como se presentó originalmente.

páginas NINGUNA, como se enmendó bajo el Artículo 19

páginas NINGUNA, presentada con la solicitud

páginas NINGUNA, presentada con la carta de _____.

[ ] los dibujos, páginas NINGUNO, como se presentaron originalmente.

páginas NINGUNO, Presentada con la demanda

páginas NINGUNO, presentada con la carta de

[ ] parte del listado de secuencias de la descripción:

páginas NINGUNA, como se presentó originalmente.

páginas NINGUNA, presentadas con la solicitud.

páginas NINGUNA, presentadas con la carta de _____.

2. Con respecto al lenguaje, todos los elementos marcados arriba están disponibles o se proporcionan por esta Autoridad en el lenguaje en el cual se presentó la solicitud internacional, salvo que se indique lo contrario bajo este punto

Estos elementos están disponibles o se proporcionan por esta Autoridad en el siguiente lenguaje: , que es:

[ ] el lenguaje de una traducción proporcionada para los propósitos de la búsqueda internacional (bajo la Regla 23.1 (b))

[ ] el lenguaje de la publicación internacional (bajo la Regla 48.3(b))

[ ] el lenguaje de la publicación para los propósitos del examen preliminar internacional (bajo la regla 55.2 y/o 55.3).

3. Con respecto a cualquier secuencia de nucleótido o aminoácido descrita en la solicitud internacional, el examen preliminar internacional se lleva a cabo en base al listado de secuencia:

[ ] contenido en la solicitud internacional en forma escrita.

[ ] presentado junto con la solicitud internacional en forma para leer en computadora.

[ ] proporcionado subsecuentemente por esta Autoridad en forma escrita.

[ ] proporcionado subsecuentemente por esta Autoridad en forma para leer en computadora

[ ] se proporciona la declaración de que el listado de secuencia subsecuentemente proporcionado no va más allá de la descripción en la solicitud internacional como se presentó.

[ ] se proporciona la declaración de que la información registrada en forma que se puede leer en computadora es idéntica al listado de secuencia como se presentó.

4. [ ] Las enmiendas han dado por resultado la cancelación de:

[ ] la descripción, páginas NINGUNA.
[ ] las reivindicaciones, Nos. NINGUNA.
[ ] los dibujos, hojas/fig. NINGUNA.

5. [ ] Este reporte se ha establecido como si (alguna de) las enmiendas no se han hecho, puesto que se han considerado que van más allá de la descripción como se presentó (Regla 70.2(c)):

* *Las hojas de reemplazo que se han presentado en la Oficina receptora en respuesta a una invitación bajo el Artículo 14 se refieren a este reporte como "presentadas originalmente" y no se anexan a este reporte ya que no contienen enmiendas (Reglas 70.16 y 70.17).*
** *Cualquier hoja de reemplazo que contenga tales enmiendas, deberá referirse bajo el punto I y anexarse a este reporte.*

REPORTE DE EXAMEN PRELIMINAR INTERNACIONAL **Solicitud Internacional No. PCT/US02/40598**

V. Declaración razonada bajo el Artículo 35(2) con respecto a la novedad, etapa inventiva o la aplicabilidad industrial; citas y explicaciones que soporten tal declaración

1. DECLARACION.

Novedad (N)	Reivindicaciones	1-26	SI
	Reivindicaciones	NINGUNA	NO
Etapa inventiva (EI)	Reivindicaciones	1-26	SI
	Reivindicaciones	NINGUNA	NO
Aplicación industrial (AI)	Reivindicaciones	1-26	SI
	Reivindicaciones	NINGUNA	NO

2. CITAS Y EXPLICACIONES

Las reivindicaciones 1-26 cumplen con los criterios establecidos en el Artículo 33(2)-(3) del PCT, debido a que el arte previo no enseña o sugiere razonablemente los compuestos o su actividad.

Las reivindicaciones 1-26 cumplen con los criterios establecidos en el Artículo 33(4) del PCT, y de esta manera tienen aplicación industrial debido a que la materia objeto reivindicada puede hacerse o usarse en la industria.

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Int'l. Application No. PCT/US02/40598

Docket No. LD0192A PCT

PCT Demand Chapter II

Express mail mailing label number EV323497241US

Date of Deposit July 9, 2003

I hereby certify that this paper or fee is being deposited with the United States Postal Service "Express Mail Post Office to Addressee" service under 37 CFR 1.10 on the date indicated above and is addressed to:
Mail Stop PCT, Commissioner for Patents, P.O. Box 1450, Alexandria, VA 22313-1450

Lisa Swidra
(Typed or printed name of person mailing paper or fee)

Lisa Swidra
(Signature of person mailing paper or fee)

1433

UNITED STATES PATENT AND TRADEMARK OFFICE

COMMISSIONER FOR PATENTS
UNITED STATES PATENT AND TRADEMARK OFFICE
WASHINGTON, D.C. 20231
www.uspto.gov

APPLICATION NUMBER	FILING DATE	GRP ART UNIT	FIL FEE REC'D	ATTY.DOCKET.NO	DRAWINGS	TOT CLAIMS	IND CLAIMS
10/025,116	12/19/2001	1614	1178	LD0192A (CIP)		21	5

CONFIRMATION NO. 4023

23914
STEPHEN B. DAVIS
BRISTOL-MYERS SQUIBB COMPANY
PATENT DEPARTMENT
P O BOX 4000
PRINCETON, NJ 08543-4000

FILING RECEIPT

"OC000000007448752"

Date Mailed: 02/08/2002

Receipt is acknowledged of this nonprovisional Patent Application. It will be considered in its order and you will be notified as to the results of the examination. Be sure to provide the U.S. APPLICATION NUMBER, FILING DATE, NAME OF APPLICANT, and TITLE OF INVENTION when inquiring about this application. Fees transmitted by check or draft are subject to collection. Please verify the accuracy of the data presented on this receipt. If an error is noted on this Filing Receipt, please write to the Office of Initial Patent Examination's Customer Service Center. Please provide a copy of this Filing Receipt with the changes noted thereon. If you received a "Notice to File Missing Parts" for this application, please submit any corrections to this Filing Receipt with your reply to the Notice. When the USPTO processes the reply to the Notice, the USPTO will generate another Filing Receipt incorporating the requested corrections (if appropriate).

Applicant(s)

Mark E. Salvati, Lawrenceville, NJ;
James Aaron Balog, Lambertville, NJ;
Dacia A. Pickering, Lawrenceville, NJ;
Soren Giese, New Hope, PA;
Aberra Fura, Lawrenceville, NJ;
Wenying Li, Middletown, CT;
Ramesh N. Patel, Bridgewater, NJ;
Ronald L. Hanson, Morris Plains, NJ;
Toomas Mitt, Plainsboro, NJ;
Jacques Y. Roberge, Princeton, NJ;
James R. Corte, Lawrenceville, NJ;
Steven H. Spergel, Warrington, PA;
Richard A. Rampulla, Flemington, NJ;

RECEIVED
U.S. Patent Law
FEB 14 2002
Docketed Item
Due Date
Attorney SB

Domestic Priority data as claimed by applicant

THIS APPLICATION IS A CIP OF 09/885,381 06/20/2001
WHICH CLAIMS BENEFIT OF 60/223,519 09/19/2000
AND CLAIMS BENEFIT OF 60/284,730 04/18/2001
AND CLAIMS BENEFIT OF 60/284,438 04/18/2001
AND A CIP OF 09/885,827 06/20/2001

Foreign Applications

If Required, Foreign Filing License Granted 02/07/2002

1434

Projected Publication Date: To Be Determined - pending completion of Missing Parts

Non-Publication Request: No

Early Publication Request: No

Title

Fused heterocyclic succinimide compounds and analogs thereof, modulators of nuclear hormone receptor function

Preliminary Class

514

LICENSE FOR FOREIGN FILING UNDER
Title 35, United States Code, Section 184
Title 37, Code of Federal Regulations, 5.11 & 5.15

GRANTED

The applicant has been granted a license under 35 U.S.C. 184, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" followed by a date appears on this form. Such licenses are issued in all applications where the conditions for issuance of a license have been met, regardless of whether or not a license may be required as set forth in 37 CFR 5.15. The scope and limitations of this license are set forth in 37 CFR 5.15(a) unless an earlier license has been issued under 37 CFR 5.15(b). The license is subject to revocation upon written notification. The date indicated is the effective date of the license, unless an earlier license of similar scope has been granted under 37 CFR 5.13 or 5.14.

This license is to be retained by the licensee and may be used at any time on or after the effective date thereof unless it is revoked. This license is automatically transferred to any related applications(s) filed under 37 CFR 1.53(d). This license is not retroactive.

The grant of a license does not in any way lessen the responsibility of a licensee for the security of the subject matter as imposed by any Government contract or the provisions of existing laws relating to espionage and the national security or the export of technical data. Licensees should apprise themselves of current regulations especially with respect to certain countries, of other agencies, particularly the Office of Defense Trade Controls, Department of State (with respect to Arms, Munitions and Implements of War (22 CFR 121-128)); the Office of Export Administration, Department of Commerce (15 CFR 370.10 (j)); the Office of Foreign Assets Control, Department of Treasury (31 CFR Parts 500+) and the Department of Energy.

NOT GRANTED

No license under 35 U.S.C. 184 has been granted at this time, if the phrase "IF REQUIRED, FOREIGN FILING LICENSE GRANTED" DOES NOT appear on this form. Applicant may still petition for a license under 37 CFR 5.12, if a license is desired before the expiration of 6 months from the filing date of the application. If 6 months has lapsed from the filing date of this application and the licensee has not received any indication of a secrecy order under 35 U.S.C. 181, the licensee may foreign file the application pursuant to 37 CFR 5.15(b).

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PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference. LD0192A	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/US02/40598	International filing date (*day/month/year*) 18 December 2002 (18.12.2002)	(Earliest) Priority Date (*day/month/year*) 19 December 2001 (19.12.2001)
Applicant BRISTOL-MYERS SQUIBB		

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

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/US02/40598

A. CLASSIFICATION OF SUBJECT MATTER
IPC(7) : C07D 491/00; A61K 31/40
US CL : 548/430, 442; 514/411
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. : 548/430, 442; 514/411

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)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	Database HCAPLUS on STN, AN 1990:440505, WARD, et al. 'Diels-Alder reactions of 2H-thiopyrans'. Tetrahedron Letters, 1990, 31(6), 845-8.	1-26
A	US 6,090,837 A (LAVIELLE et al.) 18 July 2000 (18.07.2000), columns 1-8.	1-26
A,P	US 6,384,050 B1 (TAKEMURA et al.) 07 May 2002 (02.05.2002), columns 1-22.	1-26
A,P	US 6,448,284 B1 (BACH et al.) 10 September 2002 (10.09.2002) columns 1-5.	1-26

☐ 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
"E" earlier 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
"P" 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
"&" document member of the same patent family

Date of the actual completion of the international search	Date of mailing of the international search report
23 May 2003 (23.05.2003)	30 MAY 2003
Name and mailing address of the ISA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer Deborah C Lambkin Telephone No. 703-308-1235

Form PCT/ISA/210 (second sheet) (July 1998)

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TRATADO DE COOPERACION EN MATERIA DE PATENTES
PCT
REPORTE DE BUSQUEDA INTERNACIONAL
(Artículo 18 y Reglas 43 y 44 del PCT)

Referencia al expediente del solicitante o del mandatario LD0192A	PARA ACCION ADICIONAL	ver Notificación de la Transmisión del Reporte de Búsqueda Internacional (Forma PCT/ISA/220) así como, en donde aplique el inciso 5 posterior
No. de solicitud internacional PCT/ US 02/40598	Fecha de presentación internacional (día/mes/año) 18 Diciembre 2002 (18.12.2002)	(Fecha de Prioridad) (La más cercana) (día/mes/año) 19 Diciembre 2001 (19.12.2002)
Solicitante BRISTOL-MYERS SQUIBB		

Este reporte de búsqueda internacional ha sido preparado por esta Autoridad de la Búsqueda Internacional y se transmite al solicitante de conformidad con el Artículo 18. Se transmite una copia a la Oficina Internacional.

Este reporte de búsqueda internacional consiste de un total de 2 hojas

☒ También está acompañado de una copia de cada documento de la técnica anterior citado en este reporte.

1. Bases del reporte.

a. Con respecto al Lenguaje, la búsqueda internacional se ha llevado a cabo en base a la solicitud internacional en el lenguage en el que se presentó, salvo que se indique lo contrario bajo este punto.

☐ La búsqueda internacional se ha llevado a cabo en base a la traducción de la solicitud internacional presentada a esta autoridad (Regla 23.1(b)).

b. Con respecto a cualquier secuencia de aminoácido y/o nucleótido descrito en la solicitud internacional, el reporte internacional se llevó a cabo en base el listado de secuencias:

☐ contenido en la solicitud internacional en forma escrita.

☐ presentado junto con la solicitud internacional en forma leible en computadora.

☐ presentada posteriormente a esta Autoridad en forma escrita

☐ presentada posteriormente a esta Autoridad en forma leible en computadora

☐ la declaración de que el listado de secuencia presentado posteriormente no va más alla de la descripción en la solicitud internaiconal como se presentó.

☐ la declaración de que la información registrada en la forma leible en computadora es idéntica al listado de secuencia escrito que se ha presentado

2. ☐ Ciertas reivindicaciones no son localizables (ver el Cuadro I).

3. ☐ La unidad de la invención es deficiente (ver el Cuadro II).

4. Con respecto al título,

☒ el texto se aprueba tal como lo presentó el solicitante,

☐ Esta Autoridad ha establecido que el texto sea como sigue:

5. Con respecto al resumen,

☒ el texto se aprueba tal como lo presentó el solicitante.

☐ esta Autoridad ha establecido el texto, de acuerdo con la Regla 38.2(b), tal como aparece en el Cuadro III. El solicitante puede, dentro de un mes a partir de la fecha de envío por correo de este reporte de búsqueda internacional, proporcional comentarios a esta autoridad.

6. La figura de los dibujos que se va a publicar con el resumen es la Figura No. _____

☐ como lo sugirió el solicitante. ☐ Ninguna de las figuras

☐ porque al solicitante le faltó sugerir una figura.

☐ Porque esta figura caracteriza mejor la invención.

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REPORTE DE BUSQUEDA INTERNACIONAL	No. de Solicitud Internacional PCT /US02/40598

A. CLASIFICACION DEL ASUNTO RELACIONADO

IPC (7) : C07D 491/00; A61K 31/40

US CL: 548/430, 442; 514/411

De acuerdo con la Clasificación Internacional de Patentes (IPC) o tanto la clasificación nacional como la IPC.

B. CAMPOS BUSCADOS

Documentación mínima buscada (sistema de clasificación seguido por los símbolos de clasificación)
U.S.: 548/430, 442; 514/411

Documentación buscada diferente de la documentación mínima, al grado que estos documentos se incluyan en los campos buscados.

Base de datos, electrónica, consultada durante la búsqueda internacional (nombre de la base de datos, donde se puede practicar, términos de búsqueda usados).

C. DOCUMENTOS QUE SE CONSIDERAN PERTINENTES

Categoría*	Citación del documento, con indicación, donde es apropiado, de los pasajes pertinentes	Pertinente para la reivindicación No
A	Database HVAPLUS on STN, AN 1990; 440505, WARD, et al. 'Diels-Alder reactions of 2H-thiopyrans'. Tetrahedro Letters, 1990, 31 (6). 845-8.	1-26
A	US 6,090,837 A (LAVIELLE et al.) 18 Julio 2000 (18.07.2000), columnas 1-8.	1-26
A,P	US, 6,384,050 B1 (TAKEMURA et al.) 07 Mayo 2002 (07.05.2002), columnas 1-22.	1-26
A, P	US 6,448,284 B1 (BACH et al.) 10 Septiembre 2002 (10.09.2002) columnas 1-5	1-26

☐ Documentos adicionales se listan en la continuación del cuadro C.

☐ Los miembros de la familia de patentes se listan en el anexo

* Categoría especial de los documentos citados:

"A" Documento que define el estado general de la técnica, que no se considera que es de pertinencia particular

"E" Documento anterior, pero publicado en o después de la fecha de presentación internacional

"L" Documento que puede crear dudas de la reivindicación(es) de prioridad o que se cita para establecer la fecha de publicación de otra situación u otra razón especial (como se especifique)

"O" Documento que se refiere a una descripción oral, uso, exhibición u otro medio

"P" Documento publicado antes de la fecha de presentación internacional, pero después de la fecha de prioridad reivindicada

"T" documento posterior publicado después de la fecha de presentación internacional o la fecha de prioridad, y que no provoca conflicto con la solicitud, pero se cita para entender el principio o teoría que trata la invención

"X" documento de pertinencia particular; la invención reivindicada no se puede considerar nueva o no se puede considerar que comprende un paso inventivo cuando el documento se toma solo

"Y" documento de pertinencia particular; la invención reivindicada no se puede considerar que comprende un paso inventivo cuando el documento se combina con uno o más de estos documentos, estas combinaciones son obvias para una persona experta en la técnica

"&" documento miembro de la familia de patentes

Fecha de la actual terminación de la búsqueda internacional	Fecha de envío del reporte de búsqueda internacional
23 Mayo 2003 (23.05.2003)	30/Mayo/2003
Nombre y dirección de envío ISA Comisionado de Patentes y Marcas Box PCT Washington, D.C. 20231 Fax: (703) 305-3230	Funcionario autorizado (rúbrica) Deborah C Lambkin Teléfono no. 703-308-1235

Forma PCT/ISA/210 (hoja 2) (Julio 1992)

1489 m

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

RECEIVED

BMS PATENT LAW

PCT

To:
KENNETH FEIST
BRISTIOL-MYERS SQUIBB COMPANY
P.O. BOX 4000
PRINCETON, NJ 08543-4000

JUN 02 2003

Docketed Item US-LD192-NP-105 8/30/03
Due Date US-LD192A-CIP1-105 8/30/03
Attorney SCB

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION
(PCT Rule 44.1)

	Date of Mailing (day/month/year) 30 MAY 2003
Applicant's or agent's file reference LD0192A	FOR FURTHER ACTION See paragraphs 1 and 4 below
International application No. PCT/US02/40598	International filing date (day/month/year) 18 December 2002 (18.12.2002)
Applicant BRISTOL-MYERS SQUIBB	

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 Commissioner for Patents Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized Officer Deborah C Lumbkin Telephone No. 703-308-1235

Form PCT/ISA/220 (April 2002) (See notes on accompanying sheet)

STATUS OF U.S. CASES FOR LD192 SERIES

Attorney	Dkt. No.	Country	Filing number	Type	Index	Event
BABAJKO	LD0192A	US	10/025116	CIP	1	Abandoned
BABAJKO	LD0192	US	60/233519	PSP		Expiry date
BABAJKO	LD0192	US	60/284730	PSP	1	Expiry date
BABAJKO	LD0192	US	09/885381	NP		Filing
BABAJKO	LD0192B	US	10/322077	CIP	1	Filing
BABAJKO	LD0192A	US		NP		Filing decision

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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 LD0192A (PCT)
International application No. PCT/US02/40598	International filing date *(day/month/year)* (18.12.02) 18.DECEMBER.2002	(Earliest) Priority date *(day/month/year)* (19.12.01) 19.DECEMBER.01
Title of invention FUSED HETEROCYCLIC SUCCINIMIDE COMPOUNDS AND ANALOGS THEREOF, MODULATORS OF NUCLEAR HORMONE RECEPTOR FUNCTION		

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.)*	Telephone No.
Bristol-Myers Squibb Company P.O. Box 4000 Princeton, NJ 08543-4000 United States of America	609-252-4009
	Facsimile No. 609-252-4526
	Teleprinter No.
	Applicant's registration No. with the Office

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
United States of America	United States of America

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)*

SALVATI, Mark E.
9 Tracey Drive
Lawrenceville, NJ 08648
UNITED STATES OF AMERICA

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
US	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)*

BALOG, James, Aaron
17 Terrell Road
Lambertville, NJ 08530
UNITED STATES OF AMERICA

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
US	US

[X] Further applicants are indicated on a continuation sheet.

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Sheet No. 2.

International application No.
PCT/US02/40598

Continuation of Box No. II APPLICANT(S)

If none of the following sub-boxes is used, this sheet should not be included in the demand.

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)*

PICKERING, Dacia A.
507 Drexel Avenue
Lawrenceville, NJ 08648
UNITED STATES OF AMERICA

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
Great Britain	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)*

GIESE, Soren
523 Windmere Way
New Hope, PA 18938
UNITED STATES OF AMERICA

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
Germany	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)*

FURA, Aberra
15 Cresthill Road
Lawrenceville, NJ 08648
UNITED STATES OF AMERICA

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
Ethiopia	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)*

LI, Wenying
6221 Town Place
Middletown, CT 06457
UNITED STATES OF AMERICA

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
China	US

☒ Further applicants are indicated on another continuation sheet.

Sheet No. .3.

International application No.
PCT/US02/40598

Continuation of Box No. II APPLICANT(S)

If none of the following sub-boxes is used, this sheet should not be included in the demand.

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.)*

PATEL, Ramesh, N.
572 Cabot Hill Road
Bridgewater, NJ 08807
UNITED STATES OF AMERICA

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
US	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.)*

HANSON, Ronald, L.
54 Whitewood Drive
Morris Plains, NJ 07950
UNITED STATES OF AMERICA

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
US	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.)*

MITT, Toomas
1312 Aspen Drive
Plainsboro, NJ 08536
UNITED STATES OF AMERICA

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
US	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.)*

ROBERGE, Jacques
57 Southern Way
Princeton, NJ 08540
UNITED STATES OF AMERICA

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
Canada	US

☒ Further applicants are indicated on another continuation sheet.

1494

Sheet No. .4.

International application No.
PCT/US02/40598

Continuation of Box No. II APPLICANT(S)

If none of the following sub-boxes is used, this sheet should not be included in the demand.

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.)*

CORTE, James, R.
11 Abella Court
Lawrenceville, NJ 08648
UNITED STATES OF AMERICA

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
US	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.)*

SPERGEL, Steven, H.
1807 Jericho Drive
Warrington, PA 18976
UNITED STATES OF AMERICA

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
US	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.)*

RAMPULLA, Richard, A.
5 Fairfax Court
Flemington, NJ 08822
UNITED STATES OF AMERICA

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
US	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.)*

MISRA, Raj
12 Eaton Place
Hopewell, NJ 08525
UNITED STATES OF AMERICA

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
US	US

☒ Further applicants are indicated on another continuation sheet.

1415

Sheet No. .5.

International application No.
PCT/US02/40598

Continuation of Box No. II APPLICANT(S)

If none of the following sub-boxes is used, this sheet should not be included in the demand.

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.)*

XIAO, Hai-Yun
173 Jonathan Payton Ct.
Princeton, NJ 08540
UNITED STATES OF AMERICA

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
China	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:

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 another continuation sheet.

14:15

Sheet No. 6

International application No.
PCT/US02/40598

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is [X] agent [ ] common representative

and [X] 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)*

BABAJKO, Suzanne E.
Bristol-Myers Squibb Company
P.O. Box 4000
Princeton, NJ 08543-4000
United States of America

Telephone No.
609-252-4009

Facsimile No.
609-252-4526

Teleprinter No.

Agent's registration No. with the Office
32,880

[ ] 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:

[X] the international application as originally filed

the description [X] as originally filed
[ ] as amended under Article 34

the claims [X] as originally filed
[ ] as amended under Article 19 (together with any accompanying statement)
[ ] as amended under Article 34

the drawings [X] as originally filed
[ ] as amended under Article 34

2. [ ] 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

[X] 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:

10199

Sheet No. .7.

International application No.
PCT/US02/40598

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:

			For International Preliminary Examining Authority use only	
			received	not received
1. translation of international application	:	0 sheets	☐	☐
2. amendments under Article 34	:	0 sheets	☐	☐
3. copy (or, where required, translation) of amendments under Article 19	:	0 sheets	☐	☐
4. copy (or, where required, translation) of statement under Article 19	:	0 sheets	☐	☐
5. letter	:	0 sheets	☐	☐
6. other *(specify)*	:	0 sheets	☐	☐

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

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

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).

Suzanne E. Babajko, Agent Date: July 9, 2003

Suzanne E. Babajko

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:

CHAPTER II

1498

PCT

FEE CALCULATION SHEET

Annex to the Demand

International application No. PCT/US02/40598	For International Preliminary Examining Authority use only
Applicant's or agent's file reference LD0192A PCT	Date stamp of the IPEA

Applicant
Bristol-Myers Squibb Company

CALCULATION OF PRESCRIBED FEES

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	

MODE OF PAYMENT

- [X] authorization to charge deposit account with the IPEA (see below)
- [ ] cheque
- [ ] postal money order
- [ ] bank draft
- [ ] cash
- [ ] revenue stamps
- [ ] coupons
- [ ] other *(specify)*:

AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT
(This mode of payment may not be available at all IPEAs)

IPEA/ US

- [X] Authorization to charge the total fees indicated above.
- [X] *(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.

Deposit Account No.: 19-3880

Date: July 9, 2003

Name: Suzanne E. Babalko

Signature: Suzanne E. Babalko

Customer Copy

EXPRESS MAIL

UNITED STATES POSTAL SERVICE

Post Office To Addressee

EV 323497241 US

DELIVERY (POSTAL USE ONLY)

Day of Delivery

Flat Rate Envelope

Delivery Attempt

Time

Employee Signature

Postage $ 13.65

Return Receipt Fee

Military

COD Fee

Insurance Fee

Total Postage & Fees $ 13.65

Weight 2.30 lbs.

Acceptance Clerk Initials

FROM: (PLEASE PRINT)

STEPHEN DAVIS
BRISTOL-MYERS SQUIBB CO
PO BOX 4000
PRINCETON NJ 08543-4000

LD0192A PCT (SEB)

MAIL STOP
COMMISSIONER FOR PATENTS
PO BOX 1450
ALEXANDRIA VA 22313-1450

PCT

FOR PICKUP OR TRACKING CALL 1-800-222-1811 www.usps.com

Case No.: LD0192A PCT

Application No.: PCT/US02/40598

July 9, 2003

Mailing Date: 7-9-03

Express Mail No.: EV323497241US

The patent and Trademark Office acknowledges, and has stamped hereon the date of receipt of the items checked below for PCT filing:

- ☐ Appln. Filing Papers
- ☐ Transmittal Fee:
- ☐ Search Fee:
- ☐ Basic Fee:
- ☐ Designation Fee:
- ☐ Priority Document Fee:

Demand $636.00

OT20 Rec'd PCT/PTO 09 JUL 2003

BMS-PG 6038

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

PEIST, Kenneth
Bristol-Myers Squibb Company
P.O. Box 4000
Princeton, NJ 08543-4000
United States of America

Date of mailing (day/month/year) 12 March 2003 (12.03.03)	
Applicant's or agent's file reference LD0192a	IMPORTANT NOTIFICATION
International application No. PCT/US02/40598	International filing date (day/month/year) 18 December 2002 (18.12.02)
International publication date (day/month/year) Not yet published	Priority date (day/month/year) 19 December 2001 (19.12.01)
Applicant BRISTOLS-MYERS SQUIBB COMPANY et al	

1. The applicant is hereby notified of the date of receipt (except where the letters "NR" appear in the right-hand column) by the International Bureau of the priority document(s) relating to the earlier application(s) indicated below. Unless otherwise indicated by an asterisk appearing next to a date of receipt, or by the letters "NR", in the right-hand column, the priority document concerned was submitted or transmitted to the International Bureau in compliance with Rule 17.1(a) or (b).
2. This updates and replaces any previously issued notification concerning submission or transmittal of priority documents.
3. An asterisk(*) appearing next to a date of receipt, in the right-hand column, denotes a priority document submitted or transmitted to the International Bureau but not in compliance with Rule 17.1(a) or (b). In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.
4. The letters "NR" appearing in the right-hand column denote a priority document which was not received by the International Bureau or which the applicant did not request the receiving Office to prepare and transmit to the International Bureau, as provided by Rule 17.1(a) or (b), respectively. In such a case, the attention of the applicant is directed to Rule 17.1(c) which provides that no designated Office may disregard the priority claim concerned before giving the applicant an opportunity, upon entry into the national phase, to furnish the priority document within a time limit which is reasonable under the circumstances.

Priority date	Priority application No.	Country or regional Office or PCT receiving Office	Date of receipt of priority document
19 Dece 2001 (19.12.01)	10/025,116	US	18 Febr 2003 (18.02.03)

RECEIVED
BMS PATENT LAW
APR 01 2003
Docketed Item _____
Due Date _____
Attorney _____

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. (41-22) 740-1435	Authorized officer Carlos NARANJO Telephone No. (41-22) 338 8349

PCT REQUEST

LD0192a

Original (for SUBMISSION) - printed on 06.12.2002 07:35:54 AM

0	For receiving Office use only	
0-1	International Application No.	
0-2	International Filing Date	
0-3	Name of receiving Office and "PCT International Application"	
0-4	Form - PCT/RO/101 PCT Request	
0-4-1	Prepared using	PCT-EASY Version 2.92 (updated 01.10.2002)
0-5	Petition The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty	
0-6	Receiving Office (specified by the applicant)	United States Patent and Trademark Office (USPTO) (RO/US)
0-7	Applicant's or agent's file reference	LD0192a
I	Title of invention	FUSED HETEROCYCLIC SUCCINIMIDECOMPOUNDS AND ANALOGS THEREOF, MODULATORS OF NUCLEAR HORMONE RECEPTOR FUNCTION
II	Applicant	
II-1	This person is:	applicant only
II-2	Applicant for	all designated States except US
II-4	Name	BRISTOL-MYERS SQUIBB COMPANY
II-5	Address:	P. O. Box 4000 Route 206 and Provinceline Road Princeton, NJ 08543-4000 United States of America
II-6	State of nationality	US
II-7	State of residence	US
II-8	Telephone No.	609-252-4000
II-9	Facsimile No.	609-252-4526
III-1	Applicant and/or inventor	
III-1-1	This person is:	applicant and inventor
III-1-2	Applicant for	US only
III-1-4	Name (LAST, First)	SALVATI, Mark, E.
III-1-5	Address:	9 Tracey Drive Lawrenceville, NJ 08648 United States of America
III-1-6	State of nationality	US
III-1-7	State of residence	US

1502

III-2	Applicant and/or Inventor	
III-2-1	This person is:	applicant and inventor
III-2-2	Applicant for	US only
III-2-4	Name (LAST, First)	BALOG, James, Aaron
III-2-5	Address:	17 Terrell Road Lambertville, NJ 08530 United States of America
III-2-6	State of nationality	US
III-2-7	State of residence	US
III-3	Applicant and/or Inventor	
III-3-1	This person is:	applicant and inventor
III-3-2	Applicant for	US only
III-3-4	Name (LAST, First)	PICKERING, Dacia, A.
III-3-5	Address:	507 Drexel Avenue Lawrenceville, NJ 08648 United States of America
III-3-6	State of nationality	GB
III-3-7	State of residence	US
III-4	Applicant and/or Inventor	
III-4-1	This person is:	applicant and inventor
III-4-2	Applicant for	US only
III-4-4	Name (LAST, First)	GIESE, Soren
III-4-5	Address:	523 Windmere Way New Hope, PA 18938 United States of America
III-4-6	State of nationality	DE
III-4-7	State of residence	US
III-5	Applicant and/or Inventor	
III-5-1	This person is:	applicant and inventor
III-5-2	Applicant for	US only
III-5-4	Name (LAST, First)	FURA, Aberra
III-5-5	Address:	15 Cresthill Road Lawrenceville, NJ 08648 United States of America
III-5-6	State of nationality	ET
III-5-7	State of residence	US
III-6	Applicant and/or Inventor	
III-6-1	This person is:	applicant and inventor
III-6-2	Applicant for	US only
III-6-4	Name (LAST, First)	LI, Wenying
III-6-5	Address:	6221 Town Place Middletown, CT 06457 United States of America
III-6-6	State of nationality	CN
III-6-7	State of residence	US

III-7	Applicant and/or Inventor	
III-7-1	This person is:	applicant and inventor
III-7-2	Applicant for	US only
III-7-4	Name (LAST, First)	PATEL, Ramesh, N.
III-7-5	Address:	572 Cabot Hill Road Bridgewater, NJ 08807 United States of America
III-7-6	State of nationality	US
III-7-7	State of residence	US
III-8	Applicant and/or Inventor	
III-8-1	This person is:	applicant and inventor
III-8-2	Applicant for	US only
III-8-4	Name (LAST, First)	HANSON, Ronald, L.
III-8-5	Address:	54 Whitewood Drive Morris Plains, NJ 07950 United States of America
III-8-6	State of nationality	US
III-8-7	State of residence	US
III-9	Applicant and/or Inventor	
III-9-1	This person is:	applicant and inventor
III-9-2	Applicant for	US only
III-9-4	Name (LAST, First)	MITT, Toomas
III-9-5	Address:	1312 Aspen Drive Plainsboro, NJ 08536 United States of America
III-9-6	State of nationality	US
III-9-7	State of residence	US
III-10	Applicant and/or Inventor	
III-10-1	This person is:	applicant and inventor
III-10-2	Applicant for	US only
III-10-4	Name (LAST, First)	ROBERGE, Jacques
III-10-5	Address:	57 Southern Way Princeton, NJ 08540 United States of America
III-10-6	State of nationality	CA
III-10-7	State of residence	US
III-11	Applicant and/or Inventor	
III-11-1	This person is:	applicant and inventor
III-11-2	Applicant for	US only
III-11-4	Name (LAST, First)	CORTE, James, R.
III-11-5	Address:	11 Abelia Court Lawrenceville, NJ 08648 United States of America
III-11-6	State of nationality	US
III-11-7	State of residence	US

1504

III-12	Applicant and/or Inventor:	
III-12-1	This person is:	applicant and inventor
III-12-2	Applicant for	US only
III-12-4	Name (LAST, First)	SPERGEL, Steven, H.
III-12-5	Address:	1807 Jericho Drive Warrington, PA 18976 United States of America
III-12-6	State of nationality	US
III-12-7	State of residence	US
III-13	Applicant and/or Inventor	
III-13-1	This person is:	applicant and inventor
III-13-2	Applicant for	US only
III-13-4	Name (LAST, First)	RAMPULLA, Richard, A.
III-13-5	Address:	5 Fairfax Court Flemington, NJ 08822 United States of America
III-13-6	State of nationality	US
III-13-7	State of residence	US
III-14	Applicant and/or Inventor	
III-14-1	This person is:	applicant and inventor
III-14-2	Applicant for	US only
III-14-4	Name (LAST, First)	MISRA, Raj
III-14-5	Address:	12 Eaton Place Hopewell, NJ 08525 United States of America
III-14-6	State of nationality	US
III-14-7	State of residence	US
III-15	Applicant and/or Inventor	
III-15-1	This person is:	applicant and inventor
III-15-2	Applicant for	US only
III-15-4	Name (LAST, First)	XIAO, Hai-Yun
III-15-5	Address:	173 Jonathan Dayton Ct. Princeton, NJ 08540 United States of America
III-15-6	State of nationality	CN
III-15-7	State of residence	US

PCT REQUEST

LD0182a

Original (for SUBMISSION) - printed on 08.12.2002 07:35:54 AM

IV-1	Agent or common representative; or address for correspondence The person identified below is hereby/has been appointed to act on behalf of the applicant(s) before the competent International Authorities as:	agent
IV-1-1	Name (LAST, First)	PEIST, Kenneth
IV-1-2	Address:	Bristol-Myers Squibb Company P.O. Box 4000 Princeton, NJ 08543-4000 United States of America
IV-1-3	Telephone No.	609-252-3183
IV-1-4	Facsimile No.	609-252-4526
IV-1-5	Agent's registration No.	45,006
IV-2	Additional agent(s)	additional agent(s) with same address as first named agent
IV-2-1	Name(s)	WINSLOW, Anastasia(40875); ALGIERI, Aldo(31,697); BARAJKO, Suzanne(32,880); BUCHHOLZ, Briana(39,123); D'AMICO, Stephen(46,652); DUBOFF, Samuel(25,969); GIBBONS, Maureen(44,121); HERMENAU, Ronald(34,620); KILCOYNE, John(33,100); KLEIN, Christopher(34,363); LANGE, Keith(44,201); MAKUJINA, Shah(41,174); MORSE, David(25,742); PATEL, Rana(41,412); DAVIS, Stephen(26,693); PROVOOST, Jonathan(44,292); RODNEY, Burton(22,076); RYAN, Richard(30,491); SHER, Audrey(39,024); O'BRIEN, Maureen(42,043); BELFIELD, Jing(45,914); FERGUSON, Blair(34,329); LARSEN, Scott(38,532); VANATTEN, Mary(39,408); GODDARD, Catherine, A.(46,731)

PCT REQUEST

LD0152a

Original (for SUBMISSION) - printed on 06.12.2002 07:38:54 AM

1536

V	Designation of States	
V-1	Regional Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AP: GH GM KE LS MW MZ SD SL SZ TZ UG ZM ZW and any other State which is a Contracting State of the Harare Protocol and of the PCT EA: AM AZ BY KG KZ MD RU TJ TM and any other State which is a Contracting State of the Eurasian Patent Convention and f the PCT EP: AT BE BG CH&LI CY CZ DE DK EE ES FI FR GB GR IE IT LU MC NL PT SE SK TR and any other State which is a Contracting State of the European Patent Convention and of the PCT OA: BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG and any other State which is a member State of OAPI and a Contracting State of the PCT
V-2	National Patent (other kinds of protection or treatment, if any, are specified between parentheses after the designation(s) concerned)	AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH&LI CN CO 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 SC SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZM ZW
V-3	Precautionary Designation Statement In addition to the designations made under items V-1, V-2 and V-3, the applicant also makes under Rule 4.9(b) all designations which would be permitted under the PCT except any designation(s) of the State(s) indicated under item V-5 below. The applicant declares that those additional designations are subject to confirmation and that any designation which is not confirmed before the expiration of 15 months from the priority date is to be regarded as withdrawn by the applicant at the expiration of that time limit.	
V-5	Exclusion(s) from precautionary designations	NONE
VI-1	Priority claim of earlier national application	
VI-1-1	Filing date	19 December 2001 (19.12.2001)
VI-1-2	Number	10/025,116
VI-1-3	Country	US

PCT REQUEST

LD0182a

Original (for SUBMISSION) - printed on 08.12.2002 07:35:54 AM

VI-2	Priority document request The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) identified above as item(s):	VI-1	
VII-1	International Searching Authority Chosen	United States Patent and Trademark Office (USPTO) (ISA/US)	
VIII	Declarations	Number of declarations	
VIII-1	Declaration as to the identity of the inventor	-	
VIII-2	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	-	
VIII-3	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	-	
VIII-4	Declaration of inventorship (only for the purposes of the designation of the United States of America)	-	
VIII-5	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	-	
IX	Check list	number of sheets	electronic file(s) attached
IX-1	Request (including declaration sheets)	8	-
IX-2	Description	718	-
IX-3	Claims	43	-
IX-4	Abstract	1	EZABST00.TXT
IX-5	Drawings	0	-
IX-7	TOTAL	770	
	Accompanying items	paper document(s) attached	electronic file(s) attached
IX-8	Fee calculation sheet	✓	-
IX-9	Original separate power of attorney	✓	-
IX-17	PCT-EASY diskette	-	Diskette
IX-18	Other (specified):	Certification	-
IX-19	Figure of the drawings which should accompany the abstract		
IX-20	Language of filing of the international application	English	
X-1	Signature of applicant, agent or common representative	Kenneth M. Peist	
X-1-1	Name (LAST, First)	PEIST, Kenneth	

FOR RECEIVING OFFICE USE ONLY

10-1	Date of actual receipt of the purported international application	
10-2	Drawings:	
10-2-1	Received	
10-2-2	Not received	

PCT REQUEST

Original (for SUBMISSION) - printed on 08.12.2002 07:38:54 AM

LD0192

1508

10-3	Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application	
10-4	Date of timely receipt of the required corrections under PCT Article 11(2)	
10-5	International Searching Authority	ISA/US
10-6	Transmittal of search copy delayed until search fee is paid	

FOR INTERNATIONAL BUREAU USE ONLY

11-1	Date of receipt of the record copy by the International Bureau	

PCT (ANNEX - FEE CALCULATION SHEET)

Original (for SUBMISSION) - printed on 06.12.2002 07:35:54 AM

LD0192a

(This sheet is not part of and does not count as a sheet of the international application)

0	For receiving Office use only			
0-1	International Application No.			
0-2	Date stamp of the receiving Office			
0-4	Form - PCT/RO/101 (Annex) PCT Fee Calculation Sheet			
0-4-1	Prepared using	PCT-EASY Version 2.92 (updated 01.10.2002)		
0-9	Applicant's or agent's file reference	LD0192a		
2	Applicant	BRISTOL-MYERS SQUIBB COMPANY, et al.		
12	Calculation of prescribed fees	fee amount/multiplier	Total amounts (USD)	
12-1	Transmittal fee T	⇨	240	
12-2-1	Search fee S	⇨	700	
12-2-2	International search to be carried out by	US		
12-3	International fee			
	Basic fee			
	(first 30 sheets) b1	407		
12-4	Remaining sheets	740		
12-5	Additional amount (X)	9		
12-6	Total additional amount b2	6,660		
12-7	b1 + b2 = B	7,067		
12-8	Designation fees			
	Number of designations contained in international application	95		
12-9	Number of designation fees payable (maximum 5)	5		
12-10	Amount of designation fee (X)	88		
12-11	Total designation fees D	440		
12-12	PCT-EASY fee reduction R	-125		
12-13	Total international fee (B+D-R) I	⇨	7,382	
12-14	Fee for priority document			
	Number of priority documents requested	1		
12-15	Fee per document (X)	15		
12-16	Total priority document fee P	⇨	15	
12-17	TOTAL FEES PAYABLE (T+S+I+P)	⇨	8,337	
12-19	Mode of payment	authorization to charge deposit account		
12-20	Deposit account instructions			
	The receiving Office:	United States Patent and Trademark Office (USPTO) (RO/US)		
12-20-1	Authorization to charge the total fees indicated above.	✓		

PCT (ANNEX - FEE CALCULATION SHEET)

Original (for SUBMISSION) - printed on 06.12.2002 07:35:54 AM

LD0192a

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12-20-2	Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.	✓
12-20-3	Authorization to charge the fee for priority document.	✓
12-21	Deposit account No.	19.3880
12-22	Date	06 December 2002 (06.12.2002)
12-23	Name and signature	PEIST, Kenneth

VALIDATION LOG AND REMARKS

13-2-4	Validation messages Request	Green? The title of the invention shall be short and precise. Please verify.
13-2-7	Validation messages Contents	Green? The international application contains no drawings. Please verify.
13-2-8	Validation messages Payment	Green? Please ensure that you have a valid deposit account with the receiving Office selected.

0	Para uso de la Oficina receptora únicamente	
0-1	Solicitud internacional Nº	
0-2	Fecha de presentación internacional	
0-3	Nombre de la oficina receptora y Solicitud internacional PCT	

0-4. 0-4-1	Forma – PCT/RO/101 petitoria Preparado usando	 PCT-EASY Versión 2.92 (actualizada 01.10.2002)
0-5	Petición El abajo firmante pide que la presente solicitud sea tramitada de conformidad con el Tratado de Cooperación en materia de Patentes.	
0-6	Oficina Receptora (especificada por el solicitante)	Oficina de Patentes y Marcas de los Estados Unidos (USPTO) (RO/US)
0-7	Referencia de archivo de solicitantes o agentes	LD0192a
I	TITULO DE LA INVENCION	COMPUESTOS DE SUCCINIMIDA HETEROCÍCLICOS FUSIONADOS Y ANÁLOGOS DE LOS MISMOS, MODULADORES DE LA FUNCIÓN DEL RECEPTOR DE LA HORMONA NUCLEAR.
II II-1 II-2 II-4 II-5 II-6 II-7 II-8 II-9	Solicitante Esta persona es: Solicitante para Nombre: Dirección: Estado de Nacionalidad Estado de Residencia Teléfono No. Fax No.	 Solicitante únicamente Todos los estados designados excepto US BRISTOL-MYERS SQUIBB COMPANY P.O. Box 4000 Route 206 and Provinceline Road Princeton, NJ, 08543-4000 Estados Unidos de América US US 609-252-4000 609-252-4526
III-1 III-1-1 III-1-2 III-1-4 III-1-5 II-1-6 II-1-7	Solicitante y/o inventor Esta persona es: Solicitante para Nombre (ÚLTIMO, primero) Dirección Estado de Nacionalidad Estado de Residencia	 Solicitante e inventor US únicamente SALVATI, Mark, E. 9 Tracey Drive Lawrenceville, NJ 08648 Estados Unidos de América US US
III-2 III-2-1 III-2-2 III-2-4 III-2-5 II-2-6 II-2-7	Solicitante y/o inventor Esta persona es: Solicitante para Nombre (ÚLTIMO, primero) Dirección: Estado de Nacionalidad Estado de Residencia	 Solicitante e inventor US únicamente BALOG, James, Aaron 17 Terrell Road Lambertville, NJ 08530 Estados Unidos de América US US
III-3 III-3-1	Solicitante y/o inventor Esta persona es:	 Solicitante e inventor

III-3-2	Solicitante para	US solamente
III-3-4	Nombre (ÚLTIMO, primero)	PICKERING, Dacia, A.
III-3-5	Dirección:	507 Drexel Avenue Lawrenceville, NJ 08648 Estados Unidos de América
III-3-6	Estado de Nacionalidad	GB
III-3-7	Estado de Residencia	US
III-4	Solicitante y/o inventor	
III-4-1	Esta persona es:	Solicitante e inventor
III-4-2	Solicitante para	US solamente
III-4-4	Nombre (ÚLTIMO, primero)	GIESE, Soren
III-4-5	Dirección:	523 Windmere Way New Hope, PA 18938 Estados Unidos de América
III-4-6	Estado de Nacionalidad	DE
III-4-7	Estado de Residencia	US
III-5	Solicitante y/o inventor	
III-5-1	Esta persona es:	Solicitante e Inventor
III-5-2	Solicitante para	US únicamente
III-5-4	Nombre (ÚLTIMO, primero)	FURA, Aberra
III-5-5	Dirección:	15 Cresthill Road Lawreceville, NJ 08648 Estados Unidos de América
III-5-6	Estado de Nacionalidad	ET
III-5-7	Estado de Residencia	US
III-6	Solicitante y/o inventor	
III-6-1	Esta persona es:	Solicitante e Inventor
III-6-2	Solicitante para	US únicamente
III-6-4	Nombre (ÚLTIMO, primero)	LI, Wenying
III-6-5	Dirección:	6221 Town Place Middletown, CT 06457 Estados Unidos de América
III-6-6	Estado de Nacionalidad	CN
III-6-7	Estado de Residencia	US
III-7	Solicitante y/o inventor	
III-7-1	Esta persona es:	Solicitante e Inventor
III-7-2	Solicitante para	US únicamente
III-7-4	Nombre (ÚLTIMO, primero)	PATEL, Ramesh, N.
III-7-5	Dirección:	572 Cabot Hill Road Bridgewater, NJ 08807 Estados Unidos de América
III-7-6	Estado de Nacionalidad	US
III-7-7	Estado de Residencia	US
III-8	Solicitante y/o inventor	
III-8-1	Esta persona es:	Solicitante e Inventor
III-8-2	Solicitante para	US únicamente
III-8-4	Nombre (ÚLTIMO, primero)	HANSON, Ronald, L
III-8-5	Dirección:	54 Whitewood Drive Morris Plains, NJ 07950 Estados Unidos de América
III-8-6	Estado de Nacionalidad	US
III-8-7	Estado de Residencia	US
III-9	Solicitante y/o inventor	
III-9-1	Esta persona es:	Solicitante e Inventor
III-9-2	Solicitante para	US únicamente
III-9-4	Nombre (ÚLTIMO, primero)	MITT, Toomas
III-9-5	Dirección:	1312 Aspen Drive Plainsboro, NJ 08536

		Estados Unidos de América
III-9-6	Estado de Nacionalidad	US
III-9-7	Estado de Residencia	US
III-10	Solicitante y/o inventor	
III-10-1	Esta persona es:	Solicitante e Inventor
III-10-2	Solicitante para	US únicamente
III-10-4	Nombre (ÚLTIMO, primero)	ROBERGE, Jacques
III-10-5	Dirección:	57 Southern Way Pricenton, N.J 08540 Estados Unidos de América
III-10-6	Estado de Nacionalidad	CA
III-10-7	Estado de Residencia	US
III-11	Solicitante y/o inventor	
III-11-1	Esta persona es:	Solicitante e Inventor
III-11-2	Solicitante para	US únicamente
III-11-4	Nombre (ÚLTIMO, primero)	CORTE, James, R.
III-11-5	Dirección:	11 Abelia Court Lawrenceville, NJ 08648 Estados Unidos de América
III-11-6	Estado de Nacionalidad	US
III-11-7	Estado de Residencia	US
III-12	Solicitante y/o inventor	
III-12-1	Esta persona es:	Solicitante e Inventor
III-12-2	Solicitante para	US únicamente
III-12-4	Nombre (ÚLTIMO, primero)	SPERGEL, Steven, H.
III-12-5	Dirección:	1807 Jericho Drive Warrington, PA 18976 Estados Unidos de América
III-12-6	Estado de Nacionalidad	US
III-12-7	Estado de Residencia	US
III-13	Solicitante y/o inventor	
III-13-1	Esta persona es:	Solicitante e Inventor
III-13-2	Solicitante para	US únicamente
III-13-4	Nombre (ÚLTIMO, primero)	RAMPULLA, Richard, A.
III-13-5	Dirección:	5 Fairfax Court Flemington. NJ 08822 Estados Unidos de América
III-13-6	Estado de Nacionalidad	US
III-13-7	Estado de Residencia	US
III-14	Solicitante y/o Inventor	
III-14-1	Esta persona es:	Solicitante e Inventor
III-14-2	Solicitante para	US únicamente
III-14-4	Nombre (ÚLTIMO, primero)	MISRA, Raj
III-14-5	Dirección:	12 Eaton Place Hopewell, NJ 08525 Estados Unidos de América
III-14-6	Estado de Nacionalidad	US
III-14-7	Estado de Residencia	US
III-15	Solicitante y/o Inventor	
III-15-1	Esta persona es:	Solicitante e Inventor
III-15-2	Solicitante para	US únicamente
III-15-4	Nombre (ÚLTIMO, primero)	XIAO, Hai-Yun
III-15-5	Dirección:	173 Jonathan Dayton Ct. Princeton, NJ 08540 Estados Unidos de América
III-15-6	Estado de Nacionalidad	CN

III-15-7	Estado de Residencia	US
IV-1	La persona abajo identificada se designa/ha sido designada para actuar en nombre del/ de los solicitante(s) ante las administraciones internacionales competentes como:	Agente
IV-1-1	Nombre (ÚLTIMO, primero)	PEIST, Kenneth
IV-1-2	Dirección	Bristol-Myers Squibb Company P.O. Box 4000 Princeton, NJ 08543-4000 Estados Unidos de América
IV-1-3	Teléfono No.	609-252-3183
IV-1-4	Fax No.	609-252-4526
IV-1-5	Número de registro del agente	46,006
IV-2	Agentes adicionales	Agentes adicionales con la misma dirección como el primer agente nombrado
IV-2-1	Nombre (s)	WINSLOW, Anastasia (40875); ALGIERI, Aldo (31,697); BABAJKO, Suzanne (32,880); BUCHHOLZ, Briana (39,123); D'AMICO, Stephen (46,652); DUBOFF, Samuel (25, 969); GIBBONS, Maureen (44, 121); HERMENAU, Ronald (34, 620); KILCOYNE, John (33,100); KLEIN, Christopher (34,363); LANGE, Keith (44,201); MAKUJINA, Shah (41, 174); MORSE David (25, 742); PATEL, Rena (41,412); DAVIS, Stephen (26, 693); PROVOOST, Jonathan (44, 292); RODNEY, Burton (22, 076); RYAN, Richard (30,491); SHER, Audrey (39, 024); O'BRIEN, Maureen (42,043); BELFIELD, Jing (45, 914); FERGUSON, Blair (34, 329); LARSEN, Scott (38, 532); VANATTEN, Mary (39, 408); GODDARD, Catherine, A. (46, 731)
V	Designación de estados	
V-1	Patente Regional (otros tipos de protección si los hay se especifican entre paréntesis después de la designación concerniente)	AP: GH GM KE LS MW MZ SD SL SZ TZ UG ZW ZW y cualquier otro estado que es un estado contratante del protocolo de Harare y del PCT. EA: AM AZ BY KG KZ MD RU TJ TM y cualquier otro estado que es un estado contratante de la convención de patentes eurasiáticos y del PCT EP: AT BE BG CH&LI CY CZ DE DK EE ES FI FR GB GR IE IT LU MC NL PT SE SK TR y cualquier otro estado que son un estado contratante de la convención de patentes Europea y del PCT OA: BF BJ CF CG CI CM GA GN GQ GW ML MR NE SN TD TG y cualquier otro estado que son estados miembros de OAPI y un estado contratante del estado del PCT
V-2	Patente Nacional (otros tipos de protección si los hay se especifican entre paréntesis después de la designación concerniente)	AE AG AL AM AT AU AZ BA BB BG BR BY BZ CA CH&LI CN CO 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 PH PL PT

		RO RU SD SE SG SI SK SL TJ TM TN TR TT TZ UA UG US UZ VC VN YU ZA ZW	
V-5	Declaración de Designación Precautoria Además de las designaciones hechas bajo los puntos V-1, V-2 y V-3, el solicitante también hace bajo la Regla 4.9(b) todas las designaciones que puedan permitirse bajo el PCT excepto cualquier designación de los Estados indicados bajo el punto V-6 siguiente. El solicitante declara que aquellas designaciones adicionales están sujetas a la confirmación y que cualquier designación que no se confirme antes de la expiración de 15 meses a partir de la fecha de prioridad serán apreciadas como retiradas por el solicitante en la expiración de este tiempo límite		
V-6	Exclusión(s) para designaciones preventivas	NINGUNO	
VI-1	Solicitud de reivindicación de prioridad previa nacional		
VI-1-1	Fecha de presentación	19 Diciembre 2001 (19.12.2001)	
VI-1-2	Número	10/025, 116	
VI-1-3	País	US	
VI-2	Solicitud de reivindicación de prioridad previa nacional	VI-1	
VII-1	Autoridad de Búsqueda Internacional Elegida	Oficina Europea de Patente de Estados Unidos de América (USPTO) (ISA/US)	
VIII	Declaraciones	Número de declaraciones	
VIII-1	Declaración como para la identidad del inventor	-	
VIII-2	Declaración como para la autorización del solicitante, como en la fecha de presentación internacional, para solicitar y garantizar una patente	-	
VIII-3	Declaración como para la autorización del solicitante, como en la fecha de presentación internacional, para reivindicar la prioridad de la solicitud previa	-	
VIII-4	Declaración de los inventores (sólo para los propósitos de designación de los Estados Unidos de América)	-	
VIII-5	Declaración como descripciones o excepciones no perjudiciales para carecer de novedad	-	
IX	Lista de revisión	Número de hojas	Archivos electrónicos anexos
IX -1	Petitorio	8	-
IX -2	Descripción	718	-
IX-3	Reivindicaciones	43	-
IX -4	Resumen	1	EZABST00-TXT
IX -5	Dibujos	0	-
IX-7	Total	770	
	Puntos acompañantes	Papel de documento(s) anexo	Archivo(s) electrónico anexo
IX-8	Hoja de calculo de tasa	✔	-
IX-9		✔	-
IX-17	Disco PCT-EASY	-	Disco
IX-18	Otro (especificar)	Certificación	
IX-19	Se sugiere la figura de los dibujos para acompañar el resumen en el momento de su		

	publicación.	
IX-20	Idioma de presentación de la solicitud internacional de patente	INGLES
X-1	Firma del solicitante o del mandatario	Rúbrica
X-1-1	Nombre (ÚLTIMO, primero)	PEIST, Kenneth
	PARA LA OFICINA RECEPTORA ÚNICAMENTE	
10-1	Fecha efectiva de recepción de la pretendida solicitud internacional	
10-2 10-2-1 10-2-2	Dibujos Recibidos No recibidos	
10-3	Fecha efectiva de recepción, rectificada de la recepción ulterior pero dentro del plazo, de documentos o de dibujos que completa la pretendida solicitud internacional	
10-4	Fecha de recepción, dentro del plazo de las correcciones solicitadas según el Articulo 11(2) del PCT	
10-5	Autoridad de búsqueda internacional	ISA/US
10-6	Transmisión de la copia para la búsqueda diferida hasta que se pague la tasa de búsqueda	
	PARA USO UNICAMENTE DE LA OFICINA INTERNACIONAL	
11-1	Fecha de recepción del ejemplar Original por la Oficina Internacional	

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

1517

PCT

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

(PCT Rule 47.1(c), first sentence)

To:

PEIST, Kenneth
Bristol-Myers Squibb Company
P.O. Box 4000
Princeton, NJ 08543-4000
ETATS-UNIS D'AMERIQUE

RECEIVED
BMS PATENT LAW
AUG 18 2003
Docketed Item
Due Date
Attorney SCB

Date of mailing (day/month/year) 31 July 2003 (31.07.03)	
Applicant's or agent's file reference LD0192a	IMPORTANT NOTICE

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/US02/40598	18 December 2002 (18.12.02)	19 December 2001 (19.12.01)

Applicant
BRISTOLS-MYERS SQUIBB COMPANY

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:

   None

   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:

   None

   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 31 July 2003 (31.07.03) under No. 03/062241

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 Facsimile No.(41-22) 740.14.35	Authorized officer Judith Zahra Telephone No.(41-22) 338.91.11

1518 1509

SUPERINDUSTRIA Y COMERCIO

Radicacion : 04056353 0000000 Folios: 1500
Fecha (DD): 2004-06-16 17:29:13
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2520 DIVISION DE NUEVAS CREACIONES

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

		USUARIO	RADICADOR
PATENTE DE INVENCIÓN	MODELO DE UTILIDAD	( )	( )
- Indicación de que se solicita la concesión de una patente.		( )	( )
- Datos de identificación del solicitante o de la persona que se presenta la solicitud.		( )	( )
- Descripción de la invención.		( )	( )
- Dibujos de ser estos pertinentes.		( )	( )
- Comprobante de Pago de las tasas establecidas.			
COMPLETA ( )	INCOMPLETA	( )	( )

DISEÑO INDUSTRIAL ( )

- Indicación de que se solicita el registro de Diseño Industrial	( )	( )
- Datos de identificación del solicitante o de la persona que presenta	( )	( )
- la solicitud.		
- Representación gráfica o fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.	( )	( )
Comprobante de pago de las tasas establecidas	( )	( )
COMPLETA ( ) INCOMPLETA	( )	( )

ESQUEMA DE TRAZADO . ( )

- Indicación de que solicita el registro de un Esquema de trazado.	( )	( )
- Datos de Identificacion del solicitante o de la persona que presenta La solicitud.	( )	( )
Representación gráfica del esquema de trazado	( )	( )
Comprobante de pago de las tasas establecidas.	( )	( )
COMPLETA ( ) INCOMPLETA	( )	( )

Firma Responsable:

Fecha:

1810

Industria y Comercio
SUPERINTENDENCIA

1519

SUPERINDUSTRIA Y COMERCIO

MANTENIMIENTO DE PROTOCOLOS

Número : 19358
Fecha : 07/05/1999
Conferido: BRISTOL-MYERS SQUIBB COMPANY

Pais : US ESTADOS UNIDOS DE AMERICA
Ciudad : 82 PRINCETON, NEW JERSEY
Represent: S Sustituir : S Desistir : S
No. Radicación : 99 28346 Clase: 0 Seev: 0 Seac: 0

scncia	Codigo	Ctr	Nombre
1	340	A	CASTRO DUQUE RAMIRO
2	3002		GOMEZ MEJIA HECTOR

Sede Centro: Carrera 13 No. 27-00 Pisos 2, 5, 7 y 10
Conmutador: 3 820840 Fax: 3 505220
Sede CAN: Tr. 40A No. 38-50 3153265 al 69
Fax: 3 505220. Línea 9800-910 165
Web: www.sic.gov.co e-mail: info@sic.gov.co
Bogotá D.C. - Colombia

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SUPERINDUSTRIA Y COMERCIO
Radicacion : 04056353 00000000 Folios: 1500
Fecha (AMD): 2004-06-16 17:29:13
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

04 - 56353

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE

PCT fecha presentacion: 16/06/2004.

fecha de ENTRADA EN FASE NACIONAL : 19/07/2004.

1 SOLICITUD DE:

☒ Patente de Invención. ☐ Patente de Modelo de Utilidad.

☐ Capítulo I. ☒ Capítulo II.

2 SOLICITANTE (71)	Nombre: BRISTOL – MYERS SQUIBB COMPANY Dirección: P.O. Box 4000, Route 206 and provinceline Road, Princeton, NJ 08543-4000, Estados Unidos de América Nacionalidad o Domicilio: Estados Unidos Lugar de Constitución: Estados Unidos Teléfono: Fax: E-mail	IDENTIFICACION C.C. ☐ NIT ☐ C.E. ☐ Otro ☐ Cual____ Número ____
3 REPRESENTANTE O APODERADO	Nombre: RAMIRO CASTRO DUQUE Dirección: Cra. 7 No. 16-56 Piso 9 Teléfono: 380-2200 Fax: 380-2700 E-mail:	IDENTIFICACION C.C. ☒ NIT ☐ C.E. ☐ Otro ☐ Cual____ Número 170.322 TP 1003
4 INVENTOR (ES) (72)	Nombre: EN HOJA ANEXA Dirección: Nacionalidad o Domicilio: Estados Unidos de América (Respectivamente)	

5 PCT (86)
Solicitud Internacional No. PCT/US02/40598 Fecha 18-12-2002
Publicación Internacional No. WO 03/062241 A1 Fecha 31-07-2003

6 Título (54): COMPUESTOS DE SUCCINIMIDA HETEROCICLICOS FUSIONADOS Y ANALOGOS DE LOS MISMOS, MODULADORES DE LA FUNCIÓN DEL RECEPTOR DE LA HORMONA NUCLEAR

7 Clasificación Internacional (51) A61K31/40

8 Prioridad	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
SI ☒ NO ☐	US	19-12-2001	10/025,116

9 [illegible]

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

2020-F06 (01-11-15)

Brigard & Castro
Abogados

Apartado 3692

Cra. 7 16-56
Bogotá - Colombia S.A.

Tel. Conm. 3802200
Tel./Fax: (57.1) 2827976
(57.1) 3802700

E.Mail:bricas@brigardycastro.com.co

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AS: 94.181
PCT/US01/40598
BRISTOL-MYERS SQUIBB COMPANY

1. Mark E. Salvati
   9 Tracey Drive,
   Lawrenceville, NJ 08648,
   Estados Unidos de América

2. James Aaron Balog
   17 Terrell Road,
   Lambertville, NJ 08530
   Estados Unidos de América

3. Dacia A. Pickering
   507 Drexel Avenue,
   Lawrenceville, NJ 08648
   Estados Unidos de América

4. Soren Giese
   523 Windmere Way,
   New Hope, PA 18938
   Estados Unidos de América

5. Aberra Fura
   15 Cresthill Road,
   Lawrenceville, NJ 08648,
   Estados Unidos de América

6. Wenying Li
   6221 Town Place,
   Middletown, CT 06457,
   Estados Unidos de América

7. Ramesh N. Patel
   572 Cabot Hill Road,
   Bridgewater, NJ 08807
   Estados Unidos de América

8. Ronald L. Hanson
   54 Whitewood Drive,
   Morris Plains, NJ 07950
   Estados Unidos de América

9. Toomas Mitt
   1312 Aspen Drive,
   Plainsboro, NJ 08536
   Estados Unidos de América

10. Jacques Y. Roberge
    478 Ewing Street,
    Princeton, NJ 08540
    Estados Unidos de América

11. James R. Corte
    11 Abelia Court,
    Lawrenceville, NJ 08648
    Estados Unidos de América

12. Steven H. Spergel
    1807 Jericho Drive,
    Warrington, PA 18976
    Estados Unidos de América

13. Richard A. Rampulla
    5 Fairfax Court,
    Flemington, NJ 08822
    Estados Unidos de América

14. Raj N. Misra
    12 Eaton Place,
    Hopewell, NJ 08525
    Estados Unidos de América

15. Hai-Yun Xiao
    173 Jonathan Dayton Court,
    Princeton, NJ 08540
    Estados Unidos de América

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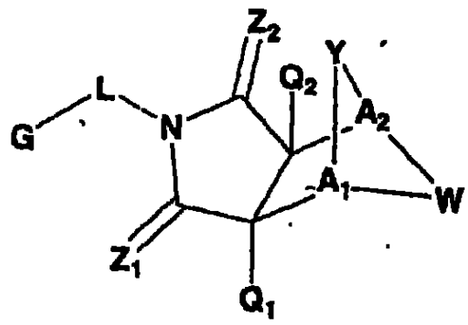
Reivindicaciones

1. Un compuesto de la siguiente fórmula:



(Ia)

caracterizado porque los símbolos tienen los siguientes significados y son, cada que se presentan, seleccionados independientemente:

G es un grupo arilo o heterociclo donde el grupo es mono- o policíclico, y el cual está opcionalmente substituido en una o más posiciones;

Z_1 es O, S, NH, o NR^6;

Z_2 es O, S, NH, o NR^6;

A_1 es CR^7 o N;

A_2 es CR^7 o N;

Y es J-J'-J" donde J es $(CR^7R^{7'})n$ y n = 0-3, J' es un enlace u O, S, S=O, SO_2, NH, NR^7, $CR^7R^{7'}$, $R^2P=O$, $R^2P=S$, $R^2OP=O$, $R^2NHP=O$, $OP=OOR^2$, $OP=ONHR^2$, OSO_2, NHNH, $NHNR^6$, NR^6NH, N=N, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, o heterociclo o heterociclo substituido, y J" es $(CR^7R^{7'})n$ y n = 0-3, donde Y no es un enlace; y

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W' es $CR^7CR^{7'}-CR^7R^{7'}$, $CR^7CR^{7'}-C=O$, $C=O-C=O$, $CR^7R^{7'}-C=CH_2$, $C=CH_2-C=CH_2$, $CR^7R^{7'}-C=NR^1$, $C=NR^1-C=NR^1$, $NR^9-CR^7R^{7'}$, $N=CR^8$, $N=N$, $NR^9-NR^{9'}$, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, o arilo o arilo substituido, en donde cuando W' no es $NR^9-CR^7R^{7'}$, $N=CR^8$, $N=N$, $NR^9-NR^{9'}$, o heterociclo o heterociclo substituido, entonces J' deberá ser O, S, S=O, SO_2, NH, NR^7, $OP=OOR^2$, $OP=ONHR^2$, OSO_2, NHNH, $NHNR^6$, NR^6NH, o N=N;

cuando W es $CR^7R^{7'}-CR^7R^{7'}$, los substituyentes R^7 y $R^{7'}$ cada que se presentan, pueden tomarse juntos para formar un sistema de anillo heterocíclico substituido o no substituido o carbocíclico substituido o no substituido que puede formarse por cualquier combinación de R^7 y $R^{7'}$ enlazado al mismo átomo de carbono;

Q_1 es H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilalquilo o arilalquilo substituido, alquinilo o alquinilo substituido, arilo o arilo substituido, heterociclo (por ejemplo heteroarilo) o heterociclo substituido (por ejemplo heteroarilo), halo, CN, $R^1OC=O$, $R^4C=O$, $R^5R^6NC=O$, $HOCR^7R^{7'}$, nitro, R^1OCH_2, R^1O, NH_2, $C=OSR^1$,

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SO_2R^1 o NR^4R^5;

Q_2 es H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilalquilo o arilalquilo substituido, alquinilo o alquinilo substituido, arilo o arilo substituido, heterociclo (por ejemplo heteroarilo) o heterociclo substituido (por ejemplo heteroarilo substituido), halo, CN, $R^1OC{=}O$, $R^4C{=}O$, $R^5R^6NC{=}O$, $HOCR^7R^{7'}$, nitro, R^1OCH_2, R^1O, NH_2, $C{=}OSR^1$, SO_2R^1, o NR^4R^5;

L es un enlace, $(CR^7R^{7'})n$, NH, NR^5, $NH(CR^7R^{7'})n$, o $NR^5(CR^7R^{7'})n$, donde n = 0-3;

R^1 y $R^{1'}$ son cada uno independientemente H, alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido, cicloalquilo o cicloalquilo substituido, cicloalquenilo o cicloalquenilo substituido, heterociclo o heterociclo substituido, cicloalquilalquilo o cicloalquilalquilo substituido, cicloalquenilalquilo o cicloalquenilalquilo substituido, heterocicloalquilo o heterocicloalquilo substituido, arilo o arilo substituido, arilalquilo o arilalquilo substituido;

R^2 es alquilo o alquilo substituido, alquenilo o alquenilo substituido, alquinilo o alquinilo substituido,

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2020
Bogotá D C

Doctor(a)
RAMIRO CASTRO DUQUE
Apoderado
BRISTOL – MYERS SQUIBB COMPANY.

Oficio N° 07157

ASUNTO:

Radicación N°	04-56353
Solicitud internacional	PCT/US02/40598
Fecha inicio fase nacional	27/06/2004
Trámite	011
Evento	379
Actuación	416
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 copia del documento en que consta la cesión del derecho de patente del inventor al solicitante o a su causante (Art. 26-k) Decisión 486).

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 CÉSPEDES DE VERGEL
Jefe de la División de Nuevas Creaciones.

El anterior requerimiento fue notificado por fijación en lista de fecha, 30 JUL 2021

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Sede Centro: Carrera 13 No. 27-00 Pisos 2, 5, 7 y 10
Conmutador: 3 820840 Fax: 3 505220
Sede CAN: Tr. 40A No. 38-50 3153265 al 69
Fax: 3 505220. Línea 9800-910 165
Web: www.sic.gov.co e-mail: info@sic.gov.co
Bogotá D.C. - Colombia