Q.F.

Industria y Comercio

SUPERINTENDENCIA

03-99304

Delegatura de propiedad Industrial

División de Nuevas Creaciones

PCT

SOLICITUD

PATENTE DE INVENCIÓN

21 **EXPEDIENTE No** 03-99304

54 **TÍTULO** Sulfona-hidroxamatos y su uso como inhibidores de proteasas

51 **CLASIFICACIÓN INTERNACIONAL**

71 **SOLICITANTE** Pharmacia Corporation

DOMICILIO Chesterfield, Missouri 63006, Estados Unidos

74 **APODERADO** Ramiro Castro Duque

22 **BOGOTÁ, D C,**

QF

202099

(FORMA P-10)

SS

PETITORIO

AS: 92.534

Industria y Comercio
SUPERINTENDENCIA

03 099304 00

Radicacion : 03099304 00000000 Folios: 1370
Fecha (AMD): 2002-11-10 17:22:24
Tramite : 011 PCT-PRIENT 3/9 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

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: **PHARMACIA CORPORATION** Dirección: P.O. BOX 1027, Chesterfield, Missouri 63006, 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 y República China (Respectivamente)	

5 PCT (86)
Solicitud Internacional No. PCT/US02/15257 Fecha 10-05-2002
Publicación Internacional No. WO 02/092588 A3 Fecha 21-11-2002

6 Título (54): SULFONA-HIDROXAMATOS AROMÁTICOS Y SU USO COMO INHIBIDORES DE PROTEASAS

7 Clasificación Internacional (51) A61K31/357

8 Prioridad SI ☒ NO ☐	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
	US	11-05-2001	60/290,375

9 Comprobante de pago No: 03-54875 **Fecha:** 07-11-2002

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

10 **ANEXOS**

- [x] Comprobante de pago de la tasa de presentación de la solicitud. $400.000
- [ ] Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- [ ] Poderes, si fuere el caso.
- [ ] Documento de cesión del inventor al solicitante o a su causante.
- [ ] Declaraciones
- [x] Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- [x] Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- [x] Copia del examen preliminar efectuado por la IPEA.
- [ ] 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. No. 322 de Bogotá D.C. NIT: 003 del C.S.J.

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

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

AA 3

AS: 92.534

LISTA DE INVENTORES

1. THOMAS E. BARTA
   1133 Maple Avenue, Apt.3-W
   Evanston, Illinois 60602
   Estados Unidos de América

2. DANIEL P. BECKER
   1800 Maplewood Lane
   Glenview, Illinois 60025
   Estados Unidos de América

3. LOUIS J. BEDELL
   208 E. Marion Avenue
   Mt. Prospect, Illinois 60070
   Estados Unidos de América

4. TERRI L. BOEHM
   928 Cleta Drive
   Ballwin, Missouri 63021
   Estados Unidos de América

5. JEFFERY N. CARROLL
   306 N. Rapp
   Columbia, Illinois 62236
   Estados Unidos de América

6. GARY A. DECRESCENZO
   7534 Spruce Hill Ct.
   St. Charles, Missouri 63304
   Estados Unidos de América

7. YVETTE M. FOBIAN
   580 Eagles Nest Ct.
   Wildwood, Missouri 63011
   Estados Unidos de América

8. JOHN N. FRESKOS
   7572 York
   Clayton, Missouri 63105
   Estados Unidos de América

9. SUSAN L. HOCKERMAN
   5319 W. Hutchingson
   Chicago, Illinois 60641
   Estados Unidos de América

10. DARREN J. KASSAB
    5 Park City Court
    O'Fallon, Missouri 63040
    Estados Unidos de América

11. STEVE A. KOLODZIEJ
    2448 Clarjon Road
    Ballwin, Missouri 63021
    Estados Unidos de América

12. JOSEPH J. MCDONALD
    1716 Timber Ridge Estate Dr.
    Wildwood, Missouri 63011
    Estados Unidos de América

13. DEBORAH A. MISCHKE
    25 White River Lane
    Defiance, Missouri 63341
    Estados Unidos de América

14. MONICA B. NORTON
    7777 Gissler Avenue
    St. Louis, Missouri 63117
    Estados Unidos de América

15. JOSEPH G. RICO
    524 Wetherby Terr. Dr.
    Ballwin, Missouri 63021
    Estados Unidos de América

16. JOHN J. TALLEY
    122 Hamilton St., Apt. 2
    Cambridge, Massachusetts
    02139, Estados Unidos

17. CLARA I. VILLAMIL
    813 Long Road
    Glenview, Illinois 60025
    Estados Unidos de América

18. LIJUAN JANE WANG
    919 Crown Pointe Est. Dr
    Wildwood, Missouri 63021
    Estados Unidos de América

4

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
Radicacion : 33099304 2003-11-10 Folios: 1392
Fecha (MSD): 2003-11-10 17:22:24
Tramite : 011 PCT-PATENT 379 FASE NACI 411 PRESENTACI
Dependencia: 2020 DIVISION DE NUEVAS CALIFICACIONES

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 03 - 54,875
FECHA : AGOSTO 5 DE 2003

***** 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	12651604	05/08/2003	19,360,000.00

***** 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	400,000.00
		TOTAL : $	400,000.00

SON: CUATROCIENTOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 November 2002 (21.11.2002)

PCT

(10) International Publication Number
WO 02/092588 A3

(51) International Patent Classification⁷: C07D 309/08, 405/12, 401/12, 211/66, 407/12, 417/12, 409/12, 413/12, A61K 31/351, A61P 35/00

(21) International Application Number: PCT/US02/15257

(22) International Filing Date: 10 May 2002 (10.05.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/290,375 11 May 2001 (11.05.2001) US

(71) Applicant (*for all designated States except US*): PHARMACIA CORPORATION [US/US]; Corporate Patent Department, 800 North Lindbergh Blvd., Mail Zone 04E, St. Louis, MO 63167 (US).

(72) Inventors; and

(75) Inventors/Applicants (*for US only*): BARTA, Thomas, E. [US/US]; Apt. 3-W, 1133 Maple Avenue, Evanston, IL 60202 (US). BECKER, Daniel, P. [US/US]; 1800 Maplewood Lane, Glenview, IL 60025 (US). BEDELL, Louis, J. [US/US]; 208 E. Marion Avenue, Mt. Prospect, IL 60070 (US). BOEHM, Terri, L. [US/US]; 928 Cleta Drive, Ballwin, MO 63021 (US). FOBIAN, Yvette, M. [US/US]; 580 Eagles Nest Ct., Wildwood, MO 63011 (US). FRESKOS, John, N. [US/US]; 7572 York, Clayton, MO 63105 (US). HOCKERMAN, Susan L. [US/US]; 5319 W. Hutchingson, Chigago, IL 60641 (US). KASSAB, Darren, J. [US/US]; 16346 Centerfield Court, Apt. E, Wildwood, MO 63040 (US). KOLODZIEJ, Steve, A. [US/US]; 2448 Clarjon Drive, Ballwin, MO 63021 (US). MCDONALD, Joseph, J. [US/US]; 1716 Timber Ridge Estate Dr., Wildwood, MO 63011 (US). NORTON, Monica, B. [US/US]; 7777 Gissler Avenue, St. Louis, MO 63117 (US). RICO, Joseph, G. [US/US]; 524 Wetherby Terr. Dr., Ballwin, MO 63021 (US). TALLEY, John, J. [US/US]; 5 Marborough Street #5, Boston, MA 02116 (US). VILLAMIL, Clara, I. [US/US]; 813 Long Road, Glenview, IL 60025 (US). WANG, Tijuan, Jane [CN/US]; 919 Crown Pointe Est. Dr., Wildwood, MO 63021 (US).

(74) Agent: GRYTE, David, M.; 800 N. Lindbergh Blvd., St. Louis, MO 63167 (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, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, 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, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, 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*

(88) Date of publication of the international search report:
27 February 2003.

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 02/092588 A3

(54) Title: AROMATIC SULFONE HYDROXAMATES AND THEIR USE AS PROTEASE INHIBITORS

(57) Abstract: This invention is directed to aromatic sulfone hydroxamates (also known as "aromatic sulfone hydroxamic acids") and salts thereof that, *inter alia*, inhibit matrix metalloproteinase (also known as "matrix metalloprotease" or "MMP") activity and/or aggrecanase activity. This invention also is directed to a prevention or treatment method that comprises administering such a compound or salt in an MMP-inhibiting and/or aggrecanase-inhibiting effective amount to an animal, particularly a mammal having (or disposed to having) a pathological condition associated with MMP and/or aggrecanase activity.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/15257

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D309/08 C07D405/12 C07D401/12 C07D211/66 C07D407/12
C07D417/12 C07D409/12 C07D413/12 A61K31/351 A61P35/00

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)
IPC 7 C07D A61K A61P

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 practical, search terms used)
CHEM ABS Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 50396 A (SEARLE) 31 August 2000 (2000-08-31) claims; example 398	1-6, 380-405
X	WO 00 69821 A (SEARLE) 23 November 2000 (2000-11-23) claims	1-6, 380-405
X	WO 99 25687 A (SEARLE) 27 May 1999 (1999-05-27) page 521 -page 535; claims 1-15; table 123	1-6,237, 238, 380-405

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in 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 document but 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
11 December 2002	23/12/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016	Francois, J

Form PCT/ISA/210 (second sheet) (July 1998)

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 02/15257

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 380 to 401 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

FURTHER INFORMATION CONTINUED FROM PCT/ISA/ 210

Continuation of Box I.2

Present claims .1 to 5,122,123,225,226,235,236,250,251,260,261,267,268,296,297,303,304,308,309,322,323,335 to 338,344,345,354,355,359 to 362,368,369,372,373,376,377 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds where A2 and A3 toegether with the carbon to which they are both attached, form an optionally-substituted piperidino or tetrahydropyrano group.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

INTERNATIONAL SEARCH REPORT

formation on patent family members

International Application No
PCT/US 02/15257

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
WO 0050396 A	31-08-2000	US 2001039287 A1	08-11-2001
		AU 3478500 A	14-09-2000
		BR 0008491 A	17-09-2002
		CN 1370144 T	18-09-2002
		CZ 20013038 A3	17-07-2002
		EP 1230219 A1	14-08-2002
		HU 0200239 A2	29-06-2002
		JP 2002537378 A	05-11-2002
		NO 20013963 A	23-10-2001
		NZ 513648 A	28-09-2001
		WO 0050396 A1	31-08-2000
WO 0069821 A	23-11-2000	AU 4797000 A	05-12-2000
		EP 1183239 A1	06-03-2002
		HU 0201680 A2	28-09-2002
		NO 20015543 A	10-01-2002
		WO 0069821 A1	23-11-2000
WO 9925687 A	27-05-1999	AU 1373299 A	07-06-1999
		BR 9814643 A	03-10-2000
		CA 2306460 A1	27-05-1999
		CN 1279669 T	10-01-2001
		EP 1042290 A1	11-10-2000
		JP 2001523662 T	27-11-2001
		NO 20002469 A	12-07-2000
		NZ 503485 A	25-10-2002
		PL 341379 A1	09-04-2001
		WO 9925687 A1	27-05-1999
		US 2001014688 A1	16-08-2001
		US 2001039287 A1	08-11-2001
		ZA 9810412 A	09-12-1999

PCT

REQUEST

The undersigned requests that the present international application be processed according to the Patent Cooperation Treaty.

For receiving Office use only

International Application No.

International Filing Date

Name of receiving Office and "PCT International Application"

Applicant's or agent's file reference *(if desired) (12 characters maximum)* 3316/0/PCT

Box No. I TITLE OF INVENTION

AROMATIC SULFONE HYDROXAMATES AND THEIR USE AS PROTEASE INHIBITORS

Box No. II APPLICANT ☐ This person is also inventor

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. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

PHARMACIA CORPORATION
A corporation of the State of Delaware
Corporate Patent Department
800 North Lindbergh Blvd., Mail Zone 04E
St. Louis, Missouri 63167 United States of America

Telephone No. 314-694-1000

Facsimile No. 314-694-9095

Teleprinter No.

Applicant's registration No. with the Office

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☒ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(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. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

BARTA, Thomas E.
1133 Maple Avenue, Apt. 3-W
Evanston, Illinois 60602
United States of America

This person is:
☐ applicant only
☒ applicant and inventor
☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on a continuation sheet.

Box No. IV 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 ☐ common representative

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.)*

GRYTE, DAVID M.
Harness, Dickey & Pierce, P.L.C.
7700 Bonhomme, Suite 400
St. Louis, Missouri 63105
United States of America

Telephone No. 314-726-7508

Facsimile No. 314-726-7501

Teleprinter No.

Agent's registration No. with the Office Reg. No. 41,809

☐ 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.

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

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. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

BECKER, Daniel P.
1800 Maplewood Lane
Glenview, Illinois 60025
United States of America

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office:

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

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. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

BEDELL, Louis J.
206 E. Marion Avenue
Mt. Prospect, Illinois 60070
United States of America

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office:

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

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. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

BOEHM, Terri L.
928 Cleta Drive
Ballwin, Missouri 63021
United States of America

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office:

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

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. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

FOBIAN, Yvette M.
580 Eagles Nest Ct.
Wildwood, Missouri 63011
United States of America

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office:

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on another continuation sheet.

12

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

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. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

FRESKOS, John N.
7572 York
Clayton, Missouri 63105
United States of America

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office:

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of:
- ☐ all designated States
- ☐ all designated States except the United States of America
- ☒ the United States of America only
- ☐ the States indicated in the Supplemental Box

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. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

HOCKERMAN, Susan L.
5319 W. Hutchingson
Chicago, Illinois 60641
United States of America

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office:

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of:
- ☐ all designated States
- ☐ all designated States except the United States of America
- ☒ the United States of America only
- ☐ the States indicated in the Supplemental Box

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. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

KASSAB, Darren J.
16346 Centerfield Court, Apt. E
Wildwood, Missouri 63040
United States of America

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office:

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of:
- ☐ all designated States
- ☐ all designated States except the United States of America
- ☒ the United States of America only
- ☐ the States indicated in the Supplemental Box

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. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

KOLODZIEJ, Steve A.
2448 Clarjon Road
Ballwin, Missouri 63021
United States of America

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office:

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of:
- ☐ all designated States
- ☐ all designated States except the United States of America
- ☒ the United States of America only
- ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on another continuation sheet.

-13

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

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. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

MCDONALD, Joseph J.
1716 Timber Ridge Estate Dr.
Wildwood, Missouri 63011
United States of America

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

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. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

NORTON, Monica B.
7777 Glasier Avenue
St. Louis, Missouri 63117
United States of America

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

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. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

RICO, Joseph G.
524 Wetherby Terr. Dr.
Ballwin, Missouri 63021
United States of America

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

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. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

TALLEY, John J.
5 Marborough Street, #5
Boston, Massachusettes 02116
United States of America

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* of nationality: US

State *(that is, country)* of residence: US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

☒ Further applicants and/or (further) inventors are indicated on another continuation sheet.

14

Continuation of Box No. III FURTHER APPLICANT(S) AND/OR (FURTHER) INVENTOR(S)

If none of the following sub-boxes is used, this sheet should not be included in the request.

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. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

VILLAMIL, Clara I.
813 Long Road
Glenview, Illinois 60025
United States of America

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* **of nationality:** US

State *(that is, country)* **of residence:** US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

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. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

WANG, Tijuan Jane
919 Crown Pointe Est. Dr
Wildwood, Missouri 63021
United States of America

This person is:
- ☐ applicant only
- ☒ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* **of nationality:** CN

State *(that is, country)* **of residence:** US

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☒ the United States of America only ☐ the States indicated in the Supplemental Box

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. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* **of nationality:**

State *(that is, country)* **of residence:**

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

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. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below.)*

This person is:
- ☐ applicant only
- ☐ applicant and inventor
- ☐ inventor only *(If this check-box is marked, do not fill in below.)*

Applicant's registration No. with the Office

State *(that is, country)* **of nationality:**

State *(that is, country)* **of residence:**

This person is applicant for the purposes of: ☐ all designated States ☐ all designated States except the United States of America ☐ the United States of America only ☐ the States indicated in the Supplemental Box

☐ Further applicants and/or (further) inventors are indicated on another continuation sheet.

Box No. V DESIGNATION OF STATES *Mark the applicable check-boxes below; at least one must be marked.*

The following designations are hereby made under Rule 4.9(a):

Regional Patent

☒ **AP** ARIPO Patent: GH Ghana, GM Gambia, KE Kenya, LS Lesotho, MW Malawi, MZ Mozambique, SD Sudan, SL Sierra Leone, SZ Swaziland, TZ United Republic of Tanzania, UG Uganda, ZM Zambia, ZW Zimbabwe, and any other State which is a Contracting State of the Harare Protocol and of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

☒ **EA** Eurasian Patent: AM Armenia, AZ Azerbaijan, BY Belarus, KG Kyrgyzstan, KZ Kazakhstan, MD Republic of Moldova, RU Russian Federation, TJ Tajikistan, TM Turkmenistan, and any other State which is a Contracting State of the Eurasian Patent Convention and of the PCT

☒ **EP** European Patent: AT Austria, BE Belgium, CH & LI Switzerland and Liechtenstein, CY Cyprus, DE Germany, DK Denmark, ES Spain, FI Finland, FR France, GB United Kingdom, GR Greece, IE Ireland, IT Italy, LU Luxembourg, MC Monaco, NL Netherlands, PT Portugal, SE Sweden, TR Turkey, and any other State which is a Contracting State of the European Patent Convention and of the PCT

☒ **OA** OAPI Patent: BF Burkina Faso, BJ Benin, CF Central African Republic, CG Congo, CI Côte d'Ivoire, CM Cameroon, GA Gabon, GN Guinea, GQ Equatorial Guinea, GW Guinea-Bissau, ML Mali, MR Mauritania, NE Niger, SN Senegal, TD Chad, TG Togo, and any other State which is a member State of OAPI and a Contracting State of the PCT *(if other kind of protection or treatment desired, specify on dotted line)* .....

National Patent *(if other kind of protection or treatment desired, specify on dotted line)*:

☒ AE United Arab Emirates	☒ GM Gambia	☒ NZ New Zealand .....
☒ AG Antigua and Barbuda	☒ HR Croatia	☒ OM Oman
☒ AL Albania	☒ HU Hungary	☒ PH Philippines .....
☒ AM Armenia	☒ ID Indonesia	☒ PL Poland .....
☒ AT Austria	☒ IL Israel	☒ PT Portugal .....
☒ AU Australia	☒ IN India	☒ RO Romania
☒ AZ Azerbaijan	☒ IS Iceland	☒ RU Russian Federation .....
☒ BA Bosnia and Herzegovina	☒ JP Japan	.....
☒ BB Barbados	☒ KE Kenya	☒ SD Sudan
☒ BG Bulgaria	☒ KG Kyrgyzstan	☒ SE Sweden
☒ BR Brazil	☒ KP Democratic People's Republic of Korea	☒ SG Singapore
☒ BY Belarus	☒ KR Republic of Korea	☒ SI Slovenia .....
☒ BZ Belize	☒ KZ Kazakhstan	☒ SK Slovakia .....
☒ CA Canada	☒ LC Saint Lucia	☒ SL Sierra Leone .....
☒ CH & LI Switzerland and Liechtenstein	☒ LK Sri Lanka	☒ TJ Tajikistan .....
☒ CN China	☒ LR Liberia	☒ TM Turkmenistan .....
☒ CO Colombia	☒ LS Lesotho	☒ TN Tunisia
☒ CR Costa Rica	☒ LT Lithuania	☒ TR Turkey .....
☒ CU Cuba	☒ LU Luxembourg	☒ TT Trinidad and Tobago .....
☒ CZ Czech Republic	☒ LV Latvia	.....
☒ DE Germany	☒ MA Morocco	☒ TZ United Republic of Tanzania
☒ DK Denmark	☒ MD Republic of Moldova	☒ UA Ukraine .....
☒ DM Dominica	.....	☒ UG Uganda .....
☒ DZ Algeria	☒ MG Madagascar	☒ US United States of America .....
☒ EC Ecuador	☒ MK The former Yugoslav Republic of Macedonia	.....
☒ EE Estonia	☒ MN Mongolia	☒ UZ Uzbekistan .....
☒ ES Spain	☒ MW Malawi	☒ VN Viet Nam .....
☒ FI Finland	☒ MX Mexico	☒ YU Yugoslavia .....
☒ GB United Kingdom	☒ MZ Mozambique	☒ ZA South Africa .....
☒ GD Grenada	☒ NO Norway	☒ ZM Zambia
☒ GE Georgia		☒ ZW Zimbabwe .....
☒ GH Ghana		

Check-boxes below reserved for designating States which have become party to the PCT after issuance of this sheet:

☒ . All other countries included in	☐	☐ .....
☐ . the PCT since the issuance of this ..	☐	☐ .....

Precautionary Designation Statement: In addition to the designations made above, the applicant also makes under Rule 4.9(b) all other designations which would be permitted under the PCT except any designation(s) indicated in the Supplemental Box as being excluded from the scope of this statement. 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. *(Confirmation (including fee) must reach the receiving Office within the 15-month time limit.)*

Supplemental Box *If the Supplemental Box is not used, this sheet should not be included in the request.*

1. *If, in any of the Boxes, except Boxes Nos. VIII(i) to (v) for which a special continuation box is provided, the space is insufficient to furnish all the information: in such case, write "Continuation of Box No...." (indicate the number of the Box) and furnish the information in the same manner as required according to the captions of the Box in which the space was insufficient, in particular:*

(i) *If more than two persons are to be indicated as applicants and/or inventors and no "continuation sheet" is available: in such case, write "Continuation of Box No. III" and indicate for each additional person the same type of information as required in Box No. III. The country of the address indicated in this Box is the applicant's State (that is, country) of residence if no State of residence is indicated below;*

(ii) *If, in Box No. II or in any of the sub-boxes of Box No. III, the indication "the States indicated in the Supplemental Box" is checked: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the applicant(s) involved and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is applicant;*

(iii) *If, in Box No. II or in any of the sub-boxes of Box No. III, the inventor or the inventor/applicant is not inventor for the purposes of all designated States or for the purposes of the United States of America: in such case, write "Continuation of Box No. II" or "Continuation of Box No. III" or "Continuation of Boxes No. II and No. III" (as the case may be), indicate the name of the inventor(s) and, next to (each) such name, the State(s) (and/or, where applicable, ARIPO, Eurasian, European or OAPI patent) for the purposes of which the named person is inventor;*

(iv) *If, in addition to the agent(s) indicated in Box No. IV, there are further agents: in such case, write "Continuation of Box No. IV" and indicate for each further agent the same type of information as required in Box No. IV;*

(v) *If, in Box No. V, the name of any State (or OAPI) is accompanied by the indication "patent of addition," or "certificate of addition," or if, in Box No. V, the name of the United States of America is accompanied by an indication "continuation" or "continuation-in-part": in such case, write "Continuation of Box No. V" and the name of each State involved (or OAPI), and after the name of each such State (or OAPI), the number of the parent title or parent application and the date of grant of the parent title or filing of the parent application;*

(vi) *If, in Box No. VI, there are more than five earlier applications whose priority is claimed: in such case, write "Continuation of Box No. VI" and indicate for each additional earlier application the same type of information as required in Box No. VI.*

2. *If, with regard to the precautionary designation statement contained in Box No. V, the applicant wishes to exclude any State(s) from the scope of that statement: in such case, write "Designation(s) excluded from precautionary designation statement" and indicate the name or two-letter code of each State so excluded.*

BOX IV - Agent or Common Representative (continued)

David M. Gryte (Reg. No. 41,809), Donald R. Holland (Reg. No. 35,197), Bryan K. Wheelock (Reg. No. 31,441), Joseph E. Walsh, Jr. (Reg. No. 36,958), Rudolph A. Telscher, Jr. (Reg. No.36,032), Elizabeth D. Odell (Reg. No.39,532), Evan R. Sotiriou (Reg. No. 46,247), Kelly K. Burris (Reg. No. 46,361), and Matthew L. Cutler (Reg. No. 43,574) of the firm of Harness, Dickey & Pierce, P.L.C (7700 Bonhomme Avenue, Suite 400, Clayton, Missouri 63105) and S. Christopher Bauer (Reg. No. 42,307), Dennis A. Bennett (Reg. No. 34,547), James C. Forbes, (Reg. No. 39,457), Kalim S. Fuzail (Reg. No. 45,805), J. Timothy Keane (Reg. No. 27,808), Robert M. Kennedy (Reg. No. 28,026), Karan B. King (Reg. No. 41,898), Verne A. Luckow (Reg. No. 45,950), Scott J. Meyer (Reg. No. 25,275), Richard A. Mueller (Reg. No. 41,094), Philip B. Polster, II (Reg. No. 43,864), Rachel Polster (Reg. 47,004), Joseph R. Schuh (Reg. No. 48,180); James M. Warner, (Reg. No. 45,199), and Scott A. Williams, (Reg. No. 39,876), of Pharmacia Corporation, (800 North Lindbergh Blvd., Mail Zone O4E, St. Louis Missouri 63167)

17

Box No. VI PRIORITY CLAIM

The priority of the following earlier application(s) is hereby claimed:

Filing date of earlier application *(day/month/year)*	Number of earlier application	Where earlier application is:		
		national application: country	regional application:* regional Office	international application: receiving Office
Item (1) 11 May 2001	60/290,375	US		
Item (2)				
Item (3)				
Item (4)				
Item (5)				

☐ Further priority claims are indicated in the Supplemental Box.

The receiving Office is requested to prepare and transmit to the International Bureau a certified copy of the earlier application(s) *(only if the earlier application was filed with the Office which for the purposes of this international application is the receiving Office)* identified above as:

☐ all items ☒ item (1) ☐ item (2) ☐ item (3) ☐ item (4) ☐ item (5) ☐ other, see Supplemental Box

** Where the earlier application is an ARIPO application, indicate at least one country party to the Paris Convention for the Protection of Industrial Property or one Member of the World Trade Organization for which that earlier application was filed (Rule 4.10(b)(ii)):* ....

.....

Box No. VII INTERNATIONAL SEARCHING AUTHORITY

Choice of International Searching Authority (ISA) *(if two or more International Searching Authorities are competent to carry out the international search, indicate the Authority chosen; the two-letter code may be used)*:

ISA / EPO .....

Request to use results of earlier search; reference to that search *(if an earlier search has been carried out by or requested from the International Searching Authority)*:

Date *(day/month/year)* Number Country *(or regional Office)*

Box No. VIII DECLARATIONS

The following declarations are contained in Boxes Nos. VIII (i) to (v) *(mark the applicable check-boxes below and indicate in the right column the number of each type of declaration)*: Number of declarations

☐	Box No. VIII (i)	Declaration as to the identity of the inventor	:
☐	Box No. VIII (ii)	Declaration as to the applicant's entitlement, as at the international filing date, to apply for and be granted a patent	:
☐	Box No. VIII (iii)	Declaration as to the applicant's entitlement, as at the international filing date, to claim the priority of the earlier application	:
☐	Box No. VIII (iv)	Declaration of inventorship (only for the purposes of the designation of the United States of America)	:
☐	Box No. VIII (v)	Declaration as to non-prejudicial disclosures or exceptions to lack of novelty	:

18

Box No. IX CHECK LIST; LANGUAGE OF FILING

This international application contains:

(a) the following number of sheets in paper form:

request (including declaration sheets)	:	9
description (excluding sequence listing part)	:	413
claims	:	213
abstract	:	1
drawings	:	0
Sub-total number of sheets	:	636
sequence listing part of description *(actual number of sheets if filed in paper form, whether or not also filed in computer readable form; see (b) below)*	:	
Total number of sheets	:	636

(b) sequence listing part of description filed in computer readable form

(i) ☐ only (under Section 801(a)(i))

(ii) ☐ in addition to being filed in paper form (under Section 801(a)(ii))

Type and number of carriers (diskette, CD-ROM, CD-R or other) on which the sequence listing part is contained *(additional copies to be indicated under item 9(ii), in right column)*: .....

This international application is accompanied by the following item(s) *(mark the applicable check-boxes below and indicate in right column the number of each item)*:

		Number of items
1. ☒ fee calculation sheet	:	1
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. ☐ priority document(s) identified in Box No. VI as item(s):	:	
7. ☐ translation of international application into (language):	:	
8. ☐ separate indications concerning deposited microorganism or other biological material	:	
9. ☐ sequence listing in computer readable form (indicate also type and number of carriers (diskette, CD-ROM, CD-R or other))		
(i) ☐ copy submitted for the purposes of international search under Rule 13*ter* only (and not as part of the international application)	:	
(ii) ☐ *(only where check-box (b)(i) or (b)(ii) is marked in left column)* additional copies including, where applicable, the copy for the purposes of international search under Rule 13*ter*	:	
(iii) ☐ together with relevant statement as to the identity of the copy or copies with the sequence listing part mentioned in left column	:	
10. ☒ other *(specify)*: Trans. to USPTO; check for $7422 ...	:	2

Figure of the drawings which should accompany the abstract:

Language of filing of the international application: English

Box No. X 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 request).

GRYTE, DAVID M. (Agent)
Reg. No., 41,809

For receiving Office use only

1. Date of actual receipt of the purported international application:	2. Drawings: ☐ received: ☐ not received:
3. Corrected date of actual receipt due to later but timely received papers or drawings completing the purported international application:	
4. Date of timely receipt of the required corrections under PCT Article 11(2):	
5. International Searching Authority (if two or more are competent): ISA /	6. ☐ Transmittal of search copy delayed until search fee is paid

For International Bureau use only

Date of receipt of the record copy by the International Bureau:

This sheet is not part of and does not count as a sheet of the international application.

PCT

FEE CALCULATION SHEET
Annex to the Request

For receiving Office use only

International Application No.

Date stamp of the receiving Office

Applicant's or agent's file reference: 3316/0/PCT

Applicant: PHARMACIA CORPORATION

CALCULATION OF PRESCRIBED FEES

1. TRANSMITTAL FEE . . . . . 240 [T]
2. SEARCH FEE . . . . . 866 [S]
   International search to be carried out by EPO
   (If two or more International Searching Authorities are competent to carry out the international search, indicate the name of the Authority which is chosen to carry out the international search.)
3. INTERNATIONAL FEE
   Basic Fee
   Where item (b) of Box No. IX applies, enter Sub-total number of sheets / Where item (b) of Box No. IX does not apply, enter Total number of sheets: 636
   [b1] first 30 sheets . . . . . 407 [b1]
   [b2] 606 (number of sheets in excess of 30) x 9 (fee per sheet) = 5454 [b2]
   [b3] additional component (only if sequence listing part of description is filed in computer readable form under Section 801(a)(i), or both in that form and on paper, under Section 801(a)(ii)):
   400 x _____ (fee per sheet) = _____ [b3]
   Add amounts entered at b1, b2 and b3 and enter total at B . . . . 5861 [B]
   Designation Fees
   The international application contains ALL designations.
   5 (number of designation fees payable *(maximum 5)*) x 88 (amount of designation fee) = 440 [D]
   Add amounts entered at B and D and enter total at I . . . . . 6301 [I]
   (Applicants from certain States are entitled to a reduction of 75% of the international fee. Where the applicant is (or all applicants are) so entitled, the total to be entered at I is 25% of the sum of the amounts entered at B and D.)
4. FEE FOR PRIORITY DOCUMENT *(If applicable)* . . . . . 15 [P]
5. TOTAL FEES PAYABLE . . . . . 7422 TOTAL
   Add amounts entered at T, S, I and P, and enter total in the TOTAL box

☐ The designation fees are not paid at this time.

MODE OF PAYMENT

☐ authorization to charge deposit account (see below) ☐ postal money order ☐ cash ☐ coupons
☒ cheque ☐ bank draft ☐ revenue stamps ☐ other *(specify)*:

AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT
(This mode of payment may not be available at all receiving Offices)

☐ Authorization to charge the total fees indicated above.
☒ *(This check-box may be marked only if the conditions for deposit accounts of the receiving Office so permit)* Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.
☐ Authorization to charge the fee for priority document.

Receiving Office: RO/ US
Deposit Account No.: 08-0750
Date: May 10, 2002
Name: David M. Gryte
Signature:

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/ EP

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
		3316/0/PCT
International application No.	International filing date *(day/month/year)*	(Earliest) Priority date *(day/month/year)*
PCT/US02/15257	10 May 2002 (10.05.02)	11 May 2001 (11.05.01)
Title of invention		
AROMATIC SULFONE HYDROXAMATES AND THEIR USE AS PROTEASE INHIBITORS		

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.
PHARMACIA CORPORATION A corporation of the State of Delaware Corporate Patent Department 800 North Lindbergh Blvd., Mail Zone 04E St. Louis, Missouri 63167 United States of America	314-694-1000
	Facsimile No. 314-694-9095
	Teleprinter No.
	Applicant's registration No. with the Office

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.)*

BARTA, Thomas E.
1133 Maple Avenue, Apt. 3-W
Evanston, Illinois 60602
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.)*

BECKER, Daniel P.
1800 Maplewood Lane
Glenview, Illinois 60025
United States of America

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
US	US

☒ Further applicants are indicated on a continuation sheet.

International application No.
PCT/US02/15257

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.)*

BEDELL, Louis J.
208 E. Marion Avenue
Mt. Prospect, Illinois 60070
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.)*

BOEHM, Terri L.
928 Cleta Drive
Ballwin, Missouri 63021
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.)*

FOBIAN, Yvette M.
580 Eagles Nest Ct.
Wildwood, Missouri 63011
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.)*

FRESKOS, John N.
7572 York
Clayton, Missouri 63105
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.

International application No.
PCT/US02/15257

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.)*

HOCKERMAN, Susan L.
5319 W. Hutchingson
Chicago, Illinois 60641
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.)*

KASSAB, Darren J.
16346 Centerfield Court, Apt. E
Wildwood, Missouri 63040
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.)*

KOLODZIEJ, Steve A.
2448 Clarjon Road
Ballwin, Missouri 63021
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.)*

MCDONALD, Joseph J.
1716 Timber Ridge Estate Dr.
Wildwood, Missouri 63011
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.

International application No.
PCT/US02/15257

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.)*

NORTON, Monica B.
7777 Gissler Avenue
St. Louis, Missouri 63117
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.)*

RICO, Joseph G.
524 Wetherby Terr. Dr.
Ballwin, Missouri 63021
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.)*

TALLEY, John J.
5 Marborough Street, #5
Boston, Massachusettes 02116
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.)*

VILLAMIL, Clara I.
813 Long Road
Glenview, Illinois 60025
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.

International application No.
PCT/US02/15257

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.)*

WANG, Tijuan Jane
919 Crown Pointe Est. Dr
Wildwood, Missouri 63021
United States of America

State *(that is, country)* of nationality:	State *(that is, country)* of residence:
CN	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.

International application No.
PCT/US02/15257

Box No. III AGENT OR COMMON REPRESENTATIVE; OR ADDRESS FOR CORRESPONDENCE

The following person is ☒ agent ☐ common representative

and ☒ 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.)*

GRYTE, DAVID M.
Harness, Dickey & Pierce, P.L.C.
7700 Bonhomme, Suite 400
St. Louis, Missouri 63105
United States of America

Telephone No.
314-726-7508

Facsimile No.
314-726-7501

Teleprinter No.

Agent's registration No. with the Office
Reg. No. 41,809

☐ **Address for correspondence:** Mark this check-box where no agent or common representative is/has been appointed and the space above is used instead to indicate a special address to which correspondence should be sent.

Box No. IV BASIS FOR INTERNATIONAL PRELIMINARY EXAMINATION

Statement concerning amendments:*

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

☒ the international application as originally filed

the description
☒ as originally filed
☐ as amended under Article 34

the claims
☒ as originally filed
☐ as amended under Article 19 (together with any accompanying statement)
☐ as amended under Article 34

the drawings
☒ 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

☒ 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:

International application No.
PCT/US02/15257

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	:	sheets	☐	☐
2. amendments under Article 34	:	sheets	☐	☐
3. copy (or, where required, translation) of amendments under Article 19	:	sheets	☐	☐
4. copy (or, where required, translation) of statement under Article 19	:	sheets	☐	☐
5. letter	:	sheets	☐	☐
6. other *(specify)*	:	sheets	☐	☐

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 *(specify)*: Copy of Power of Attorney

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

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

David M. Gryte
Reg. No. 41,809

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:

27

CHAPTER II

PCT

FEE CALCULATION SHEET

Annex to the Demand

International application No. PCT/US02/15257	For International Preliminary Examining Authority use only
Applicant's or agent's file reference 3316/0/PCT	Date stamp of the IPEA

Applicant

Pharmacia Corporation

CALCULATION OF PRESCRIBED FEES

1. Preliminary examination fee	EUR 1530	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.)*	EUR 159	H	
3. Total of prescribed fees Add the amounts entered at P and H and enter total in the TOTAL box	EUR 1689 TOTAL		

MODE OF PAYMENT

☒	authorization to charge deposit account with the IPEA (see below)	☐	cash
☐	cheque	☐	revenue stamps
☐	postal money order	☐	coupons
☐	bank draft	☐	other *(specify)*:

AUTHORIZATION TO CHARGE (OR CREDIT) DEPOSIT ACCOUNT
(This mode of payment may not be available at all IPEAs)

IPEA/ EP

☒ Authorization to charge the total fees indicated above.

☐ *(This check-box may be marked only if the conditions for deposit accounts of the IPEA so permit)* Authorization to charge any deficiency or credit any overpayment in the total fees indicated above.

Deposit Account No.: 28300413

Date: December 6, 2002

Name: David M. Gryte

Signature:

See Notes to the fee calculation sheet

2nd search report dated 2/23/03

PATENT COOPERATION TREATY

From the INTERNATIONAL SEARCHING AUTHORITY

PCT

NOTIFICATION OF TRANSMITTAL OF THE INTERNATIONAL SEARCH REPORT OR THE DECLARATION

(PCT Rule 44.1)

To:
PHARMACIA CORPORATION
CORPORATE PATENT DEPARTEMENT
Attn. WARNER,James M.
800 N. Lindbergh Blvd.
Mail Zone 04E
St.Louis,MO 63167
UNITED STATES OF AMERICA

RECEIVED
JAN 14 2003
WARNER, DICKEY & PIERCE
ST. LOUIS, MISSOURI

Applicant's or agent's file reference 3316/0/PCT	Date of mailing (day/month/year) 23/12/2002
International application No. PCT/US 02/15257	FOR FURTHER ACTION See paragraphs 1 and 4 below
Applicant PHARMACIA CORPORATION	International filing date (day/month/year) 10/05/2002

1. [X] 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 2 months from the date of transmittal of the International Search Report; however, for more details, see the notes on the accompanying sheet.

   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. Further action(s): The applicant is reminded of the following:

   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 90bis.1 and 90bis.3, respectively, before the completion of the technical preparations for international publication.

   Within 19 months from the priority date, 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).

   Within 20 months from the priority date, the applicant must perform the prescribed acts for entry into the national phase before all designated Offices which have not been elected in the demand or in a later election within 19 months from the priority date or could not be elected because they are not bound by Chapter II.

Name and mailing address of the International Searching Authority European Patent Office, P.B. 5818 Patentlaan 2 NL-2280 HV Rijswijk Tel. (+31-70) 340-2040. Tx. 31 651 epo nl.	Authorized officer Eva Bleijs

NOTES TO FORM PCT/ISA/220

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

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

INSTRUCTIONS CONCERNING AMENDMENTS UNDER ARTICLE 19

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

What parts of the international application may be amended?

Under Article 19, only the claims may be amended.

During the international phase, the claims may also be amended (or further amended) under Article 34 before the International Preliminary Examining Authority. The description and drawings may only be amended under Article 34 before the International Examining Authority.

Upon entry into the national phase, all parts of the international application may be amended under Article 28 or, where applicable, Article 41.

When?

Within 2 months from the date of transmittal of the international search report or 16 months from the priority date, whichever time limit expires later. It should be noted, however, that the amendments will be considered as having been received on time if they are received by the International Bureau after the expiration of the applicable time limit but before the completion of the technical preparations for international publication (Rule 48.1).

Where not to file the amendments?

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

Where a demand for international preliminary examination has been/is filed, see below.

How?

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

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

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

The amendments must be made in the language in which the international application is to be published.

What documents must/may accompany the amendments?

Letter (Section 205(b)):

The amendments must be submitted with a letter.

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

The letter must be in English or French, at the choice of the applicant. However, if the language of the international application is English, the letter must be in English; if the language of the international application is French, the letter must be in French.

NOTES TO FORM PCT/ISA/220 (continued)

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

(i) the claim is unchanged;

(ii) the claim is cancelled;

(iii) the claim is new;

(iv) the claim replaces one or more claims as filed;

(v) the claim is the result of the division of a claim as filed.

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

1. [Where originally there were 48 claims and after amendment of some claims there are 51]:
"Claims 1 to 29, 31, 32, 34, 35, 37 to 48 replaced by amended claims bearing the same numbers; claims 30, 33 and 36 unchanged; new claims 49 to 51 added."

2. [Where originally there were 15 claims and after amendment of all claims there are 11]:
"Claims 1 to 15 replaced by amended claims 1 to 11."

3. [Where originally there were 14 claims and the amendments consist in cancelling some claims and in adding new claims]:
"Claims 1 to 6 and 14 unchanged; claims 7 to 13 cancelled; new claims 15, 16 and 17 added." or
"Claims 7 to 13 cancelled; new claims 15, 16 and 17 added; all other claims unchanged."

4. [Where various kinds of amendments are made]:
"Claims 1-10 unchanged; claims 11 to 13, 15 and 16 cancelled; claims 14, 15 and 16 replaced by amended claims 14; claim 17 subdivided into amended claims 15, 16 and 17; new claims 20 and 21 added."

"Statement under article 19(1)" (Rule 46.4)

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

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

It must be in the language in which the international application is to be published.

It must be brief, not exceeding 500 words if in English or if translated into English.

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

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

Consequence if a demand for international preliminary examination has already been filed

If, at the time of filing any amendments under Article 19, a demand for international preliminary examination has already been submitted, the applicant must preferably, at the same time of filing the amendments with the International Bureau, also file a copy of such amendments with the International Preliminary Examining Authority (see Rule 66.2(a), first sentence).

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

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

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

31

PATENT COOPERATION TREATY

PCT

INTERNATIONAL SEARCH REPORT

(PCT Article 18 and Rules 43 and 44)

Applicant's or agent's file reference	FOR FURTHER ACTION	see Notification of Transmittal of International Search Report (Form PCT/ISA/220) as well as, where applicable, item 5 below.
3316/0/PCT		
International application No.	International filing date (day/month/year)	(Earliest) Priority Date (day/month/year)
PCT/US 02/15257	10/05/2002	11/05/2001
Applicant		
PHARMACIA CORPORATION		

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

This International Search Report consists of a total of 5 sheets.

[X] 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. [X] Certain claims were found unsearchable (See Box I).

3. [ ] Unity of invention is lacking (see Box II).

4. With regard to the title,

[X] 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,

[X] 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.

[X] None of the figures.

INTERNATIONAL SEARCH REPORT

International Application No
PCT/US 02/15257

A. CLASSIFICATION OF SUBJECT MATTER
IPC 7 C07D309/08 C07D405/12 C07D401/12 C07D211/66 C07D407/12
C07D417/12 C07D409/12 C07D413/12 A61K31/351 A61P35/00

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)
IPC 7 C07D A61K A61P

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 practical, search terms used)
CHEM ABS Data, PAJ

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 00 50396 A (SEARLE) 31 August 2000 (2000-08-31) claims; example 398	1-6, 380-405
X	WO 00 69821 A (SEARLE) 23 November 2000 (2000-11-23) claims	1-6, 380-405
X	WO 99 25687 A (SEARLE) 27 May 1999 (1999-05-27) page 521 -page 535; claims 1-15; table 123	1-6,237, 238, 380-405

☐ Further documents are listed in the continuation of box C.

☒ Patent family members are listed in 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 document but 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
11 December 2002	23/12/2002

Name and mailing address of the ISA	Authorized officer
European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl,	Francois, J

Continuation of Box I.2

Present claims .1 to 5,122,123,225,226,235,236,250,251,260,261,267,268,296,297,303,304,308,309,322,323,335 to 338,344,345,354,355,359 to 362,368,369,372,373,376,377 relate to an extremely large number of possible compounds. Support within the meaning of Article 6 PCT and/or disclosure within the meaning of Article 5 PCT is to be found, however, for only a very small proportion of the compounds claimed. In the present case, the claims so lack support, and the application so lacks disclosure, that a meaningful search over the whole of the claimed scope is impossible. Consequently, the search has been carried out for those parts of the claims which appear to be supported and disclosed, namely those parts relating to the compounds where A2 and A3 toegether with the carbon to which they are both attached, form an optionally-substituted piperidino or tetrahydropyrano group.

The applicant's attention is drawn to the fact that claims, or parts of claims, relating to inventions in respect of which no international search report has been established need not be the subject of an international preliminary examination (Rule 66.1(e) PCT). The applicant is advised that the EPO policy when acting as an International Preliminary Examining Authority is normally not to carry out a preliminary examination on matter which has not been searched. This is the case irrespective of whether or not the claims are amended following receipt of the search report or during any Chapter II procedure.

34

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US 02/15257

Box I Observations where certain claims were found unsearchable (Continuation of item 1 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. [X] Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 380 to 401 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.

2. [X] Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:

see FURTHER INFORMATION sheet PCT/ISA/210

3. [ ] Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box II Observations where unity of invention is lacking (Continuation of item 2 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. [ ] As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.

2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.

3. [ ] As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:

4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

[ ] The additional search fees were accompanied by the applicant's protest.

[ ] No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

Information on patent family members

International Application No
PCT/US 02/15257

Patent document cited in search report	Publication date	Patent family member(s)		Publication date
WO 0050396 A	31-08-2000	US	2001039287 A1	08-11-2001
		AU	3478500 A	14-09-2000
		BR	0008491 A	17-09-2002
		CN	1370144 T	18-09-2002
		CZ	20013038 A3	17-07-2002
		EP	1230219 A1	14-08-2002
		HU	0200239 A2	29-06-2002
		JP	2002537378 A	05-11-2002
		NO	20013963 A	23-10-2001
		NZ	513648 A	28-09-2001
		WO	0050396 A1	31-08-2000
WO 0069821 A	23-11-2000	AU	4797000 A	05-12-2000
		EP	1183239 A1	06-03-2002
		HU	0201680 A2	28-09-2002
		NO	20015543 A	10-01-2002
		WO	0069821 A1	23-11-2000
WO 9925687 A	27-05-1999	AU	1373299 A	07-06-1999
		BR	9814643 A	03-10-2000
		CA	2306460 A1	27-05-1999
		CN	1279669 T	10-01-2001
		EP	1042290 A1	11-10-2000
		JP	2001523662 T	27-11-2001
		NO	20002469 A	12-07-2000
		NZ	503485 A	25-10-2002
		PL	341379 A1	09-04-2001
		WO	9925687 A1	27-05-1999
		US	2001014688 A1	16-08-2001
		US	2001039287 A1	08-11-2001
		ZA	9810412 A	09-12-1999

6794-0000C/POA
One month resp
3/3/03

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

PCT

To:
GRYTE, David M.
HARNESS DICKEY & PIERCE, PLC
7700 Bonhomme, Suite 400
St. Louis, MI 63105
ETATS-UNIS D'AMERIQUE

RECEIVED
FEB 10 2003
HARNESS, DICKEY & PIERCE
ST. LOUIS, MISSOURI

WRITTEN OPINION
(PCT Rule 66)

Date of mailing (day/month/year)	03/02/2003
Applicant's or agent's file reference: 3316/0/PCT	REPLY DUE: within 1 / 00 months/days from the above date of mailing

International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/US 02/ 15257	10/05/2002	11/05/2001

International Patent Classification (IPC) or both national classification and IPC
C07D309/08

Applicant
PHARMACIA CORPORATION et al.

1. This written opinion is the first drawn up by this International Preliminary Examining Authority.

2. This opinion contains indications relating to the following items:

- I [X] Basis of the opinion
- II [ ] Priority
- III [X] Non-establishment of opinion with regard to novelty, inventive step and industrial applicability
- IV [ ] Lack of unity of invention
- V [X] Reasoned statement under Rule 66.2(a)(ii) 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

3. The applicant is invited to reply to this opinion.

When? See the time limit indicated above. The applicant may, before the expiration of that time limit, request this Authority to grant an extension, see Rule 66.2(d).

How? By submitting a written reply, accompanied, where appropriate, by amendments, according to Rule 66.3. For the form and the language of the amendments, see Rules 66.8 and 66.9.

Also For an additional opportunity to submit amendments, see Rule 66.4.
For the examiner's obligation to consider amendments and/or arguments, see Rule 66.4bis.
For an informal communication with the examiner, see Rule 66.6.

If no reply is filed, the international preliminary examination report will be established on the basis of this opinion.

4. The final date by which the international preliminary examination report must be established according to Rule 69.2 is: 11/09/2003

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	Examiner Formalities officer (incl. extension of time limits) Tel. (+49-89) 2399 2828

Form PCT/IPEA/408 (cover sheet) (march 2002)

I. **Basis of the opinion**

The basis of this written opinion is the application as originally filed.

III. **Non-establishment of opinion with regard to novelty, inventive step and industrial applicability**

The question of whether the claimed invention appears to be novel, to involve an inventive step, or to be industrially applicable has not been and will not be the subject of the international preliminary examination in respect of the claims which have not been searched (Article 17(2)(a) or (3) and Rule 66.1(e) PCT; see also international search report).

V. **Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability**

1. To the extent that the international preliminary examination has been carried out (see item III above), the following is pointed out:

2. In light of the documents cited in the international search report, it is considered that the invention as defined in at least some of the claims, which have been the subject of an international search report, does not appear to meet the criteria mentioned in Article 33(1) PCT, i.e. does not appear to be novel and/or to involve an inventive step (see international search report, in particular the documents cited X and/or Y and corresponding claim references).

3. If amendments are filed, the applicant should comply with the requirements of Rule 66.8 PCT and indicate the basis of the amendments in the documents of the application as originally filed (Article 34 (2) (b) PCT) otherwise these amendments may not be taken into consideration for the establishment of the international preliminary examination report. The attention of the applicant is drawn to the fact that if the application contains an unnecessary plurality of independent claims, no examination of any of the claims will be carried out.

NB: Should the applicant decide to request detailed substantive examination, then an international preliminary examination report will normally be established directly. Exceptionally the examiner may draw up a second written opinion, should this be explicitly requested.

6794-000005 OA

International Preliminary report

38-G

PATENT COOPERATION TREATY

RECEIVED

MAR 31 2003

PCT

HARNESS, DICKEY & PIERCE
ST. LOUIS, MISSOURI

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITY

To:
GRYTE, David M.
HARNESS DICKEY & PIERCE, PLC
7700 Bonhomme, Suite 400
St. Louis, MI 63105
ETATS-UNIS D'AMERIQUE

NOTIFICATION OF TRANSMITTAL OF INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Rule 71.1)

Date of mailing *(day/month/year)*	24/03/2003
Applicant's or agent's file reference: 3316/0/PCT	IMPORTANT NOTIFICATION

International application No.	International filing date *(day/month/year)*	Priority date *(day/month/year)*
PCT/US 02/ 15257	10/05/2002	11/05/2001

Applicant

PHARMACIA CORPORATION et al.

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.

The applicant's attention is drawn to Article 33(5), which provides that the criteria of novelty, inventive step and industrial applicability described in Article 33(2) to (4) merely serve the purposes of international preliminary examination and that "any Contracting State may apply additional or different criteria for the purposes of deciding whether, in that State, the claimed inventions is patentable or not" (see also Article 27(5)). Such additional criteria may relate, for example, to exemptions from patentability, requirements for enabling disclosure, clarity and support for the claims.

Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	FERRO VASCONCELOS M Tel. (+49-89) 2399 2828

Form PCT/IPEA/416 (August 2002) P20473

Orb

PATENT COOPERATION TREATY

PCT

39

INTERNATIONAL PRELIMINARY EXAMINATION REPORT

(PCT Article 36 and Rule 70)

(Rationalised Report according to the Notice of the President of the EPO published in the OJ11/2001)

Applicant's or agent's file reference	FOR FURTHER ACTION	See Notification of Transmittal of International Preliminary Examination Report (Form PCT/IPEA/416)
3316/0/PCT		
International application No.	International filing date (day/month/year)	Priority date (day/month/year)
PCT/US 02/ 15257	10/05/2002	11/05/2001
International Patent Classification (IPC) or national classification and IPC		
C07D309/08		
Applicant		
PHARMACIA CORPORATION et al.		

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 consists 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 opinion 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
06/12/2002	19/03/2003
Name and mailing address of the IPEA/	Authorized officer
European Patent Office D-80298 Munich Tel. (+49-89) 2399-0, Tx: 523656 epmu d Fax: (+49-89) 2399-4465	VERHULST W Tel. (+49-89) 2399 2828

Form PCT/IPEA/409 (cover sheet) P20476 (October 2002)

I. Basis of the report,

The basis of this international preliminary examination is the application as originally filed.

III. Non-establishment of opinion with regard to novelty, inventive step and industrial applicability

The question of whether the claimed invention appears to be novel, to involve an inventive step, or to be industrially applicable has not been the subject of the international preliminary examination in respect of the claims which have not been searched (Article 17(2)(a) or (3) and Rule 66.1(e) PCT); see also international search report).

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability

To the extent that the international preliminary examination has been carried out (see item III above), the following is pointed out:

In light of the documents cited in the international search report, it is considered that the invention as defined in at least some of the claims, which have been the subject of an international search report, does not appear to meet the criteria mentioned in Article 33(1) PCT, i.e. does not appear to be novel and/or to involve an inventive step (see international search report, in particular the documents cited X and/or Y and corresponding claim references).

PATENT COOPERATION TREATY

6794-000005/kn
Record of change
PCT

41

From the INTERNATIONAL BUREAU

RECEIVED
SEP 10 2003
HARNESS, DICKEY & PIERCE
ST. LOUIS, MISSOURI

To:

GRYTE, David, M.
Harness, Dickey & Pierce, PLC
7700 Bonhomme, Suite 400
St. Louis, MI 63105
United States of America

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

Date of mailing (day/month/year)	
28 August 2003 (28.08.03)	
Applicant's or agent's file reference	**IMPORTANT NOTIFICATION**
3316/0/PCT	
International application No.	**International filing date (day/month/year)**
PCT/US02/15257	10 May 2002 (10.05.02)

1. The following indications appeared on record concerning:

[X] the applicant [X] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[X] the person [ ] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
CARROLL, Jeffery, N. 306 N. Rapp Columbia, IL 62236 United States of America	US	US
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:
The person identified in Box 2 has been added to the records as inventor/applicant for the US only.

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Jean-Luc MARTIN
Facsimile No. (41-22) 338.87.40	Telephone No. (41-22) 338 9887

Form PCT/IB/308 (March 1994)

PATENT COOPERATION TREATY

42 M

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

GRYTE, David, M.
Harness, Dickey & Pierce, PLC
7700 Bonhomme, Suite 400
St. Louis, MI 63105
United States of America

Date of mailing (day/month/year)	
29 August 2003 (29.08.03)	
Applicant's or agent's file reference: 3318/0/PCT	IMPORTANT NOTIFICATION
International application No.: PCT/US02/15257	International filing date (day/month/year): 10 May 2002 (10.05.02)

1. The following indications appeared on record concerning:

[X] the applicant [X] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[X] the person [ ] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
DECRESCENZO, Gary, A. 7534 Spruce Hill Court St. Charles, MO 63304 United States of America	US	US
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:
The person identified in Box 2 has been added to the records as inventor/applicant for the US only.

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Jean-Luc MARTIN
Facsimile No. (41-22) 338.87.40	Telephone No. (41-22) 338 9887

Form PCT/IB/308 (March 1994)

43

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

GRYTE, David, M.
Harness, Dickey & Pierce, PLC
7700 Bonhomme, Suite 400
St. Louis, MI 63105
United States of America

Date of mailing (day/month/year): 29 August 2003 (29.08.03)	
Applicant's or agent's file reference: 3316/0/PCT	IMPORTANT NOTIFICATION
International application No.: PCT/US02/15257	International filing date (day/month/year): 10 May 2002 (10.05.02)

1. The following indications appeared on record concerning:

[X] the applicant [X] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[X] the person [ ] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
MISCHKE, Deborah, A. 25 White River Lane Defiance, MO 63341 United States of America	US	US
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:
The person identified in Box 2 has been added to the records as inventor/applicant for the US only.

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[ ] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Jean-Luc MARTIN
Facsimile No. (41-22) 338.87.40	Telephone No. (41-22) 338 8887

Form PCT/IB/308 (March 1994) 005228663

6794-000057/PCA

PATENT COOPERATION TREATY

44

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

GRYTE, David, M.
Harness, Dickey & Pierce, PLC
7700 Bonhomme, Suite 400
St. Louis, MI 63105
United States of America

Date of mailing (day/month/year)	
23 April 2003 (23.04.03)	
Applicant's or agent's file reference	IMPORTANT NOTIFICATION
3316/0/PCT	
International application No.	International filing date (day/month/year)
PCT/US02/15257	10 May 2002 (10.05.02)

1. The following indication appeared on record concerning:

[X] the applicant [ ] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
PHARMACIA CORPORATION Corporate Patent Department 800 North Lindbergh Blvd. Mail Zone 04E St. Louis, MO 63167 United States of America	US	US
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [X] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
PHARMACIA CORPORATION P.O.Box 1027 Chesterfield, Missouri 63006 United States of America	US	US
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Tewfik BENYAHIA
Facsimile No. (41-22) 338.87.40	Telephone No. (41-22) 338 8459

Form PCT/IB/306 (March 1994) 005587500

JR
AMD

PATENT COOPERATION TREATY

45

PCT

From the INTERNATIONAL BUREAU

To:

GRYTE, David, M.
Harness, Dickey & Pierce, PLC
7700 Bonhomme, Suite 400
St. Louis, MI 63105
United States of America

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

Date of mailing (day/month/year)	
23 April 2003 (23.04.03)	
Applicant's or agent's file reference	IMPORTANT NOTIFICATION
3316/0/PCT	
International application No.	International filing date (day/month/year)
PCT/US02/15257	10 May 2002 (10.05.02)

1. The following indications appeared on record concerning:

[X] the applicant [X] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
KASSAB, Darren, J. 16346 Centerfield Court, Apt. E Wildwood, MO 63040 United States of America	US	US
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [X] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
KASSAB, Darren, J. 5 Park City Court O'Fallon, Missouri 63040 United States of America	US	US
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Tewfik BENYAHIA
Facsimile No. (41-22) 338.87.40	Telephone No. (41-22) 338 8459

Form PCT/IB/308 (March 1994) 005587507

PATENT COOPERATION TREATY

46

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

GRYTE, David, M.
Harness, Dickey & Pierce, PLC
7700 Bonhomme, Suite 400
St. Louis, MI 63105
United States of America

Date of mailing (day/month/year)	
23 April 2003 (23.04.03)	
Applicant's or agent's file reference	IMPORTANT NOTIFICATION
3316/0/PCT-	
International application No.	International filing date (day/month/year)
PCT/US02/15257	10 May 2002 (10.05.02)

1. The following indications appeared on record concerning:

[X] the applicant [X] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
TALLEY, John, J. 6 Marborough Street #5 Boston, MA 02116 United States of America	US	US
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [ ] the name [X] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
TALLEY, John, J. 122 Hamilton St., Apt. 2 Cambridge, Massachusetts 02139 United States of America	US	US
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Tewfik BENYAHIA
Facsimile No. (41-22) 338.87.40	Telephone No. (41-22) 338 8468

Form PCT/IB/308 (March 1994) 005587623

PATENT COOPERATION TREATY

47

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

(PCT Rule 92bis.1 and Administrative Instructions, Section 422)

To:

GRYTE, David, M.
Harness, Dickey & Pierce, PLC
7700 Bonhomme, Suite 400
St. Louis, MI 63105
United States of America

Date of mailing (day/month/year)	
23 April 2003 (23.04.03)	
Applicant's or agent's file reference	IMPORTANT NOTIFICATION
3316/0/PCT	
International application No.	International filing date (day/month/year)
PCT/US02/15257	10 May 2002 (10.05.02)

1. The following indications appeared on record concerning:

[X] the applicant [X] the inventor [ ] the agent [ ] the common representative

Name and Address	State of Nationality	State of Residence
WANG, Tijuan, Jane 919 Crown Pointe Est. Dr. Wildwood, MO 63021 United States of America	CN	US
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

2. The International Bureau hereby notifies the applicant that the following change has been recorded concerning:

[ ] the person [X] the name [ ] the address [ ] the nationality [ ] the residence

Name and Address	State of Nationality	State of Residence
WANG, Lijuan, Jane 919 Crown Pointe Est. Dr. Wildwood, MO 63021 United States of America	CN	US
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

4. A copy of this notification has been sent to:

[X] the receiving Office
[ ] the International Searching Authority
[X] the International Preliminary Examining Authority
[ ] the designated Offices concerned
[X] the elected Offices concerned
[ ] other:

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Tewfik BENYAHIA
Facsimile No. (41-22) 338.87.40	Telephone No. (41-22) 338 8459

Form PCT/IB/308 (March 1994)

PATENT COOPERATION TREATY

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION CONCERNING SUBMISSION OR TRANSMITTAL OF PRIORITY DOCUMENT

(PCT Administrative Instructions, Section 411)

To:

GRYTE, David, M.
Harness, Dickey & Pierce, P.L.C.
Suite 400
7700 Bonhomme
St. Louis, MO 63105
ETATS-UNIS D'AMERIQUE

Date of mailing (day/month/year)	
12 July 2002 (12.07.02)	
Applicant's or agent's file reference	**IMPORTANT NOTIFICATION**
3316/0/PCT	
International application No.	**International filing date (day/month/year)**
PCT/US02/15257	10 May 2002 (10.05.02)
International publication date (day/month/year)	**Priority date (day/month/year)**
Not yet published	11 May 2001 (11.05.01)
Applicant	
PHARMACIA CORPORATION 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
11 May 2001 (11.05.01)	60/290,375	US	05 July 2002 (05.07.02)

The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland	Authorized officer Carine SEVILLANO (Fax 022 338 87 40)
Facsimile No. (41-22) 740.14.35	Telephone No. (41-22) 338.83.38

Form PCT/IB/304 (July 1998)

004972053

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

(19) World Intellectual Property Organization
International Bureau

(43) International Publication Date
21 November 2002 (21.11.2002)

PCT

(10) International Publication Number
WO 02/092588 A2

(51) International Patent Classification[7]: C07D 309/08, 405/12, 401/12, 211/66, 407/12, 417/12, 409/12, 413/12, A61K 31/351, A61P 35/00

(21) International Application Number: PCT/US02/15257

(22) International Filing Date: 10 May 2002 (10.05.2002)

(25) Filing Language: English

(26) Publication Language: English

(30) Priority Data:
60/290,375 11 May 2001 (11.05.2001) US

(71) Applicant *(for all designated States except US)*: PHARMACIA CORPORATION [US/US]; Corporate Patent Department, 800 North Lindbergh Blvd., Mail Zone 04E, St. Louis, MO 63167 (US).

(72) Inventors; and
(75) Inventors/Applicants *(for US only)*: BARTA, Thomas, E. [US/US]; Apt. 3-W, 1133 Maple Avenue, Evanston, IL 60202 (US). BECKER, Daniel, P. [US/US]; 1800 Maplewood Lane, Glenview, IL 60025 (US). BEDELL, Louis, J. [US/US]; 208 E. Marion Avenue, Mt. Prospect, IL 60070 (US). BOEHM, Terri, L. [US/US]; 928 Cleta Drive, Ballwin, MO 63021 (US). FOBIAN, Yvette, M. [US/US]; 580 Eagles Nest Ct., Wildwood, MO 63011 (US). FRESKOS, John, N. [US/US]; 7572 York, Clayton, MO 63105 (US). HOCKERMAN, Susan L. [US/US]; 5319 W. Hutchinson, Chicago, IL 60641 (US). KASSAB, Darren, J. [US/US]; 16346 Centerfield Court, Apt. E, Wildwood, MO 63040 (US). KOLODZIEJ, Steve, A. [US/US]; 3448 Clarjon Drive, Ballwin, MO 63021 (US). MCDONALD, Joseph, J. [US/US]; 1716 Timber Ridge Estate Dr., Wildwood, MO 63011 (US). NORTON, Maulen, B. [US/US]; 7777 Glazier Avenue, St. Louis, MO 63117 (US). RICO, Joseph, G. [US/US]; 524 Wetherby Terr. Dr., Ballwin, MO 63021 (US). TALLEY, John, J. [US/US]; 5 Marlborough Street #5, Boston, MA 02116 (US). VILLAMIL, Clara, I. [US/US]; 813 Long Road, Glenview, IL 60025 (US). WANG, Tijuan, Jane [CN/US]; 919 Crown Pointe Est. Dr., Wildwood, MO 63021 (US).

(74) Agent: GRYTE, David, M.; 800 N. Lindbergh Blvd., St. Louis, MO 63167 (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, SD, SE, SG, SI, SK, SL, TJ, TM, TN, TR, TT, TZ, UA, UG, US, UZ, 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, CH, CY, DE, DK, ES, FI, FR, GB, GR, IE, IT, LU, MC, NL, PT, SE, TR), OAPI patent (BF, BJ, CF, CG, CI, CM, GA, GN, GQ, GW, ML, MR, NE, SN, TD, TG).

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

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 02/092588 A2

(54) Title: AROMATIC SULFONE HYDROXAMATES AND THEIR USE AS PROTEASE INHIBITORS

(57) Abstract: This invention is directed to aromatic sulfone hydroxamates (also known as "aromatic sulfone hydroxamic acids") and salts thereof that, *inter alia*, inhibit matrix metalloproteinase (also known as "matrix metalloproteases" or "MMP") activity and/or aggrecanase activity. This invention also is directed to a prevention or treatment method that comprises administering such a compound or salt in an MMP-inhibiting and/or aggrecanase-inhibiting effective amount to an animal, particularly a mammal having (or disposed to having) a pathological condition associated with MMP and/or aggrecanase activity.

50

AROMATIC SULFONE HYDROXAMATES AND THEIR USE AS PROTEASE INHIBITORS

PRIORITY CLAIM TO RELATED PATENT APPLICATION

[1] This patent claims priority to U.S. Provisional Patent Application Serial No. 60/290,375 (filed May 11, 2001). The entire text of U.S. Provisional Patent Application Serial No. 60/290,375 is incorporated by reference into this patent.

FIELD OF THE INVENTION

[2] This invention is directed generally to proteinase (also known as "protease") inhibitors, and, more particularly, to aromatic sulfone hydroxamates (also known as "aromatic sulfone hydroxamic acids") that, *inter alia*, inhibit matrix metalloproteinase (also known as "matrix metalloprotease" or "MMP") activity and/or aggrecanase activity. This invention also is directed to compositions of such inhibitors, intermediates for the syntheses of such inhibitors, methods for making such inhibitors, and methods for preventing or treating conditions associated with MMP activity and/or aggrecanase activity, particularly pathological conditions.

BACKGROUND OF THE INVENTION

[3] Connective tissue is a required component of all mammals. It provides rigidity, differentiation, attachments, and, in some cases, elasticity. Connective tissue components include, for example, collagen, elastin, proteoglycans, fibronectin, and laminin. These biochemicals make up (or are components of) structures, such as skin, bone, teeth, tendon, cartilage, basement membrane, blood vessels, cornea, and vitreous humor.

[4] Under normal conditions, connective tissue turnover and/or repair processes are in equilibrium with connective tissue production. Degradation of connective tissue is carried out by the action of proteinases released from resident tissue cells and/or invading inflammatory or tumor cells.

[5] Matrix metalloproteinases, a family of zinc-dependent proteinases, make up a major class of enzymes involved in degrading connective tissue. Matrix metalloproteinases are divided into classes, with some members having several different

names in common use. Examples are: MMP-1 (also known as collagenase 1, fibroblast collagenase, or EC 3.4.24.3); MMP-2 (also known as gelatinase A, 72kDa gelatinase, basement membrane collagenase, or EC 3.4.24.24), MMP-3 (also known as stromelysin 1 or EC 3.4.24.17), proteoglycanase, MMP-7 (also known as matrilysin), MMP-8 (also known as collagenase II, neutrophil collagenase, or EC 3.4.24.34), MMP-9 (also known as gelatinase B, 92kDa gelatinase, or EC 3.4.24.35), MMP-10 (also known as stromelysin 2 or EC 3.4.24.22), MMP-1 I (also known as stromelysin 3), MMP-12 (also known as metalloelastase, human macrophage elastase or HME), MMP- 13 (also known as collagenase 111), and MMP- 14 (also known as MT1-MMP or membrane MMP). *See, generally*, Woessner, J.F., "The Matrix Metalloprotease Family" in *Matrix Metalloproteinases*, pp.1-14 (Edited by Parks, W.C. & Mecham, R.P., Academic Press, San Diego, CA 1998).

[6] Excessive breakdown of connective tissue by MMPs is a feature of many pathological conditions. Inhibition of MMPs therefore provides a control mechanism for tissue decomposition to prevent and/or treat these pathological conditions. Such pathological conditions generally include, for example, tissue destruction, fibrotic diseases, pathological matrix weakening, defective injury repair, cardiovascular diseases, pulmonary diseases, kidney diseases, liver diseases, ophthalmologic diseases, and diseases of the central nervous system. Specific examples of such conditions include, for example, rheumatoid arthritis, osteoarthritis, septic arthritis, multiple sclerosis, a decubitis ulcer, corneal ulceration, epidermal ulceration, gastric ulceration, tumor metastasis, tumor invasion, tumor angiogenesis, periodontal disease, liver cirrhosis, fibrotic lung disease, emphysema, otosclerosis, atherosclerosis, proteinuria, coronary thrombosis, dilated cardiomyopathy, congestive heart failure, aortic aneurysm, epidermolysis bullosa, bone disease, Alzheimer's disease, defective injury repair *(e.g.*, weak repairs, adhesions such as post-surgical adhesions, and scarring), post-myocardial infarction, bone disease, and chronic obstructive pulmonary disease.

[7] Matrix metalloproteinases also are involved in the biosynthesis of tumor necrosis factors (TNFs). Tumor necrosis factors are implicated in many pathological conditions. TNF-α, for example, is a cytokine that is presently thought to be produced initially as a 28 kD cell-associated molecule. It is released as an active, 17 kD form that can mediate a large number of deleterious effects *in vitro* and *in* vivo. TNF-α can cause

52

and/or contribute to the effects of inflammation (*e.g.*, rheumatoid arthritis), autoimmune disease, graft rejection, multiple sclerosis, fibrotic diseases, cancer, infectious diseases (*e.g.*, malaria, mycobacterial infection, meningitis, etc.), fever, psoriasis, cardiovascular diseases (*e.g.*, post-ischemic reperfusion injury and congestive heart failure), pulmonary diseases, hemorrhage, coagulation, hyperoxic alveolar injury, radiation damage, and acute phase responses like those seen with infections and sepsis and during shock (*e.g.*, septic shock and hemodynamic shock). Chronic release of active TNF-α can cause cachexia and anorexia. TNF-α also can be lethal.

[8] Inhibiting TNF (and related compounds) production and action is an important clinical disease treatment. Matrix metalloproteinase inhibition is one mechanism that can be used. MMP (*e.g.*, collagenase, stromelysin, and gelatinase) inhibitors, for example, have been reported to inhibit TNF-α release. *See, e.g.*, Gearing et al. *Nature* 376, 555-557 (1994). *See also*, McGeehan et al. *See also*, *Nature* 376, 558-561 (1994). MMP inhibitors also have been reported to inhibit TNF-α convertase, a metalloproteinase involved in forming active TNF-α. *See, e.g.*, WIPO Int'l Pub. No. WO 94/24140. *See also*, WIPO Int'l Pub. No. WO 94/02466. *See also*, WIPO Int'l Pub. No. WO 97/20824.

[9] Matrix metalloproteinases also are involved in other biochemical processes in mammals. These include control of ovulation, post-partum uterine involution, possibly implantation, cleavage of APP (β-amyloid precursor protein) to the amyloid plaque, and inactivation of (α_1-protease inhibitor (α_1 -PI). Inhibiting MMPs therefore may be a mechanism that may be used to control of fertility. In addition, increasing and maintaining the levels of an endogenous or administered serine protease inhibitor (*e.g.*, α_1 -PI) supports the treatment and prevention of pathological conditions such as emphysema, pulmonary diseases, inflammatory diseases, and diseases of aging (*e.g.*, loss of skin or organ stretch and resiliency).

[10] Numerous metalloproteinase inhibitors are known. *See, generally*, Brown, P.D., "Synthetic Inhibitors of Matrix Metalloproteinases," in *Matrix Metalloproteinases*, pp. 243-61 (Edited by Parks, W.C. & Mecham, R.P., Academic Press, San Diego, CA 1998).

[11] Metalloproteinase inhibitors include, for example, natural biochemicals, such as tissue inhibitor of metalloproteinase (TIMP), α2-macroglobulin, and their analogs and derivatives. These are high-molecular-weight protein molecules that form inactive complexes with metalloproteinases.

[12] A number of smaller peptide-like compounds also have been reported to inhibit metalloproteinases. Mercaptoamide peptidyl derivatives, for example, have been reported to inhibit angiotensin converting enzyme (also known as ACE) *in vitro* and *in vivo*. ACE aids in the production of angiotensin II, a potent pressor substance in mammals. Inhibiting ACE leads to lowering of blood pressure.

[13] A wide variety of thiol compounds have been reported to inhibit MMPs. *See, e.g.*, WO95/12389. *See also*, WO96/11209. *See also*, U.S. Patent No. 4,595,700. *See also*, U.S. Patent No. 6.013,649.

[14] A wide variety of hydroxamate compounds also have been reported to inhibit MMPs. Such compounds reportedly include hydroxamates having a carbon backbone. *See, e.g.*, WIPO Int'l Pub. No. *WO* 95/29892. *See also*, WIPO Int'l Pub. No. WO 97/24117. *See also*, WIPO Int'l Pub. No. WO 97/49679. *See also*, European Patent No. EP 0 780 386. Such compounds also reportedly include hydroxamates having peptidyl backbones or peptidomimetic backbones. *See, e.g*, WIPO Int'l Pub. No. WO 90/05719. *See also*, WIPO Int'l Pub. No. WO 93/20047. *See also*, WIPO Int'l Pub. No. WO 95/09841. *See also*, WIPO Int'l Pub. No. WO 96/06074. *See also*, Schwartz et al., Progr. *Med. Chem.*, 29:271-334(1992). *See also*, Rasmussen et al., *Pharmacol. Ther.*, 75(1): 69-75 (1997). *See also*, Denis et al., *Invest New Drugs*, 15(3): 175-185 (1997). Various piperazinylsulfonylmethyl hydroxamates and piperidinylsulfonylmethyl hydroxamates have additionally been reported to inhibit MMPs. *See*, WIPO Int'l Pub. No. WO 00/46221. And various aromatic sulfone hydroxamates have been reported to inhibit MMPs. *See*, WIPO Int'l Pub. No. WO 99/25687. *See also*, WIPO Int'l Pub. No. WO 00/50396. *See also*, WIPO Int'l Pub. No. WO 00/69821.

[15] It is often advantageous for an MMP inhibitor drug to target a certain MMP(s) over another MMP(s). For example, it is typically preferred to inhibit MMP-2, MMP-3, MMP-9, and/or MMP-13 (particularly MMP-13) when treating and/or preventing cancer, inhibiting of metastasis, and inhibiting angiogenesis. It also is typically preferred to inhibit MMP-13 when preventing and/or treating osteoarthritis. *See, e.g.*, Mitchell et

54

al., J *Clin. Invest.*, 97:761-768 (1996). *See also*, Reboul et al., *J Clin. Invest.*, 97:2011-2019 (1996). Normally, however, it is preferred to use a drug that has little or no inhibitory effect on MMP-1 and MMP-14. This preference stems from the fact that both MMP-1 and MMP-14 are involved in several homeostatic processes, and inhibition of MMP-1 and/or MMP-14 consequently tends to interfere with such processes.

[16] Many known MMP inhibitors exhibit the same or similar inhibitory effects against each of the MMPs. For example, batimastat (a peptidomimetic hydroxamate) has been reported to exhibit IC_{50} values of from about 1 to about 20 nM against each of MMP-1, MMP-2, MMP-3, MMP-7, and MMP-9. Marimastat (another peptidomimetic hydroxamate) has been reported to be another broad-spectrum MMP inhibitor with an enzyme inhibitory spectrum similar to batimastat, except that Marimastat reportedly exhibited an IC_{50} value against MMP-3 of 230 nM. *See* Rasmussen et al., *Pharmacol. Ther.*, 75(1): 69-75 (1997).

[17] Meta analysis of data from Phase I/II studies using Marimastat in patients with advanced, rapidly progressive, treatment-refractory solid tumor cancers (colorectal, pancreatic, ovarian, and prostate) indicated a dose-related reduction in the rise of cancer-specific antigens used as surrogate markers for biological activity. Although Marimastat exhibited some measure of efficacy via these markers, toxic side effects reportedly were observed. The most common drug-related toxicity of Marimastat in those clinical trials was musculoskeletal pain and stiffness, often commencing in the small joints in the hands, and then spreading to the arms and shoulder. A short dosing holiday of 1-3 weeks followed by dosage reduction reportedly permits treatment to continue. *See* Rasmussen et al., *Pharmacol. Ther.*, 75(1): 69-75 (1997). It is thought that the lack of specificity of inhibitory effect among the MMPs may be the cause of that effect.

[18] Another enzyme implicated in pathological conditions associated with excessive degradation of connective tissue is aggrecanase, particularly aggrecanase-1 (also known as ADAMTS-4). Specifically, articular cartilage contains large amounts of the proteoglycan aggrecan. Proteoglycan aggrecan provides mechanical properties that help articular cartilage in withstanding compressive deformation during joint articulation. The loss of aggrecan fragments and their release into synovial fluid caused by proteolytic cleavages is a central pathophysiological event in osteoarthritis and rheumatoid arthritis. It has been reported that two major cleavage sites exist in the proteolytically sensitive

55

interglobular domains at the N-terminal region of the aggrecan core protein. One of those sites has been reported to be cleaved by several matrix metalloproteases. The other site, however, has been reported to be cleaved by aggrecanase-1. Thus, inhibiting excessive aggrecanase activity provides an additional and/or alternative prevention or treatment method for inflammatory conditions. *See generally*, Tang, B. L., "ADAMTS: A Novel Family of Extracellular Matrix Proteases," *Int'l Journal of Biochemistry & Cell Biology*, 33, pp. 33-44 (2001). Such diseases reportedly include, for example, osteoarthritis, rheumatoid arthritis, joint injury, reactive arthritis, acute pyrophosphate arthritis, and psoriatic arthritis. *See, e.g.*, European Patent Application Publ. No. EP 1 081 137 A1.

[19] In addition to inflammatory conditions, there also is evidence that inhibiting aggrecanase may be used for preventing or treating cancer. For example, excessive levels of aggrecanase-1 reportedly have been observed with a glioma cell line. It also has been postulated that the enzymatic nature of aggrecanase and its similarities with the MMPs would support tumor invasion, metastasis, and angiogenesis. *See* Tang, *Int'l Journal of Biochemistry & Cell Biology*, 33, pp. 33-44 (2001).

[20] Various hydroxamate compounds have been reported to inhibit aggrecanase-1. Such compounds include, for example, those described in European Patent Application Publ. No. EP 1 081 137 A1. Such compounds also include, for example, those described in WIPO PCT Int'l Publ. No. WO 00/09000. Such compounds further include, for example, those described in WIPO PCT Int'l Publ. No. WO 00/59874.

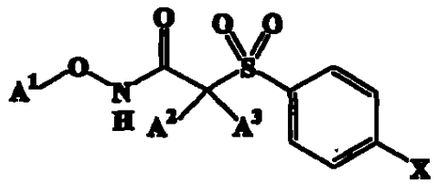
[21] In view of the importance of hydroxamate compounds in the prevention or treatment of several pathological conditions and the lack of enzyme specificity exhibited by two of the more potent MMP-inhibitor drugs that have been in clinical trials, there continues to be a need for hydroxamates having greater enzyme specificity (preferably toward MMP-2, MMP-9, MMP- 13, and/or aggrecanase (particularly toward MMP-13 in some instances, toward both MMP-2 and MMP-9 in other instances, and aggrecanase in yet other instances), while exhibiting little or no inhibition of MMP-1 and/or MMP-14. The following disclosure describes hydroxamate compounds that tend to exhibit such desirable activities.

56

SUMMARY OF THE INVENTION

[22] This invention is directed to hydroxamate compounds (and salts thereof) that inhibit pathological protease activity (particularly compounds that inhibit MMP-2, MMP-9, MMP- 13, and/or aggrecanase activity), while generally exhibiting relatively little or no inhibition against MMP-1 and MMP-14 activity. This invention also is directed to a method for inhibiting MMP activity and/or aggrecanase activity, particularly pathological MMP and/or aggrecanase activity. Such a method is particularly suitable to be used with mammals, such as humans, other primates (*e.g.*, monkeys, chimpanzees, etc.), companion animals (*e.g.*, dogs, cats, horses, etc.), farm animals (*e.g.*, goats, sheep, pigs, cattle, etc.), laboratory animals (*e.g.*, mice, rats, etc.), and wild and zoo animals (*e.g.*, wolves, bears, deer, etc.).

[23] Briefly, therefore, the invention is directed in part to a compound or salt thereof. The compound has a structure corresponding to Formula I:



I

Here:

A^1 is -H, alkylcarbonyl, alkoxycarbonyl, carbocyclylcarbonyl, carbocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclylalkylcarbonyl, carbocyclyloxycarbonyl, carbocyclylalkoxycarbonyl, aminoalkylcarbonyl, alkyl(thiocarbonyl), alkoxy(thiocarbonyl), carbocyclyl(thiocarbonyl), carbocyclylalkyl(thiocarbonyl), heterocyclyl(thiocarbonyl), heterocyclylalkyl(thiocarbonyl), carbocyclyloxy(thiocarbonyl), carbocyclylalkoxy(thiocarbonyl), or aminoalkyl(thiocarbonyl). Except where A^1 is -H, any member of this group optionally is substituted (*i.e.*, it may be either unsubstituted or substituted).

A^2 and A^3, together with the carbon atom to which they are both attached, form an optionally-substituted heterocyclyl containing from 5 to 8 ring members.

[24] In a preferred embodiment of the invention, X is $-E^1-E^2-E^3-E^4-E^5$. In this embodiment:

E^1 is -O-, -$S(O)_2$-, -S(O)-, -S-, -$N(R^1)$-, -C(O)-$N(R^1)$-, -$N(R^1)$-C(O)-, or -$C(R^1)(R^2)$-.

E^2 forms a link of at least 2 carbon atoms between E^1 and E^3. E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of this group optionally is substituted.

E^3 is -C(O)-, -O-(CO)-, -C(O)-O-, -$C(NR^3)$-, -$N(R^4)$-, -C(O)-$N(R^4)$-, -$N(R^4)$-C(O)-, -$N(R^4)$-C(O)-$N(R^5)$-, -S-, -S(O)-, -$N(R^4)$-$S(O)_2$-, -$S(O)_2$-$N(R^4)$-, -C(O)-$N(R^4)$-$N(R^5)$-C(O)-, -$C(R^4)(R^6)$-C(O)-, or -$C(R^7)(R^8)$-.

E^4 is a bond, alkyl, or alkenyl. The alkyl and alkenyl optionally are substituted.

E^5 is -H, -OH, alkyl, alkenyl, alkynyl, alkoxy, alkoxyalkyl, carbocyclyl, or heterocyclyl. Except where E^5 is except -H or -OH, any member of this group optionally is substituted. E^5 is not -H when both E^3 is -$C(R^7)(R^8)$- and E^4 is a bond.

R^1 and R^2 are independently selected from the group consisting of -H and alkyl. The alkyl optionally is substituted. Neither R^1 nor R^2 forms a ring structure with E^2, E^3, E^4, or E^5.

R^3 is -H or -OH.

R^4 and R^5 are independently selected from the group consisting of -H, alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, and heterocyclylalkyl. Except for -H, any member of this group optionally is substituted. Neither R^4 nor R^5 forms a ring structure with E^2, E^4, or E^5.

R^6 is -CN or -OH.

R^7 is -H, halogen, -OH, alkyl, alkoxy, or alkoxyalkyl. The alkyl, alkoxy, and alkoxyalkyl optionally are substituted.

R^8 is -OH or alkoxy. The alkoxy optionally is substituted.

[25] In another preferred embodiment of the invention, X is -E^1-E^2-E^3-E^4-E^5. In this embodiment:

E^1 is -O-, -$S(O)_2$-, -S(O)-, -S-, -$N(R^1)$-, -C(O)-$N(R^1)$-, -$N(R^1)$-C(O)-, or -$C(R^1)(R^2)$-.

58

E^2 forms a link of at least 2 carbon atoms between E^1 and E3. E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of this group optionally is substituted.

E^3 is carbocyclyl or heterocyclyl. The carbocyclyl and heterocyclyl have 5 or 6 ring members and optionally are substituted.

E^4 is a bond, alkyl, alkenyl, -O-, or $-N(R^3)-$. The alkyl and alkenyl optionally are substituted.

E^5 is carbocyclyl or heterocyclyl. The carbocyclyl and heterocyclyl optionally are substituted.

R^1 and R^2 are independently selected from the group consisting of -H and alkyl. The alkyl optionally is substituted. Neither R^1 nor R^2 forms a ring structure with E^2, E^3, E^4, or E^5.

R^3 is -H or alkyl. The alkyl optionally is substituted.

[16] In another preferred embodiment of the invention, X is $-E^1-E^2-C(E^6)=C(E^7)-E^3-E^4-E^5$. In this embodiment:

E^1 is -O-, $-S(O)_2-$, -S(O)-, $-N(R^1)-$, $-C(O)-N(R^1)-$, $-N(R^1)-C(O)-$, or $-C(R^1)(R^2)-$.

E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of this group optionally is substituted.

E^4 is a bond or alkyl. The alkyl optionally is substituted.

E^5 is alkyl, alkenyl, alkynyl, alkoxy, alkoxyalkyl, carbocyclyl, or heterocyclyl. Any member of this group optionally is substituted.

E^6 is -H, halogen, or alkyl. The alkyl optionally is substituted.

E^7 is -H, alkyl, alkenyl, alkynyl, $-S(O)_2-R^3$, $-NO_2$, $-C(O)-N(R^3)(R^4)$, $-(C)(OR^3)$, carbocyclyl, carbocyclylalkyl, alkoxycarbocyclyl, -CN, -C=N-OH, or -C=NH. The alkyl, alkenyl, alkynyl, carbocyclyl, carbocyclylalkyl, and alkoxycarbocyclyl optionally are substituted.

R^1 and R^2 are independently selected from the group consisting of -H and alkyl. The alkyl optionally is substituted. Neither R^1 nor R^2 forms a ring structure with E^2, E^4, E^5, E^6, or E^7.

59

R^3 and R^4 are independently selected from the group consisting of -H, alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, heterocyclylalkyl. Except where the member is -H, any member of this group optionally is substituted.

[27] In another preferred embodiment of the invention, X is $-E^1-E^2-E^3-E^4-E^5$. In this embodiment:

E^1 is -O-, $-S(O)_2-$, -S(O)-, $-N(R^3)-$, $-C(O)-N(R^3)-$, $-N(R^3)-C(O)-$, or $-C(R^1)(R^2)-$.

E^2 is a bond, alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Except where the member is a bond, any member of such group optionally is substituted.

E^3 is carbonylpyrrollidinyl. The carbonylpyrrollidinyl optionally is substituted.

E^4 is a bond, alkyl, or alkenyl. The alkyl and alkenyl optionally and substituted.

E^5 is alkyl, alkenyl, alkynyl, alkoxy, alkoxyalkyl, carbocyclyl, or heterocyclyl. Any member of this group optionally is substituted.

R^1 and R^2 are independently selected from the group consisting of -H and alkyl. The alkyl optionally is substituted. Neither R^1 nor R^2 forms a ring structure with E^2, E^3, E^4, or E^5.

[28] In another preferred embodiment of the invention, X is $-E^1-E^2-E^5$. In this embodiment:

E^1 is -O-, $-S(O)_2-$, -S(O)-, $-N(R^1)-$, $-C(O)-N(R^1)-$, $-N(R^1)-C(O)-$, or $-C(R^1)(R^2)-$.

E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of this group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, alkyl, and haloalkyl.

E^5 is alkyl, alkenyl, alkynyl, cycloalkyl, cyclopentenyl, cyclopentadienyl, cyclohexenyl, or cyclohexadienyl. The cycloalkyl, cyclopentenyl, cyclopentadienyl, cyclohexenyl, and cyclohexadienyl optionally are substituted. The alkyl, alkenyl, and alkynyl (a) contain at least 4 carbon atoms, and (b)

60

optionally are substituted with one or more substituents selected from the group consisting of -OH, -NO_2, -CN, and halogen.

R^1 and R^2 are independently selected from the group consisting of -H and alkyl. The alkyl optionally is substituted. Neither R^1 nor R^2 forms a ring structure with E^5.

[29] In another preferred embodiment of the invention, X is -E^1-E^2-E^3-E^4-E^5. In this embodiment:

E^1 is -O-, -$S(O)_2$-, -S(O)-, -$N(R^1)$-, -C(O)-$N(R^1)$-, -$N(R^1)$-C(O)-, or -$C(R^1)(R^2)$-.

E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of this group optionally is substituted.

E^3 is carbonylpiperidinyl. The carbonylpiperidinyl optionally is substituted.

E^4 is a bond, alkyl, or alkenyl. The alkyl and alkenyl optionally are substituted.

E^5 is alkyl, alkenyl, alkynyl, alkoxy, alkoxyalkyl, carbocyclyl, or heterocyclyl. Any member of this group optionally is substituted.

R^1 and R^2 are independently selected from the group consisting of -H and alkyl. The alkyl optionally is substituted. Neither R^1 nor R^2 forms a ring structure with E^2, E^3, E^4, or E^5.

[30] In another preferred embodiment of the invention, X is -E^1-E^2-E^5. In this embodiment:

E^1 is -O-, -$S(O)_2$-, -S(O)-, -$N(R^1)$-, -C(O)-$N(R^1)$-, -$N(R^1)$-C(O)-, or -$C(R^1)(R^2)$-.

E^2 forms a link of at least 3 carbon atoms between E^1 and E^5. E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of this group optionally is substituted.

E^5 is optionally-substituted heterocyclyl, optionally-substituted fused-ring carbocyclyl, or substituted single-ring carbocyclyl.

R^1 and R^2 are independently selected from the group consisting of -H and alkyl. The alkyl optionally is substituted. Neither R^1 nor R^2 forms a ring structure with E^5.

61

[31] In another preferred embodiment of the invention, X is $-E^1-E^2-E^5$. In this embodiment:

E^1 is -O-, $-S(O)_2-$, -S(O)-, $-N(R^1)-$, $-C(O)-N(R^1)-$, $-N(R^1)-C(O)-$, or $-C(R^1)(R^2)-$.

E^2 forms a link of at least 4 carbon atoms between E^1 and E^5. E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of this group optionally is substituted.

E^5 is -OH or optionally-substituted carbocyclyl.

R^1 and R^2 are independently selected from the group consisting of -H and alkyl. The alkyl optionally is substituted. Neither R^1 nor R^2 forms a ring structure with E^5.

[32] In another preferred embodiment of the invention, X is $-E^1-E^2-O-E^4-E^5$. In this embodiment:

E^1 is $-S(O)_2-$, -S(O)-, $-N(R^1)-$, $-C(O)-N(R^1)-$, $-N(R^1)-C(O)-$, or $-C(R^1)(R^2)-$.

E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of this group optionally is substituted.

E^4 is a bond, alkyl, or alkenyl. The alkyl and alkenyl optionally are substituted.

E^5 is alkyl, alkenyl, alkynyl, alkoxy, alkoxyalkyl, carbocyclyl, or heterocyclyl. Any member of this group optionally is substituted.

R^1 and R^2 are independently selected from the group consisting of -H and alkyl. The alkyl optionally is substituted. Neither R^1 nor R^2 forms a ring structure with E^2, E^4, or E^5.

[33] In another preferred embodiment of the invention, X is $-O-E^2-O-E^5$. In this embodiment:

E^2 comprises at least 3 carbon atoms. E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of this group optionally is substituted.

E^5 is -H, alkyl, alkenyl, alkynyl, alkoxyalkyl, carbocyclyl, carbocyclylalkoxyalkyl, heterocyclyl, heterocyclylalkyl, or heterocyclylalkoxyalkyl. The alkyl, alkenyl, alkynyl, and alkoxyalkyl optionally are substituted with one or more substituents independently selected from the

group consisting of halogen, -OH, -NO_2, and -CN. the carbocyclyl, carbocyclylalkoxyalkyl, heterocyclyl, heterocyclylalkyl, and heterocyclylalkoxyalkyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, alkyl, haloalkyl, alkoxy, haloalkoxy, alkoxyalkyl, halogen-substituted alkoxyalkyl, -$N(R^3)(R^4)$, -$C(O)(R^5)$, -S-R^3, -$S(O)_2$-R^3, carbocyclyl, halocarbocyclyl, carbocyclylalkyl, and halogen-substituted carbocyclylalkyl.

R^1 and R^2 are independently selected from the group consisting of -H, alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, and heterocyclylalkyl. Except where the member is -H., any member of this group optionally is substituted with one or more halogen.

R^3 is -H, alkyl, -O-R^4, -$N(R^4)(R^5)$, carbocyclylalkyl, or heterocyclylalkyl. The alkyl, carbocyclylalkyl, and heterocyclylalkyl optionally are substituted with one or more halogen.

R^4 and R^5 are independently selected from the group consisting of -H, alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, and heterocyclylalkyl. Except where the member is -H, any member of this group optionally is substituted with one or more halogen.

[34] In another preferred embodiment of the invention, X is -O-E^2-O-E^4-E^5. In this embodiment:

E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of this group optionally is substituted. An atom in E^2 optionally is bound to an atom in E^5 to form a ring.

E^4 is a bond, alkyl, or alkenyl. The alkyl and alkenyl optionally are substituted.

E^5 is:

an optionally-substituted radical selected from the group consisting of alkenyl, alkynyl, alkoxy, alkoxyalkyl, fused-ring carbocyclyl, and heterocyclyl;

single-ring carbocyclyl substituted with one or more substituents independently selected from the group consisting of -OH, -NO_2, -CN, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5,

63

carbocyclyl, halocarbocyclyl, carbocyclylalkyl, halogen-substituted carbocyclylalkyl, heterocyclyl, haloheterocyclyl, heterocyclylalkyl, and halogen-substituted heterocyclylalkyl; or

single-ring carbocyclyl having multiple substitutions.

R^1 and R^2 are independently selected from the group consisting of -H, alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, and heterocyclylalkyl. Except where the member is -H, any member of this group optionally is substituted with one or more halogen.

R^3 is -H, alkyl, -O-R^4, -N(R^4)(R^5), carbocyclylalkyl, or heterocyclylalkyl. The alkyl, carbocyclylalkyl, and heterocyclylalkyl optionally are substituted with one or more halogen.

R^4 and R^5 are independently selected from the group consisting of -H, alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, and heterocyclylalkyl. Except where the member is -H, any member of this group optionally is substituted with one or more halogen.

[35] In another preferred embodiment of the invention, X is -E^1-E^2-$S(O)_2$-E^4-E^5. In this embodiment:

E^1 is -$S(O)_2$-, -S(O)-, -N(R^1)-, -C(O)-N(R^1)-, -N(R^1)-C(O)-, or -C(R^1)(R^2)-.

E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of this group optionally is substituted.

E^4 is a bond, alkyl, or alkenyl. The alkyl and alkenyl optionally are substituted.

E^5 is alkyl, alkenyl, alkynyl, alkoxy, alkoxyalkyl, carbocyclyl, or heterocyclyl. Any member of this group optionally is substituted.

R^1 and R^2 are independently selected from the group consisting of -H and alkyl. The alkyl optionally is substituted. Neither R^1 nor R^2 forms a ring structure with E^2, E^4, or E^5.

[36] In another preferred embodiment of the invention, X is -O-E^2-$S(O)_2$-E^4-E^5. In this embodiment:

E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of this group optionally is substituted.

E^4 is alkyl or alkenyl. The alkyl and alkenyl optionally are substituted.

E^5 is -H, alkyl, alkenyl, alkynyl, alkoxy, carbocyclyl, or heterocyclyl. Any member of this group optionally is substituted.

[37] In another preferred embodiment of the invention, X is $-O-E^2-S(O)_2-E^5$. In this embodiment:

E^2 comprises less than 5 carbon atoms. E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of this group optionally is substituted.

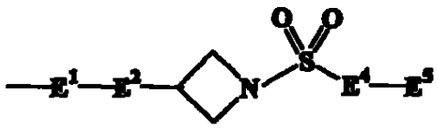
E^5 is alkyl, alkenyl, alkynyl, alkoxyalkyl, carbocyclyl, or heterocyclyl. Any member of this group optionally is substituted.

[38] In another preferred embodiment of the invention, X is $-O-E^2-S(O)_2-E^5$. In this embodiment:

E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of this group optionally is substituted.

E^5 is alkyl, alkenyl, alkynyl, alkoxyalkyl, saturated carbocyclyl, partially saturated carbocyclyl, or heterocyclyl. Any member of this group optionally is substituted.

[39] In another preferred embodiment of the invention, X is:



In this embodiment:

E^1 $-S(O)_2-$, $-S(O)-$, $-N(R^1)-$, $-C(O)-N(R^1)-$, $-N(R^1)-C(O)-$, or $-C(R^1)(R^2)-$.

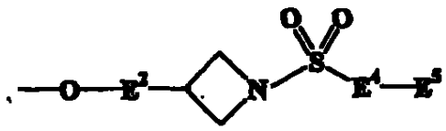
E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of this group optionally is substituted.

E^4 is a bond, alkyl, or alkenyl. The alkyl and alkenyl optionally are substituted.

E^5 is alkyl, alkenyl, alkynyl, alkoxy, alkoxyalkyl, carbocyclyl, or heterocyclyl. Any member of this group optionally is substituted.

R^1 and R^2 are independently selected from the group consisting of -H and alkyl. The alkyl optionally is substituted. Neither R^1 nor R^2 forms a ring structure with E^2, E^4, or E^5.

[40] In another preferred embodiment of the invention, X is:



In this embodiment:

E^2 is a bond, alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of this group optionally is substituted.

E^4 is a bond, alkyl, or alkenyl. The alkyl and alkenyl optionally are substituted.

E^5 is substituted carbocyclyl or optionally-substituted heterocyclyl. The carbocyclyl is substituted with:

two or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, alkyl, haloalkyl, alkoxy, haloalkoxy, alkoxyalkyl, halogen-substituted alkoxyalkyl, $-N(R^3)(R^4)$, $-C(O)(R^5)$, $-S-R^3$, $-S(O)_2-R^3$, carbocyclyl, halocarbocyclyl, carbocyclylalkyl, and halogen-substituted carbocyclylalkyl; or

a substituent selected from the group consisting of halogen, -OH, $-NO_2$, -CN, $-C(O)-O-R^3$, $-S-R^3$, $-S(O)_2-R^3$, carbocyclyl, halocarbocyclyl, carbocyclylalkyl, and halogen-substituted carbocyclylalkyl.

The heterocyclyl, on the other hand, optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, alkyl, haloalkyl, alkoxy, haloalkoxy, alkoxyalkyl, halogen-substituted alkoxyalkyl, $-N(R^3)(R^4)$, $-C(O)(R^5)$, $-S-R^3$, $-S(O)_2-R^3$, carbocyclyl, halocarbocyclyl, carbocyclylalkyl, and halogen-substituted carbocyclylalkyl.

R^3 and R^4 are independently selected from the group consisting of -H, alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, and heterocyclylalkyl. Except where the member is -H, any member of this group optionally is substituted with one or more halogen.

R^5 is -H, alkyl, $-O-R^6$, $-N(R^6)(R^7)$, carbocyclylalkyl, or heterocyclylalkyl. The alkyl, carbocyclylalkyl, and heterocyclylalkyl optionally are substituted with one or more halogen.

R^6 and R^7 are independently selected from the group consisting of -H, alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, and heterocyclylalkyl. Except where the member is -H, any member of this group optionally is substituted with one or more halogen.

[41] In another preferred embodiment of the invention, X is $-E^1-E^2-E^5$. In this embodiment:

E^1 is -O-, $-S(O)_2-$, -S(O)-, -S-, $-N(R^1)-$, $-C(O)-N(R^1)-$, $-N(R^1)-C(O)-$, or $-C(R^1)(R^2)-$.

E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of such group optionally is substituted.

E^5 is substituted heterocyclyl.

R^1 and R^2 are independently selected from the group consisting of -H and alkyl. The alkyl optionally is substituted.

Neither R^1 nor R^2 forms a ring structure with E^5.

[42] In another preferred embodiment of the invention, X is $-E^1-E^2-E^5$. In this embodiment:

E^1 is -O-, $-S(O)_2-$, -S(O)-, $-N(R^1)-$, $-C(O)-N(R^1)-$, $-N(R^1)-C(O)-$, or $-C(R^1)(R^2)-$.

E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of such group optionally is substituted. In addition, E^2 comprises at least two carbon atoms.

E^5 is optionally-substituted heterocyclyl.

R^1 and R^2 are independently selected from the group consisting of -H and alkyl. The alkyl optionally is substituta.

Neither R^1 nor R^2 forms a ring structure with E^5.

[43] In another preferred embodiment of the invention, X is $-E^1-E^2-E^3-E^4-E^5$. In this embodiment:

E^1 is -O-, $-S(O)_2-$, -S(O)-, -S-, $-N(R^1)-$, $-C(O)-N(R^1)-$, $-N(R^1)-C(O)-$, or $-C(R^1)(R^2)-$.

E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of such group optionally is substituted.

67

E^3 is -C(O)-, -O-(CO)-, -C(O)-O-, -C(NR^3)-, -N(R^4)-, -N(R^4)-C(NR^3)-, -C(NR^3)-N(R^4)-, -C(O)-N(R^4)-, -N(R^4)-C(O)-, -N(R^4)-C(O)-N(R^5)-, -S-, -S(O)-, -N(R^4)-S(O)$_2$-, -S(O)$_2$-N(R^4)-, -C(O)-N(R^4)-N(R^5)-C(O)-, -C(R^4)(R^6)-C(O)-, or -C(R^7)(R^8)-.

E^4 is a bond, alkyl, or alkenyl. The alkyl and alkenyl optionally are substituted.

E^5 is carbocyclyl or heterocyclyl. The carbocyclyl and heterocyclyl are:

substituted with a substituent selected from the group consisting of optionally-substituted carbocyclyl, optionally-substituted carbocyclylalkyl, optionally-substituted heterocyclyl, and optionally-substituted heterocyclylalkyl; and

optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO$_2$, -CN, alkyl, alkoxy, alkoxyalkyl, -N(R^{11})(R^{12}), -C(O)(R^{13}), -S-R^{11}, -S(O)$_2$-R^{11}, carbocyclyl, carbocyclylalkyl, haloalkyl, haloalkoxy, halogen-substituted alkoxyalkyl, halocarbocyclyl, halogen-substituted carbocyclylalkyl, hydroxycarbocyclyl, and heteroaryl.

R^1 and R^2 are independently selected from the group consisting of -H and alkyl, wherein the alkyl optionally is substituted.

R^3 is -H or -OH.

R^4 and R^5 are independently selected from the group consisting of -H, alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, and heterocyclylalkyl, wherein any member (except -H) of such group optionally is substituted.

R^6 is -CN or -OH.

R^7 is -H, halogen, -OH, alkyl, alkoxy, or alkoxyalkyl. The alkyl, alkoxy, and alkoxyalkyl optionally are substituted.

R^8 is -OH or alkoxy. The alkoxy optionally is substituted.

R^{11} and R^{12} are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl. Any member (except -H) of such group optionally is substituted with one or more halogen.

R^{13} is -H, C_1-C_8-alkyl, -O-R^{14}, -N(R^{14})(R^{15}), carbocyclyl-C_1-C_8-alkyl, heterocyclyl-C_1-C_8-alkyl, halo-C_1-C_8-alkyl, halogen-substituted carbocyclyl-C_1-C_8-alkyl, or halogen-substituted heterocyclyl-C_1-C_8-alkyl.

R^{14} and R^{15} are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl. Any member (except -H) of such group optionally is substituted with one or more halogen.

Neither R^1 nor R^2 forms a ring structure with E^2, E^3, E^4, or E^5.

Neither R^6 nor R^5 forms a ring structure with E^2, E^4, or E^5.

[44] This invention also is directed, in part, to a method for preventing or treating a condition associated with pathological matrix metalloprotease activity in a mammal having the condition or predisposed to having the condition. The method comprises administering an above-described compound or a pharmaceutically acceptable salt thereof to the mammal in an amount that is therapeutically-effective to prevent or treat the condition.

[45] This invention also is directed, in part, to a method for preventing or treating a pathological condition in a mammal having the condition or predisposed to having the condition. The method comprises administering an above-described compound or a pharmaceutically acceptable salt thereof to the mammal in an amount that is therapeutically-effective to prevent or treat the condition. In this embodiment, the pathological condition comprises tissue destruction, a fibrotic disease, pathological matrix weakening, defective injury repair, a cardiovascular disease, a pulmonary disease, a kidney disease, a liver disease, an ophthalmologic disease, and a central nervous system disease.

[46] This invention also is directed, in part, to a method for preventing or treating a pathological condition in a mammal having the condition or predisposed to having the condition. The method comprises administering an above-described compound or a pharmaceutically acceptable salt thereof to the mammal in an amount that is therapeutically-effective to prevent or treat the condition. In this embodiment, the pathological condition comprises osteoarthritis, rheumatoid arthritis, septic arthritis, tumor invasion, tumor metastasis, tumor angiogenesis, a decubitis ulcer, a gastric ulcer, a corneal ulcer, periodontal disease, liver cirrhosis, fibrotic lung disease, otosclerosis,

69

atherosclerosis, multiple sclerosis, dilated cardiomyopathy, epidermal ulceration, epidermolysis bullosa, aortic aneurysm, defective injury repair, an adhesion, scarring, congestive heart failure, post myocardial infarction, coronary thrombosis, emphysema, proteinuria, Alzheimer's disease, bone disease, and chronic obstructive pulmonary disease.

[47] This invention also is directed, in part, to a method for preventing or treating a condition associated with pathological TNF-α convertase activity in a mammal having the condition or predisposed to having the condition. The method comprises administering an above-described compound or a pharmaceutically acceptable salt thereof to the mammal in an amount that is therapeutically-effective to prevent or treat the condition.

[48] This invention also is directed, in part, to a method for preventing or treating a condition associated with pathological aggrecanase activity in a mammal having the condition or predisposed to having the condition. The method comprises administering an above-described compound or a pharmaceutically acceptable salt thereof to the mammal in an amount that is therapeutically-effective to prevent or treat the condition.

[49] This invention also is directed, in part, to pharmaceutical compositions comprising a therapeutically-effective amount of an above-described compound or a pharmaceutically-acceptable salt thereof.

[50] This invention also is directed, in part, to a use of an above-described compound or a pharmaceutically acceptable salt thereof to prepare a medicament for treating a condition associated with pathological matrix metalloprotease activity.

[51] This invention also is directed, in part, to a use of an above-described compound or a pharmaceutically acceptable salt thereof to prepare a medicament for treating a condition associated with pathological TNF-α convertase activity.

[52] This invention also is directed, in part, to a use of an above-described compound or a pharmaceutically acceptable salt thereof to prepare a medicament for treating a condition associated with pathological aggrecanase activity.

[53] Further benefits of Applicants' invention will be apparent to one skilled in the art from reading this patent.

70

DETAILED DESCRIPTION OF THE PREFERRED EMBODIMENTS

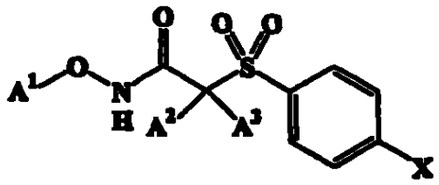
[54] This detailed description of preferred embodiments is intended only to acquaint others skilled in the art with Applicants' invention, its principles, and its practical application so that others skilled in the art may adapt and apply the invention in its numerous forms, as they may be best suited to the requirements of a particular use. This detailed description and its specific examples, while indicating preferred embodiments of this invention, are intended for purposes of illustration only. This invention, therefore, is not limited to the preferred embodiments described in this patent, and may be variously modified.

A. Compounds of This Invention

[55] In accordance with this invention, it has been found that certain aromatic sulfone hydroxamates tend to be effective for inhibiting MMPs, particularly those associated with excessive (or otherwise pathological) breakdown of connective tissue. Specifically, Applicants have found that these hydroxamates tend to be effective for inhibiting proteases (particularly MMP-2, MMP-9, MMP- 13, other MMP's associated with pathological conditions, and/or aggrecanase) that are often particularly destructive to tissue if present or generated in abnormally excessive quantities or concentrations. Moreover, Applicants have discovered that these hydroxamates tend to be selective toward inhibiting pathological protease activity, while avoiding excessive inhibition of other proteases (particularly MMP-1 and/or MMP-14) that are typically essential to normal bodily function *(e.g.,* tissue turnover and repair).

A-1. Preferred Compound Structures

[56] As noted above, the compound of this invention generally has a structure corresponding to Formula I:



I

[57] A^1 is -H, alkylcarbonyl, alkoxycarbonyl, carbocyclylcarbonyl, carbocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclylalkylcarbonyl, carbocyclyloxycarbonyl, carbocyclylalkoxycarbonyl, aminoalkylcarbonyl, alkyl(thiocarbonyl), alkoxy(thiocarbonyl), carbocyclyl(thiocarbonyl), carbocyclylalkyl(thiocarbonyl), heterocyclyl(thiocarbonyl), heterocyclylalkyl(thiocarbonyl), carbocyclyloxy(thiocarbonyl), carbocyclylalkoxy(thiocarbonyl), or aminoalkyl(thiocarbonyl). Except where the member is -H, any member of this group optionally is substituted.

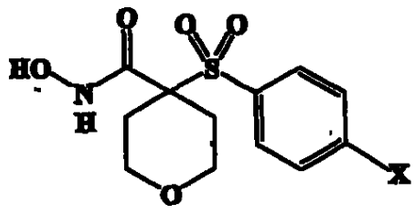
[58] In some preferred embodiments, A^1 is -H, C_1-C_8-alkylcarbonyl, C_1-C_8-alkoxycarbonyl, carbocyclylcarbonyl, carbocyclyl-C_1-C_8-alkylcarbonyl, heterocyclylcarbonyl, heterocyclyl-C_1-C_8-alkylcarbonyl, carbocyclyloxycarbonyl, carbocyclyl-C_1-C_8-alkoxycarbonyl, $N(R^A)(R^B)$-C_1-C_8-alkylcarbonyl, C_1-C_8-alkyl(thiocarbonyl), C_1-C_8-alkoxy(thiocarbonyl), carbocyclyl(thiocarbonyl), carbocyclyl-C_1-C_8-alkyl(thiocarbonyl), heterocyclyl(thiocarbonyl), heterocyclyl-C_1-C_8-alkyl(thiocarbonyl), carbocyclyloxy(thiocarbonyl), carbocyclyl-C_1-C_8-alkoxy(thiocarbonyl), or $N(R^A)(R^B)$-C_1-C_8-alkyl(thiocarbonyl). R^A and R^B are independently selected from the group consisting of -H, C_1-C_8-alkyl, C_1-C_8-alkoxycarbonyl, C_1-C_8-alkylcarbonyl, carbocyclyl-C_1-C_8-alkyl, and carbocyclyl-C_1-C_8-alkoxycarbonyl.

[59] In generally more preferred embodiments, A^1 is -H.

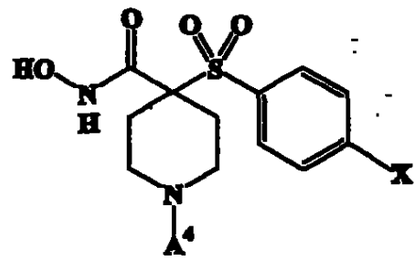
[60] A^2 and A^3, together with the carbon atom to which they are both attached, form an optionally-substituted heterocyclyl containing from 5 to 8 ring members (*i.e.*, from 5 to 8 atoms are bound together to form the ring (or rings) of the heterocyclyl).

[61] In some preferred embodiments, A^2 and A^3, together with the carbon atom to which they both are attached, form an optionally-substituted heterocyclyl containing either 5 or 6 ring members.

[62] In some preferred embodiments, the compound corresponds in structure to one of the following formulas:



I-A



I-B

[63] A^4 is -H, alkyl, alkylcarbonyl, alkylcarbonylalkyl, alkylcarbonylalkylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkoxycarbonylalkylcarbonyl, alkylsulfonyl, alkyliminocarbonyl, alkenyl, alkynyl, alkoxyalkyl, alkylthioalkyl, alkylsulfonylalkyl, alkylsulfoxidoalkyl, alkylthioalkenyl, alkylsulfoxidoalkenyl, alkylsulfonylalkenyl, carbocyclyl, carbocyclylalkyl, carbocyclylalkoxyalkyl, carbocyclylcarbonyl, carbocyclylsulfonyl, carbocyclyliminocarbonyl, carbocyclyloxycarbonyl, carbocyclylthioalkyl, carbocyclylsulfoxidoalkyl, carbocyclylsulfonylalkyl, carbocyclylthioalkenyl, carbocyclylsulfoxidoalkenyl, carbocyclylsulfonylalkenyl, heterocyclyl, heterocyclylalkyl, heterocyclylalkoxyalkyl, heterocyclylcarbonyl, heterocyclylthioalkyl, heterocyclylsulfoxidoalkyl, heterocyclylsulfonylalkyl, heterocyclylthioalkenyl, heterocyclylsulfoxidoalkenyl, heterocyclylsulfonylalkenyl, heterocyclylsulfonyl, heterocyclyliminocarbonyl, heterocyclylalkylcarbonyl, heterocyclylcarbonylalkylcarbonyl, heterocyclylsulfonyl, heterocyclylcarbonylalkyl, aminoalkylcarbonyl, aminocarbonyl, aminocarbonylalkylcarbonyl, aminosulfonyl, aminosulfonylalkyl, aminoalkyl, aminocarbonylalkyl, or aminoalkylsulfonyl. Except where the member is -H, any member of this group optionally is substituted.

[64] In some preferred embodiments, A^4 is -H, C_1-C_8-alkyl, C_1-C_8-alkylcarbonyl, C_1-C_8-alkylcarbonyl-C_1-C_8-alkyl,

C_1-C_8-alkylcarbonyl-C_1-C_8-alkylcarbonyl, C_1-C_8-alkoxycarbonyl, C_1-C_8-alkoxycarbonyl-C_1-C_8-alkyl, C_1-C_8-alkoxycarbonyl-C_1-C_8-alkylcarbonyl, C_1-C_8-alkylsulfonyl, C_1-C_8-alkyliminocarbonyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, C_1-C_8-alkoxy-C_1-C_8-alkyl, C_1-C_8-alkylthio-C_1-C_8-alkyl, C_1-C_8-alkylthio-C_2-C_8-alkenyl, C_1-C_8-alkylsulfoxido-C_1-C_8-alkyl, C_1-C_8-alkylsulfoxido-C_2-C_8-alkenyl, C_1-C_8-alkylsulfonyl-C_1-C_8-alkyl, C_1-C_8-alkylsulfonyl-C_2-C_8-alkenyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, carbocyclyl-C_1-C_8-alkoxy-C_1-C_8-alkyl, carbocyclylcarbonyl, carbocyclylsulfonyl, carbocyclyliminocarbonyl, carbocyclyloxycarbonyl, carbocyclylthio-C_1-C_8-alkyl, carbocyclylthio-C_2-C_8-alkenyl, carbocyclylsulfoxido-C_1-C_8-alkyl, carbocyclylsulfoxido-C_2-C_8-alkenyl, carbocyclylsulfonyl-C_1-C_8-alkyl, carbocyclylsulfonyl-C_2-C_8-alkenyl, heterocyclyl, heterocyclyl-C_1-C_8-alkyl, heterocyclyl-C_1-C_8-alkoxy-C_1-C_8-alkyl, heterocyclylcarbonyl, heterocyclylthio-C_1-C_8-alkyl, heterocyclylsulfoxido-C_1-C_8-alkyl, heterocyclylsulfonyl-C_1-C_8-alkyl, heterocyclylthio-C_2-C_8-alkenyl, heterocyclylsulfoxido-C_2-C_8-alkenyl, heterocyclylsulfonyl-C_2-C_8-alkenyl, heterocyclylsulfonyl, heterocyclyliminocarbonyl, heterocyclyl-C_1-C_8-alkylcarbonyl, heterocyclylcarbonyl-C_1-C_8-alkylcarbonyl, heterocyclylsulfonyl, heterocyclylcarbonyl-C_1-C_8-alkyl, $N(R^C)(R^D)$-C_1-C_8-alkylcarbonyl, $N(R^C)(R^D)$-carbonyl, $N(R^C)(R^D)$-carbonyl-C_1-C_8-alkylcarbonyl, $N(R^C)(R^D)$-sulfonyl, $N(R^C)(R^D)$-sulfonyl-C_1-C_8-alkyl, $N(R^C)(R^D)$-C_1-C_8-alkyl, $N(R^C)(R^D)$-carbonyl-C_1-C_8-alkyl, or $N(R^C)(R^D)$-C_1-C_8-alkylsulfonyl. Any substitutable member of this group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -CN, -C(O)-OH, -SH, $-SO_3H$, and NO_2.

[65] R^C and R^D are independently selected from the group consisting of -H, -OH, C_1-C_8-alkyl, C_1-C_8-alkyl-carbonyl, C_1-C_8-alkoxy-C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, C_1-C_8-alkyl-thio-C_1-C_8-alkyl, C_1-C_8-alkyl-sulfoxido-C_1-C_8-alkyl, C_1-C_8-alkyl-sulfonyl-C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, carbocyclylcarbonyl, carbocyclyl-C_1-C_8-alkoxy-C_1-C_8-alkyl, carbocyclylthio-C_1-C_8-alkyl, carbocyclylsulfoxido-C_1-C_8-alkyl, carbocyclylsulfonyl-C_1-C_8-alkyl, heterocyclyl, heterocyclyl-C_1-C_8-alkyl, heterocyclyl-C_1-C_8-alkoxy-C_1-C_8-alkyl, heterocyclylcarbonyl,

74

heterocyclylthio-C_1-C_6-alkyl, heterocyclylsulfoxido-C_1-C_6-alkyl, heterocyclylsulfonyl-C_1-C_6-alkyl, aminocarbonyl-C_1-C_6-alkyl, C_1-C_6-alkyloxycarbonylamino-C_1-C_6-alkyl, and amino-C_1-C_6-alkyl. Except where the member is -H or OH, any member of this group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -CN, -C(O)-OH, -SH, $-SO_3H$, and NO_2. The nitrogen of the amino-C_1-C_6-alkyl optionally is substituted with 1 or 2 substituents independently selected from the group consisting of C_1-C_6-alkyl, C_1-C_6-alkylcarbonyl, carbocyclyl, and carbocyclyl-C_1-C_6-alkyl. No greater than one of R^C or R^D is -OH.

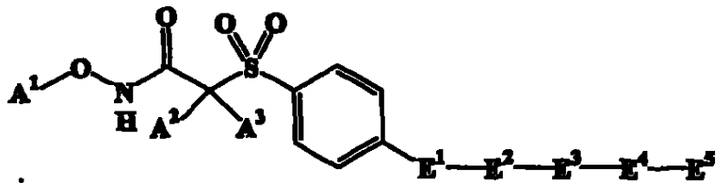
[66] In some preferred embodiments, A^4 is -H, C_1-C_6-alkyl (often preferably C_1-C_4-alkyl, and more preferably ethyl), C_1-C_6-alkoxy-C_1-C_6-alkyl (often preferably C_1-C_2-alkoxy-C_1-C_3-alkyl, and more preferably methoxyethyl), carbocyclyl (often preferably C_3-C_6-cycloalkyl or phenyl, and more preferably cyclopropyl), carbocyclyl-C_1-C_6-alkyl (often preferably C_3-C_6-cycloalkyl-C_1-C_3-alkyl or phenyl-C_1-C_3-alkyl, and more preferably cyclopropylmethyl or benzyl), C_1-C_6-alkylsulfonyl (often preferably C_1-C_2-alkylsulfonyl, and more preferably methylsulfonyl), C_3-C_6-alkenyl (often preferably C_3-C_4-alkenyl, and more preferably C_3-alkenyl), C_3-C_6-alkynyl (often preferably C_3-C_4-alkynyl, and more preferably C_3-alkynyl). Except where the member is -H, any member of these groups optionally is substituted with halogen, but more typically is preferably not substituted with halogen.

[67] In some preferred embodiments, A^4 is -H, ethyl, methoxyethyl, cyclopropyl, cyclopropylmethyl, or benzyl.

[68] X may be selected from a wide range of substituents. The following discussion describes several specific preferred embodiments encompassing the substituents that Applicants have found to be generally preferred.

Preferred Embodiment No. 1

[69] In some embodiments of this invention, the compound has a structure corresponding to Formula II:



II

[70] A^1, A^2, and A^3 are as defined above for Formula I.

[71] E^1 is -O-, -$S(O)_2$-, -S(O)-, -$N(R^1)$-, -C(O)-$N(R^1)$-, -$N(R^1)$-C(O)-, or -$C(R^1)(R^2)$-. E^1 alternatively may be -S-.

[72] E^2 forms a link of at least 2 carbon atoms between E^1 and E^3. E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of this group optionally is substituted.

[73] In some preferred embodiments, E^2 is C_2-C_{20}-alkyl, cycloalkyl, C_1-C_{10}-alkylcycloalkyl, cycloalkyl-C_1-C_{10}-alkyl, or C_1-C_{10}-alkylcycloalkyl-C_1-C_{10}-alkyl. Any member of this group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, C_1-C_8-alkyl, and halo-C_1-C_8-alkyl.

[74] In some preferred embodiments, E^2 is C_2-C_8-alkyl optionally substituted with one or more halogen.

[75] In some preferred embodiments, E^2 is C_2-C_8-alkyl.

[76] In some preferred embodiments, E^2 is C_2-C_6-alkyl.

[77] E^3 is -C(O)-, -O-(CO)-, -C(O)-O-, -$C(NR^3)$-, -$N(R^4)$-, -C(O)-$N(R^4)$-, -$N(R^4)$-C(O)-, -$N(R^4)$-C(O)-$N(R^5)$-, -S-, -S(O)-, -$N(R^4)$-$S(O)_2$-, -$S(O)_2$-$N(R^4)$-, -C(O)-$N(R^4)$-$N(R^5)$-C(O)-, -$C(R^4)(R^6)$-C(O)-, or -$C(R^7)(R^8)$-.

[78] E^4 is a bond, alkyl, or alkenyl. The alkyl and alkenyl optionally are substituted.

[79] In some preferred embodiments, E^4 is a bond, C_1-C_{20}-alkyl, or C_2-C_{20}-alkenyl. The C_1-C_{20}-alkyl andC_2-C_{20}-alkenyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen and carbocyclyl. This carbocyclyl, in turn, optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_8-alkyl, C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, halo-C_1-C_8-alkyl, halo-C_1-C_8-alkoxy, halogen-substituted

C_1-C_6-alkoxy-C_1-C_6-alkyl, halocarbocyclyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl.

[80] In some preferred embodiments, E^4 a bond, C_1-C_3-alkyl, or C_2-C_3-alkenyl. The C_1-C_3-alkyl, and C_2-C_3-alkenyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen and carbocyclyl. This carbocyclyl, in turn, optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, halocarbocyclyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl.

[81] In some preferred embodiments, E^4 is a bond, C_1-C_3-alkyl, or C_2-C_3-alkenyl.

[82] E^5 is -H, -OH, alkyl, alkenyl, alkynyl, alkoxy, alkoxyalkyl, carbocyclyl, or heterocyclyl. Except where E^5 is -H or -OH, any member of this group optionally is substituted. E^5 is not -H when both E^3 is -$C(R^7)(R^8)$- and E^4 is a bond.

[83] In some preferred embodiments, E^5 is -H, -OH, C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, C_1-C_{20}-alkoxy, C_1-C_{20}-alkoxy-C_1-C_{20}-alkyl, carbocyclyl, or heterocyclyl. The C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, C_1-C_{20}-alkoxy, and C_1-C_{20}-alkoxy-C_1-C_{20}-alkyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, and -CN. The carbocyclyl and heterocyclyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^{11})(R^{12})$, -$C(O)(R^{13})$, -S-R^{11}, -$S(O)_2$-R^{11}, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, halocarbocyclyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl. The carbocyclyl and heterocyclyl also optionally are substituted with one or more substituents independently selected from the group consisting of C_1-C_6-alkylcarbocyclyl, halogen-substituted C_1-C_6-alkylcarbocyclyl, hydroxycarbocyclyl, and heterocyclyl.

[84] In some preferred embodiments, E^5 is -H, -OH, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, carbocyclyl, or heterocyclyl.

77

The C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkoxy, and C_1-C_6-alkoxy-C_1-C_6-alkyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, and -CN. The carbocyclyl and heterocyclyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^{11})(R^{12})$, $-C(O)(R^{13})$, $-S-R^{11}$, $-S(O)_2-R^{11}$, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, halocarbocyclyl, halogen-substituted carbocyclyl-C_1-C_6-alkyl, C_1-C_6-alkylcarbocyclyl, halogen-substituted C_1-C_6-alkylcarbocyclyl, hydroxycarbocyclyl, and heteroaryl.

[85] In some preferred embodiments, E^5 is furanyl, tetrahydropyranyl, dihydrofuranyl, tetrahydrofuranyl, thiophenyl, dihydrothiophenyl, tetrahydrothiophenyl, pyrrolyl, isopyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, isoimidazolyl, imidazolinyl, imidazolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, triazolyl, tetrazolyl, dithiolyl, oxathiolyl, oxazolyl, isoxazolyl, oxazolidinyl, isoxazolidinyl, thiazolyl, isothiazolyl, thiazolinyl, isothiazolinyl, thiazolidinyl, isothiazolidinyl, thiodiazolyl, oxathiazolyl, oxadiazolyl, oxatriazolyl, dioxazolyl, oxathiazolyl, oxathiolyl, oxathiolanyl, pyranyl, dihydropyranyl, pyridinyl, piperidinyl, diazinyl, piperazinyl, triazinyl, oxazinyl, isoxazinyl, oxathiazinyl, oxadiazinyl, morpholinyl, azepinyl, oxepinyl, thiepinyl, diazepinyl, indolizinyl, pyrindinyl, pyranopyrrolyl, 4H-quinolizinyl, purinyl, naphthyridinyl, pyridopyridinyl, pteridinyl, indolyl, isoindolyl, indoleninyl, isoindazolyl, benzazinyl, phthalazinyl, quinoxalinyl, quinazolinyl, benzodiazinyl, benzopyranyl, benzothiopyranyl, benzoxazolyl, indoxazinyl, anthranilyl, benzodioxolyl, benzodioxanyl, benzoxadiazolyl, benzofuranyl, isobenzofuranyl, benzothienyl, isobenzothienyl, benzothiazolyl, benzothiadiazolyl, benzimidazolyl, benzotriazolyl, benzoxazinyl, benzisoxazinyl, tetrahydroisoquinolinyl, carbazolyl, xanthenyl, or acridinyl. Such substituent optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^{11})(R^{12})$, $-C(O)(R^{13})$, $-S-R^{11}$, $-S(O)_2-R^{11}$, aryl, aryl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, haloaryl, and halogen-substituted aryl-C_1-C_6-alkyl. Any member of such group also optionally is substituted with one or more substituent

independent selected from the group consisting of C_1-C_6-alkylaryl, halogen-substituted C_1-C_6-alkylaryl, hydroxyaryl, and heteroaryl.

[86] In some preferred embodiments, E^5 is indolizinyl, pyrindinyl, pyranopyrrolyl, 4H-quinolizinyl, purinyl, naphthyridinyl, pyridopyridinyl, pteridinyl, indolyl, isoindolyl, indoleninyl, isoindazolyl, benzazinyl, phthalazinyl, quinoxalinyl, quinazolinyl, benzodiazinyl, benzopyranyl, benzothiopyranyl, benzoxazolyl, indoxazinyl, anthranilyl, benzodioxolyl, benzodioxanyl, benzoxadiazolyl, benzofuranyl, isobenzofuranyl, benzothienyl, isobenzothienyl, benzothiazolyl, benzothiadiazolyl, benzimidazolyl, benzotriazolyl, benzoxazinyl, benzisoxazinyl, tetrahydroisoquinolinyl, or pyridofuranyl. Such substituent optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^{11})(R^{12})$, $-C(O)(R^{13})$, $-S-R^{11}$, $-S(O)_2-R^{11}$, aryl, aryl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, haloaryl, halogen-substituted aryl-C_1-C_6-alkyl. Such substituent also optionally is substituted with one or more substituents independently selected from the group consisting of C_1-C_6-alkylaryl, halogen-substituted C_1-C_6-alkylaryl, hydroxyaryl, and heteroaryl.

[87] In some preferred embodiments, E^5 is benzazinyl, benzofuranyl, or tetrahydroisoquinolinyl. Such substituent optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^{11})(R^{12})$, $-C(O)(R^{13})$, $-S-R^{11}$, $-S(O)_2-R^{11}$, aryl, aryl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, haloaryl, and halogen-substituted aryl-C_1-C_6-alkyl. Such substituent also optionally is substituted with one or more substituents independently selected from the group consisting of C_1-C_6-alkylaryl, halogen-substituted C_1-C_6-alkylaryl, hydroxyaryl, and heteroaryl.

[88] In some preferred embodiments, E^5 is indolyl, benzoxazolyl, benzothienyl, benzothiazolyl, or pyridofuranyl. Such substituent any member of such group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^{11})(R^{12})$, $-C(O)(R^{13})$, $-S-R^{11}$, $-S(O)_2-R^{11}$, aryl, aryl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted

79

C_1-C_6-alkoxy-C_1-C_6-alkyl, haloaryl, and halogen-substituted aryl-C_1-C_6-alkyl. Such substituent also optionally is substituted with one or more substituents independently selected from the group consisting of C_1-C_6-alkylaryl, halogen-substituted C_1-C_6-alkylaryl, hydroxyaryl, and heteroaryl.

[89] R^1 and R^2 are independently selected from the group consisting of -H and alkyl. The alkyl optionally is substituted. Neither R^1 nor R^2 forms a ring structure with E^2, E^3, E^4, or E^5.

[90] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_6-alkyl, and halo-C_1-C_6-alkyl.

[91] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_6-alkyl, and halo-C_1-C_6-alkyl.

[92] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H, and C_1-C_6-alkyl.

[93] R^3 is -H or -OH.

[94] R^4 and R^5 are independently selected from the group consisting of -H, alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, and heterocyclylalkyl. Except for -H, any member of this group optionally is substituted. Neither R^4 nor R^5 forms a ring structure with E^2, E^4, or E^5.

[95] In some preferred embodiments, R^4 and R^5 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[96] In some preferred embodiments, R^4 and R^5 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group optionally is substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[97] R^6 is -CN or -OH.

[98] R^7 is -H, halogen, -OH, alkyl, alkoxy, or alkoxyalkyl. The alkyl, alkoxy, and alkoxyalkyl optionally are substituted.

80

[99] In some preferred embodiments, R^7 is -H, halogen, -OH, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, or halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl.

[100] In some preferred embodiments, R^7 is -H, halogen, -OH, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, or halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl.

[101] In some preferred embodiments, R^7 is -H, halogen, -OH, C_1-C_6-alkyl, C_1-C_6-alkoxy, or C_1-C_6-alkoxy-C_1-C_6-alkyl.

[102] R^8 is -OH or alkoxy. The alkoxy optionally is substituted.

[103] In some preferred embodiments, R^8 is -OH, C_1-C_6-alkoxy, or halo-C_1-C_6-alkoxy.

[104] In some preferred embodiments, R^8 is -OH, C_1-C_6-alkoxy, or halo-C_1-C_6-alkoxy.

[105] In some preferred embodiments, R^8 is -OH or C_1-C_6-alkoxy.

[106] R^{11} and R^{12} are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[107] In some preferred embodiments, R^{11} and R^{12} are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[108] R^{13} is -H, C_1-C_6-alkyl, -O-R^{14}, -N(R^{14})(R^{15}), carbocyclyl-C_1-C_6-alkyl, heterocyclyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halogen-substituted carbocyclyl-C_1-C_6-alkyl, or halogen-substituted heterocyclyl-C_1-C_6-alkyl.

[109] In some preferred embodiments, R^{13} is -H, C_1-C_6-alkyl, -O-R^{14}, -N(R^{14})(R^{15}), carbocyclyl-C_1-C_6-alkyl, heterocyclyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halogen-substituted carbocyclyl-C_1-C_6-alkyl, or halogen-substituted heterocyclyl-C_1-C_6-alkyl.

81

[110] In some preferred embodiments, R^{13} is -H, C_1-C_6-alkyl, -O-R^{14}, -N(R^{14})(R^{15}), carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl.

[111] R^{14} and R^{15} are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but typically is preferably not substituted with halogen.

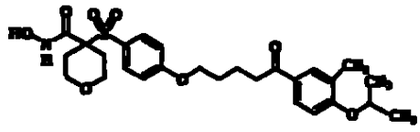
[112] In some preferred embodiments, R^{14} and R^{15} are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but typically is preferably not substituted with halogen.

Preferred Embodiment No. 1-a: E^3 is -C(O)-

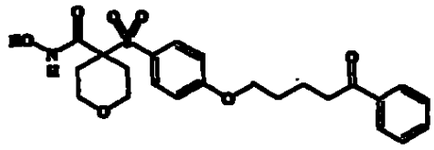
[113] In some embodiments, E^3 is -C(O)-.

[114] In some such embodiments, E^5 is optionally-substituted carbocyclyl, and often preferably optionally-substituted cycloalkyl or optionally-substituted aryl.

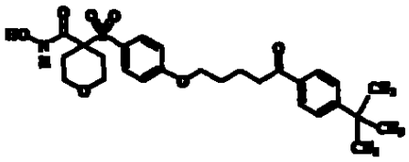
[115] In some preferred embodiments, for example, E^5 is optionally-substituted phenyl. Such compounds include, for example:



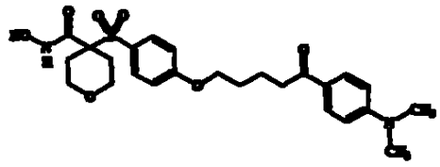
IIA-1



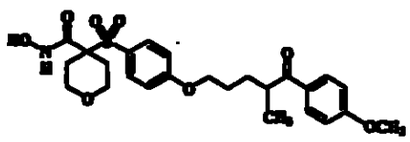
IIA-2



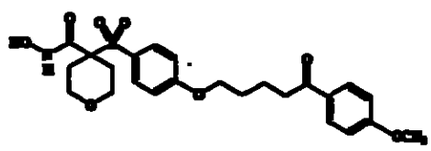
IIA-3



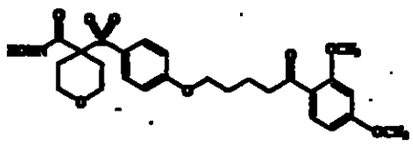
IIA-4



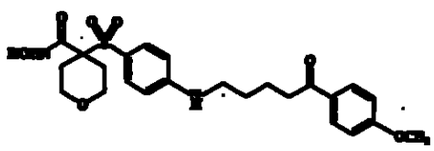
IIA-5



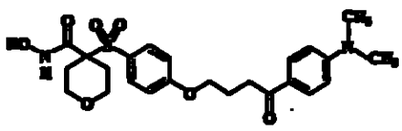
IIA-6



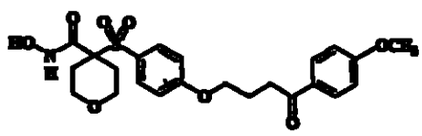
IIA-7



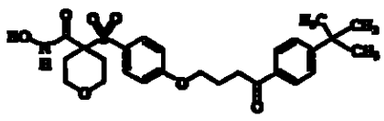
IIA-8



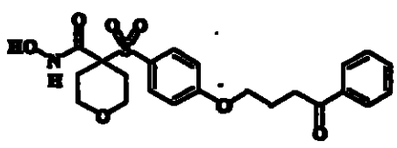
IIA-9



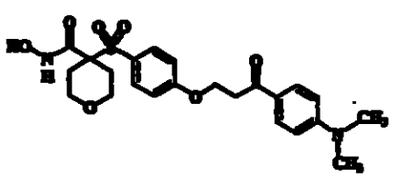
IIA-10



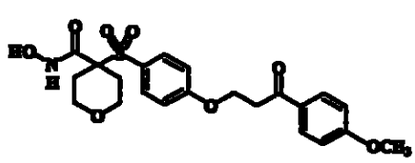
IIA-11



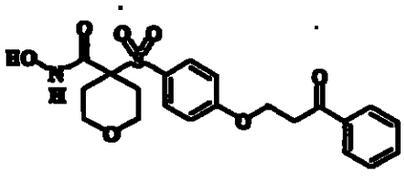
IIA-12



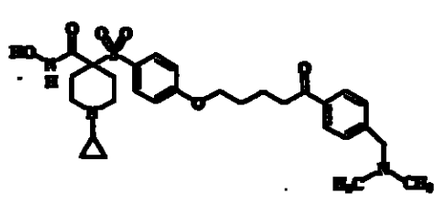
IIA-13



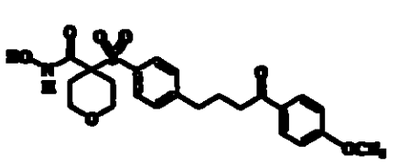
IIA-14



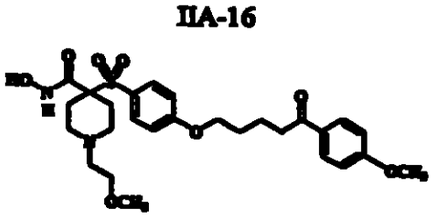
IIA-15



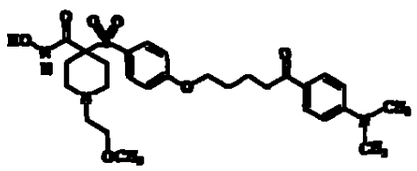
IIA-16



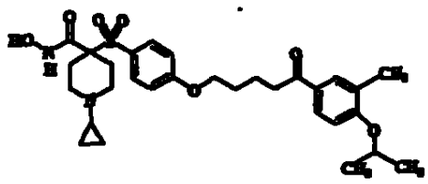
IIA-17



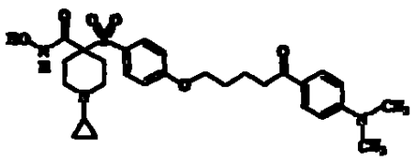
IIA-18



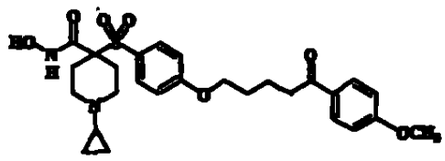
IIA-19



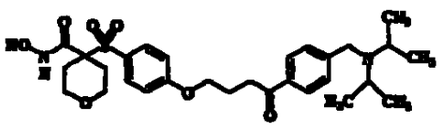
IIA-20



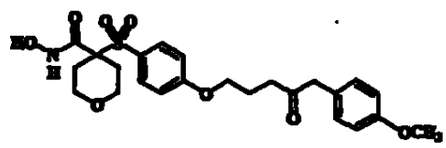
IIA-21



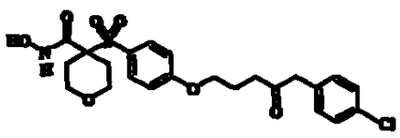
IIA-22



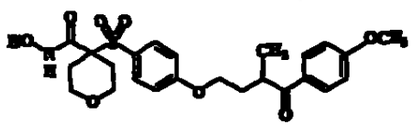
IIA-23



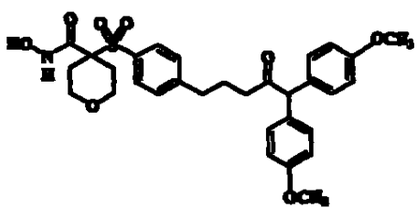
IIA-24



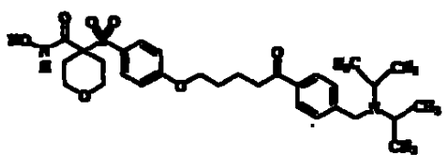
IIA-25



IIA-26



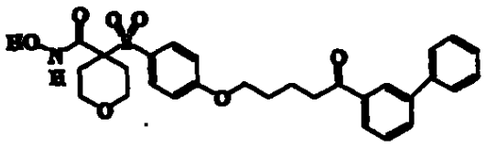
IIA-27



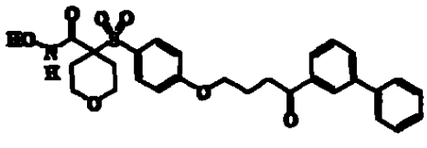
IIA-28

Such compounds also include compounds wherein E^5 is phenyl substituted with one or more substituents independently selected from the group consisting of aryl, haloaryl, aryl-C_1-C_6-alkyl, and halogen-substituted aryl-C_1-C_6-alkyl. Here, the phenyl also optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^{11})(R^{12})$, -$C(O)(R^{13})$, -S-R^{11}, -$S(O)_2$-R^{11}, aryl, aryl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, haloaryl, halogen-substituted aryl-C_1-C_6-alkyl, C_1-C_6-alkylaryl,

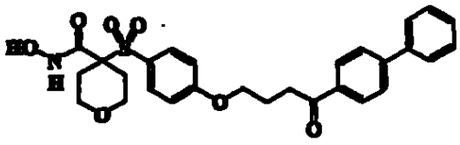
halogen-substituted C_1-C_6-alkylaryl, hydroxyaryl, and heteroaryl. Such compounds include, for example:



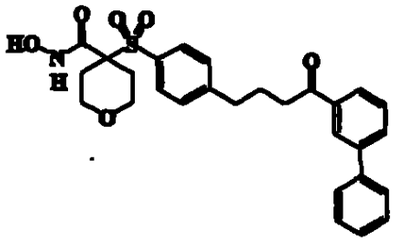
IIA-29



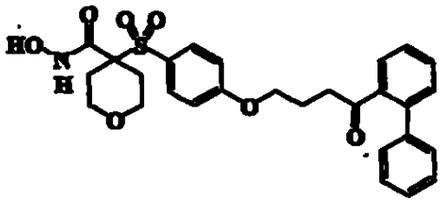
IIA-30



IIA-31

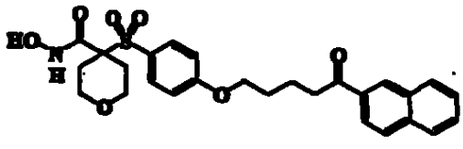


IIA-32

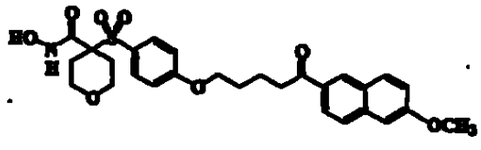


IIA-33

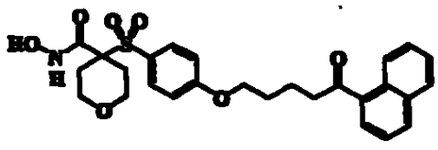
[116] In other preferred embodiments, E^5 is optionally-substituted naphthalenyl. Such compounds include, for example:



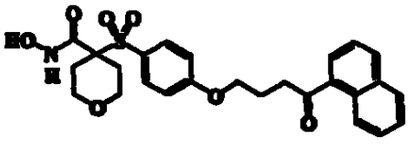
IIA-34



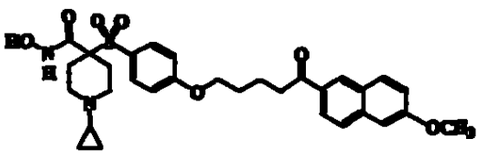
IIA-35



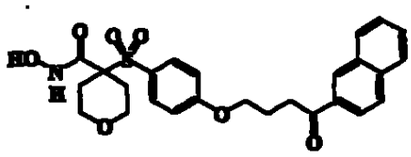
IIA-36



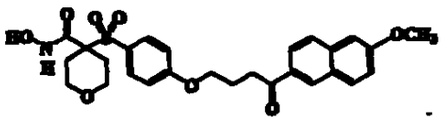
IIA-37



IIA-38

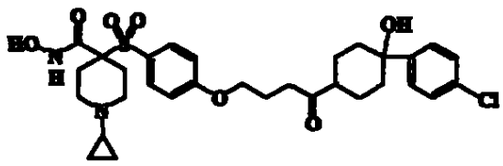


IIA-39



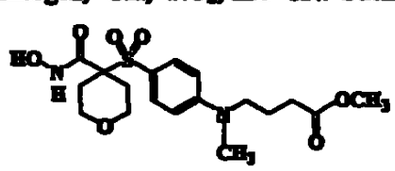
IIA-40

[117] In yet other preferred embodiments, E^5 is optionally-substituted C_3-C_6-cycloalkyl. Such compounds include, for example:

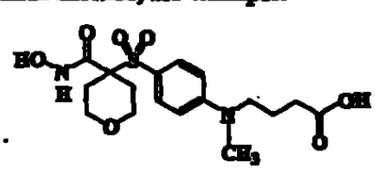


IIA-41.

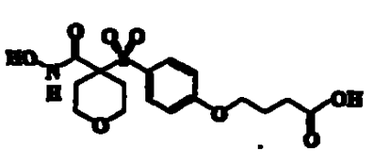
[118] In some preferred embodiments, E^5 is -H, -OH, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkoxy, or C_1-C_6-alkoxy-C_1-C_6-alkyl. The C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkoxy, and C_1-C_6-alkoxy-C_1-C_6-alkyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, and -CN. Such compounds include, for example:



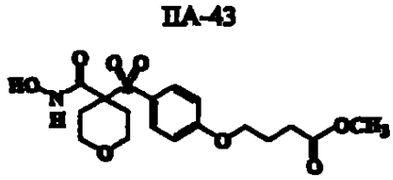
IIA-42



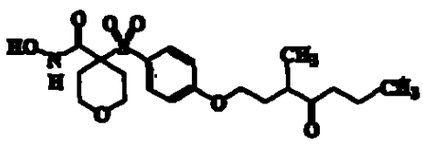
IIA-43



IIA-44

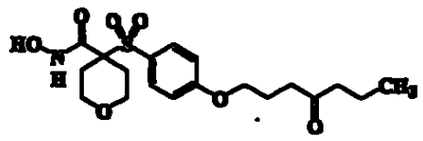


IIA-45

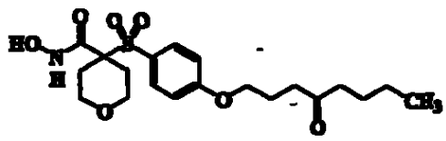


IIA-46

Other such compounds include, for example:

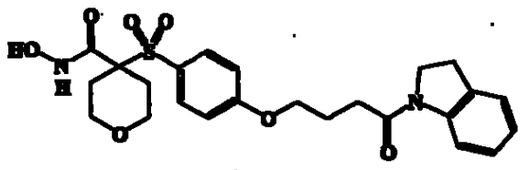


IIA-47



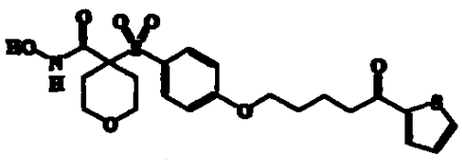
IIA-48

[119] In other preferred embodiments, E^5 is optionally-substituted heterocyclyl. In one such embodiment, E^5 is optionally-substituted thiophenyl. Such compounds include, for example:

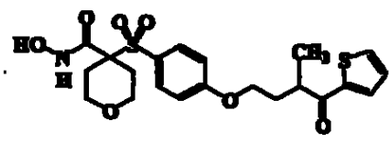


IIA-49

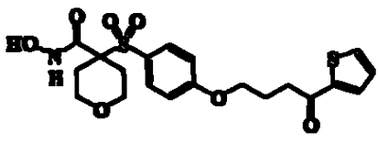
Other such compounds include, for example:



IIA-50



IIA-51



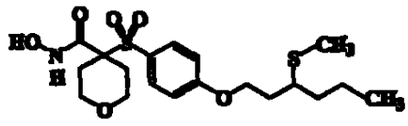
IIA-52

Preferred Embodiment No. 1-b: E^5 is -S-

[120] In some embodiments, E^5 is -S-.

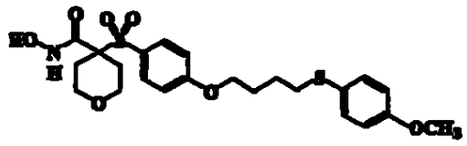
[121] In some such embodiments, E^5 is -H, -OH, C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, C_1-C_8-alkoxy, or C_1-C_8-alkoxy-C_1-C_8-alkyl. The C_1-C_8-alkyl,

C_2-C_8-alkenyl, C_2-C_8-alkynyl, C_1-C_8-alkoxy, and C_1-C_8-alkoxy-C_1-C_8-alkyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, and -CN. Such compounds include, for example:

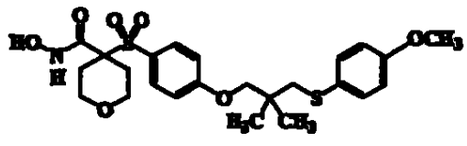


IIB-1

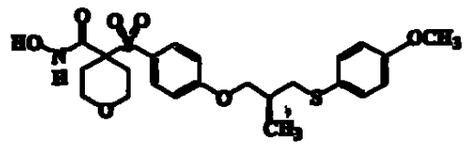
[122] In some preferred embodiments, E^5 is optionally-substituted carbocyclyl, often preferably optionally-substituted aryl, and more preferably optionally-substituted phenyl. Such compounds include, for example:



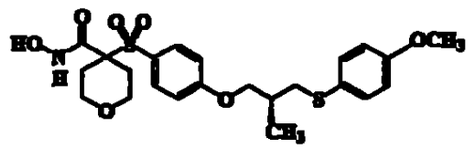
IIB-2



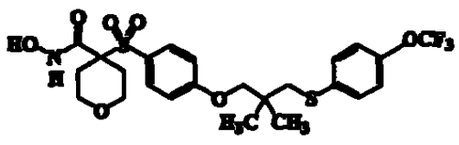
IIB-3



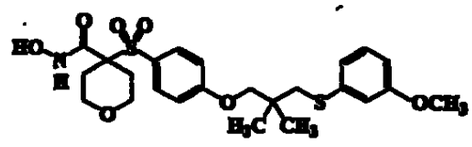
IIB-4



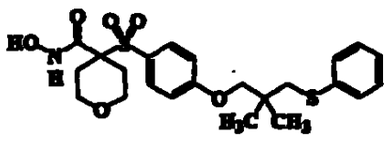
IIB-5



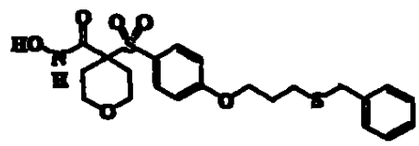
IIB-6



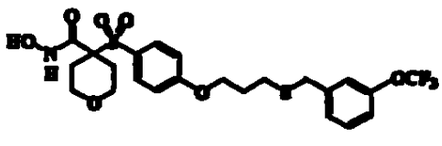
IIB-7



IIB-8

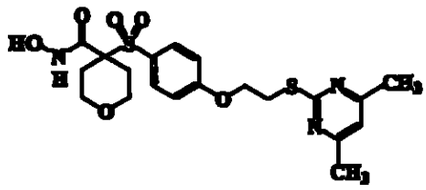


IIB-9

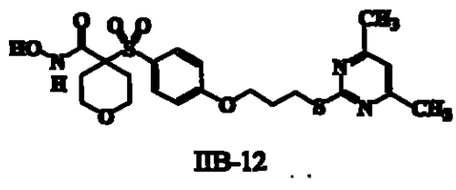


IIB-10

[123] In some preferred embodiments, E^5 is optionally-substituted heterocyclyl. In one such embodiment, E^5 is optionally-substituted pyrimidinyl. Such compounds include, for example:

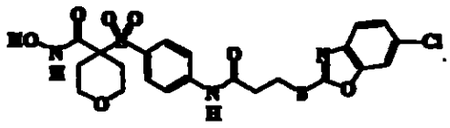


IIB-11

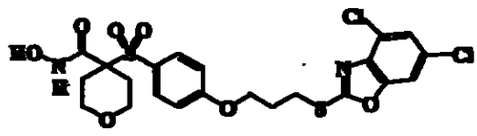


IIB-12

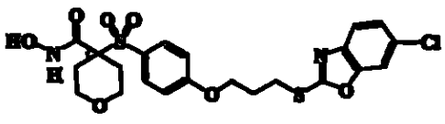
In another such embodiment, E^5 is optionally-substituted 2-fused-ring heterocyclyl. In some preferred embodiments, E^5 is optionally-substituted benzoxazolyl or optionally-substituted benzothiazolyl. Such compounds include, for example:



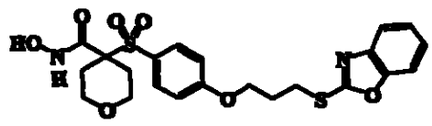
IIB-13



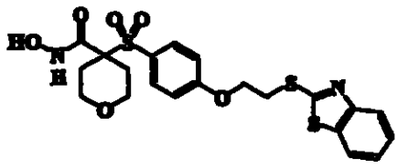
IIB-14



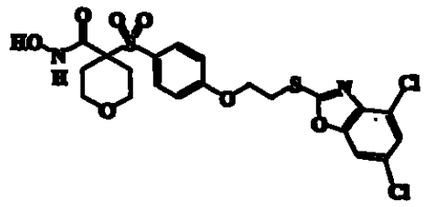
IIB-15



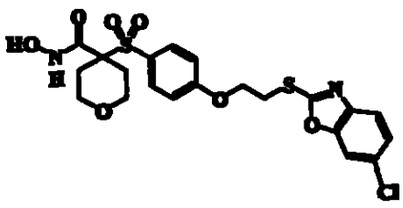
IIB-16



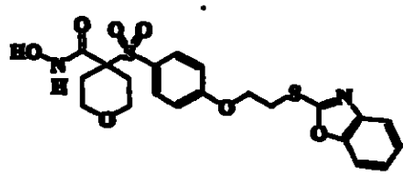
IIB-17



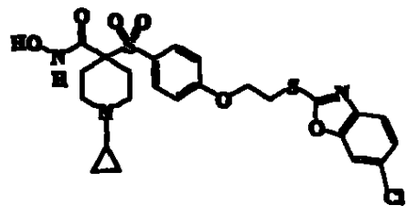
IIB-18



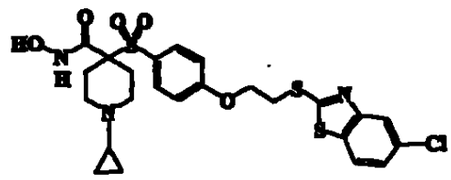
IIB-19



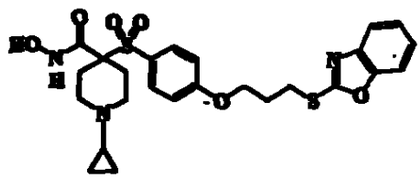
IIB-20



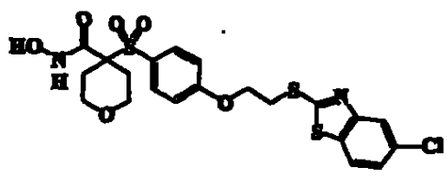
IIB-21



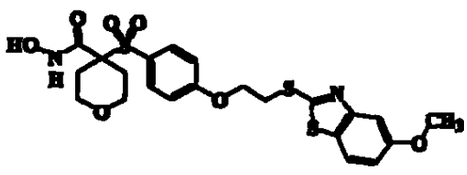
IIB-22



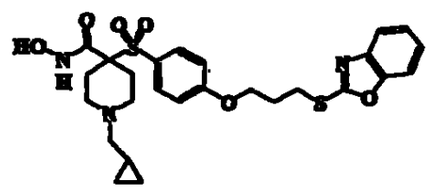
IIB-23



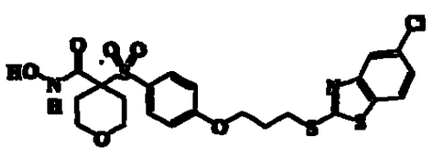
IIB-24



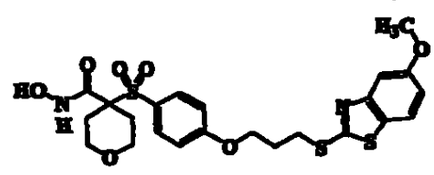
IIB-25



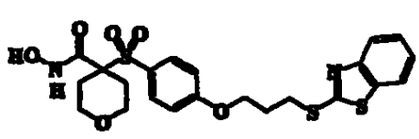
IIB-26



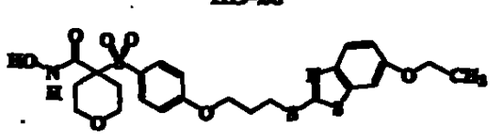
IIB-27



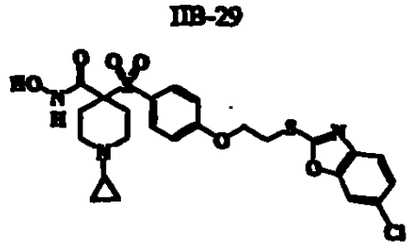
IIB-28



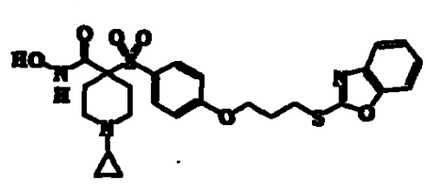
IIB-29



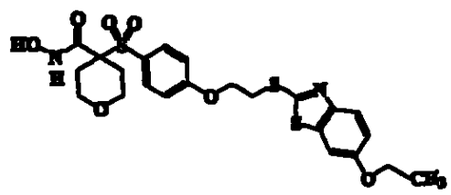
IIB-30



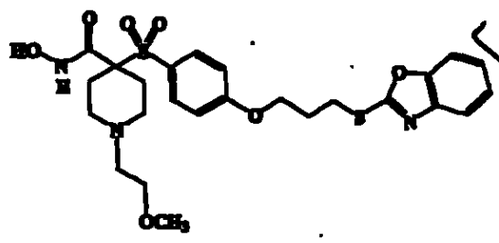
IIB-31



IIB-32

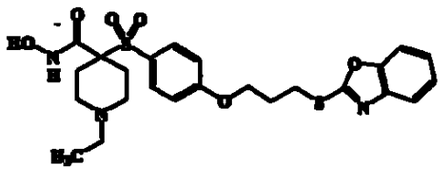


IIB-33

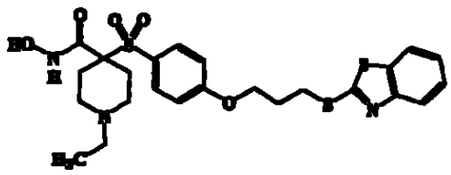


IIB-34

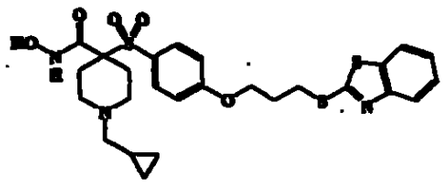
Other such compounds include, for example:



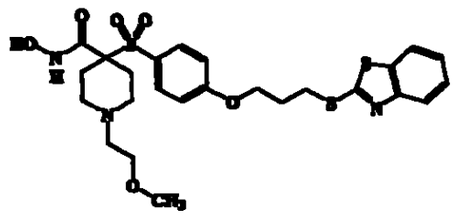
IIB-35



IIB-36



IIB-37

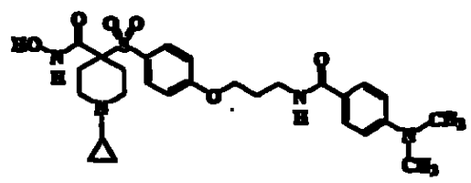


IIB-38

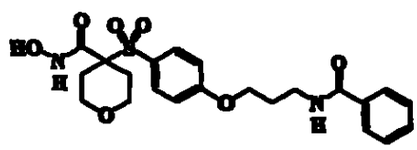
Preferred Embodiment No. 1-c: E^3 is -N(R^4)-C(O)-

[124] In some embodiments, E^3 is -N(R^4)-C(O)-.

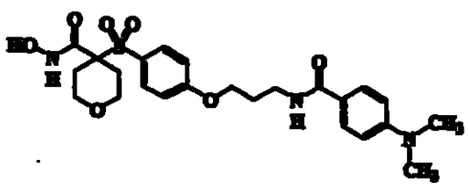
[125] In some such embodiments, E^5 is optionally-substituted carbocyclyl. In some preferred embodiments, E^5 is optionally-substituted phenyl. Such compounds include, for example:



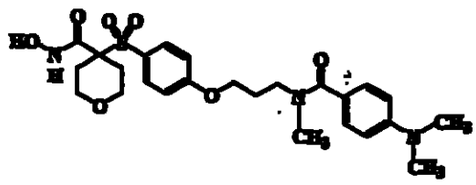
IIC-1



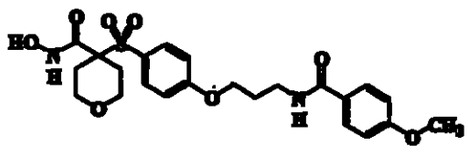
IIC-2



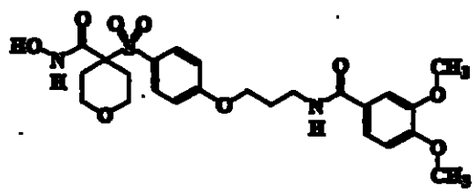
IIC-3



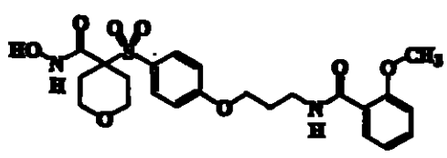
IIC-4



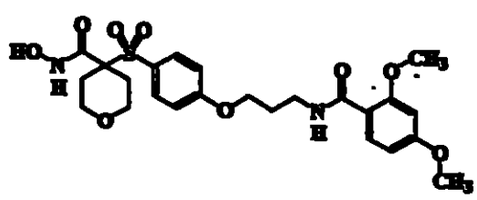
IIC-5



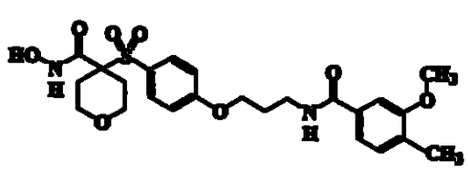
IIC-6



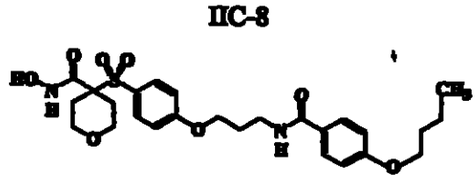
IIC-7



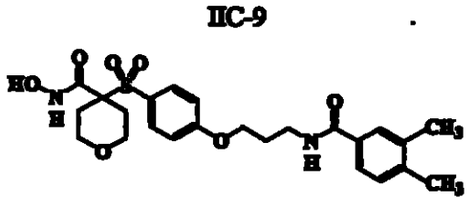
IIC-8



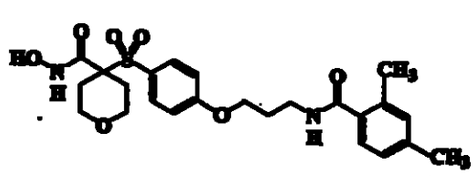
IIC-9



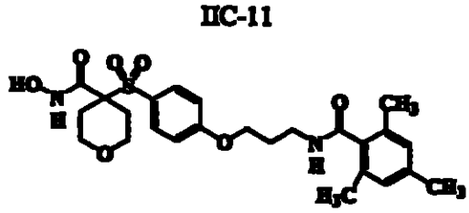
IIC-10



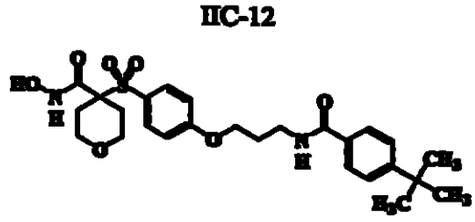
IIC-11



IIC-12

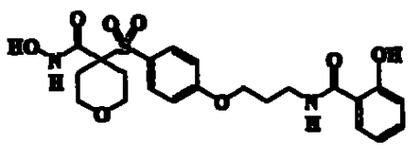


IIC-13

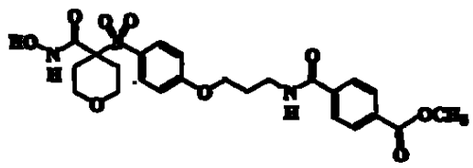


IIC-14

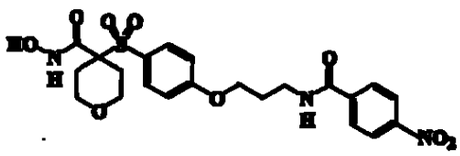
92



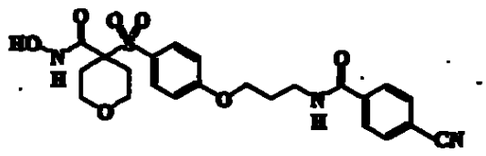
IIC-15



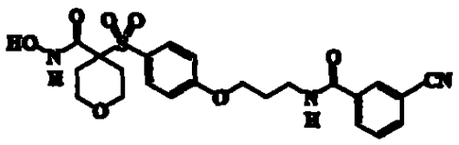
IIC-16



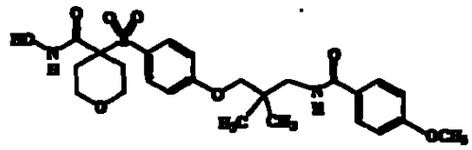
IIC-17



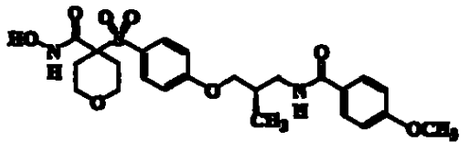
IIC-18



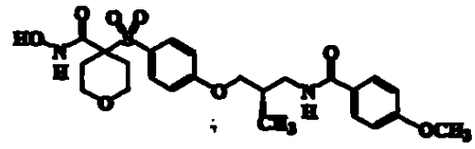
IIC-19



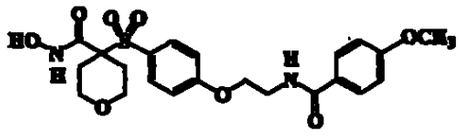
IIC-20



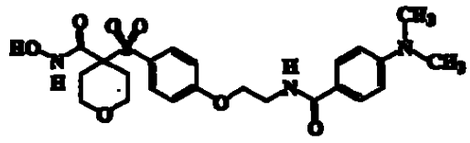
IIC-21



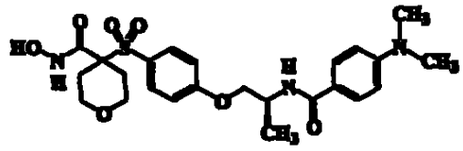
IIC-22



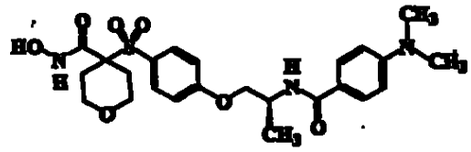
IIC-23



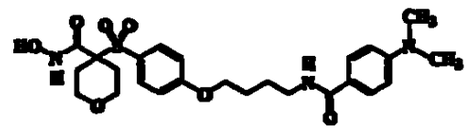
IIC-24



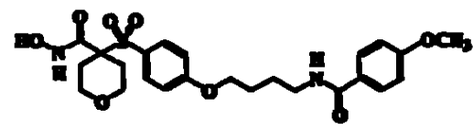
IIC-25



IIC-26

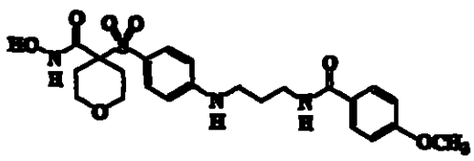


IIC-27

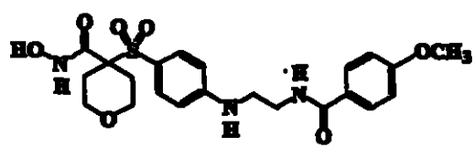


IIC-28

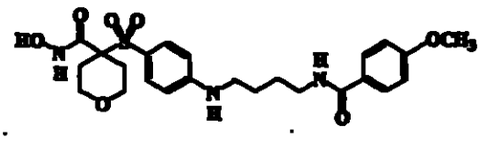
93



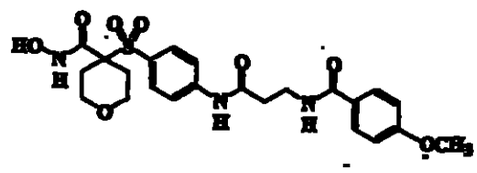
IIC-29



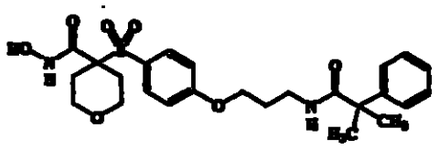
IIC-30



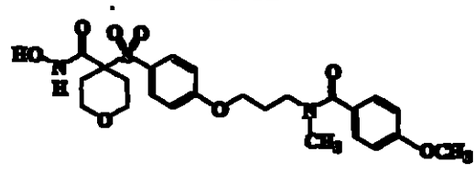
IIC-31



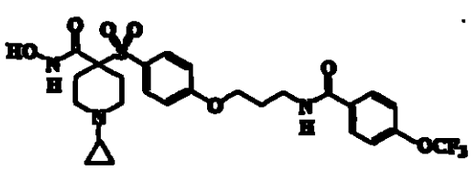
IIC-32



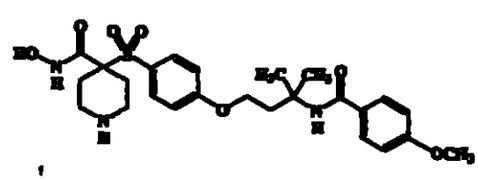
IIC-33



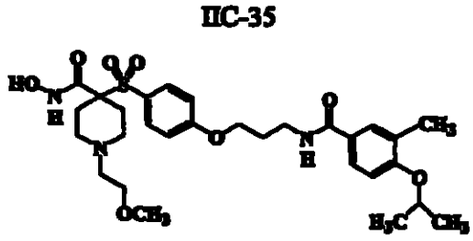
IIC-34



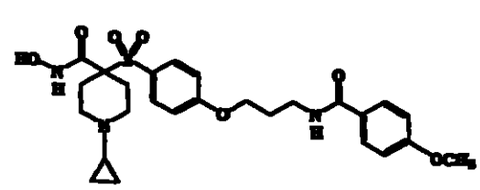
IIC-35



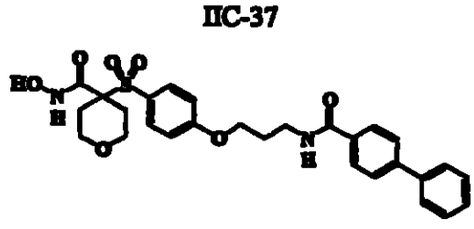
IIC-36



IIC-37

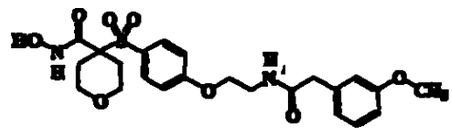


IIC-38

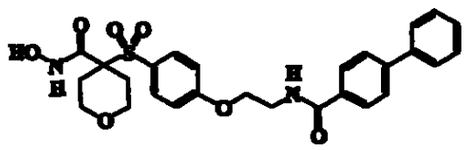


IIC-39

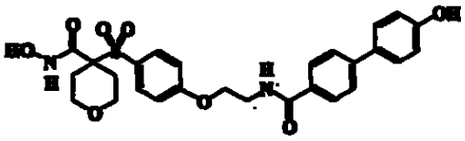
Other such compounds include, for example:



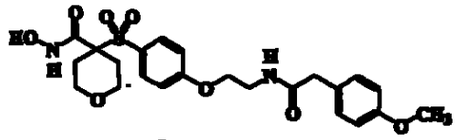
IIC-40



IIC-41

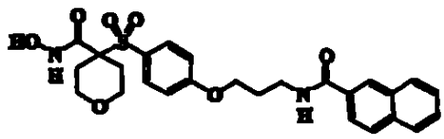


IIC-42

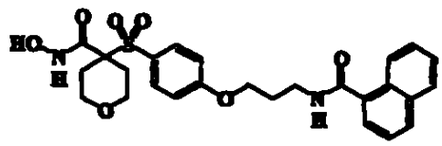


IIC-43

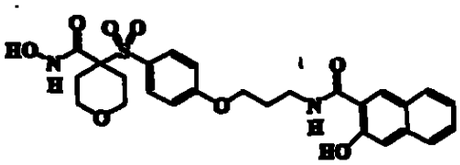
[126] In some preferred embodiments, E^5 is optionally-substituted naphthalenyl. Such compounds include, for example:



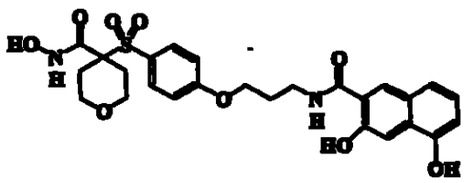
IIC-44



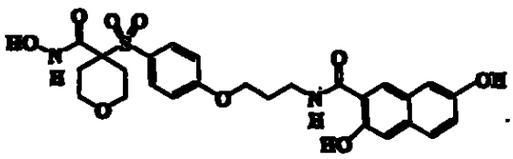
IIC-45



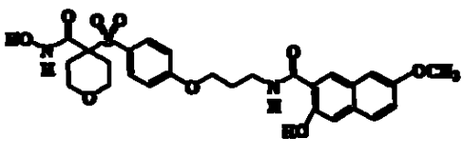
IIC-46



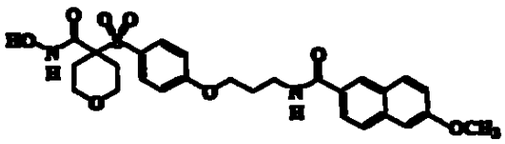
IIC-47



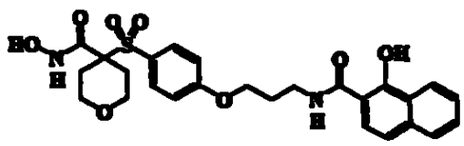
IIC-48



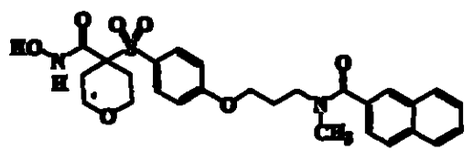
IIC-49



IIC-50

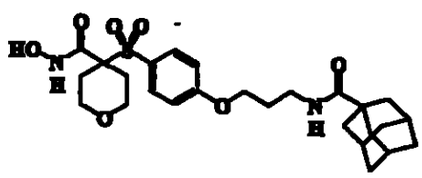


IIC-51



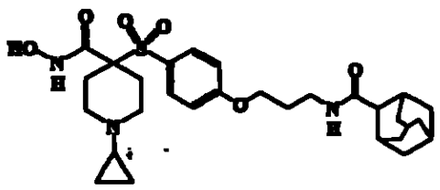
IIC-52

[127] In some preferred embodiments, E^5 is optionally-substituted cycloalkyl. Such compounds include, for example, fused-ring cycloalkyls. These compounds include, for example:

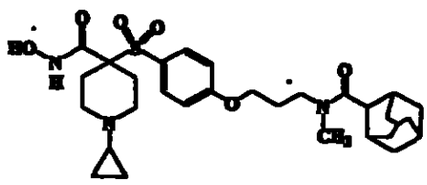


IIC-53

These compounds also include, for example:

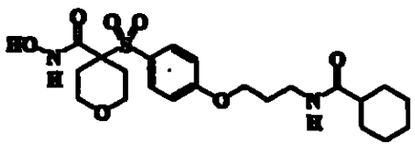


IIC-54

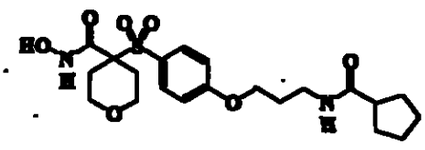


IIC-55

[128] In some preferred embodiments, E^5 is optionally-substituted C_5-C_6-cycloalkyl. These compounds include, for example:

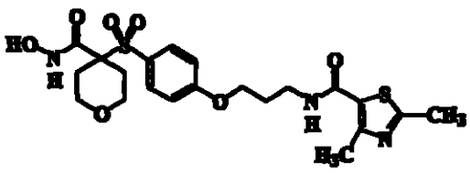


IIC-56

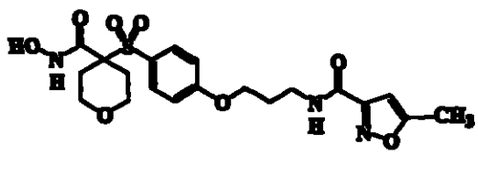


IIC-57

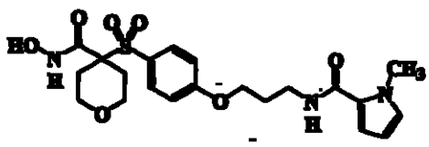
[129] In some preferred embodiments, E^5 is optionally-substituted heterocyclyl. In one such embodiment, E^5 is an optionally-substituted heterocyclyl selected from the group consisting of pyridinyl, pyrrolyl, isopyrrolyl, oxazolyl, isoxazole, thiazolyl, furanyl, and morpholinyl. In another such embodiment, E^5 is an optionally-substituted heterocyclyl selected from the group consisting of tetrazolyl, imidazolyl, and thienyl. Compounds of these embodiments include, for example:



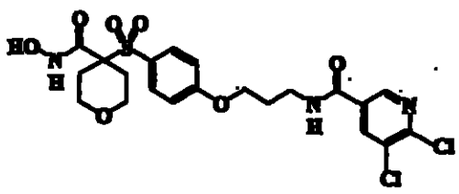
IIC-58



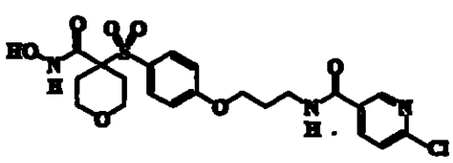
IIC-59



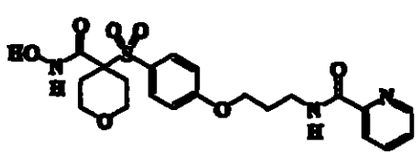
IIC-60



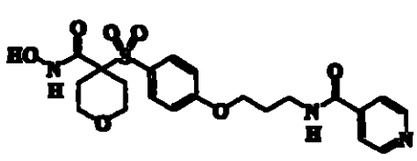
IIC-61



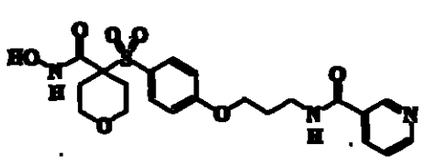
IIC-62



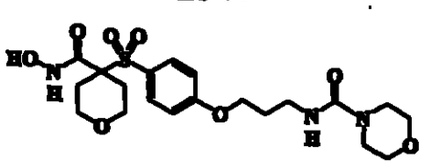
IIC-63



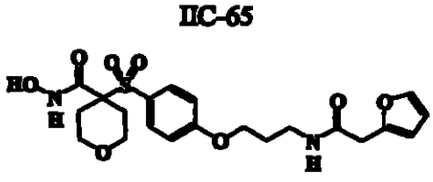
IIC-64



IIC-65

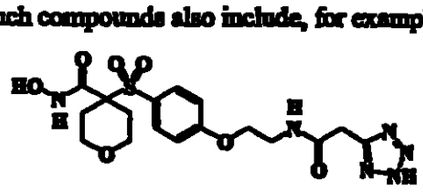


IIC-66

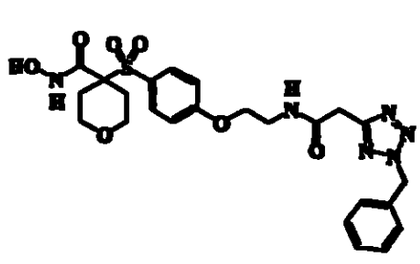


IIC-67

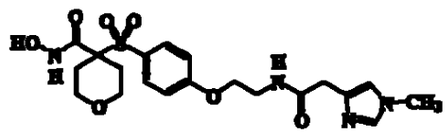
Such compounds also include, for example:



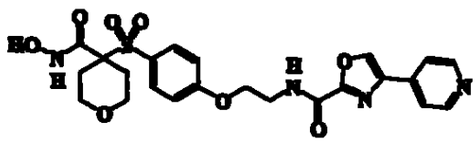
IIC-68



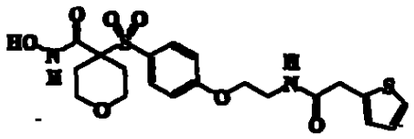
IIC-69



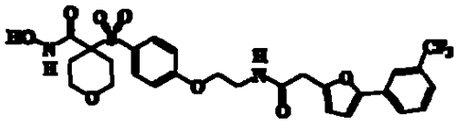
IIC-70



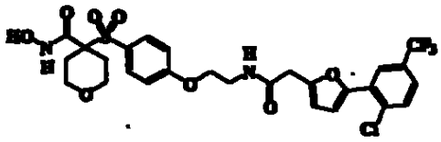
IIC-71



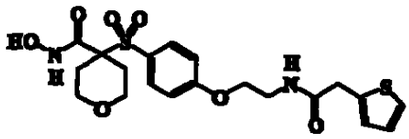
IIC-72



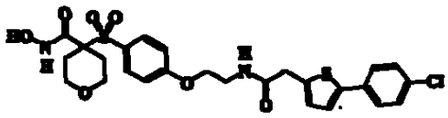
IIC-73



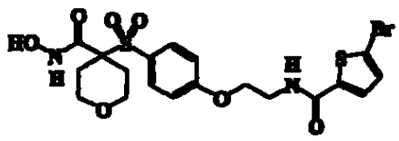
IIC-74



IIC-75

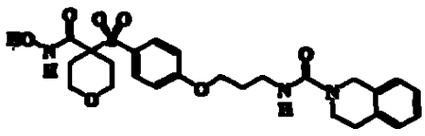


IIC-76

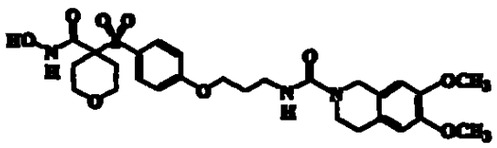


IIC-77

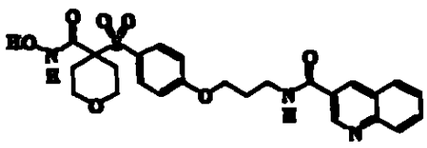
[138] In some preferred embodiments, E^5 is optionally-substituted 2-fused-ring heterocyclyl. In some more preferred embodiments, E^5 is an optionally-substituted heterocyclyl selected from the group consisting of benzazinyl, benzofuranyl, tetrahydroisoquinolinyl or pyridofuranyl. In some other more preferred embodiments, E^5 is an optionally-substituted heterocyclyl selected from the group consisting of indolyl, benzoxazolyl, benzothienyl, and benzothiazolyl. Compounds of such embodiments include, for example:



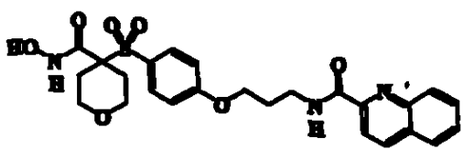
IIC-78



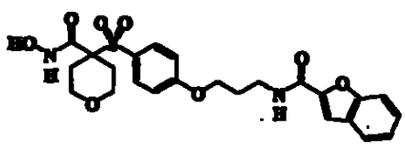
IIC-79



IIC-80

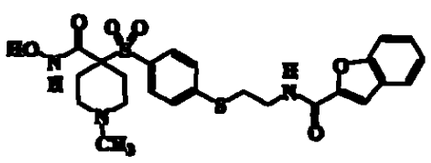


IIC-81

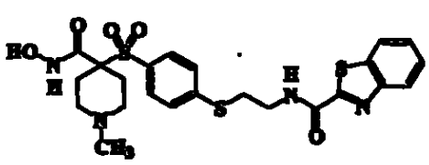


IIC-82

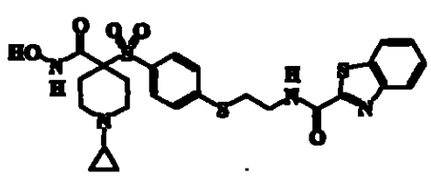
Other such compounds include, for example:



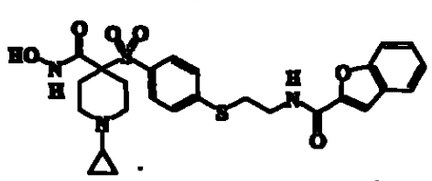
IIC-83



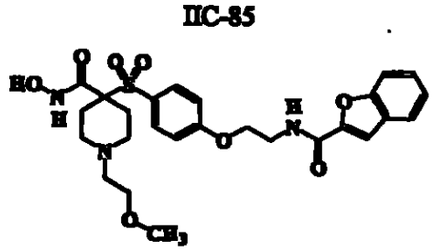
IIC-84



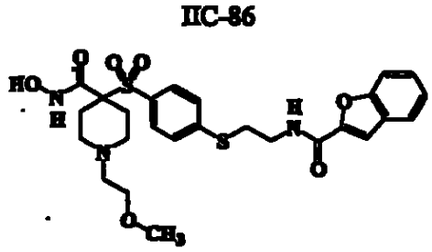
IIC-85



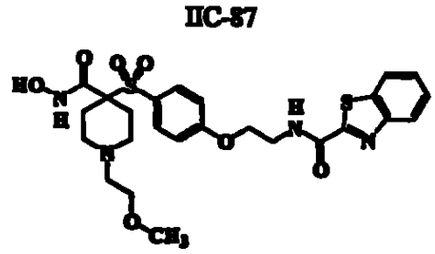
IIC-86



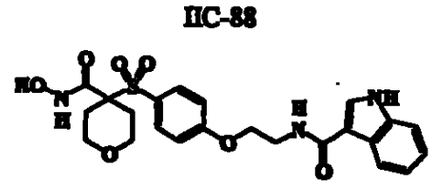
IIC-87



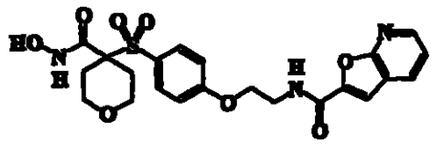
IIC-88



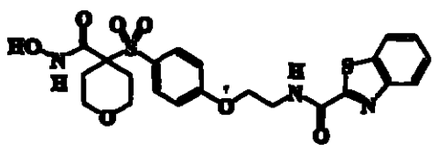
IIC-89



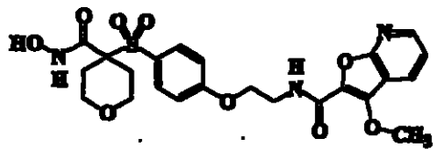
IIC-90



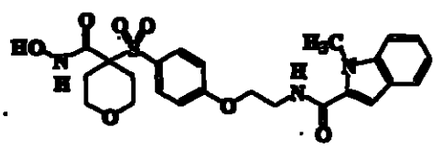
IIC-91



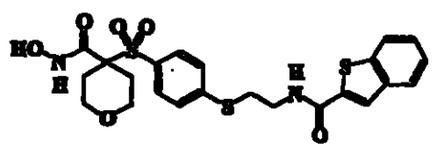
IIC-92



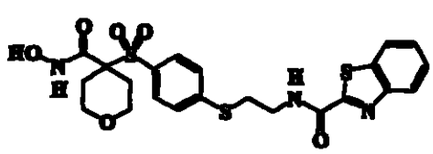
IIC-93



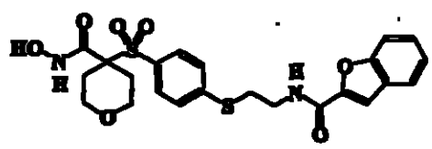
IIC-94



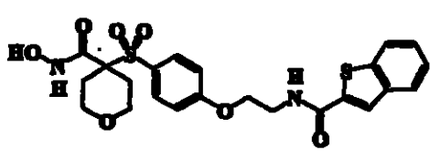
IIC-95



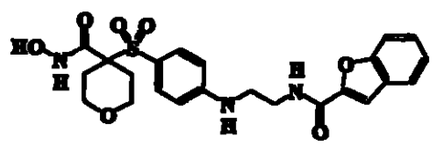
IIC-96



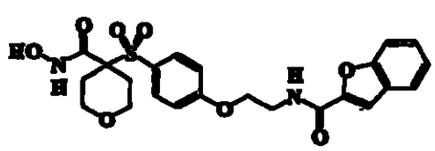
IIC-97



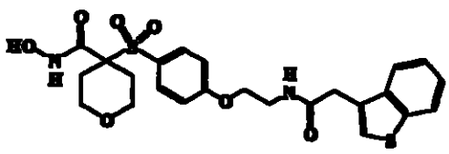
IIC-98



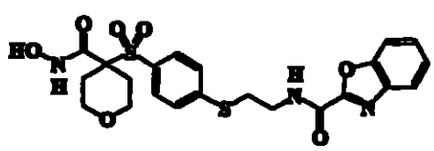
IIC-99



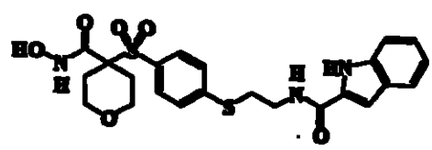
IIC-100



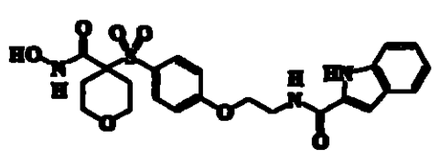
IIC-101



IIC-102



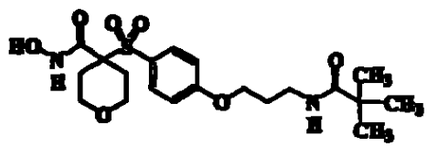
IIC-103



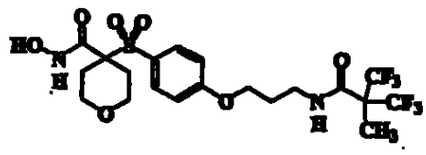
IIC-104

[131] In some preferred embodiments, E^5 is -OH, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkoxy, or C_1-C_6-alkoxy-C_1-C_6-alkyl. Except where the member is

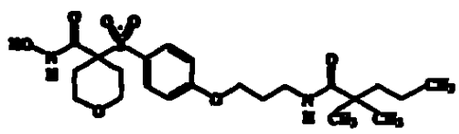
-OH, any member of this group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, and -CN. Such compounds include, for example:



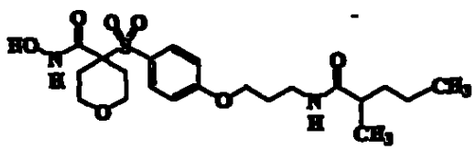
IIC-105



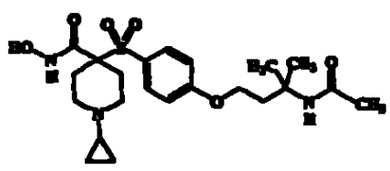
IIC-106



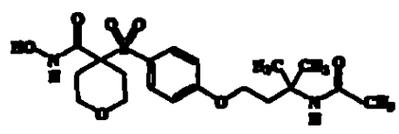
IIC-107



IIC-108



IIC-109



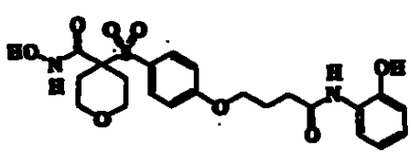
IIC-110

Preferred Embodiment No. 1-d: E^3 is -C(O)-N(R^4)-

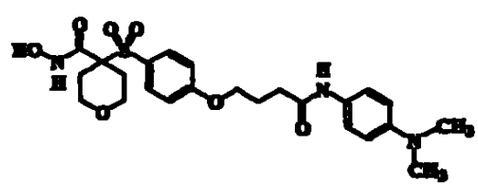
[132] In some embodiments, E^3 is -C(O)-N(R^4)-.

[133] In some such embodiments, for example, E^5 is optionally-substituted carbocyclyl, often preferably optionally-substituted aryl.

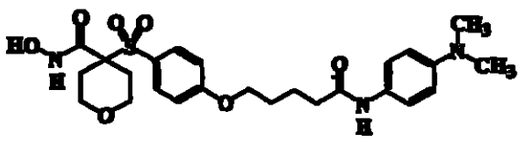
[134] In some preferred embodiments, E^5 is optionally-substituted phenyl. Such compounds include, for example:



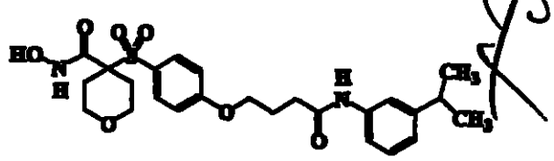
IID-1



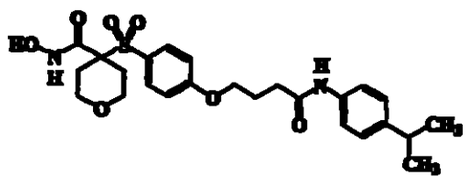
IID-2



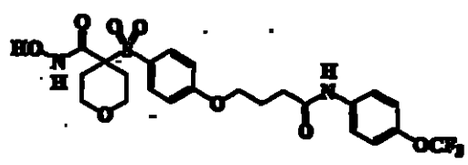
IID-3



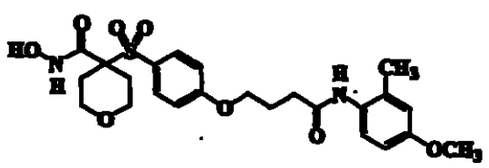
IID-4



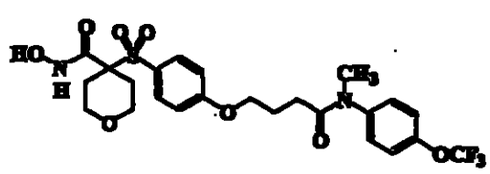
IID-5



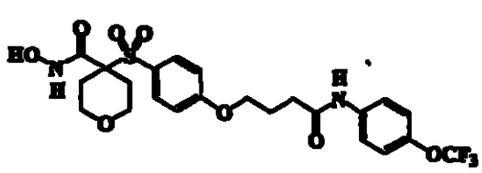
IID-6



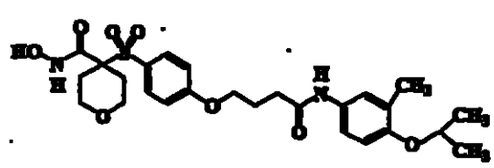
IID-7



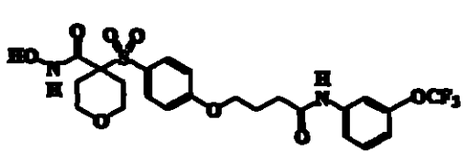
IID-8



IID-9

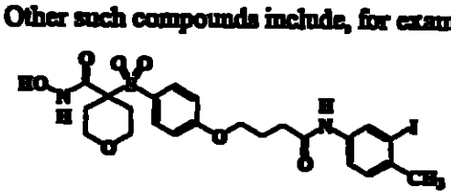


IID-10

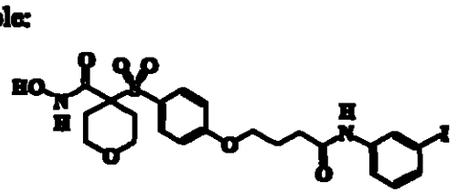


IID-11

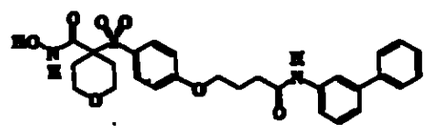
Other such compounds include, for example:



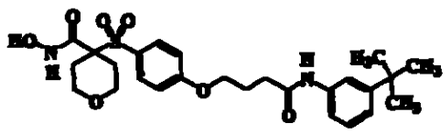
IID-12



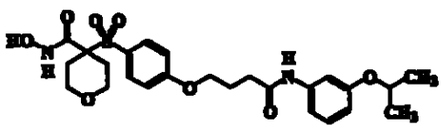
IID-13



IID-14

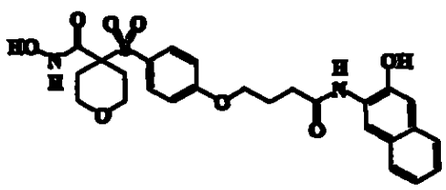


IID-15



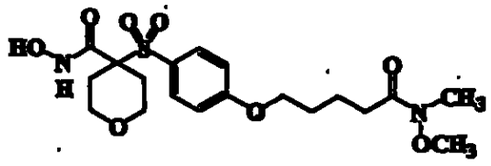
IID-16

[135] In some preferred embodiments, E^5 is optionally-substituted naphthalenyl. These compounds include, for example:



IID-17

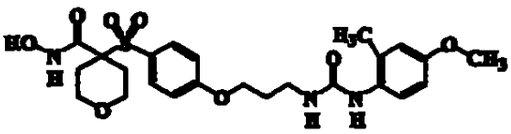
[136] In some preferred embodiments, E^5 is -OH, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkoxy, or C_1-C_6-alkoxy-C_1-C_6-alkyl. Except where the member is -OH, any member of this group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, and -CN. Such compounds include, for example:



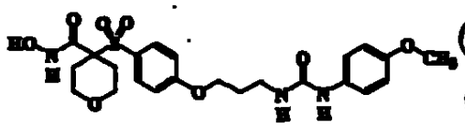
IID-18

Preferred Embodiment No. 1-e: E^3 is $-N(R^4)-C(O)-N(R^5)-$

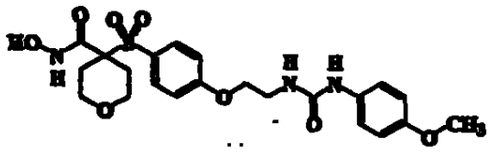
[137] In some embodiments, E^3 is $-N(R^4)-C(O)-N(R^5)-$. In some such embodiments, for example, E^5 is optionally-substituted carbocyclyl, often preferably optionally-substituted aryl, and more preferably optionally-substituted phenyl. Such compounds include, for example:



IIE-1



IIE-2

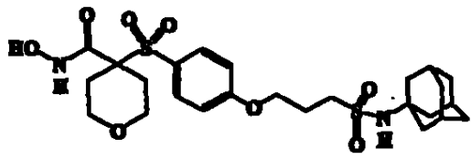


IIE-3

Preferred Embodiment No. 1-f: E^3 is $-S(O)_2-N(R^4)-$

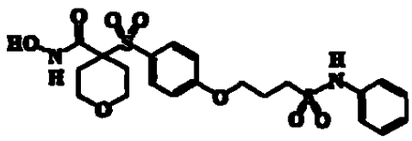
[138] In some embodiments, E^3 is $-S(O)_2-N(R^4)-$.

[139] In some such embodiments, E^5 is optionally-substituted carbocyclyl. The carbocyclyl may be, for example, cycloalkyl. Such compounds include, for example:

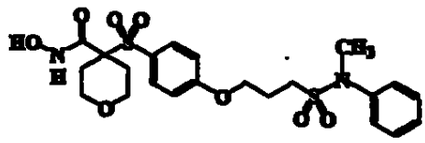


IIF-1

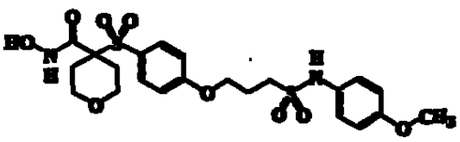
In some preferred embodiments, the carbocyclyl is aryl (preferably phenyl). Such compounds include, for example:



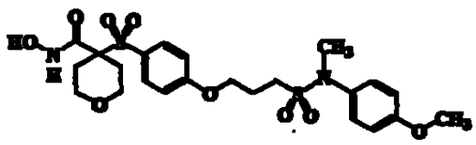
IIF-2



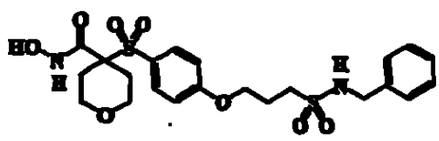
IIF-3



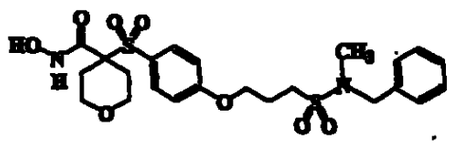
IIF-4



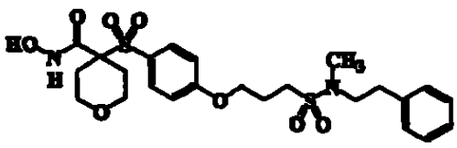
IIF-5



IIF-6

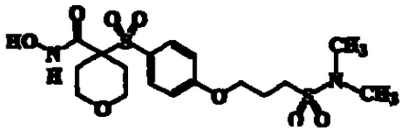


IIF-7

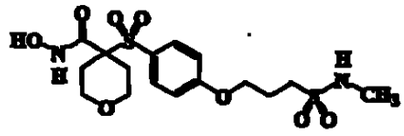


IIF-8

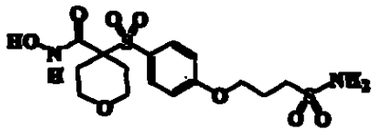
[140] In some preferred embodiments, E^3 is -H, -OH, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkoxy, or C_1-C_6-alkoxy-C_1-C_6-alkyl. Except where the member is -H or -OH, any member of this group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, and -CN. Such compounds include, for example:



IIF-9



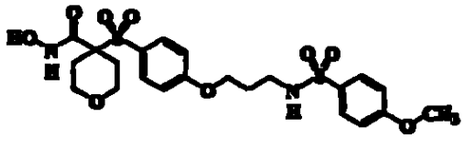
IIF-10



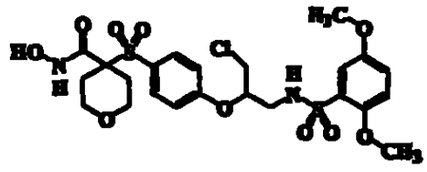
IIF-11

Preferred Embodiment No. 1-g: E^3 is $-N(R^4)-S(O)_2-$

[141] In some embodiments, E^3 is $-N(R^4)-S(O)_2-$. In some such embodiments, E^5 is optionally-substituted carbocyclyl, often preferably optionally-substituted aryl, and more preferably optionally-substituted phenyl. Such compounds include, for example:



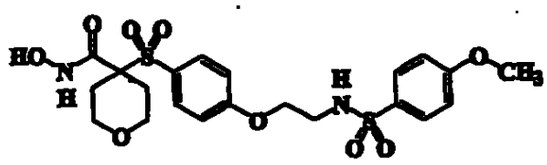
IIG-1



IIG-2

105

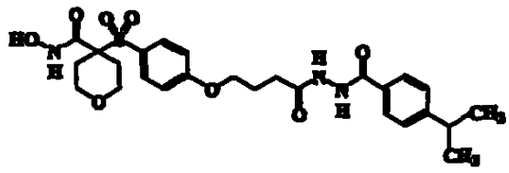
Other such compounds include, for example:



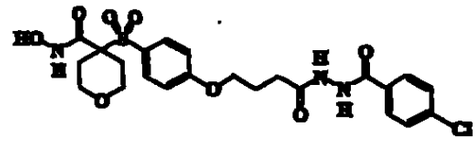
IIG-3

Preferred Embodiment No. 1-h: E^3 is -C(O)-N(R^4)-N(R^5)-C(O)-

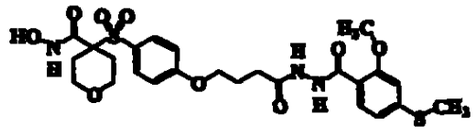
[142] In some embodiments, E^3 is -C(O)-N(R^4)-N(R^5)-C(O)-. In some such embodiments, E^5 is optionally-substituted carbocyclyl, often preferably optionally-substituted aryl, and more preferably optionally-substituted phenyl. Such compounds include, for example:



IIH-1



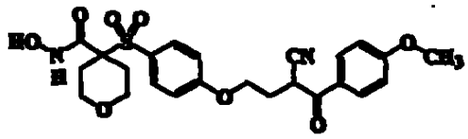
IIH-2



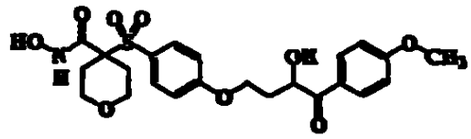
IIH-3

Preferred Embodiment No. 1-i: E^3 is -C(R^4)(R^5)-C(O)-

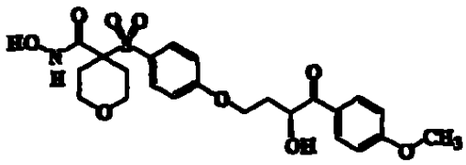
[143] In some embodiments, E^3 is -C(R^4)(R^5)-C(O)-. In some such embodiments, E^5 is optionally-substituted carbocyclyl, often preferably optionally-substituted aryl, and more preferably optionally-substituted phenyl. Such compounds include, for example:



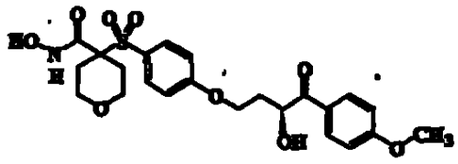
III-1



III-2



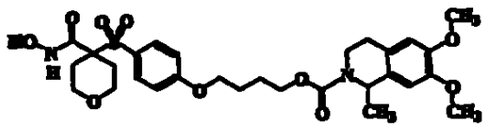
III-3



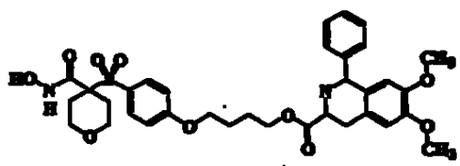
III-4

Preferred Embodiment No. 1-j: E^3 is -O-C(O)-

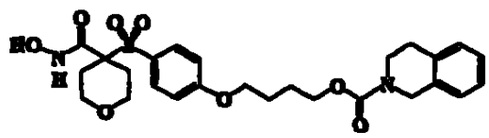
[144] In some embodiments, E^3 is *-O-C(O)-*. In some such embodiments, E^5 is optionally-substituted heterocyclyl. In some preferred embodiments, E^5 is an optionally-substituted 2-fused-ring heterocyclyl. In some embodiments, for example, E^5 is optionally-substituted tetrahydroisoquinolinyl . Such compounds include, for example:



III-1



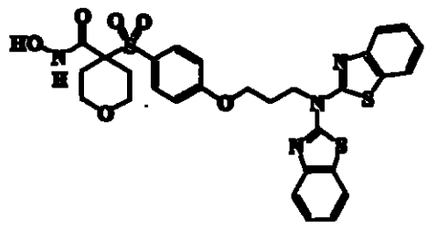
III-2



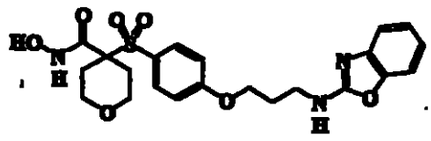
III-3

Preferred Embodiment No. 1-k: E^3 is -N(R^4)-

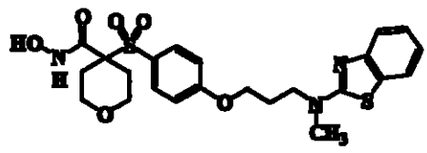
[145] In some embodiments, E^3 is *-N(R^4)-*. In some such embodiments, E^5 is optionally-substituted heterocyclyl. In some preferred embodiments, E^5 is optionally-substituted 2-fused-ring heterocyclyl. In some embodiments, for example, E^5 is optionally-substituted benzoxazolyl, benzothiazolyl, or benzimidazolyl. Such compounds include, for example:



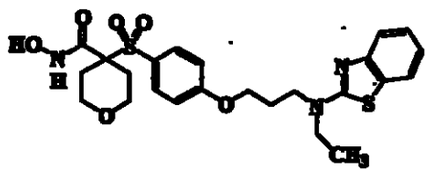
IIK-1



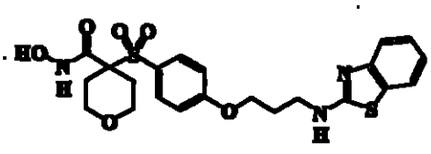
IIK-2



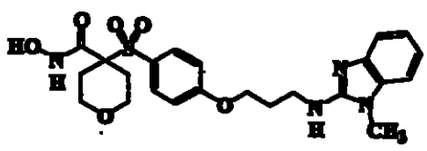
IIK-3



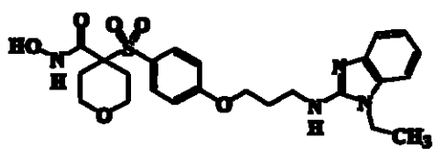
IIK-4



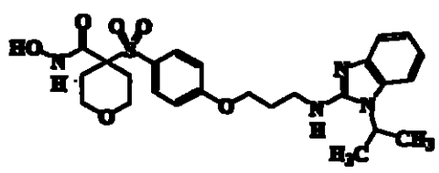
IIK-5



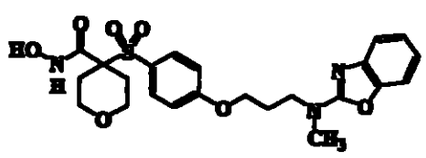
IIK-6



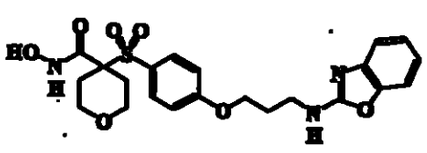
IIK-7



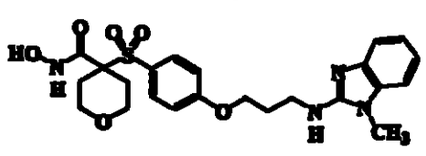
IIK-8



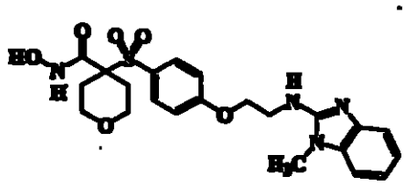
IIK-9



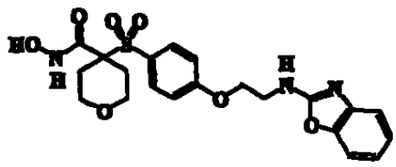
IIK-10



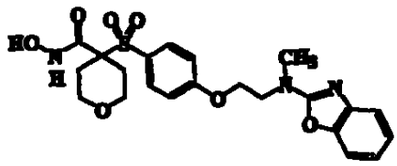
IIK-11



IIK-12



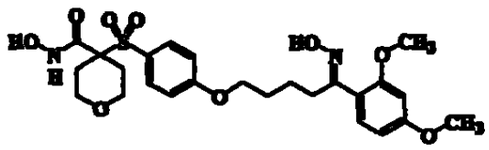
IIK-13



IIK-14

Preferred Embodiment No. 1-l: E^3 is $-C(NR^5)-$

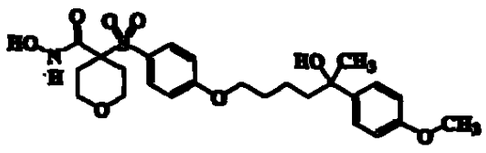
[146] In some embodiments, E^3 is $-C(NR^5)-$. In some such embodiments, E^5 is optionally-substituted carbocyclyl, often preferably optionally-substituted aryl, and more preferably optionally-substituted phenyl. Such compounds include, for example:



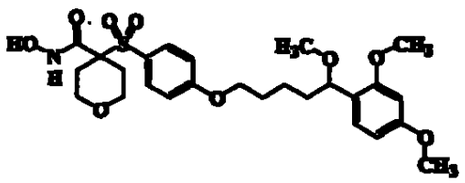
IIL-1

Preferred Embodiment No. 1-m: E^3 is $-C(R^7)(R^8)-$

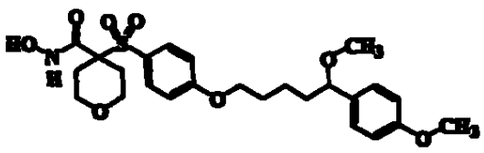
[147] In some embodiments, E^3 is $-C(R^7)(R^8)-$. In some such embodiments, E^5 is optionally-substituted carbocyclyl, often preferably optionally-substituted aryl, and more preferably optionally-substituted phenyl. Such compounds include, for example:



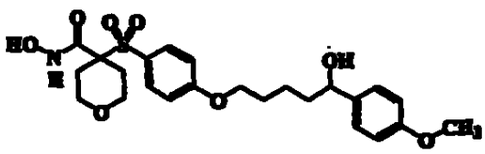
IIM-1



IIM-2



IIM-3

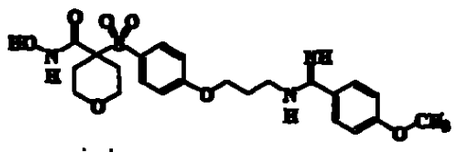


IIM-4

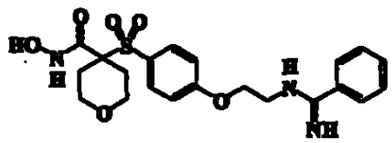
109

Preferred Embodiment No. 1-n: E^3 is $-N(R^4)-C(NR^3)-$

[148] In some embodiments, E^3 is $-N(R^4)-C(NR^3)-$. In some such embodiments, E^5 is optionally-substituted carbocyclyl, often preferably optionally-substituted aryl, and more preferably optionally-substituted phenyl. Such compounds include, for example:



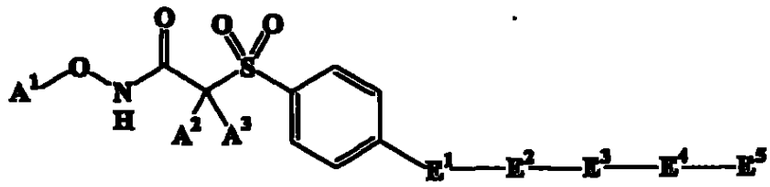
IIN-1



IIN-2

Preferred Embodiment No. 2

[149] In some embodiments of this invention, the compound has a structure corresponding to Formula III:



III

[150] A^1, A^2, and A^3 are as defined above for Formula I.

[151] E^1 is $-O-$, $-S(O)_2-$, $-S(O)-$, $-N(R^1)-$, $-C(O)-N(R^1)-$, $-N(R^1)-C(O)-$, or $-C(R^1)(R^2)-$. E^1 alternatively may be $-S-$.

[152] E^2 forms a link of at least 2 carbon atoms between E^1 and E^3. E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of this group optionally is substituted.

[153] In some preferred embodiments, E^2 is C_2-C_{20}-alkyl, cycloalkyl, C_1-C_{10}-alkylcycloalkyl, cycloalkyl-C_1-C_{10}-alkyl, or C_1-C_{10}-alkylcycloalkyl-C_1-C_{10}-alkyl. Any member of this group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, C_1-C_6-alkyl, and halo-C_1-C_6-alkyl.

[154] In some preferred embodiments, E^2 is C_2-C_6-alkyl optionally substituted with one or more halogen.

110

[155] In some preferred embodiments, E^2 is C_2-C_5-alkyl optionally substituted with one or more halogen.

[156] In some preferred embodiments, E^2 is C_2-C_5-alkyl.

[157] In some preferred embodiments, E^2 is $-(CH_2)_m-$, wherein m is from 2 to 5.

[158] E^3 is carbocyclyl or heterocyclyl. This carbocyclyl and heterocyclyl have 5 or 6 ring members and optionally are substituted.

[159] In some preferred embodiments, E^3 is carbocyclyl or heterocyclyl wherein the carbocyclyl and heterocyclyl have 5 or 6 ring members and optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, keto, C_1-C_8-alkyl, C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl. Except where the substituent is halogen, -OH, or keto, any of these substituents optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, C_1-C_8-alkyl, C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, C_1-C_8-alkylthio, halo-C_1-C_8-alkyl, halo-C_1-C_8-alkoxy, halo-C_1-C_8-alkylthio, and halogen-substituted C_1-C_8-alkoxy-C_1-C_8-alkyl.

[160] In some preferred embodiments, E^3 is carbocyclyl or heterocyclyl wherein the carbocyclyl and heterocyclyl have 5 or 6 ring members and optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, keto, C_1-C_8-alkyl, C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl. Except where the substituent is halogen, -OH, or keto, any substituent of this group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, C_1-C_8-alkyl, C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, C_1-C_8-alkylthio, halo-C_1-C_8-alkyl, halo-C_1-C_8-alkoxy, halogen-substituted C_1-C_8-alkoxy-C_1-C_8-alkyl, and halo-C_1-C_8-alkylthio.

[161] E^4 is a bond, alkyl, alkenyl, -O-, or $-N(R^5)-$. The alkyl and alkenyl optionally are substituted.

[162] In some preferred embodiments, E^4 is a bond, -O-, $-N(R^5)-$, C_1-C_{20}-alkyl, or C_2-C_{20}-alkenyl. The C_1-C_{20}-alkyl and C_2-C_{20}-alkenyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen and carbocyclyl optionally substituted with one or more substituents independently selected

from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halocarbocyclyl, halogen-substituted carbocyclyl-C_1-C_6-alkyl, and halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl.

[163] In some preferred embodiments, E^4 is a bond, -O-, -$N(R^3)$-, C_1-C_3-alkyl, or C_2-C_3-alkenyl. The C_1-C_3-alkyl and C_2-C_3-alkenyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen and carbocyclyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, halocarbocyclyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl.

[164] In some preferred embodiments, E^4 is a bond, -O-, -$N(R^3)$-, C_1-C_3-alkyl, or C_2-C_3-alkenyl.

[165] In some preferred embodiments, E^4 is a bond.

[166] E^5 is carbocyclyl or heterocyclyl. The carbocyclyl and heterocyclyl optionally are substituted. In some preferred embodiments, the carbocyclyl and heterocyclyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, keto, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^6)(R^7)$, -$C(O)(R^8)$, -S-R^6, -$S(O)_2$-R^6, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, halocarbocyclyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl. The carbocyclyl and heterocyclyl also optionally are substituted with one or more substituents independently selected from the group consisting of C_2-C_6-alkenyl and C_2-C_6-alkynyl.

[167] In some preferred embodiments, E^5 is pyridinyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^6)(R^7)$, -$C(O)(R^8)$, -S-R^6, -$S(O)_2$-R^6, phenyl, phenyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, halophenyl, and halogen-substituted phenyl-C_1-C_6-alkyl. The pyridinyl also is optionally substituted with

one or more substituents independently selected from the group consisting of C_2-C_6-alkenyl and C_2-C_6-alkynyl.

[168] In some preferred embodiments, E^5 is piperidinyl, piperazinyl, imidazolyl, furanyl, thienyl, pyrimidyl, benzodioxolyl, benzodioxanyl, benzofuryl, or benzothienyl. Such substituent optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^6)(R^7)$, -$C(O)(R^8)$, -S-R^6, -$S(O)_2$-R^6, phenyl, phenyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, halophenyl, and halogen-substituted phenyl-C_1-C_6-alkyl. Such substituent also optionally is substituted with one or more substituents independently selected from the group consisting of C_2-C_6-alkenyl and C_2-C_6-alkynyl.

[169] In some preferred embodiments, E^5 is phenyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^6)(R^7)$, -$C(O)(R^8)$, -S-R^6, -$S(O)_2$-R^6, phenyl, phenyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, halophenyl, and halogen-substituted phenyl-C_1-C_6-alkyl. The phenyl also is optionally substituted with one or more substituents independently selected from the group consisting of C_2-C_6-alkenyl and C_2-C_6-alkynyl.

[170] In some preferred embodiments, E^5 is naphthalenyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^6)(R^7)$, -$C(O)(R^8)$, -S-R^6, -$S(O)_2$-R^6, phenyl, phenyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, halophenyl, and halogen-substituted phenyl-C_1-C_6-alkyl. The naphthalenyl also is optionally substituted with one or more substituents independently selected from the group consisting of C_2-C_6-alkenyl and C_2-C_6-alkynyl.

[171] R^1 and R^2 are independently selected from the group consisting of -H and alkyl. The alkyl optionally is substituted. Neither R^1 nor R^2 forms a ring structure with E^2, E^3, E^4, or E^5.

[172] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_6-alkyl, and halo-C_1-C_6-alkyl.

[173] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_6-alkyl, and halo-C_1-C_6-alkyl.

[174] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H and C_1-C_6-alkyl.

[175] R^3 is -H or alkyl. The alkyl optionally is substituted.

[176] In some preferred embodiments, R^3 is -H, C_1-C_6-alkyl, or halo-C_1-C_6-alkyl.

[177] In some preferred embodiments, R^3 is -H, C_1-C_6-alkyl, or halo-C_1-C_6-alkyl.

[178] In some preferred embodiments, R^3 is -H or C_1-C_6-alkyl.

[179] R^6 and R^7 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, heterocyclyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halocarbocyclyl, halogen-substituted carbocyclyl-C_1-C_6-alkyl, haloheterocyclyl, and halogen-substituted heterocyclyl-C_1-C_6-alkyl.

[180] In some preferred embodiments, R^6 and R^7 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[181] R^8 is -H, C_1-C_8-alkyl, -O-R^9, -N(R^9)(R^{10}), carbocyclyl-C_1-C_6-alkyl, heterocyclyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halogen-substituted carbocyclyl-C_1-C_6-alkyl, or halogen-substituted heterocyclyl-C_1-C_6-alkyl.

[182] In some preferred embodiments, R^8 is -H, C_1-C_6-alkyl, -O-R^9, -N(R^9)(R^{10}), carbocyclyl-C_1-C_6-alkyl, heterocyclyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halogen-substituted carbocyclyl-C_1-C_6-alkyl, or halogen-substituted heterocyclyl-C_1-C_6-alkyl.

[183] In some preferred embodiments, R^8 is -H, C_1-C_6-alkyl, -O-R^9, -N(R^9)(R^{10}), carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl.

[184] R^9 and R^{10} are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, heterocyclyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halocarbocyclyl, halogen-substituted carbocyclyl-C_1-C_6-alkyl, haloheterocyclyl, and halogen-substituted heterocyclyl-C_1-C_6-alkyl.

[185] In some preferred embodiments, R^9 and R^{10} are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, heterocyclyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halocarbocyclyl,

halogen-substituted carbocyclyl-C_1-C_6-alkyl, haloheterocyclyl, and halogen-substituted heterocyclyl-C_1-C_6-alkyl.

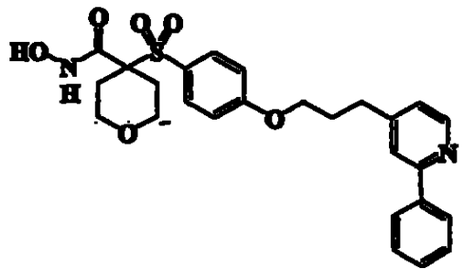
[186] In some preferred embodiments, R^9 and R^{10} are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, and heterocyclyl, heterocyclyl-C_1-C_6-alkyl.

Preferred Embodiment No. 2-a: E^3 is optionally-substituted heterocyclyl

[187] In some embodiments, E^3 is optionally-substituted heterocyclyl.

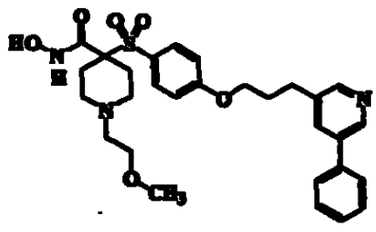
[188] In some preferred embodiments E^3 is an optionally-substituted heterocyclyl that contains only one heteroatom ring member. Examples of often suitable heterocyclyls include furanyl, tetrahydropyranyl, dihydrofuranyl, tetrahydrofuranyl, thiophenyl, dihydrothiophenyl, tetrahydrothiophenyl, pyrrolinyl, pyrrolyl, isopyrrolyl, pyrrolidinyl, pyridinyl, piperidinyl, pyranyl, dihydropyranyl, and tetrahydropyranyl.

[189] In some preferred embodiments, E^3 is optionally-substituted pyridinyl. In some such embodiments, E^3 is optionally-substituted phenyl. Such compounds include, for example:

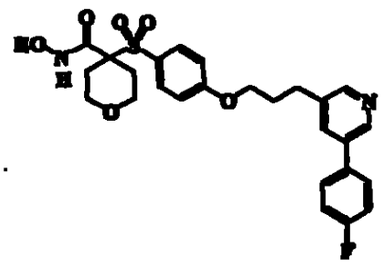


IIIA-1

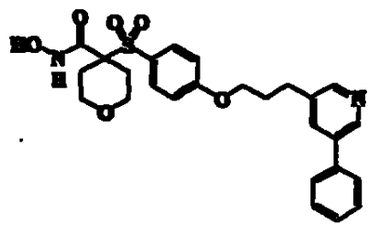
Such compounds also include, for example:



IIIA-2

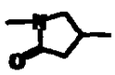


IIIA-3

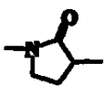


IIIA-4

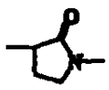
[190] In some preferred embodiments, E^3 is an optionally-substituted heterocyclyl selected from the group consisting of:



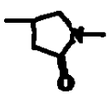
E-1



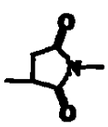
E-2



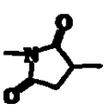
E-3



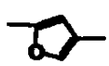
E-4



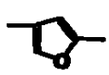
E-5



E-6



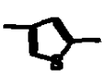
E-7



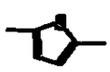
E-8



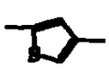
E-9



E-10



E-11



E-12



E-13



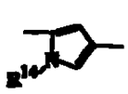
E-14



E-15



E-16



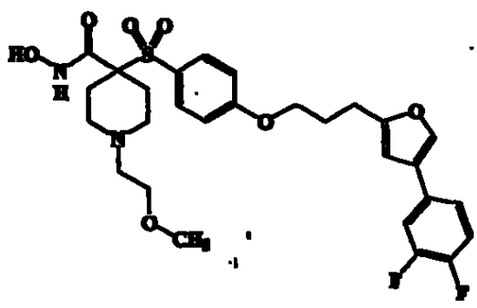
E-17

Any member of this group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the substituent is halogen or -OH, any substituent of this group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, C_1-C_6-alkylthio, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, and

116

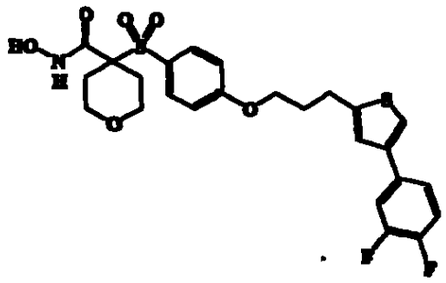
halo-C_1-C_6-alkylthio. R^{14} is selected from the group consisting of halogen, -OH, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is halogen or -OH, any member of this group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, C_1-C_6-alkylthio, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, and halo-C_1-C_6-alkylthio.

[191] In some preferred embodiments, E^3 is optionally-substituted furanyl. In one such embodiment, for example, E^3 is optionally-substituted phenyl. Such compounds include, for example:

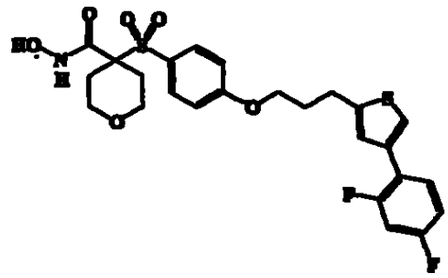


IIIA-5

[192] In some preferred embodiments, E^3 is optionally-substituted thienyl. In some such embodiments, E^3 is optionally-substituted phenyl. Such compounds include, for example:

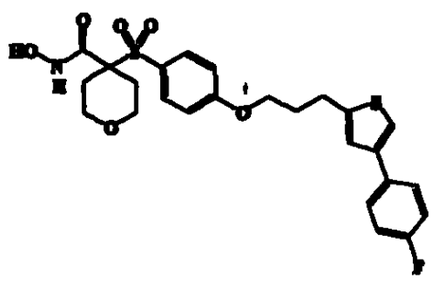


IIIA-6

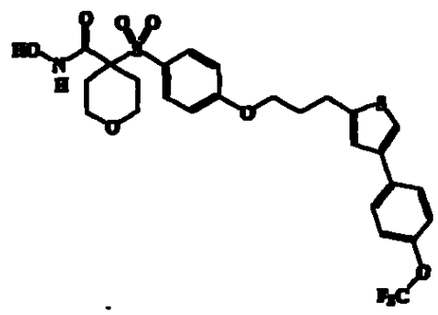


IIIA-7

117

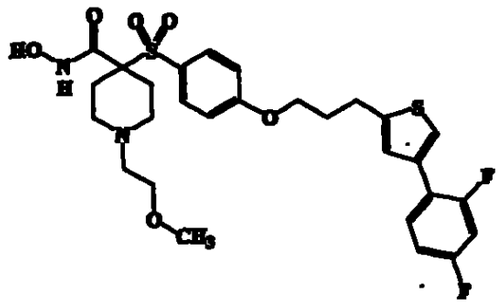


IIIA-8



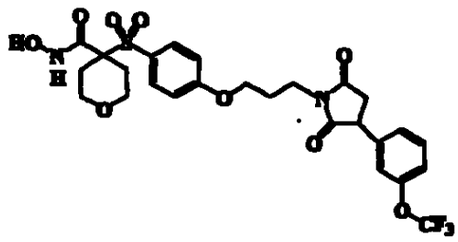
IIIA-9

Such compounds also include, for example:

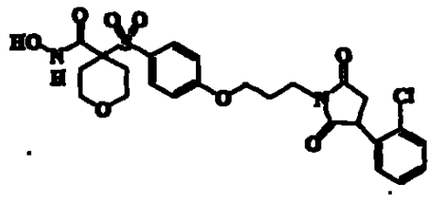


IIIA-10

[193] In some preferred embodiments, E^3 is optionally-substituted pyrrolidinyl. In some such embodiments, for example, E^3 is optionally-substituted phenyl. Such compounds include, for example:



IIIA-11

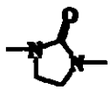


IIIA-12

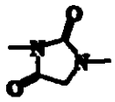
[194] E^3 also may be, for example, an optionally-substituted heterocyclyl that contains no greater and no less than two heteroatom ring members. Suitable heterocyclyls include, for example, pyrazolyl, pyrazolinyl, pyrazolidinyl, imidazolyl, isoimidazolyl, imidazolinyl, imidazolidinyl, dithiolyl, thiazolyl, isothiazolyl, thiazolinyl, isothiazolinyl, thiazolidinyl, isothiazolidinyl, oxathiolyl, oxathiolanyl, oxazolyl, isoxazolyl, oxazolidinyl,

isoxazolidinyl, pyrazinyl, piperazinyl, pyrimidinyl, pyridazinyl, oxazinyl, and morpholinyl.

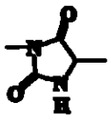
[195] In some preferred embodiments, B^3 is an optionally-substituted heterocyclyl selected from the group consisting of:

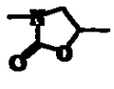

E-18

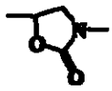

E-19

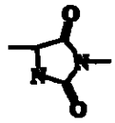

E-20


E-21


E-22


E-23


E-24


E-25


E-1


E-1


E-1

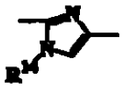

E-1


E-26


E-27


E-28


E-29


E-30


E-31

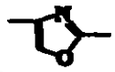

E-32


E-33

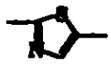

E-34

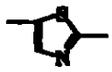

E-35

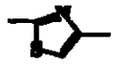

E-36

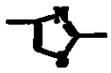

E-37


E-38


E-39


E-40

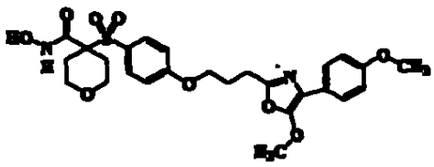

E-41


E-42

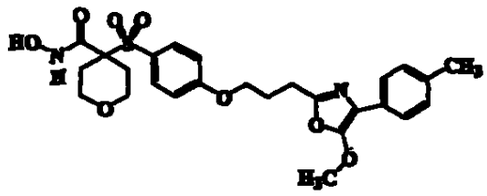
Any member of this group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, C_1-C_6-alkyl,

C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the substituent is halogen or -OH, any substituent of this group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, C_1-C_6-alkylthio, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, and halo-C_1-C_6-alkylthio. Such substituents also optionally are substituted with one or more substituents independently selected from the group consisting of C_2-C_6-alkenyl and C_2-C_6-alkynyl. R^{14} is as defined above where E^3 contains only one heteroatom in its ring.

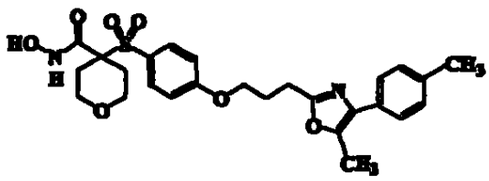
[196] In some particularly preferred embodiments, E^3 is an optionally-substituted heterocyclyl selected from the group consisting of oxazolyl and isoxazolyl. In some such embodiment, for example, E^5 is optionally-substituted carbocyclyl, often preferably optionally-substituted aryl, and more preferably optionally-substituted phenyl. Such compounds include, for example:



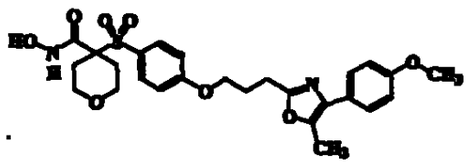
IIIA-13



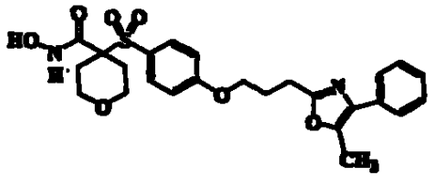
IIIA-14



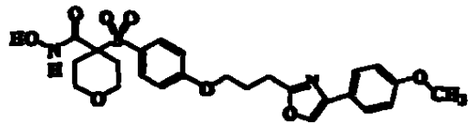
IIIA-15



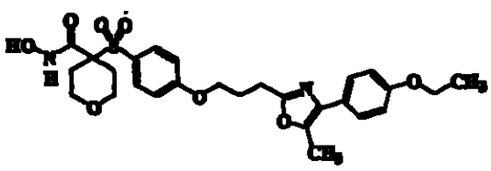
IIIA-16



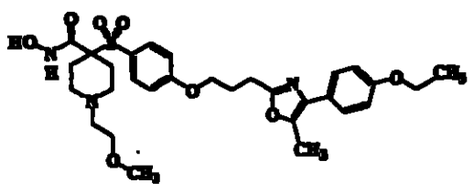
IIIA-17



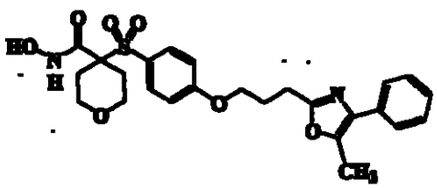
IIIA-18



IIIA-19

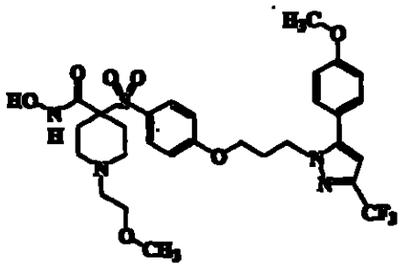


IIIA-20

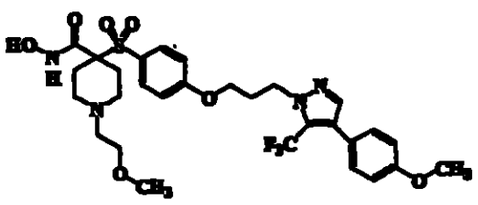


IIIA-21

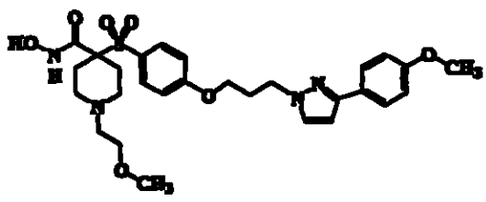
[197] In some preferred embodiments, E^3 is an optionally-substituted heteroaryl selected from the group consisting of pyrazolyl and isoimidazolyl. In some such embodiments, E^5 is optionally-substituted carbocyclyl, often preferably optionally-substituted aryl, and more preferably optionally-substituted phenyl. Such compounds include, for example:



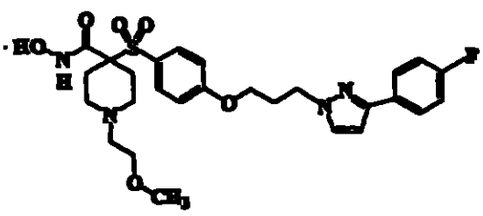
IIIA-22



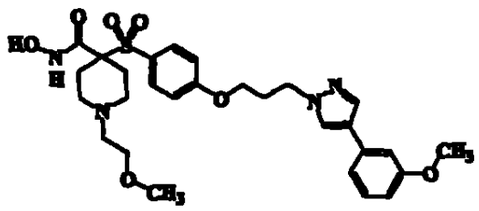
IIIA-23



IIIA-24

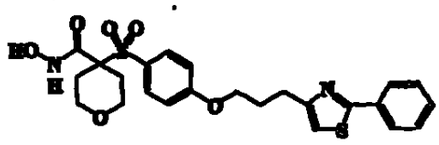


IIIA-25



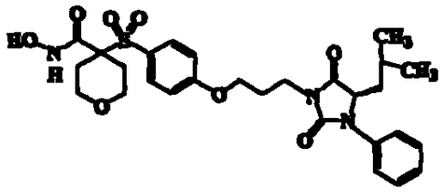
IIIA-26

[198] In some preferred embodiments, E^3 is an optionally-substituted heteroaryl selected from the group consisting of thiazolyl and isothiazolyl. In one such embodiment, for example, E^5 is optionally-substituted carbocyclyl, often preferably optionally-substituted aryl, and more preferably optionally-substituted phenyl. Such compounds include, for example:

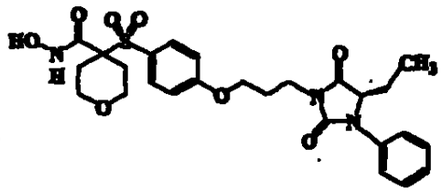


IIIA-27

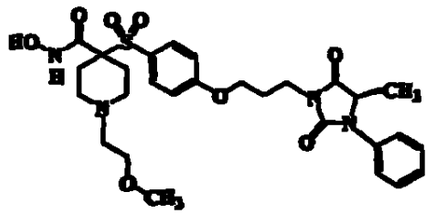
[199] In some preferred embodiments, E^3 is an optionally-substituted heteroaryl selected from the group consisting of pyrazolidinyl and imidazolidinyl. In some such embodiments, E^5 is optionally-substituted carbocyclyl. In some preferred embodiments, E^5 is optionally-substituted aryl, often preferably optionally-substituted phenyl. Such compounds include, for example:



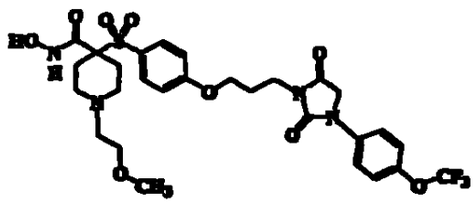
IIIA-28



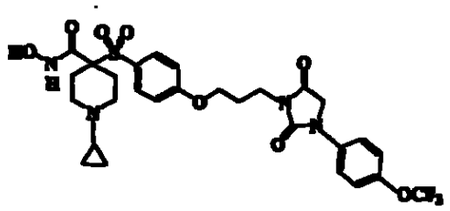
IIIA-29



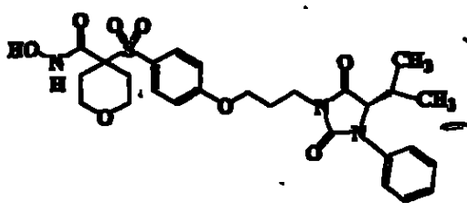
IIIA-30



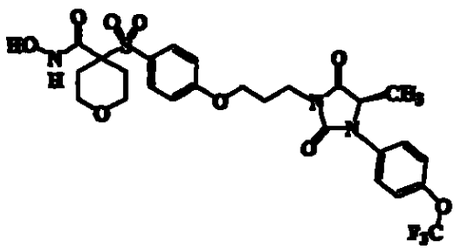
IIIA-31



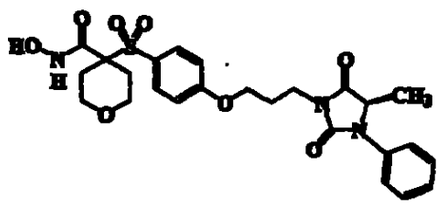
IIIA-32



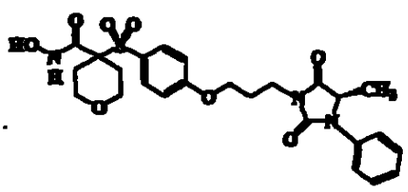
IIIA-33



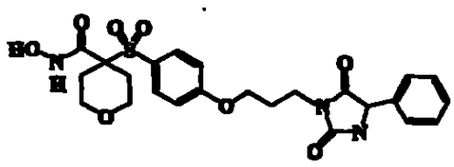
IIIA-34



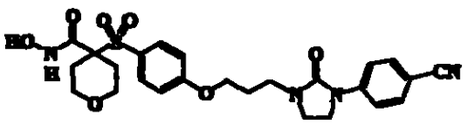
IIIA-35



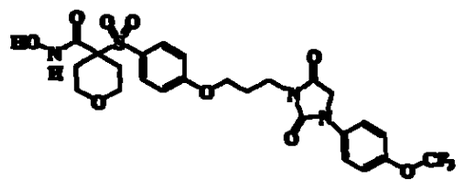
IIIA-36



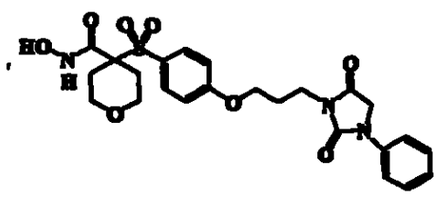
IIIA-37



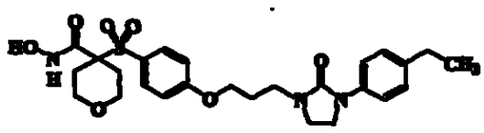
IIIA-38



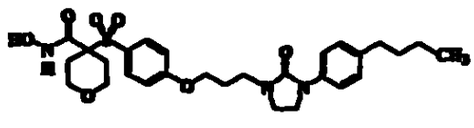
IIIA-39



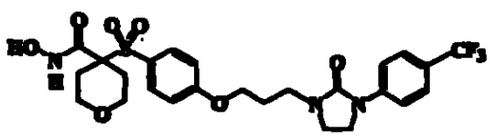
IIIA-40



IIIA-41

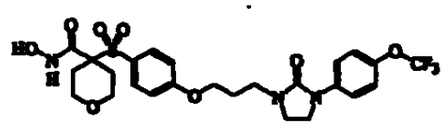


IIIA-42

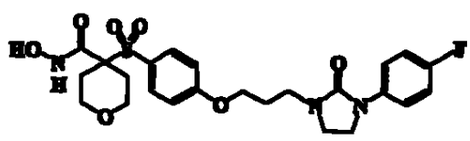


IIIA-43

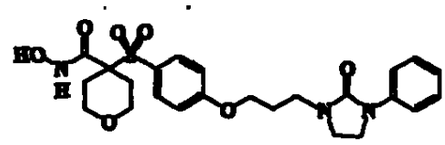
123



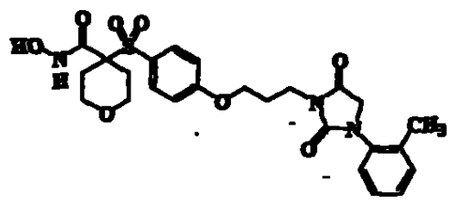
IIIA-44



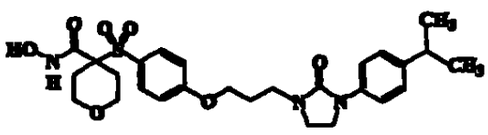
IIIA-45



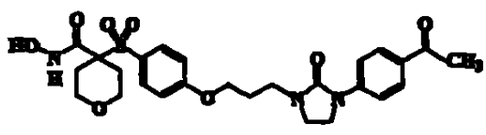
IIIA-46



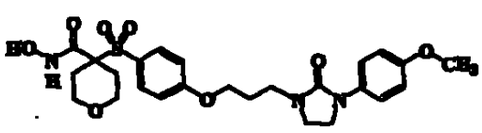
IIIA-47



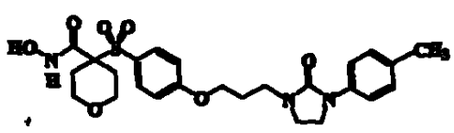
IIIA-48



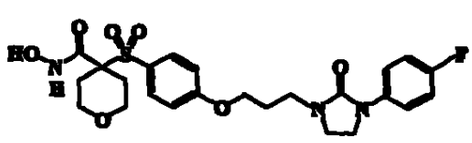
IIIA-49



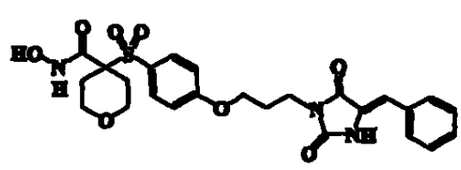
IIIA-50



IIIA-51

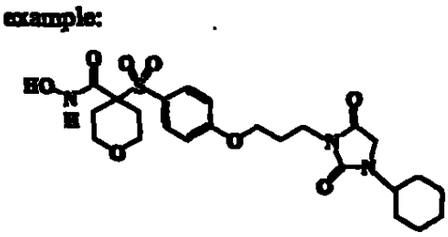


IIIA-52



IIIA-53

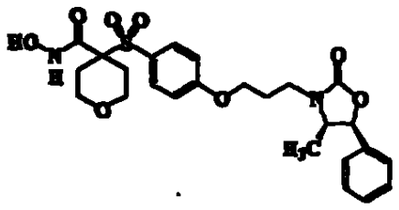
In other preferred embodiments, E^5 is optionally substituted C_3-C_6-cycloalkyl. Such compounds include, for example:



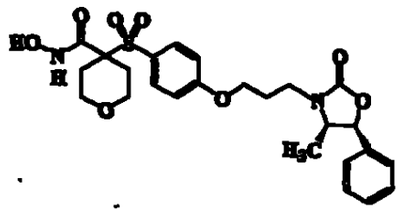
IIIA-54

[288] In some preferred embodiments, E^5 is optionally-substituted oxazolidinyl. In some such embodiments, E^5 is optionally-substituted carbocyclyl, often preferably

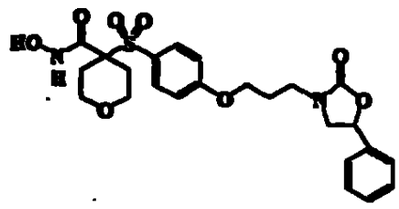
optionally-substituted aryl, and more preferably optionally-substituted phenyl. Such compounds include, for example:



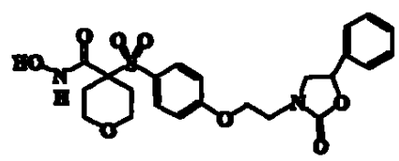
IIIA-55



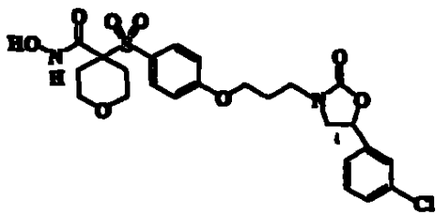
IIIA-56



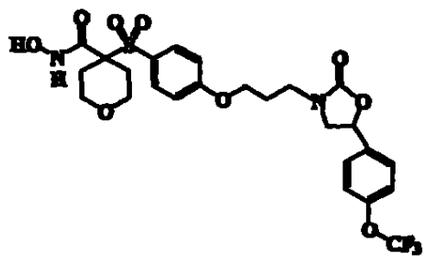
IIIA-57



IIIA-58



IIIA-59



IIIA-60

[201] E^3 also may be, for example, an optionally-substituted heterocyclyl that contains no greater and no less than 3 heterostom ring members. Often suitable heterocyclyls include, for example, oxadiazolyl, thiadiazolyl, and triazolyl. Here, the triazolyl optionally is substituted.

[202] In some preferred embodiments, E^3 is an optionally-substituted heteroaryl selected from the group consisting of:



E-43



E-44



E-45



E-46



E-47



E-48



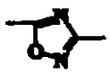
E-49



E-50



E-51



E-52



E-53



E-54

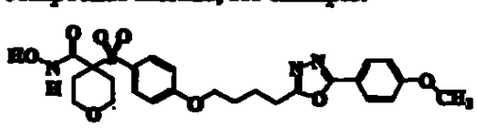


E-55

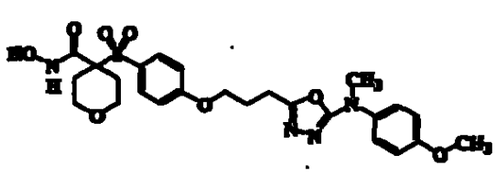
Any member of this group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the substituent is halogen or -OH, any substituent of this group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, C_1-C_6-alkylthio, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, and halo-C_1-C_6-alkylthio. R^{14} is as defined above for heterocyclyls containing 1 or 2 heteroatom ring members.

[283] In some preferred embodiments, E^3 is oxadiazolyl.

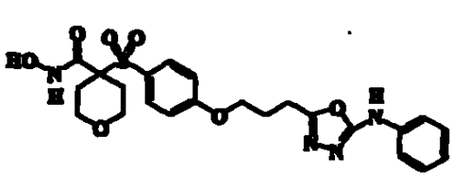
[284] In some such embodiments, E^3 is optionally-substituted phenyl. Such compounds include, for example:



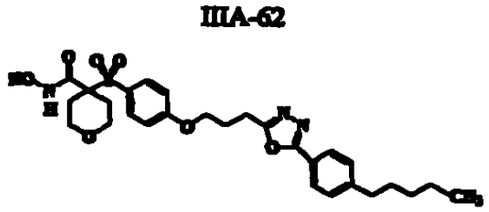
IIIA-61



IIIA-62

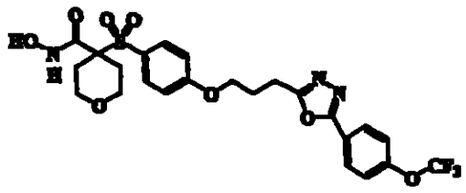


IIIA-63

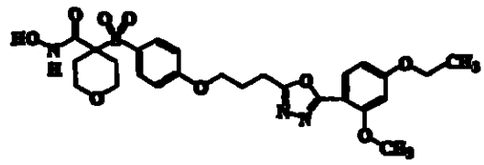


IIIA-64

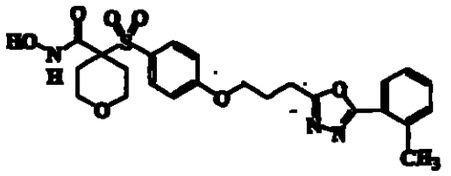
126



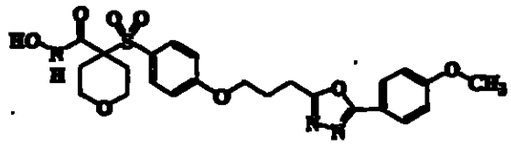
IIIA-65



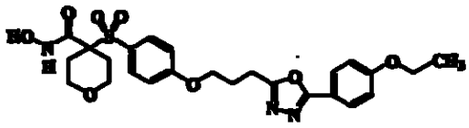
IIIA-66



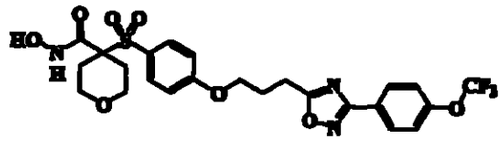
IIIA-67



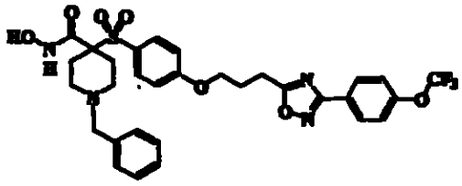
IIIA-68



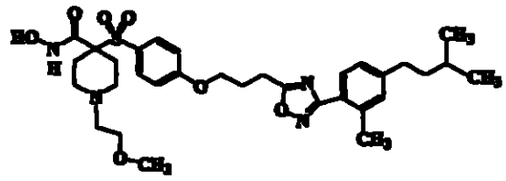
IIIA-69



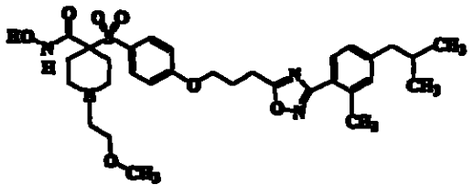
IIIA-70



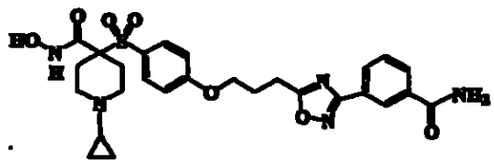
IIIA-71



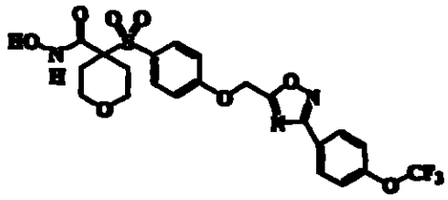
IIIA-72



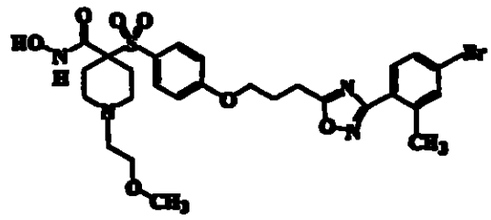
IIIA-73



IIIA-74

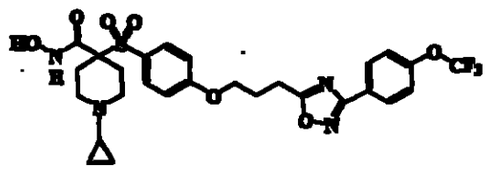


IIIA-75

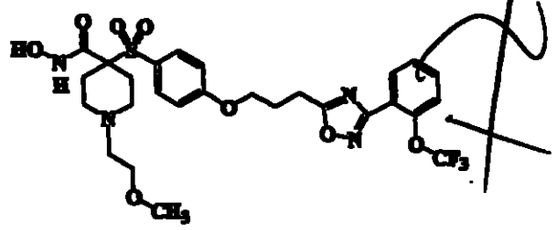


IIIA-76

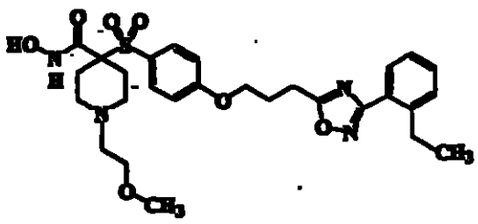
127



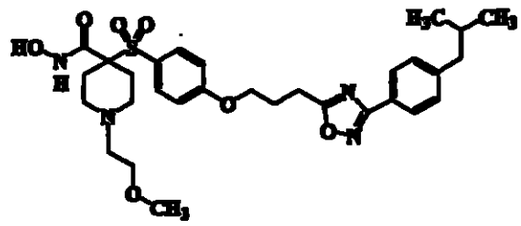
IIIA-77



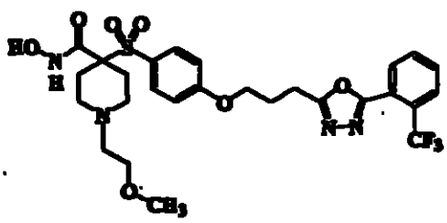
IIIA-78



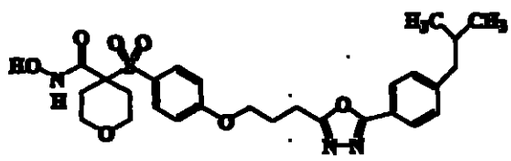
IIIA-79



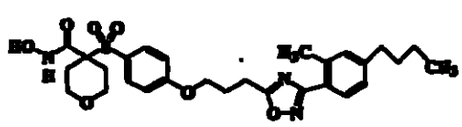
IIIA-80



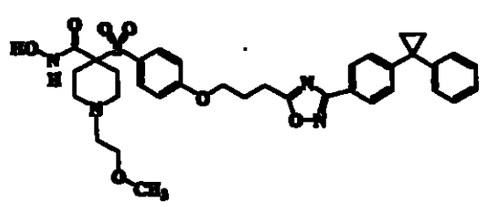
IIIA-81



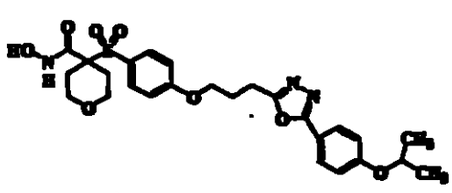
IIIA-82



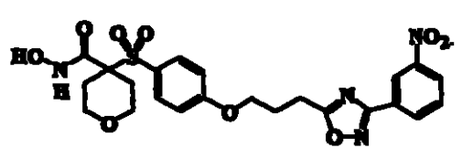
IIIA-83



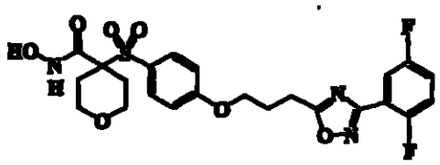
IIIA-84



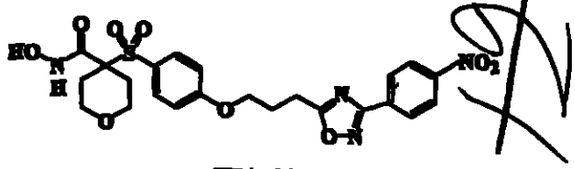
IIIA-85



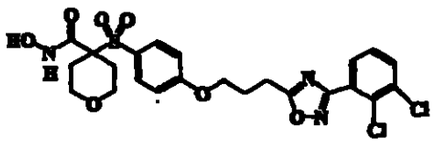
IIIA-86



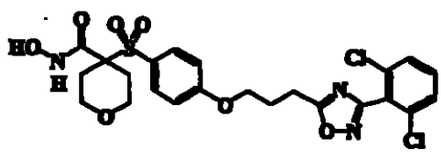
IIIA-87



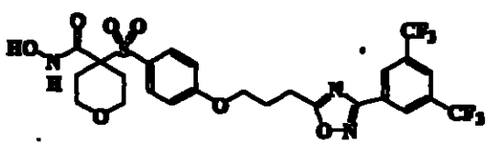
IIIA-88



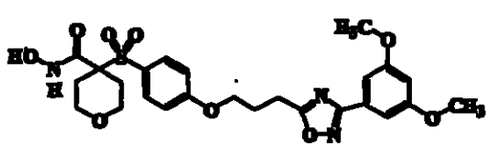
IIIA-89



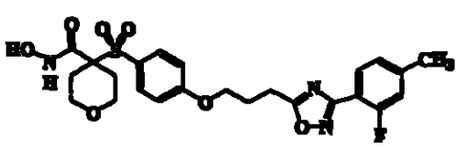
IIIA-90



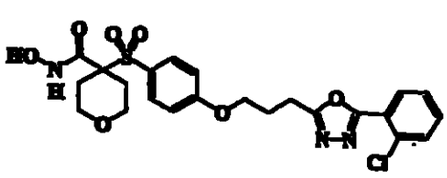
IIIA-91



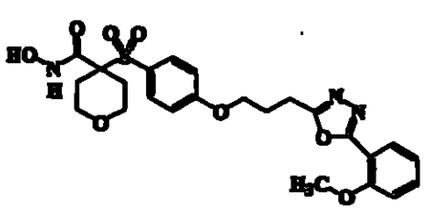
IIIA-92



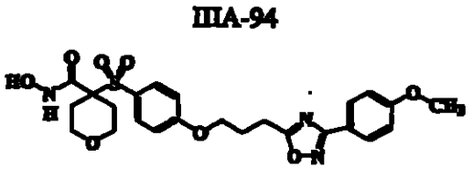
IIIA-93



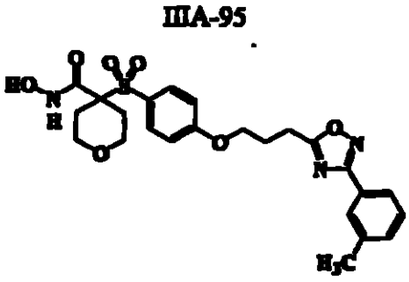
IIIA-94



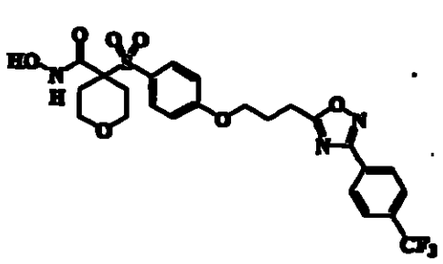
IIIA-95



IIIA-96

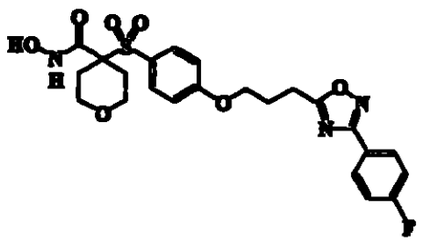


IIIA-97

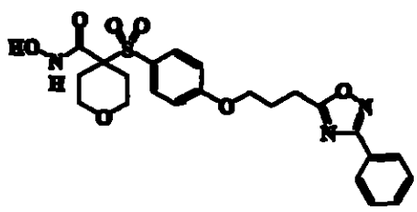


IIIA-98

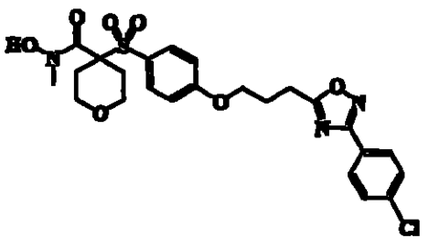
129



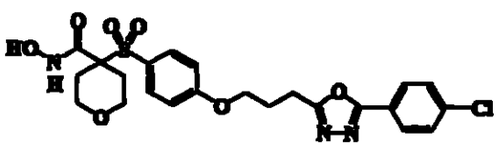
IIIA-99



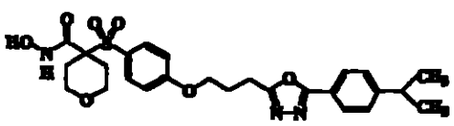
IIIA-100



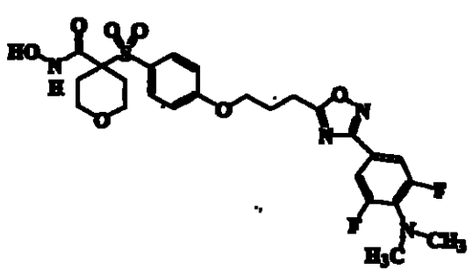
IIIA-101



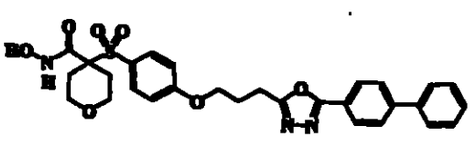
IIIA-102



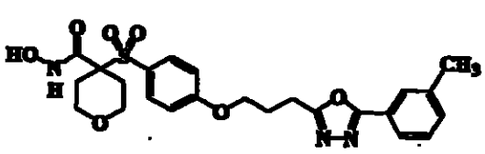
IIIA-103



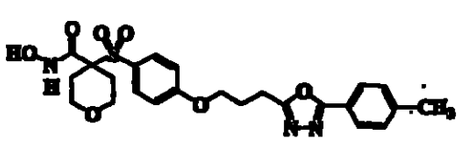
IIIA-104



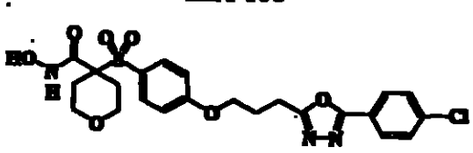
IIIA-105



IIIA-106

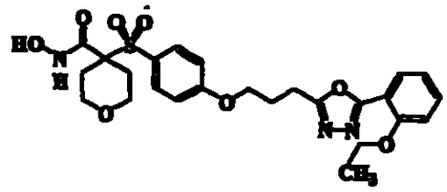


IIIA-107

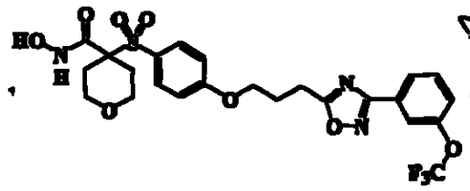


IIIA-108

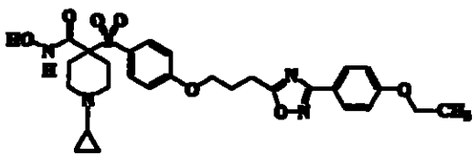
130



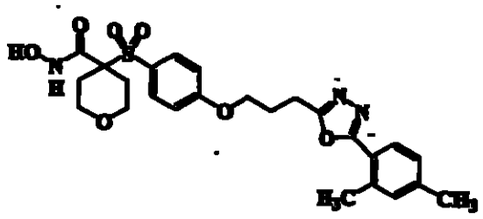
IIIA-109



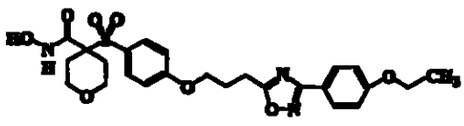
IIIA-110



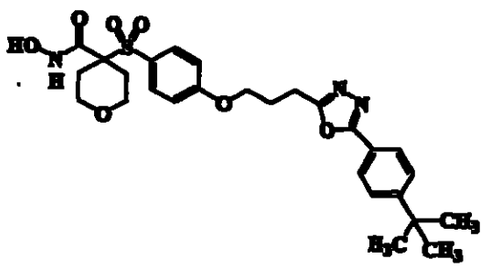
IIIA-111



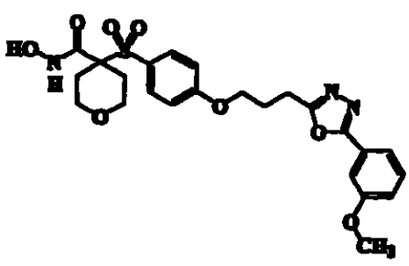
IIIA-112



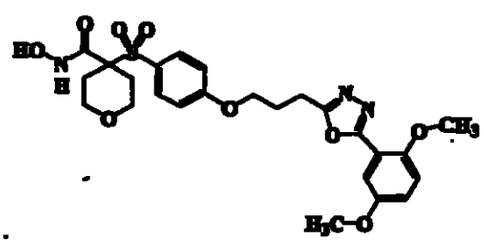
IIIA-113



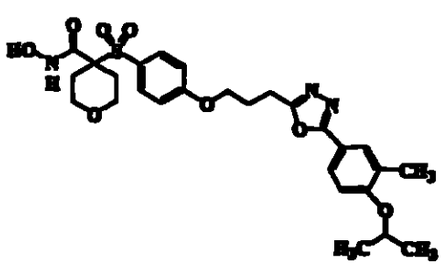
IIIA-114



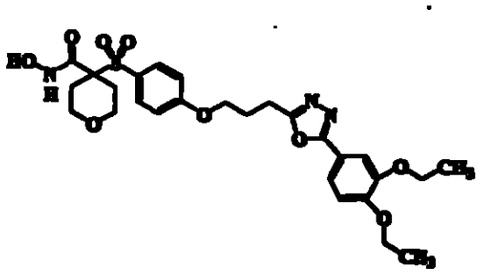
IIIA-115



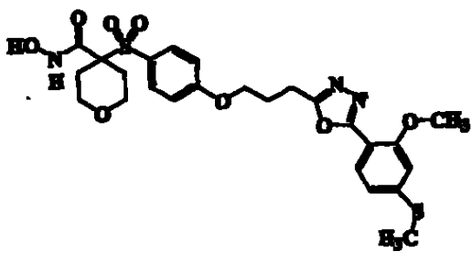
IIIA-116



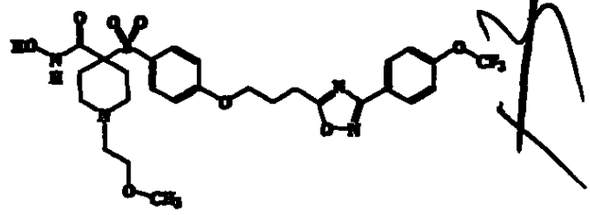
IIIA-117



IIIA-118

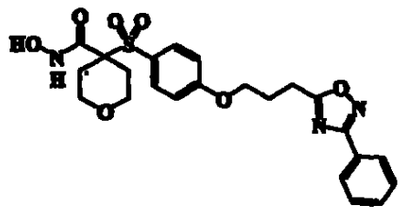


IIIA-119

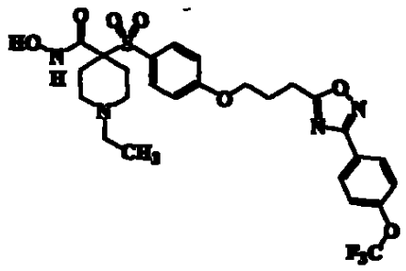


IIIA-120

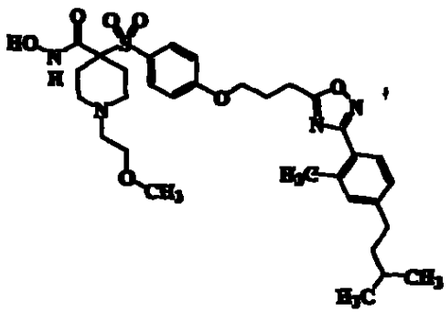
Such compounds also include, for example:



IIIA-121

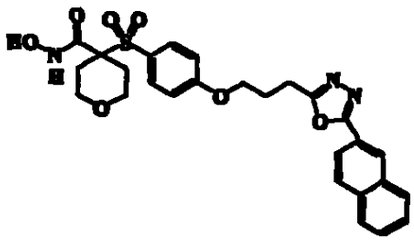


IIIA-122

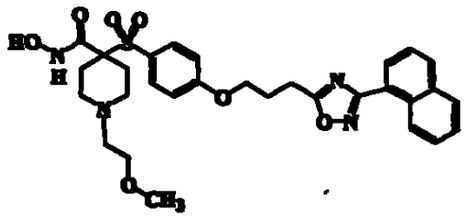


IIIA-123

[285] In other embodiments, E^5 is optionally-substituted naphthalenyl. Such compounds include, for example:



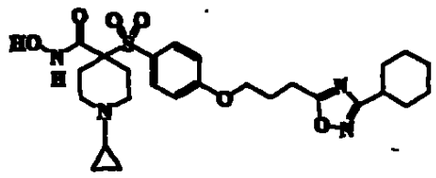
IIIA-124



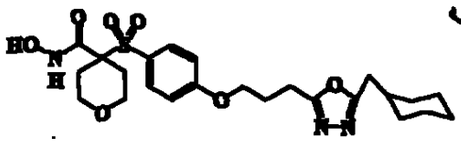
IIIA-125

132

[206] In other embodiments, E^5 is optionally-substituted C_3-C_6-cycloalkyl. Such compounds include, for example:

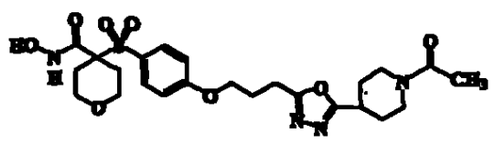


IIIA-126

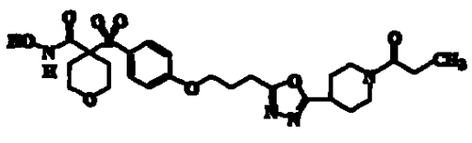


IIIA-127

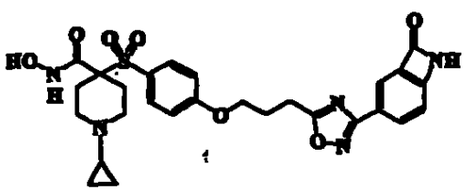
[207] In yet other embodiments, E^5 is optionally-substituted heterocyclyl. Such compounds include, for example:



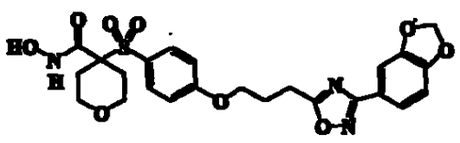
IIIA-128



IIIA-129

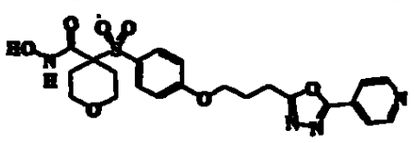


IIIA-130

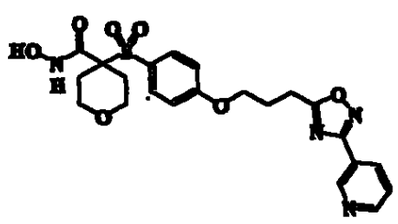


IIIA-131

Such compounds also include, for example:



IIIA-132



IIIA-133

[208] E^3 also may be, for example, an optionally-substituted heterocyclyl that contains at least 4 heteroatom ring members.

[209] In some preferred embodiments, E^3 is selected from the group consisting of:



E-56

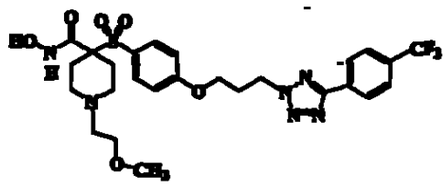


E-57

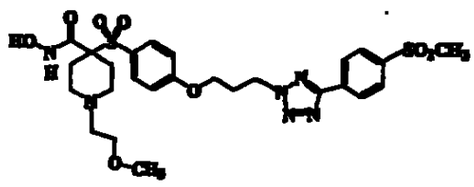


E-58

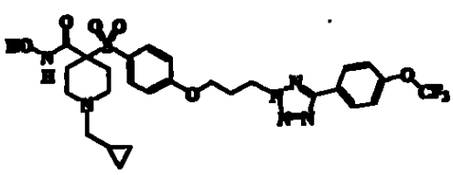
In some such embodiments, E^5 is optionally-substituted carbocyclyl, often preferably optionally-substituted aryl, and more preferably optionally-substituted phenyl. Such compounds include, for example:



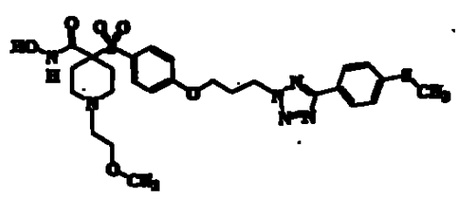
IIIA-134



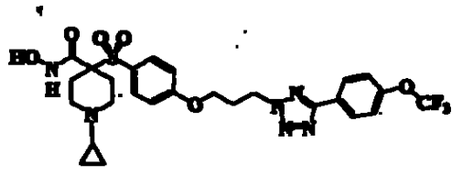
IIIA-135



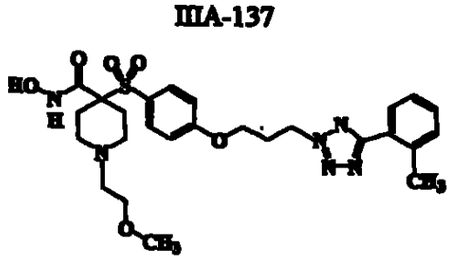
IIIA-136



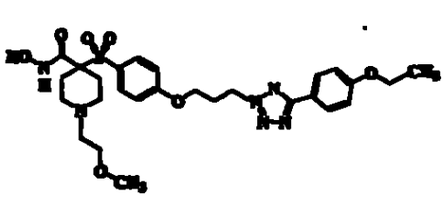
IIIA-137



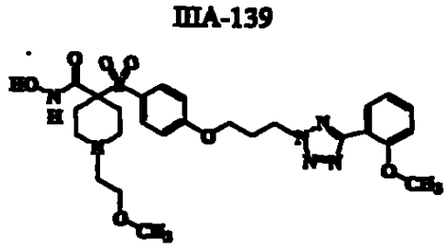
IIIA-138



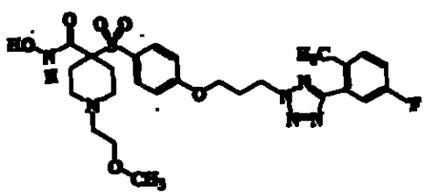
IIIA-139



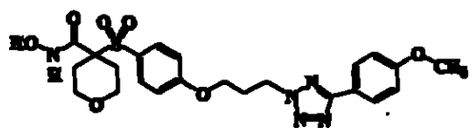
IIIA-140



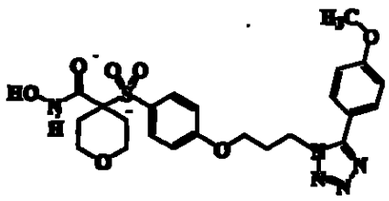
IIIA-141



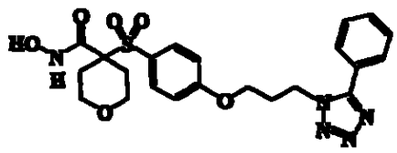
IIIA-142



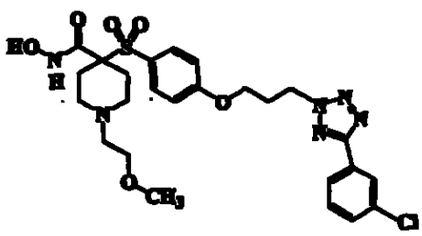
IIIA-143



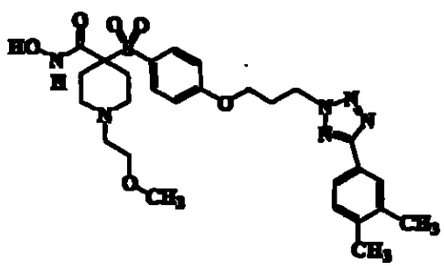
IIIA-144



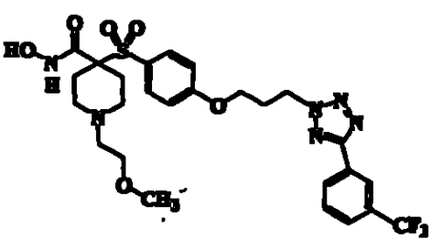
IIIA-145



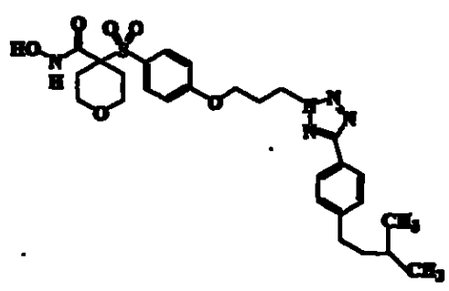
IIIA-146



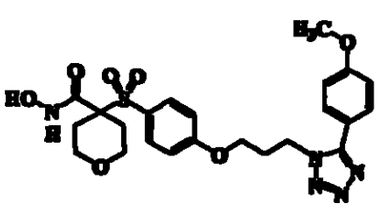
IIIA-147



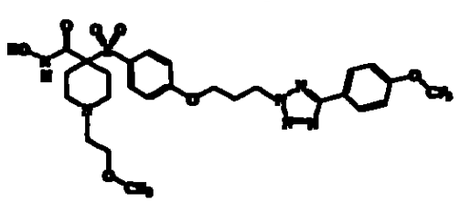
IIIA-148



IIIA-149

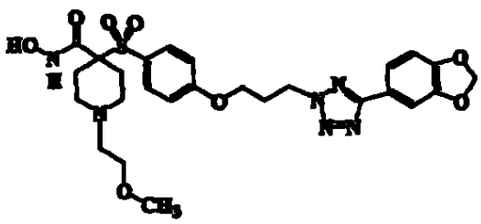


IIIA-150

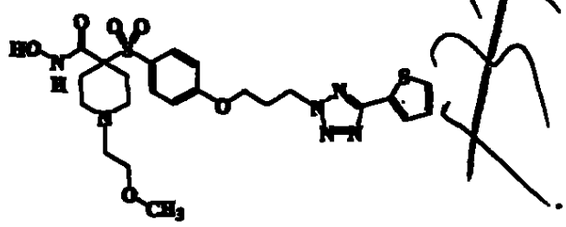


IIIA-151

In other such embodiments, E^5 is optionally-substituted heterocyclyl. Such compounds include, for example:



IIIA-152



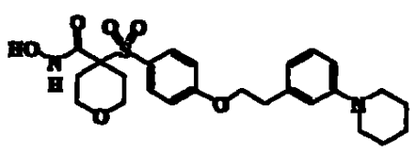
IIIA-153

Preferred Embodiment No. 2-b: E^3 is optionally substituted carbocyclyl

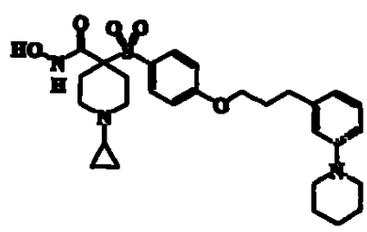
[210] In some embodiments, E^3 is an optionally-substituted carbocyclyl. E^3 may be, for example, an optionally-substituted carbocyclyl selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclopentadienyl, cyclohexyl, cyclohexenyl, cyclohexadienyl, phenyl, naphthalenyl, tetrahydronaphthalenyl, indenyl, isoindenyl, indanyl, bicyclodecanyl, anthracenyl, phenanthrene, benzonaphthenyl, fluorenenyl, decalinyl, and norpinanyl.

[211] In some preferred embodiments, E^3 is optionally-substituted phenyl. In one such embodiment, for example, E^3 is optionally-substituted heterocyclyl.

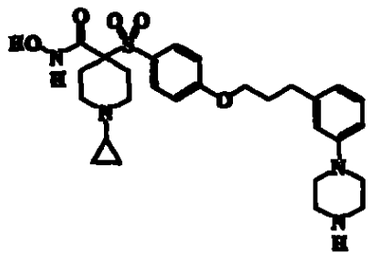
[212] In some such embodiments, E^3 is optionally-substituted heterocycloalkyl. Examples of such compounds include, for example:



IIIB-1

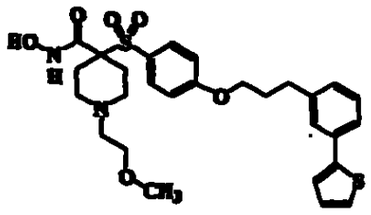


IIIB-2

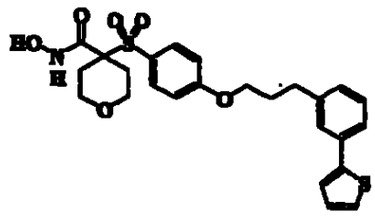


IIIB-3

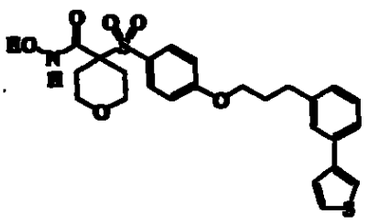
[213] In other preferred embodiments, E^5 is optionally-substituted, 5-member heteroaryl. Examples of such compounds include, for example:



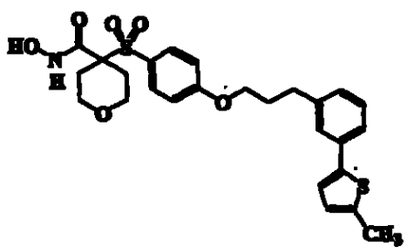
IIIB-4



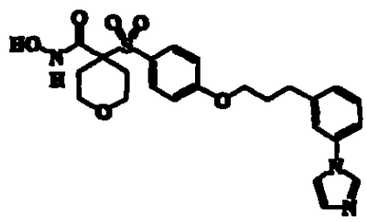
IIIB-5



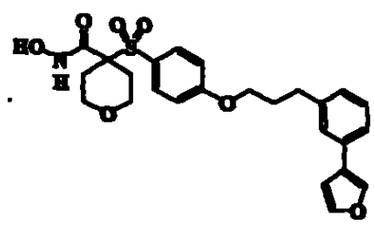
IIIB-6



IIIB-7

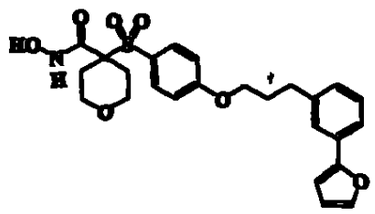


IIIB-8



IIIB-9

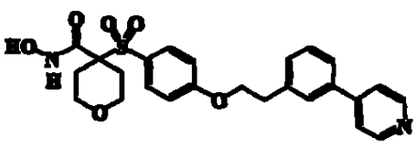
Such compounds also include, for example:



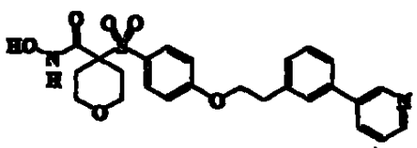
IIIB-10

[214] In other preferred embodiments, E^5 is optionally-substituted, 6-member heteroaryl.

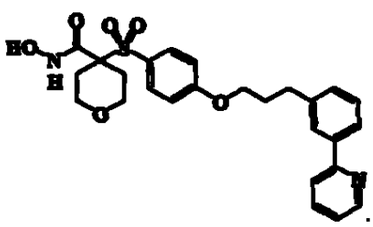
[215] In other preferred embodiments, E^5 is optionally-substituted pyridinyl. Such compounds include, for example:



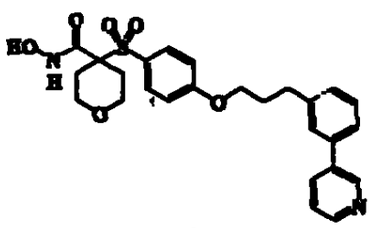
IIIB-11



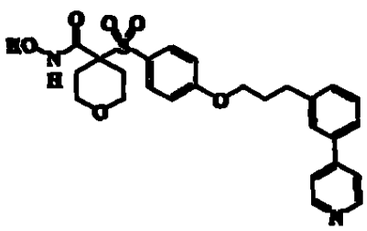
IIIB-12



IIIB-13

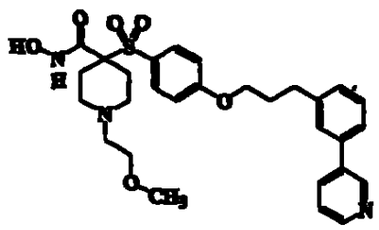


IIIB-14

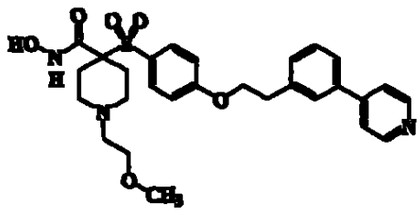


IIIB-15

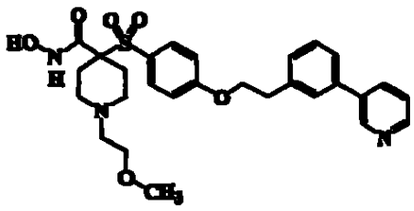
Such compounds also include, for example:



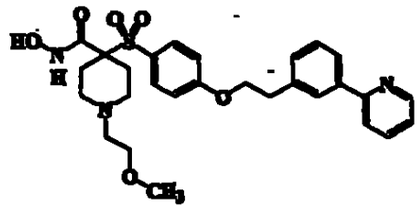
IIIB-16



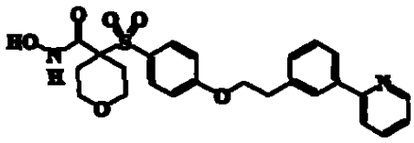
IIIB-17



IIIB-18

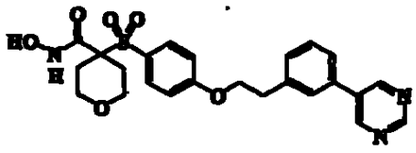


IIIB-19



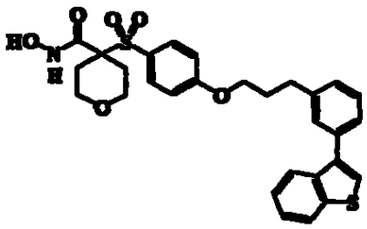
IIIB-20

[216] In other preferred embodiments, E^5 is optionally-substituted pyrimidinyl. Such compounds include, for example:

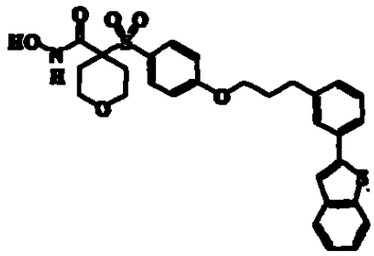


IIIB-21

[217] In other preferred embodiments, E^5 is optionally-substituted, multi-ring heterocyclyl. Such compounds include, for example:

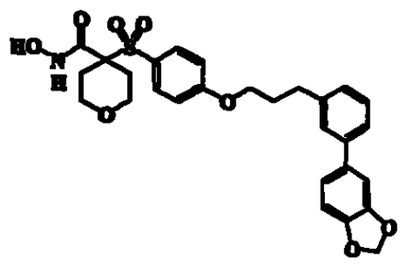


IIIB-22

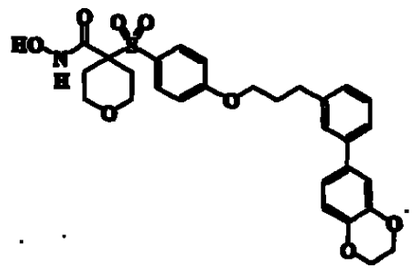


IIIB-23

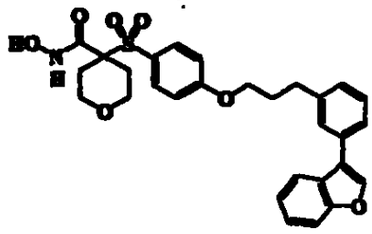
139



IIIB-24



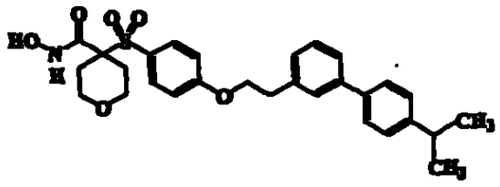
IIIB-25



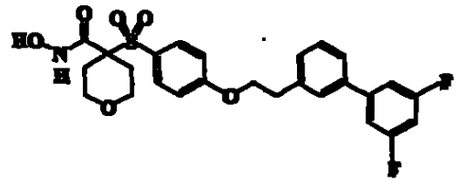
IIIB-26

[218] In some preferred embodiments, for example, E^5 is optionally-substituted carbocyclyl, often preferably optionally-substituted aryl,

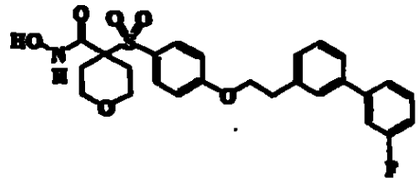
[219] In some preferred embodiments, E^5 is optionally-substituted phenyl. Such compounds include, for example:



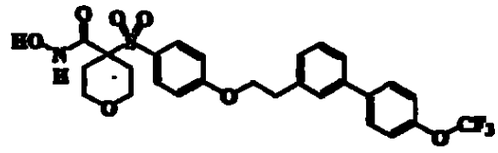
IIIB-27



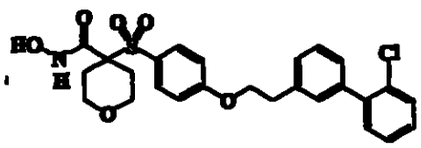
IIIB-28



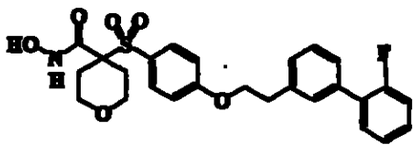
IIIB-29



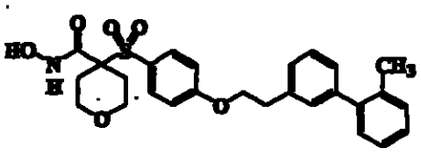
IIIB-30



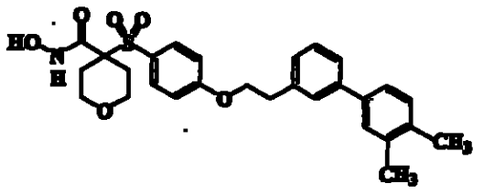
IIIB-31



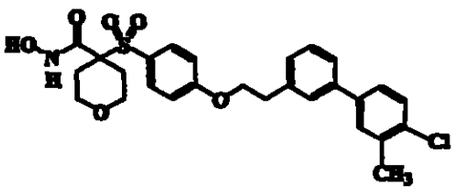
IIIB-32



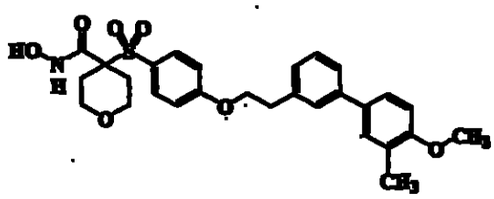
IIIB-33



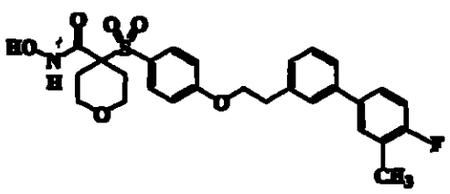
IIIB-34



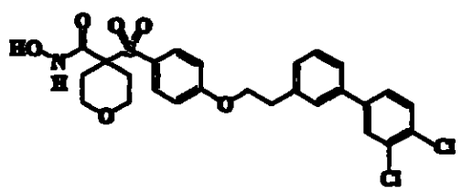
IIIB-35



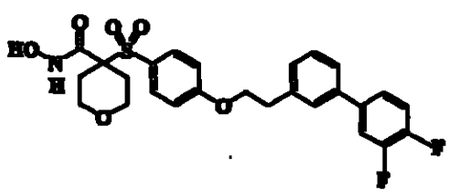
IIIB-36



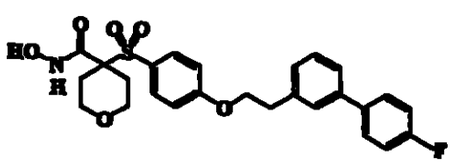
IIIB-37



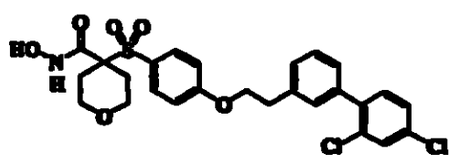
IIIB-38



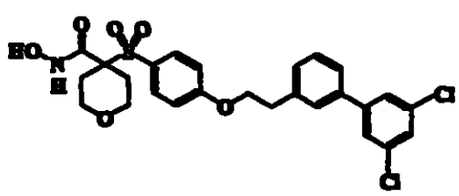
IIIB-39



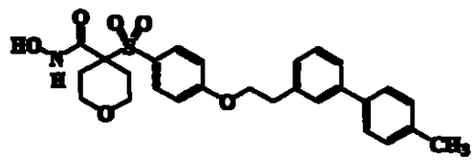
IIIB-40



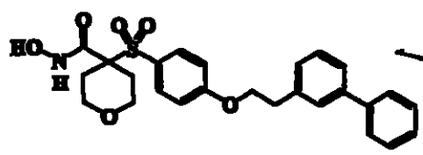
IIIB-41



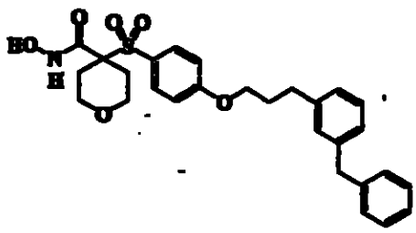
IIIB-42



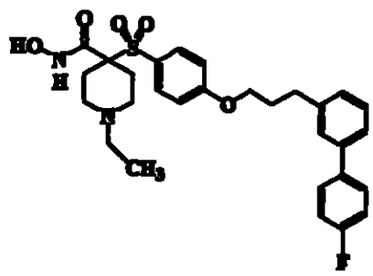
IIIB-43



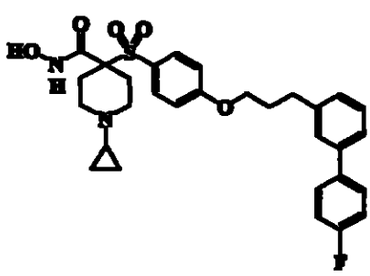
IIIB-44



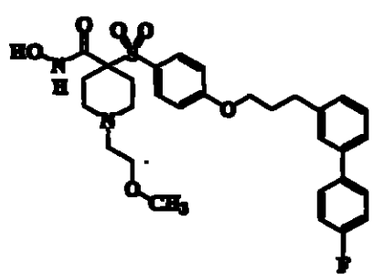
IIIB-45



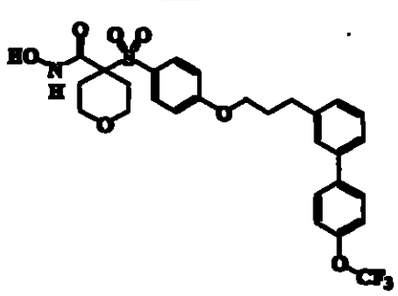
IIIB-46



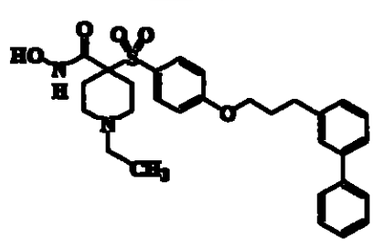
IIIB-47



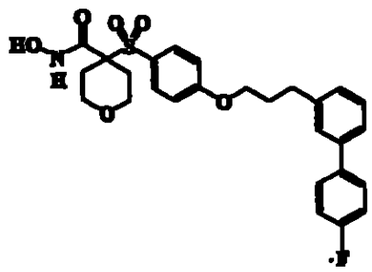
IIIB-48



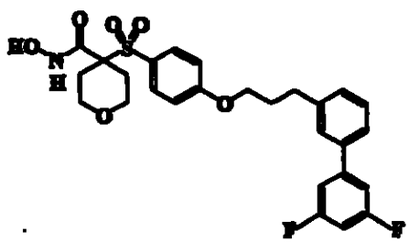
IIIB-49



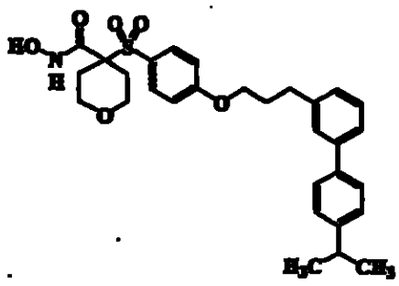
IIIB-50



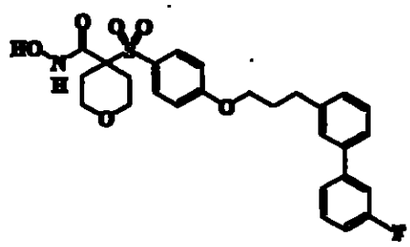
IIIB-51



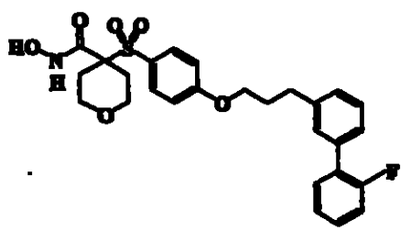
IIIB-52



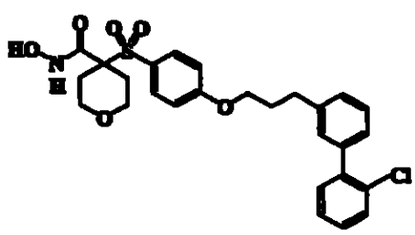
IIIB-53



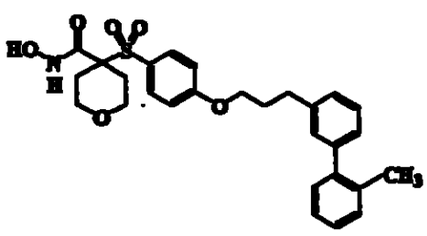
IIIB-54



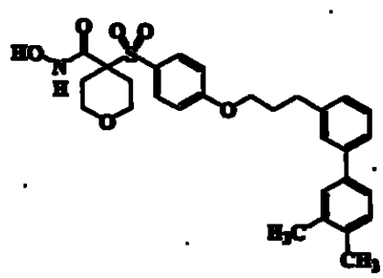
IIIB-55



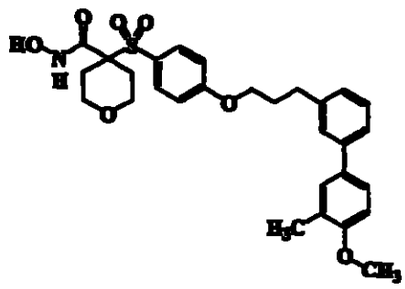
IIIB-56



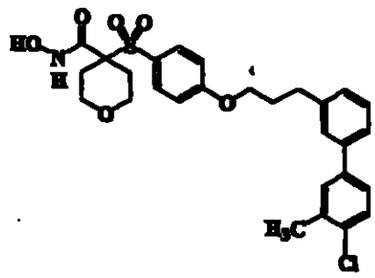
IIIB-57



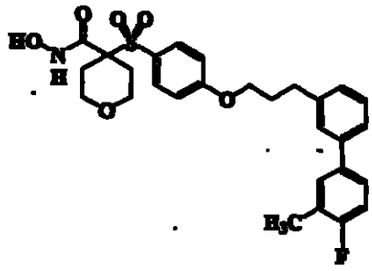
IIIB-58



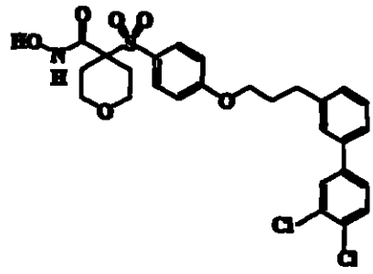
IIIB-59



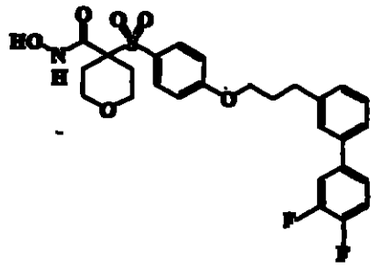
IIIB-60



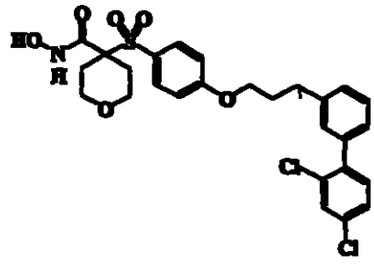
IIIB-61



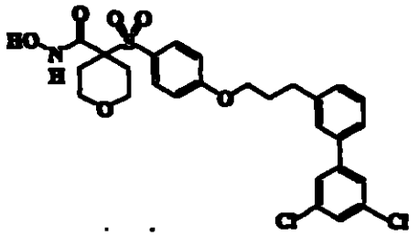
IIIB-62



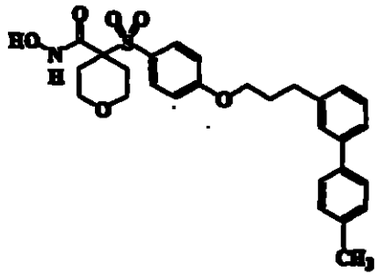
IIIB-63



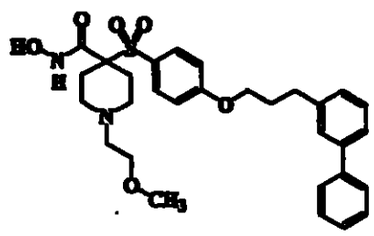
IIIB-64



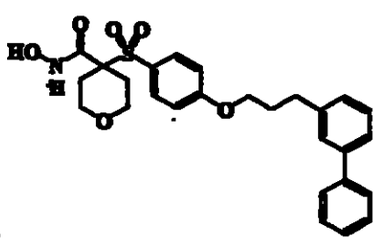
IIIB-65



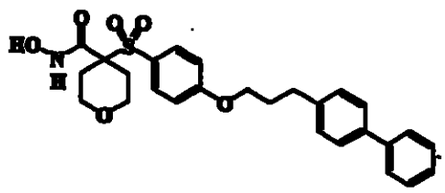
IIIB-66



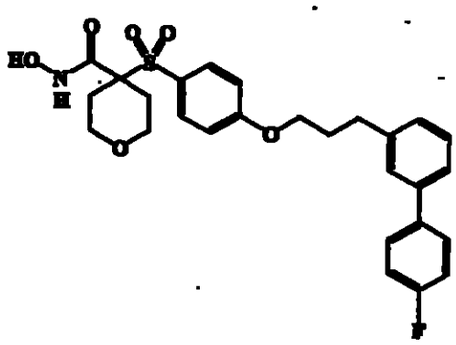
IIIB-67



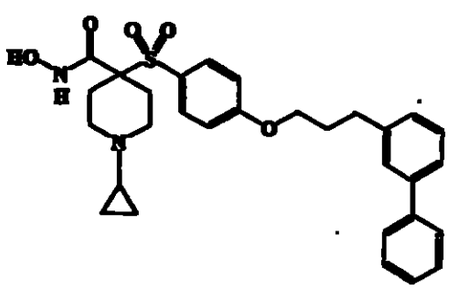
IIIB-68



IIIB-69

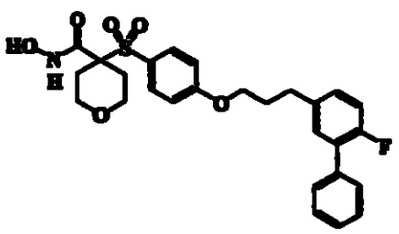


IIIB-70

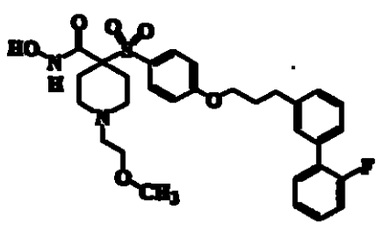


IIIB-71

Other such compounds include, for example:

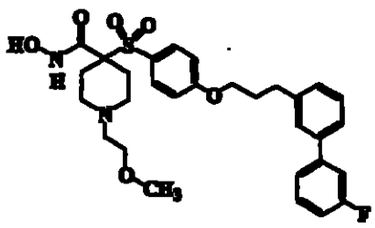


IIIB-72

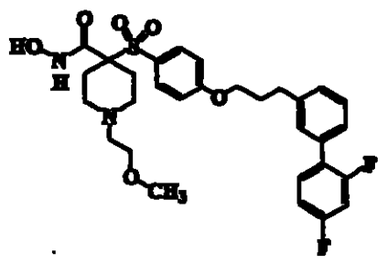


IIIB-73

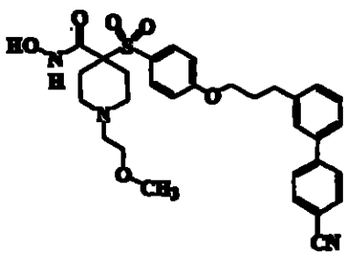
145



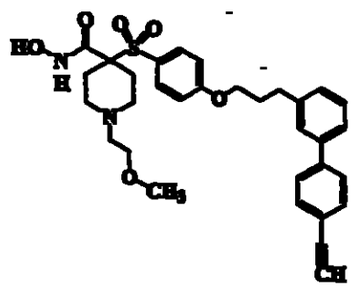
IIIB-74



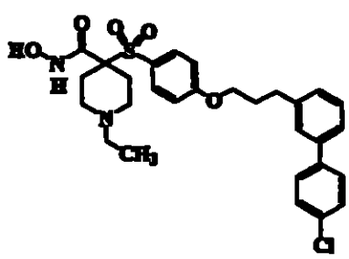
IIIB-75



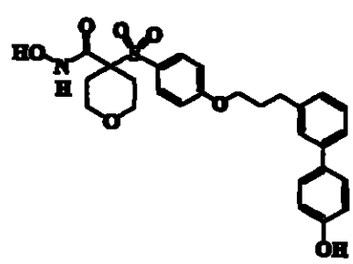
IIIB-76



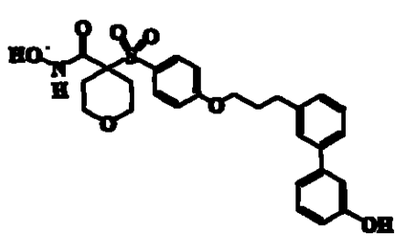
IIIB-77



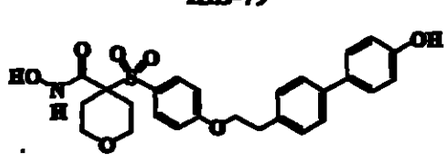
IIIB-78



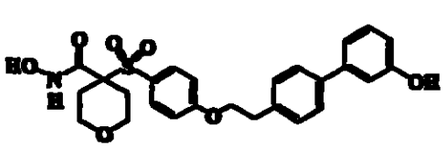
IIIB-79



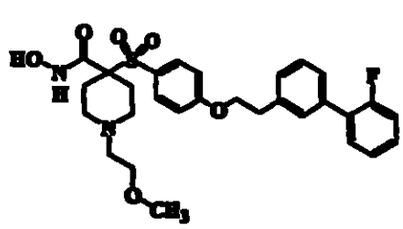
IIIB-80



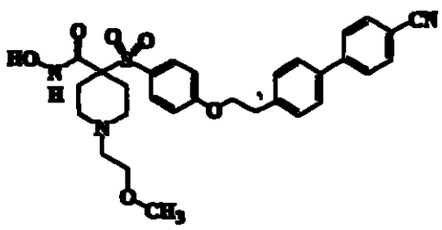
IIIB-81



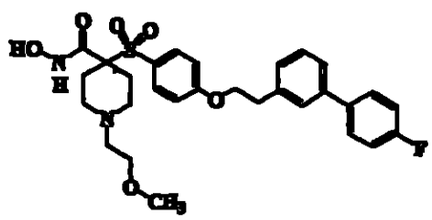
IIIB-82



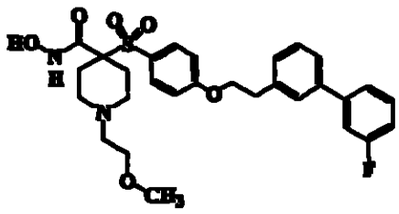
IIIB-83



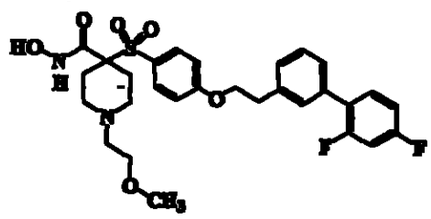
IIIB-84



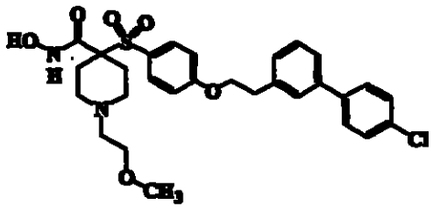
IIIB-85



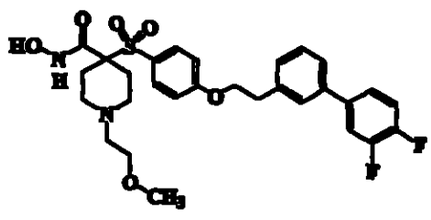
IIIB-86



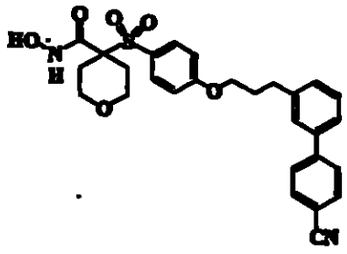
IIIB-87



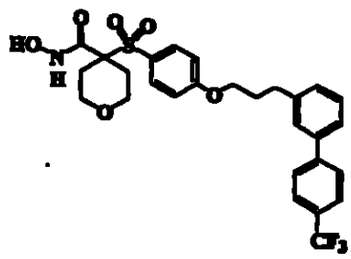
IIIB-88



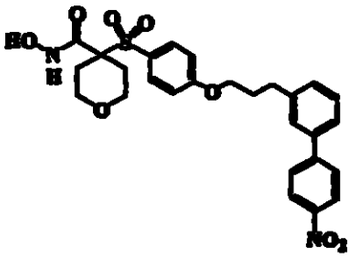
IIIB-89



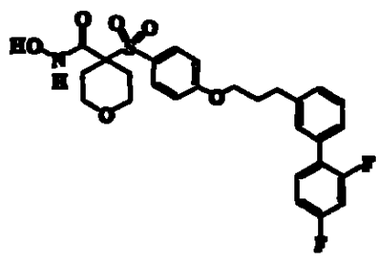
IIIB-90



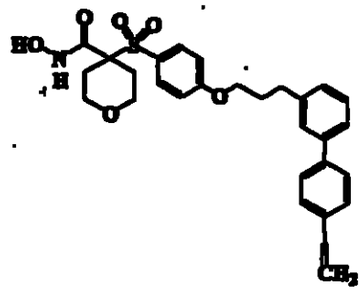
IIIB-91



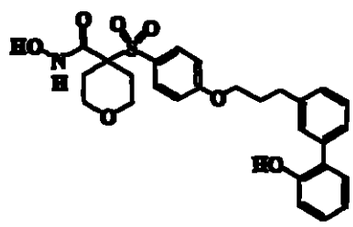
IIIB-92



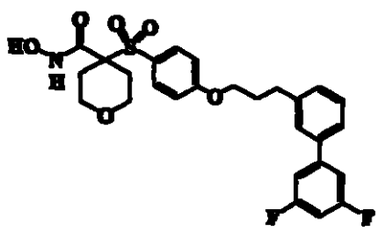
IIIB-93



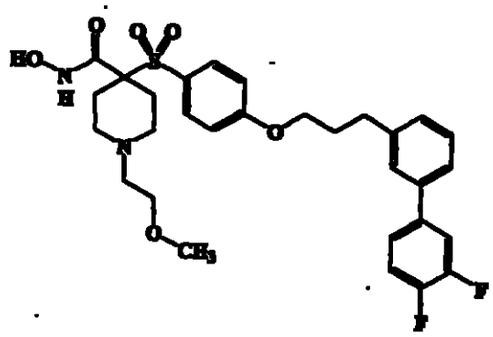
IIIB-94



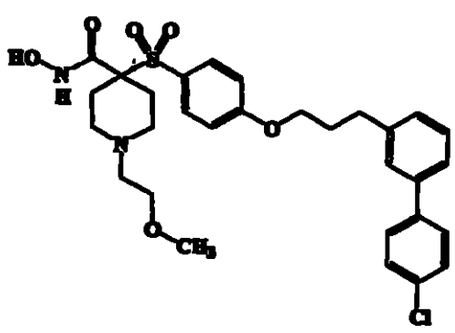
IIIB-95



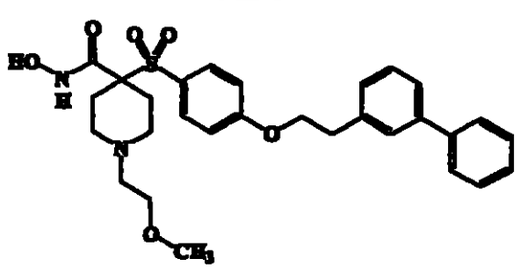
IIIB-96



IIIB-97



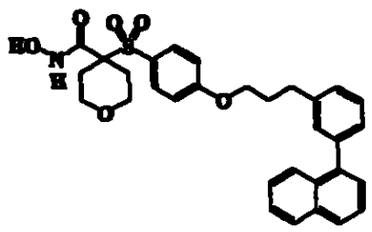
IIIB-98



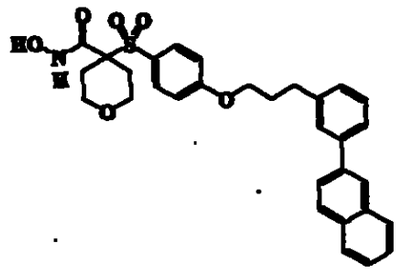
IIIB-99

[228] In other preferred embodiments, E^5 is optionally-substituted naphthalenyl. Such compounds include, for example:

148



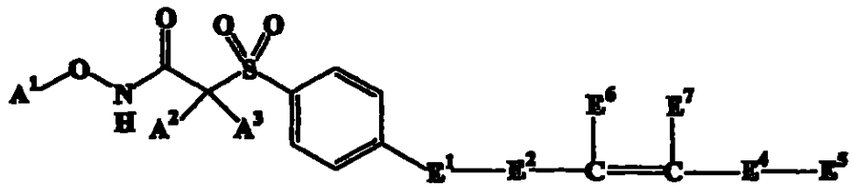
IIIB-100



IIIB-101

Preferred Embodiment No. 3

[221] In some embodiments of this invention, the compound has a structure corresponding to Formula IV:



IV

[222] A^1, A^2, and A^3 are as defined above for Formula I.

[223] E^1 is s -O-, $-S(O)_2-$, -S(O)-, $-N(R^1)-$, $-C(O)-N(R^1)-$, $-N(R^1)-C(O)-$, or $-C(R^1)(R^2)-$.

[224] E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of this group optionally is substituted.

[225] In some preferred embodiments, E^2 is C_1-C_{20}-alkyl, cycloalkyl, C_1-C_{10}-alkylcycloalkyl, cycloalkyl-C_1-C_{10}-alkyl, or C_1-C_{10}-alkylcycloalkyl-C_1-C_{10}-alkyl. Any member of this group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, C_1-C_6-alkyl, and halo-C_1-C_6-alkyl.

[226] In some preferred embodiments, E^2 is C_1-C_6-alkyl, cycloalkyl, C_1-C_6-alkylcycloalkyl, cycloalkyl-C_1-C_6-alkyl, or C_1-C_6-alkylcycloalkyl-C_1-C_6-alkyl. Any member of this group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, C_1-C_2-alkyl, and halo-C_1-C_2-alkyl.

149

[227] In some preferred embodiments, E^2 is C_1-C_6-alkyl, cycloalkyl, C_1-C_6-alkylcycloalkyl, cycloalkyl-C_1-C_6-alkyl, or C_1-C_6-alkylcycloalkyl-C_1-C_6-alkyl. Any member of this group optionally is substituted with one or more C_1-C_2-alkyl.

[228] E^4 is a bond or alkyl. The alkyl optionally is substituted.

[229] In some preferred embodiments, E^4 is a bond, C_1-C_{20}-alkyl, or halo-C_1-C_{20}-alkyl.

[230] In some preferred embodiments, E^4 is a bond, C_1-C_3-alkyl, or halo-C_1-C_3-alkyl.

[231] In some preferred embodiments, E^4 is a bond or C_1-C_3-alkyl.

[232] In some preferred embodiments, E^4 is a bond.

[233] E^5 is alkyl, alkenyl, alkynyl, alkoxy, alkoxyalkyl, carbocyclyl, or heterocyclyl. Any member of this group optionally is substituted.

[234] In some preferred embodiments, E^5 is C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, C_1-C_{20}-alkoxy, C_1-C_{20}-alkoxy-C_1-C_{20}-alkyl, carbocyclyl, or heterocyclyl. The C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, C_1-C_{20}-alkoxy, and C_1-C_{20}-alkoxy-C_1-C_{20}-alkyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, and -CN. The carbocyclyl and heterocyclyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, keto, C_1-C_8-alkyl, halo-C_1-C_8-alkyl, C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, halo-C_1-C_8-alkoxy, -$N(R^7)(R^8)$, -$C(O)(R^9)$, -S-R^7, -$S(O)_2$-R^7, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_8-alkyl, and halogen-substituted C_1-C_8-alkoxy-C_1-C_8-alkyl.

[235] In some preferred embodiments, E^5 is C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, carbocyclyl, or heterocyclyl. The C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, C_1-C_8-alkoxy, and C_1-C_8-alkoxy-C_1-C_8-alkyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, and -CN. The carbocyclyl and heterocyclyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, keto, C_1-C_8-alkyl, halo-C_1-C_8-alkyl, C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, halo-C_1-C_8-alkoxy, -$N(R^7)(R^8)$, -$C(O)(R^9)$, -S-R^7, -$S(O)_2$-R^7, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_8-alkyl, and halogen-substituted C_1-C_8-alkoxy-C_1-C_8-alkyl.

150

[236] E^6 is -H, halogen, or alkyl. The alkyl optionally is substituted.

[237] In some preferred embodiments, E^6 is -H, halogen, or C_1-C_6-alkyl. The C_1-C_6-alkyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[238] In some preferred embodiments, E^6 is -H, halogen, or C_1-C_6-alkyl. The C_1-C_6-alkyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[239] E^7 is -H, alkyl, alkenyl, alkynyl, $-S(O)_2-R^3$, $-NO_2$, $-C(O)-N(R^3)(R^4)$, $-(C)(OR^3)$, carbocyclyl, carbocyclylalkyl, alkoxycarbocyclyl, -CN, -C=N-OH, or -C=NH. The alkyl, alkenyl, alkynyl, carbocyclyl, carbocyclylalkyl, and alkoxycarbocyclyl optionally are substituted.

[240] In some preferred embodiments, E^7 is -H, C_1-C_6-alkyl, C_1-C_6-alkenyl, C_1-C_6-alkynyl, $-S(O)_2-R^3$, $-NO_2$, $-C(O)-N(R^3)(R^4)$, $-(C)(OR^3)$, carbocyclyl, carbocycyl-C_1-C_6-alkyl, C_1-C_6-alkoxycarbocyclyl, -CN, -C=N-OH, or -C=NH. The C_1-C_6-alkyl, C_1-C_6-alkenyl, C_1-C_6-alkynyl, carbocyclyl, carbocycyl-C_1-C_6-alkyl, or C_1-C_6-alkoxycarbocyclyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[241] In some preferred embodiments, E^7 is -H, C_1-C_6-alkyl, C_1-C_6-alkenyl, C_1-C_6-alkynyl, $-S(O)_2-R^3$, $-NO_2$, $-C(O)-N(R^3)(R^4)$, $-(C)(OR^3)$, carbocyclyl, carbocycyl-C_1-C_6-alkyl, C_1-C_6-alkoxycarbocyclyl, -CN, -C=N-OH, or -C=NH. The C_1-C_6-alkyl, C_1-C_6-alkenyl, C_1-C_6-alkynyl, carbocyclyl, carbocycyl-C_1-C_6-alkyl, or C_1-C_6-alkoxycarbocyclyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[242] R^1 and R^2 are independently selected from the group consisting of -H and alkyl. The alkyl optionally is substituted. Neither R^1 nor R^2 forms a ring structure with E^2, E^4, E^5, E^6, or E^7.

[243] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_6-alkyl, and halo-C_1-C_6-alkyl.

[244] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_6-alkyl, and halo-C_1-C_6-alkyl.

[245] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H and C_1-C_6-alkyl.

151

[246] R^3 and R^4 are independently selected from the group consisting of -H, alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, and heterocyclylalkyl. Except where the member is -H, any member of this group optionally is substituted.

[247] In some preferred embodiments, R^3 and R^4 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[248] In some preferred embodiments, R^3 and R^4 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[249] R^7 and R^8 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[250] In some preferred embodiments, R^7 and R^8 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

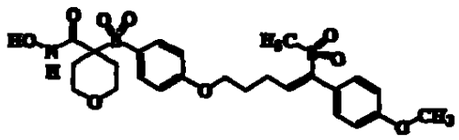
[251] R^9 is -H, C_1-C_6-alkyl, -O-R^{10}, -N(R^{10})(R^{11}), carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl. The C_1-C_6-alkyl, carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[252] In some preferred embodiments, R^9 is -H, C_1-C_6-alkyl, -O-R^{10}, -N(R^{10})(R^{11}), carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl. The C_1-C_6-alkyl, carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

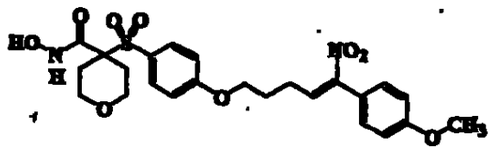
[253] R^{10} and R^{11} are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[254] In some preferred embodiments, R^{10} and R^{11} are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

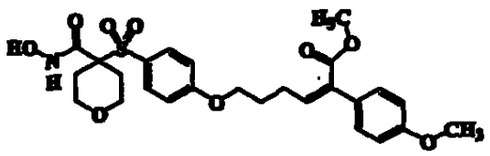
[255] In some preferred embodiments, E^5 is optionally-substituted carbocyclyl or optionally-substituted heterocyclyl. For example, in some such embodiments, E^5 is optionally-substituted carbocyclyl, often preferably optionally-substituted aryl, and more preferably optionally-substituted phenyl. Such compounds include, for example:



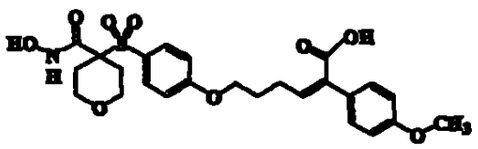
IV-1



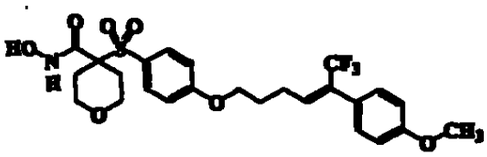
IV-2



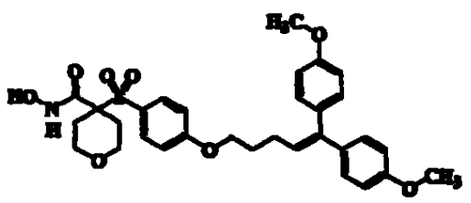
IV-3



IV-4

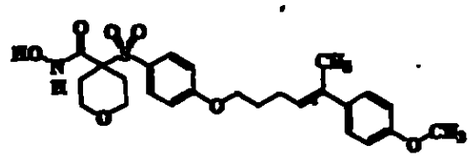


IV-5

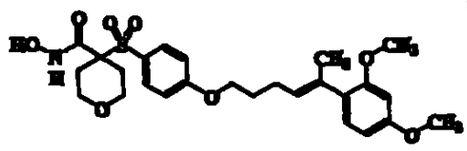


IV-6

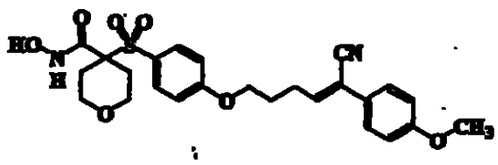
153



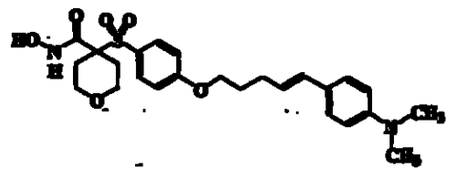
IV-7



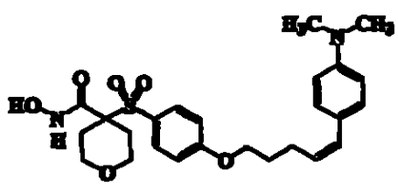
IV-8



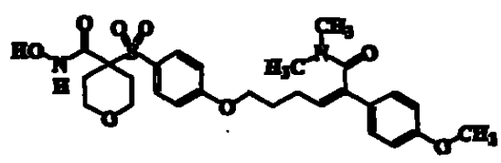
IV-9



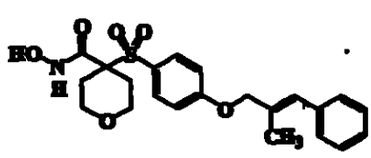
IV-10



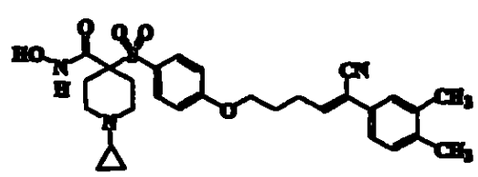
IV-11



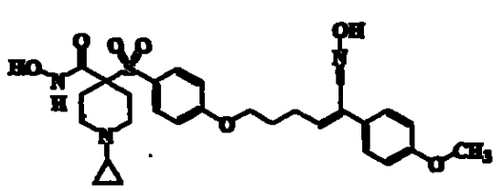
IV-12



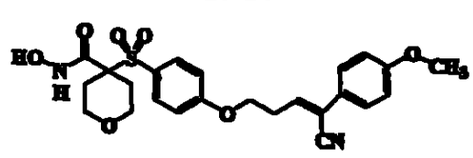
IV-13



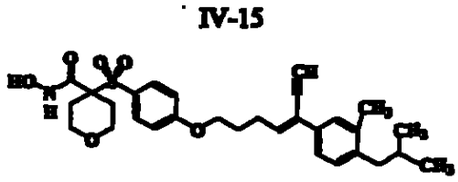
IV-14



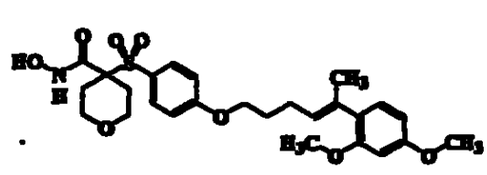
IV-15



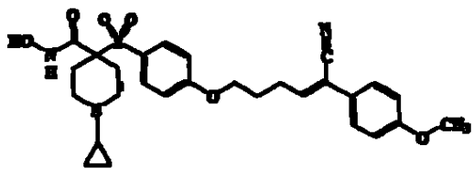
IV-16



IV-17



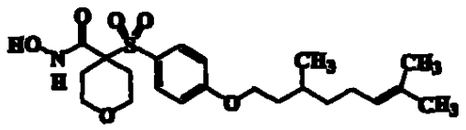
IV-18



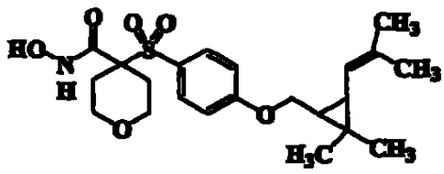
IV-19

[256] In some preferred embodiments, E^5 is C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkoxy, or C_1-C_6-alkoxy-C_1-C_6-alkyl. Any member of this group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, and -CN.

[257] In some preferred embodiments, E^5 is optionally-substituted C_1-C_6-alkyl, with the C_1-C_6-alkyl often being more preferably unsubstituted. Such compounds include, for example:



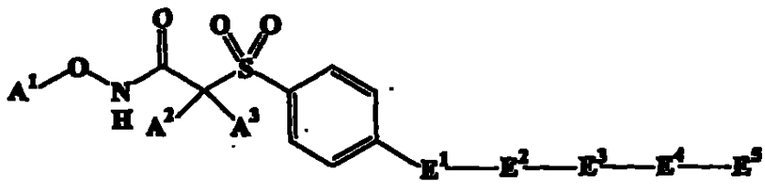
IV-20



IV-21

Preferred Embodiment No. 4

[258] In some embodiments of this invention, the compound has a structure corresponding to Formula V:



V

[259] A^1, A^2, and A^3 are as defined above for Formula I.

[260] E^1 is -O-, -$S(O)_2$-, -S(O)-, -$N(R^3)$-, -C(O)-$N(R^3)$-, -$N(R^3)$-C(O)-, or -$C(R^1)(R^2)$-.

[261] E^2 is a bond, alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Except where the member is a bond, any member of such group optionally is substituted.

155

[262] In some preferred embodiments, E^2 is a bond, C_1-C_{20}-alkyl, cycloalkyl, C_1-C_{10}-alkylcycloalkyl, cycloalkyl-C_1-C_{10}-alkyl, or C_1-C_{10}-alkylcycloalkyl-C_1-C_{10}-alkyl. Any member of this group (except for the bond) optionally is substituted with one or more substituents independently selected from the group consisting of halogen, C_1-C_6-alkyl, and halo-C_1-C_6-alkyl.

[263] In some preferred embodiments, E^2 is a bond, C_1-C_6-alkyl, or halo-C_1-C_6-alkyl.

[264] In some preferred embodiments E^2 is a bond or C_1-C_6-alkyl.

[265] E^3 is carbonylpyrrollidinyl. The carbonylpyrrollidinyl optionally is substituted.

[266] In some preferred embodiments, E^3 is carbonylpyrrollidinyl wherein the carbonylpyrrollidinyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[267] E^4 is a bond, alkyl, or alkenyl. The alkyl and alkenyl optionally are substituted.

[268] In some preferred embodiments, E^4 is a bond, C_1-C_{20}-alkyl, halo-C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, or halo-C_2-C_{20}-alkenyl.

[269] In some preferred embodiments, E^4 is a bond, C_1-C_3-alkyl, halo-C_1-C_3-alkyl, C_2-C_3-alkenyl, or halo-C_2-C_3-alkenyl.

[270] In some preferred embodiments, E^4 is a bond, C_1-C_3-alkyl, or C_2-C_3-alkenyl.

[271] In some preferred embodiments, E^4 is a bond.

[272] E^5 is alkyl, alkenyl, alkynyl, alkoxy, alkoxyalkyl, carbocyclyl, or heterocyclyl. Any member of this group optionally is substituted.

[273] In some preferred embodiments, E^5 is C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, C_1-C_{20}-alkoxy, C_1-C_{20}-alkoxy-C_1-C_{20}-alkyl, carbocyclyl, or heterocyclyl. The C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, C_1-C_{20}-alkoxy, and C_1-C_{20}-alkoxy-C_1-C_{20}-alkyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, and -CN. The carbocyclyl and heterocyclyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, keto, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy,

156

C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl.

[274] In some preferred embodiments, E^5 is C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, carbocyclyl, or heterocyclyl. The C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkoxy, and C_1-C_6-alkoxy-C_1-C_6-alkyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, and -CN. The carbocyclyl and heterocyclyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, keto, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl.

[275] R^1 and R^2 are independently selected from the group consisting of -H and alkyl. The alkyl optionally is substituted. Neither R^1 nor R^2 forms a ring structure with E^2, E^3, E^4, or E^5.

[276] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_6-alkyl, and halo-C_1-C_6-alkyl.

[277] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_6-alkyl, and halo-C_1-C_6-alkyl.

[278] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H and C_1-C_6-alkyl.

[279] R^5 and R^6 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[280] In some preferred embodiments, R^5 and R^6 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member

of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

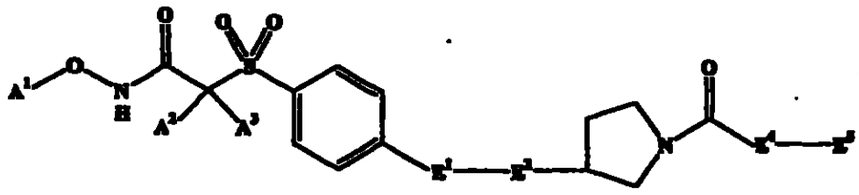
[281] R^7 is -H, C_1-C_8-alkyl, -O-R^8, -N(R^8)(R^9), carbocyclyl-C_1-C_8-alkyl, or heterocyclyl-C_1-C_8-alkyl. The C_1-C_8-alkyl, carbocyclyl-C_1-C_8-alkyl, or heterocyclyl-C_1-C_8-alkyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[282] In some preferred embodiments, R^7 is -H, C_1-C_6-alkyl, -O-R^8, -N(R^8)(R^9), carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl. The C_1-C_6-alkyl, carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[283] R^8 and R^9 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

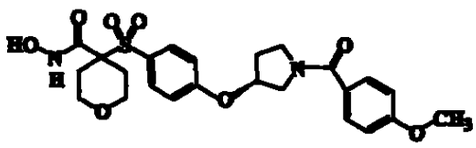
[284] In some preferred embodiments, R^8 and R^9 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[285] In some preferred embodiments, the compound has a structure corresponding to Formula V-A:

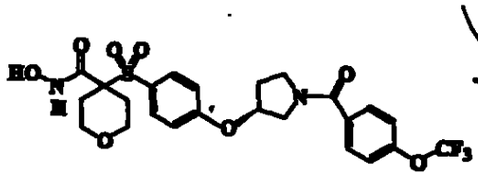


V-A

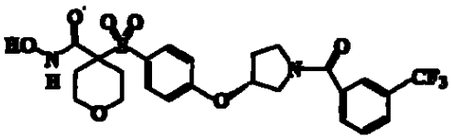
[286] In some preferred embodiments, E^5 is optionally-substituted carbocyclyl or optionally substituted heterocyclyl. For example, in some such embodiments, E^5 is optionally substituted carbocyclyl, often preferably optionally-substituted aryl, and more preferably optionally-substituted phenyl. Such compounds include, for example:



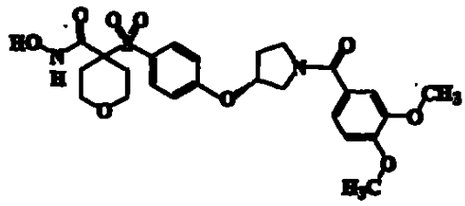
V-1



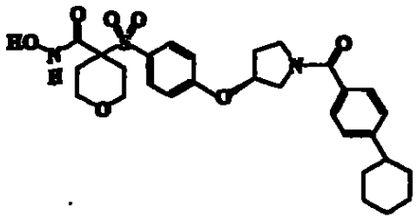
V-2



V-3

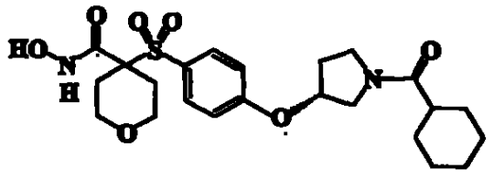


V-4



V-5

[287] In some preferred embodiments, E^5 is optionally-substituted C_3-C_8-cycloalkyl. Such compounds include, for example:

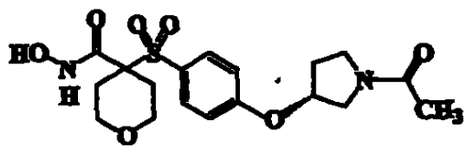


V-6

[288] In some preferred embodiments, E^5 is C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, C_1-C_8-alkoxy, or C_1-C_8-alkoxy-C_1-C_8-alkyl. The C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, C_1-C_8-alkoxy, and C_1-C_8-alkoxy-C_1-C_8-alkyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, and -CN.

[289] In some preferred embodiments, E^5 is optionally-substituted C_1-C_8-alkyl, with C_1-C_8-alkyl often being more preferred. Such compounds include, for example:

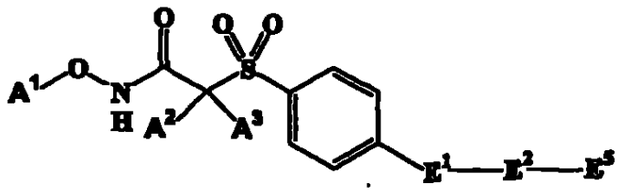
159



V-7

Preferred Embodiment No. 5

[290] In some embodiments of this invention, the compound has a structure corresponding to Formula VI:



VI

[291] A^1, A^2, and A^3 are as defined above for Formula I.

[292] E^1 is -O-, $-S(O)_z$-, -S(O)-, $-N(R^1)$-, $-C(O)-N(R^1)$-, $-N(R^1)-C(O)$-, or $-C(R^1)(R^2)$-.

[293] E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of this group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, alkyl, and haloalkyl.

[294] In some preferred embodiments, E^2 is C_1-C_{20}-alkyl, cycloalkyl, C_1-C_{10}-alkylcycloalkyl, cycloalkyl-C_1-C_{10}-alkyl, or C_1-C_{10}-alkylcycloalkyl-C_1-C_{10}-alkyl. Any member of this group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, C_1-C_6-alkyl, and halo-C_1-C_6-alkyl.

[295] In some preferred embodiments, E^2 is C_1-C_6-alkyl, cycloalkyl, C_1-C_6-alkylcycloalkyl, cycloalkyl-C_1-C_6-alkyl, or C_1-C_6-alkylcycloalkyl-C_1-C_6-alkyl. Any member of this group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, C_1-C_2-alkyl, and halo-C_1-C_2-alkyl.

160

[296] In some preferred embodiments, E^2 is C_1-C_6-alkyl, cycloalkyl, C_1-C_6-alkylcycloalkyl, cycloalkyl-C_1-C_6-alkyl, or C_1-C_6-alkylcycloalkyl-C_1-C_6-alkyl. Any member of this group optionally is substituted with one or more C_1-C_2-alkyl.

[297] E^5 is alkyl, alkenyl, alkynyl, cycloalkyl, cyclopentenyl, cyclopentadienyl, cyclohexenyl, or cyclohexadienyl. Here, the cycloalkyl, cyclopentenyl, cyclopentadienyl, cyclohexenyl, and cyclohexadienyl optionally are substituted. The alkyl, alkenyl, and alkynyl (a) contain at least 4 carbon atoms, and (b) optionally are substituted with one or more substituents selected from the group consisting of -OH, -NO_2, -CN, and halogen.

[298] In some preferred embodiments, E^5 is C_4-C_{20}-alkyl, C_4-C_{20}-alkenyl, C_4-C_{20}-alkynyl, cycloalkyl, cyclopentenyl, cyclopentadienyl, cyclohexenyl, or cyclohexadienyl. The C_4-C_{20}-alkyl, C_4-C_{20}-alkenyl, and C_4-C_{20}-alkynyl optionally are substituted with one or more substituents independently selected from the group consisting of -OH, -NO_2, -CN, and halogen. The cycloalkyl, cyclopentenyl, cyclopentadienyl, cyclohexenyl, and cyclohexadienyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, keto, C_1-C_8-alkyl, halo-C_1-C_8-alkyl, C_1-C_8-alkoxy, halo-C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, halogen-substituted C_1-C_8-alkoxy-C_1-C_8-alkyl, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_8-alkyl, and halogen-substituted carbocyclyl-C_1-C_8-alkyl.

[299] In some preferred embodiments, E^5 is C_4-C_8-alkyl, C_4-C_8-alkenyl, C_4-C_8-alkynyl, cycloalkyl, cyclopentenyl, cyclopentadienyl, cyclohexenyl, or cyclohexadienyl. The C_4-C_8-alkyl, C_4-C_8-alkenyl, and C_4-C_8-alkynyl optionally are substituted with one or more substituents independently selected from the group consisting of -OH, -NO_2, -CN, and halogen. The cycloalkyl, cyclopentenyl, cyclopentadienyl, cyclohexenyl, and cyclohexadienyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, keto, C_1-C_8-alkyl, halo-C_1-C_8-alkyl, C_1-C_8-alkoxy, halo-C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, halogen-substituted C_1-C_8-alkoxy-C_1-C_8-alkyl, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_8-alkyl, and halogen-substituted carbocyclyl-C_1-C_8-alkyl.

161

[300] R^1 and R^2 are independently selected from the group consisting of -H and alkyl. The alkyl optionally is substituted. Neither R^1 nor R^2 forms a ring structure with R^3.

[301] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_6-alkyl, and halo-C_1-C_6-alkyl.

[302] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_6-alkyl, and halo-C_1-C_6-alkyl.

[303] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H and C_1-C_6-alkyl.

[304] R^5 and R^6 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[305] In some preferred embodiments, R^5 and R^6 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

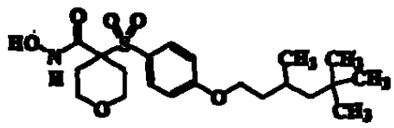
[306] R^7 is -H, C_1-C_6-alkyl, -O-R^8, -N(R^8)(R^9), carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl. The C_1-C_6-alkyl, carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[307] In some preferred embodiments, R^7 is -H, C_1-C_6-alkyl, -O-R^8, -N(R^8)(R^9), carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl. The C_1-C_6-alkyl, carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

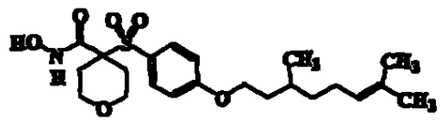
[308] R^8 and R^9 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[309] In some preferred embodiments, R^8 and R^9 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

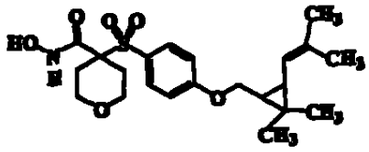
[310] In some preferred embodiments, E^5 is C_4-C_8-alkyl, C_4-C_8-alkenyl, or C_4-C_8-alkynyl. The C_4-C_8-alkyl, C_4-C_8-alkenyl, and C_4-C_8-alkynyl optionally are substituted with one or more substituents independently selected from the group consisting of -OH, -NO_2, -CN, and halogen. Such compounds include, for example:



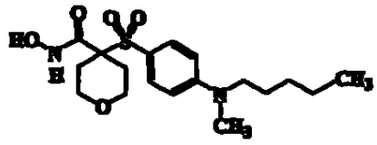
VI-1



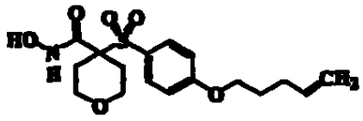
VI-2



VI-3

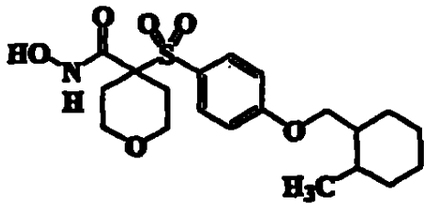


VI-4

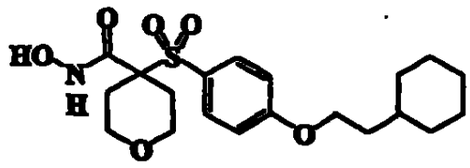


VI-5

[311] In some preferred embodiments, E^5 is optionally-substituted carbocyclyl. In some such embodiments, E^5 is optionally-substituted C_3-C_6-cycloalkyl. Such compounds include, for example:

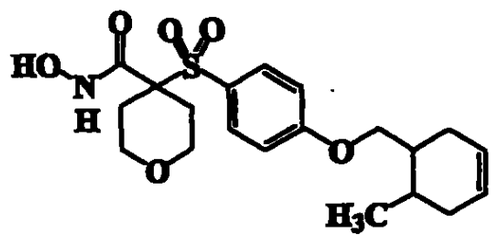


VI-6



VI-7

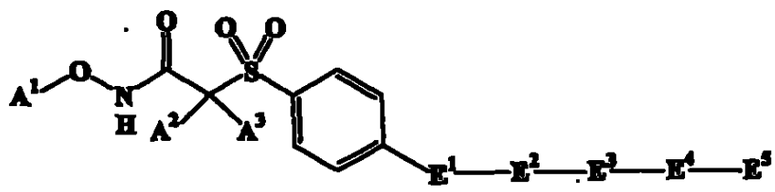
In other such embodiments, E^5 is an optionally-substituted, partially-saturated carbocyclyl selected from the group consisting of cyclopentenyl, cyclopentadienyl, cyclohexenyl, and cyclohexadienyl. Such compounds include, for example:



VI-8

Preferred Embodiment No. 6

[312] In some embodiments of this invention, the compound has a structure corresponding to Formula VII:



VII

[313] A^1, A^2, and A^3 are as defined above for Formula I.

[314] E^1 is -O-, $-S(O)_2-$, -S(O)-, $-N(R^1)-$, $-C(O)-N(R^1)-$, $-N(R^1)-C(O)-$, or $-C(R^1)(R^2)-$.

[315] E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of this group optionally is substituted.

[316] In some preferred embodiments, E^2 is C_1-C_{20}-alkyl, cycloalkyl, C_1-C_{10}-alkylcycloalkyl, cycloalkyl-C_1-C_{10}-alkyl, or C_1-C_{10}-alkylcycloalkyl-C_1-C_{10}-alkyl. Any member of this group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, C_1-C_6-alkyl, and halo-C_1-C_6-alkyl.

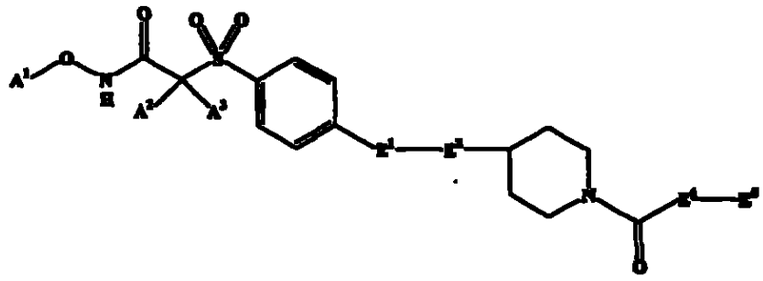
[317] In some preferred embodiments, E^2 is C_1-C_6-alkyl optionally substituted with one or more halogen.

[318] In some preferred embodiments, E^2 is C_1-C_6-alkyl.

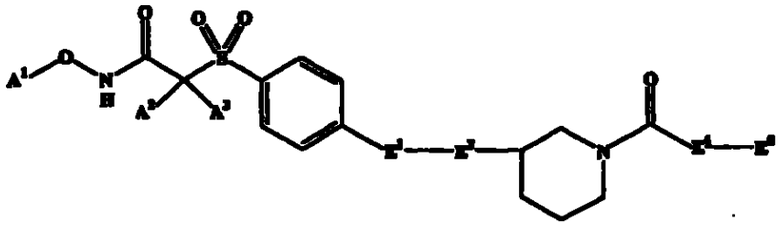
[319] E^3 is carbonylpiperidinyl. The carbonylpiperidinyl optionally is substituted.

[320] In some preferred embodiments, E^3 is carbonylpiperidinyl wherein the carbonylpiperidinyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[321] In some preferred embodiments, the compound has a structure corresponding to one of the following formulas:



VII-A



VII-B

[322] E^4 is a bond, alkyl, or alkenyl. The alkyl and alkenyl optionally are substituted.

[323] In some preferred embodiments, E^4 is a bond, C_1-C_{20}-alkyl, halo-C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, or halo-C_2-C_{20}-alkenyl.

[324] In some preferred embodiments, E^4 is a bond, C_1-C_3-alkyl, halo-C_1-C_3-alkyl, C_2-C_3-alkenyl, or halo-C_2-C_3-alkenyl.

[325] In some preferred embodiments, E^4 is a bond, C_1-C_3-alkyl, or C_2-C_3-alkenyl.

[326] In some preferred embodiments, E^4 is a bond.

[327] E^5 is alkyl, alkenyl, alkynyl, alkoxy, alkoxyalkyl, carbocyclyl, or heterocyclyl. Any member of this group optionally is substituted.

[328] In some preferred embodiments, E^5 is C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, C_1-C_{20}-alkoxy, C_1-C_{20}-alkoxy-C_1-C_{20}-alkyl, carbocyclyl, or heterocyclyl. The C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, C_1-C_{20}-alkoxy, and C_1-C_{20}-alkoxy-C_1-C_{20}-alkyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, and -CN. The carbocyclyl and heterocyclyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, keto, C_1-C_8-alkyl, halo-C_1-C_8-alkyl, C_1-C_8-alkoxy, halo-C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, halogen-substituted C_1-C_8-alkoxy-C_1-C_8-alkyl, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbocyclyl, halocarbocyclyl, and carbocyclyl-C_1-C_8-alkyl.

[329] In some preferred embodiments, E^5 is C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, carbocyclyl, or heterocyclyl. Here, the C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, C_1-C_8-alkoxy, and C_1-C_8-alkoxy-C_1-C_8-alkyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, and -CN. The carbocyclyl and heterocyclyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, keto, C_1-C_8-alkyl, halo-C_1-C_8-alkyl, C_1-C_8-alkoxy, halo-C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, halogen-substituted C_1-C_8-alkoxy-C_1-C_8-alkyl, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_8-alkyl, and halogen-substituted carbocyclyl-C_1-C_8-alkyl.

[330] R^1 and R^2 are independently selected from the group consisting of -H and alkyl. The alkyl optionally is substituted. Neither R^1 nor R^2 forms a ring structure with E^2, E^3, E^4, or E^5.

[331] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_8-alkyl, and halo-C_1-C_8-alkyl.

[332] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_8-alkyl, and halo-C_1-C_8-alkyl.

[333] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H and C_1-C_8-alkyl.

[334] R^5 and R^6 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and

heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[335] In some preferred embodiments, R^5 and R^6 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

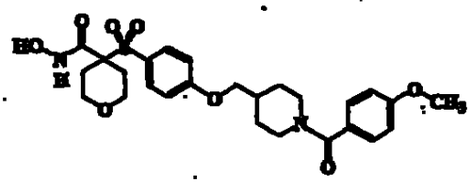
[336] R^7 is -H, C_1-C_6-alkyl, -O-R^8, -N(R^8)(R^8), carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl. The C_1-C_6-alkyl, carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[337] In some preferred embodiments, R^7 is -H, C_1-C_6-alkyl, -O-R^8, -N(R^8)(R^8), carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl. The C_1-C_6-alkyl, carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

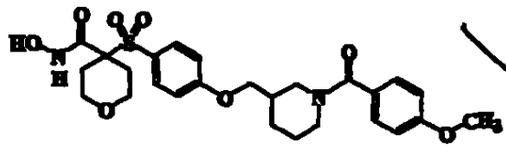
[338] R^8 and R^9 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[339] In some preferred embodiments, R^8 and R^9 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[340] In some preferred embodiments, E^5 is optionally-substituted carbocyclyl or optionally substituted heterocyclyl. In some such embodiments, E^5 is optionally-substituted aryl, often preferably optionally-substituted phenyl. Such compounds include, for example:



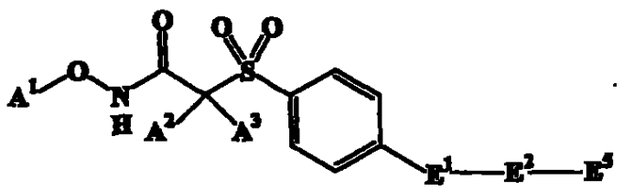
VII-1



VII-2

Preferred Embodiment No. 7

[341] In some embodiments of this invention, the compound has a structure corresponding to Formula VIII:



VIII

[342] A^1, A^2, and A^3 are as defined above for Formula I.

[343] E^1 is -O-, $-S(O)_2-$, -S(O)-, $-N(R^1)-$, $-C(O)-N(R^1)-$, $-N(R^1)-C(O)-$, or $-C(R^1)(R^2)-$.

[344] E^2 forms a link of at least 3 carbon atoms between E^1 and E^5. E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of this group optionally is substituted.

[345] In some preferred embodiments, E^2 is C_3-C_{20}-alkyl, cycloalkyl, C_1-C_{10}-alkyl-cycloalkyl, cycloalkyl-C_1-C_{10}-alkyl, or C_1-C_{10}-alkyl-cycloalkyl-C_1-C_{10}-alkyl. Any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[346] In some preferred embodiments, E^2 is C_3-C_6-alkyl optionally substituted with one or more halogen.

[347] In some preferred embodiments, E^2 is C_3-C_6-alkyl.

[348] E^5 is optionally-substituted heterocyclyl, optionally-substituted fused-ring carbocyclyl, or substituted single-ring carbocyclyl.

[349] In some preferred embodiments, E^5 is single-ring carbocyclyl, fused-ring carbocyclyl, or heterocyclyl.

[350] Here, the single-ring carbocyclyl is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, keto, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_z$-R^5, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, halogen-substituted carbocyclyl-C_1-C_6-alkyl. The single-ring carbocyclyl also optionally is substituted on the same atom with two substituents independently selected from the group consisting of alkyl and haloalkyl, the two substituents together forming C_3-C_6-cycloalkyl or halo-C_3-C_6-cycloalkyl.

[351] In some preferred embodiments, the single-ring carbocyclyl is substituted with one or more substituents independently selected from the group consisting of and halogen, -OH, -NO_2, -CN, keto, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_z$-R^5, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl. The single-ring carbocyclyl also optionally is substituted on the same atom with two substituents independently selected from the group consisting of alkyl and haloalkyl, the two substituents together forming C_3-C_6-cycloalkyl or halo-C_3-C_6-cycloalkyl.

[352] The heterocyclyl and fused-ring carbocyclyl optionally are substituted with one or more substituents independently selected from the group consisting of and halogen, -OH, -NO_2, -CN, keto, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_z$-R^5, carbocyclyl, halocarbocyclyl, and carbocyclyl-C_1-C_6-alkyl. The heterocyclyl and fused-ring carbocyclyl also optionally are substituted on the same atom with two substituents independently selected from the group consisting of alkyl and haloalkyl, the two substituents together forming C_3-C_6-cycloalkyl or halo-C_3-C_6-cycloalkyl.

[353] In some preferred embodiments, the heterocyclyl and fused-ring carbocyclyl optionally are substituted with one or more substituents independently selected from the group consisting of and halogen, -OH, -NO_2, -CN, keto, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl,

halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl. The heterocyclyl and fused-ring carbocyclyl also optionally are substituted on the same atom with two substituents independently selected from the group consisting of alkyl and haloalkyl, the two substituents together forming C_3-C_6-cycloalkyl or halo-C_3-C_6-cycloalkyl.

[354] R^1 and R^2 are independently selected from the group consisting of -H and alkyl. The alkyl optionally is substituted. Neither R^1 nor R^2 forms a ring structure with E^5.

[355] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_6-alkyl, and halo-C_1-C_6-alkyl.

[356] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_6-alkyl, and halo-C_1-C_6-alkyl.

[357] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H and C_1-C_6-alkyl.

[358] R^5 and R^6 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[359] In some preferred embodiments, R^5 and R^6 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[360] R^7 is -H, C_1-C_6-alkyl, -O-R^8, -$N(R^8)(R^5)$, carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl. The C_1-C_6-alkyl, carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[361] In some preferred embodiments, R^7 is -H, C_1-C_6-alkyl, -O-R^8, -$N(R^8)(R^5)$, carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl. The C_1-C_6-alkyl,

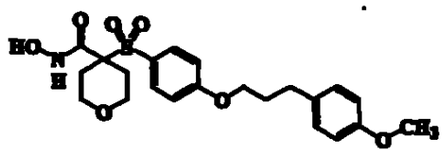
carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[362] R^8 and R^9 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

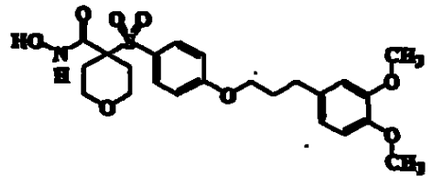
[363] In some preferred embodiments, R^8 and R^9 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[364] In some preferred embodiments, E^5 is a substituted single-ring carbocyclyl. E^5 may be, for example a substituted single-ring carbocyclyl selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclopentadienyl, cyclohexyl, cyclohexenyl, cyclohexadienyl, and phenyl.

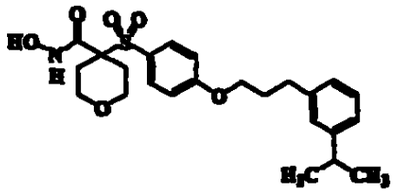
[365] In some preferred embodiments, E^5 is substituted phenyl. Such compounds include, for example:



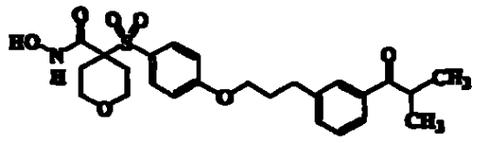
VIII-1



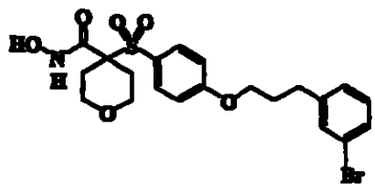
VIII-2



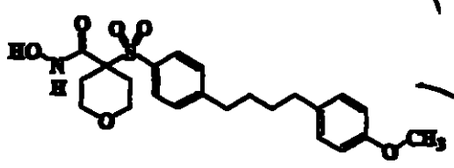
VIII-3



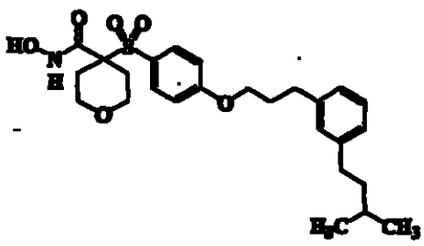
VIII-4



VIII-5

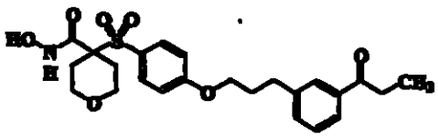


VIII-6

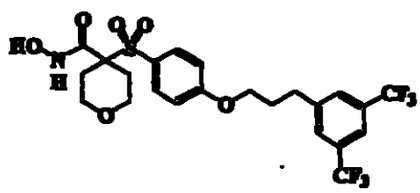


VIII-7

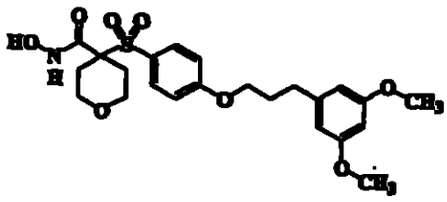
Such compounds also include, for example:



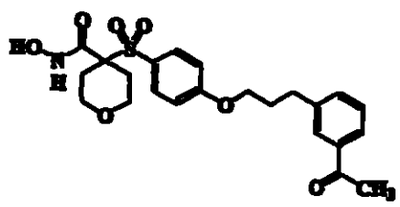
VIII-8



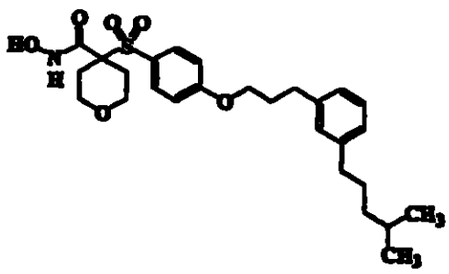
VIII-9



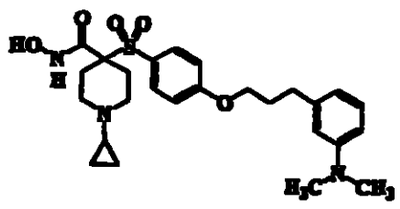
VIII-10



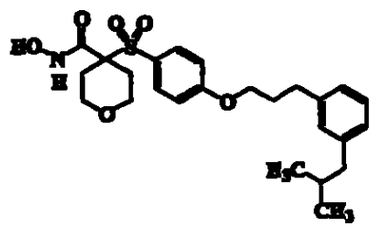
VIII-11



VIII-12



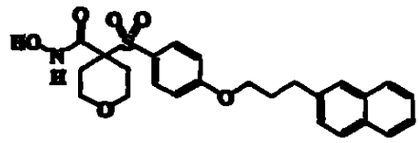
VIII-13



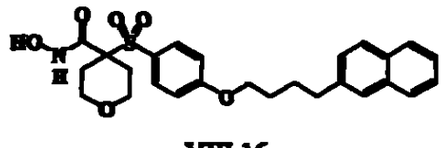
VIII-14

[366] In some preferred embodiments, E^5 is optionally-substituted fused-ring carbocyclyl. E^5 may be, for example, optionally-substituted fused-ring carbocyclyl selected from the group consisting of naphthalenyl, tetrahydronaphthalenyl, indenyl, isoindenyl, indanyl, bicyclodecanyl, anthracenyl, phenanthrene, benzonaphthenyl, fluorenyl, decalinyl, and norpinanyl.

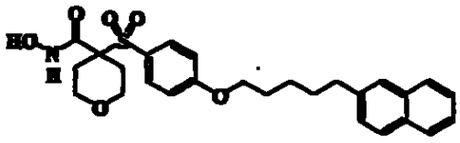
[367] In some preferred embodiments, E^5 is optionally-substituted naphthalenyl. Such compounds include, for example:



VIII-15



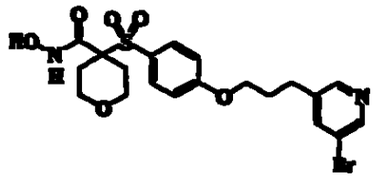
VIII-16



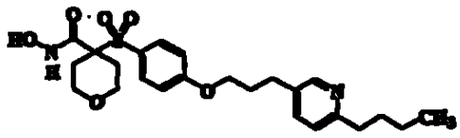
VIII-17

[368] In some preferred embodiments, E^5 is optionally-substituted, single-ring heterocyclyl.

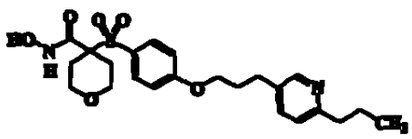
[369] In some preferred embodiments, E^5 is an optionally-substituted pyridinyl. Such compounds include, for example:



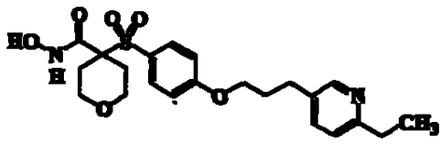
VIII-18



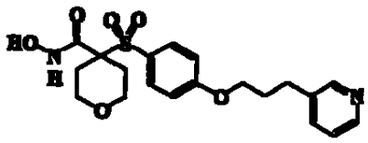
VIII-19



VIII-20

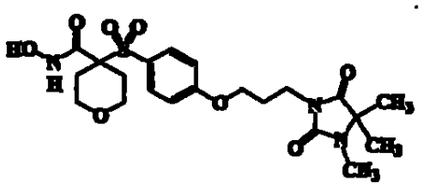


VIII-21

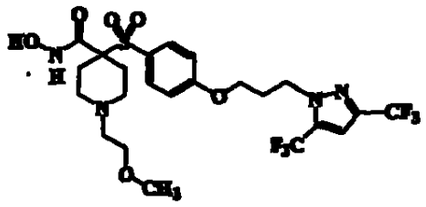


VIII-22

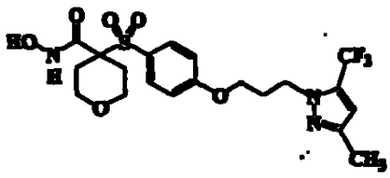
[370] In some preferred embodiments, E^5 is an optionally-substituted heterocyclyl selected from the group consisting of imidazolyl, imidazolinyl, imidazolidinyl, pyrazolyl, pyrazolinyl, and pyrazolidinyl. Such compounds include, for example:



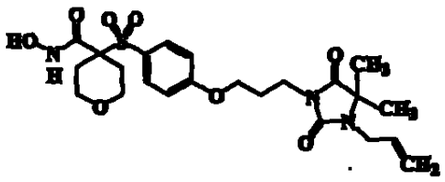
VIII-23



VIII-24



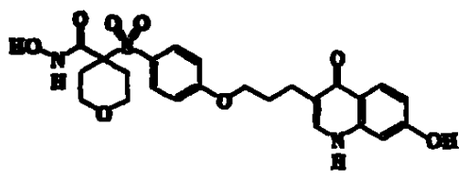
VIII-25



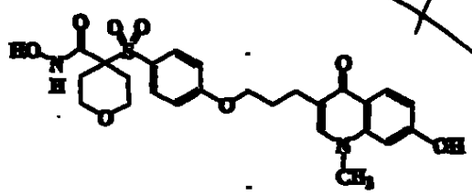
VIII-26

[371] In some preferred embodiments, E^5 is optionally-substituted fused-ring heterocyclyl. E^5 may be, for example, an optionally-substituted fused-ring heterocyclyl selected from the group consisting of indolizinyl, pyrindinyl, pyranopyrrolyl, 4H-quinolizinyl, purinyl, naphthyridinyl, pyridopyridinyl, pteridinyl, indolyl, isoindolyl, indoleninyl, isoindazolyl, benzazinyl, phthalazinyl, quinoxalinyl, quinazolinyl, benzodiazinyl, benzopyranyl, benzothiopyranyl, benzoxazolyl, indoxazinyl, anthranilyl, benzodioxolyl, benzodioxanyl, benzoxadiazolyl, benzofuranyl, isobenzofuranyl, benzothienyl, isobenzothienyl, benzothiazolyl, benzothiadiazolyl, benzimidazolyl,

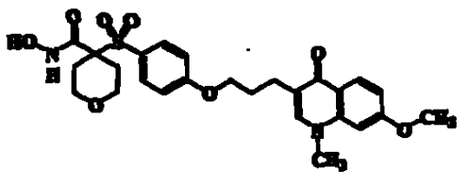
benzotriazolyl, benzoxazinyl, benzisoxazinyl, tetrahydroisoquinolinyl , carbazolyl, xanthenyl, and acridinyl. Compounds wherein B^5 is an optionally-substituted fused-ring heterocyclyl include, for example:



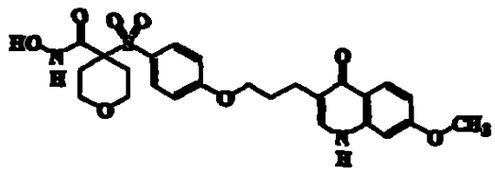
VIII-27



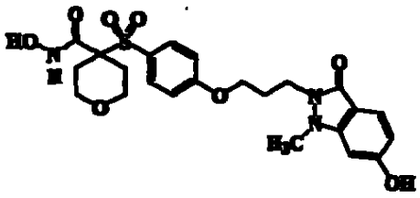
VIII-28



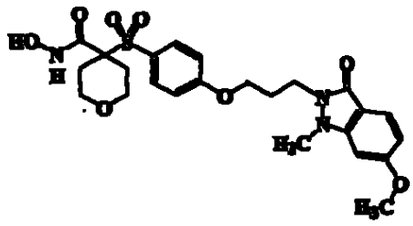
VIII-29



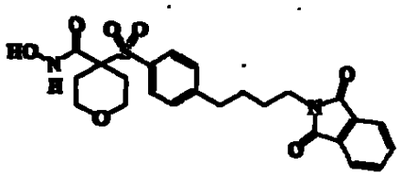
VIII-30



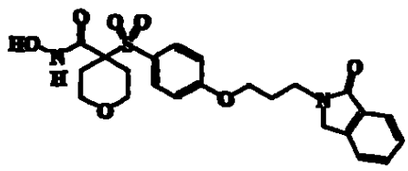
VIII-31



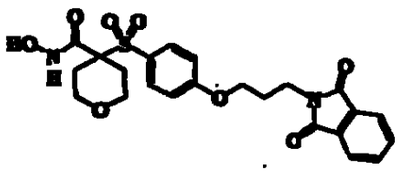
VIII-32



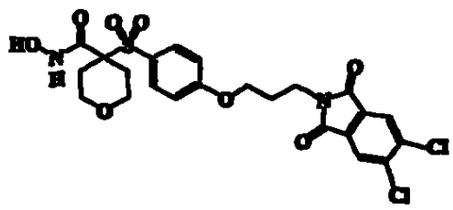
VIII-33



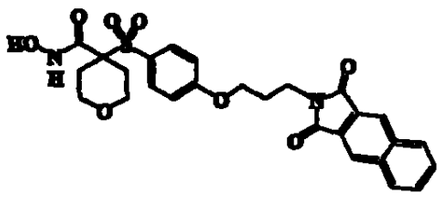
VIII-34



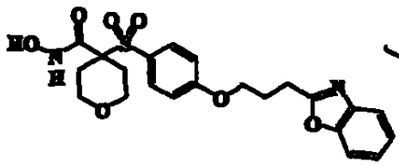
VIII-35



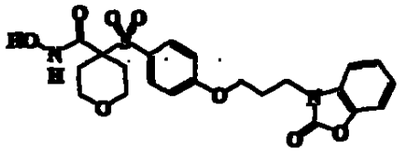
VIII-36



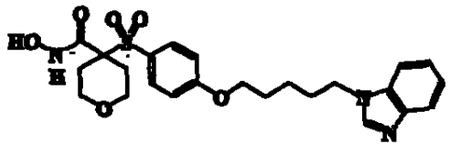
VIII-37



VIII-38

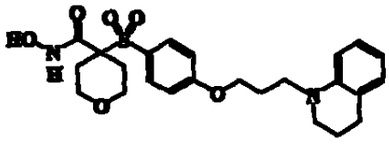


VIII-39

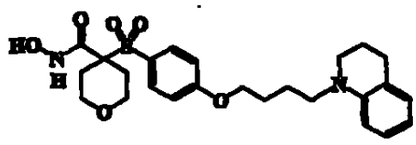


VIII-40

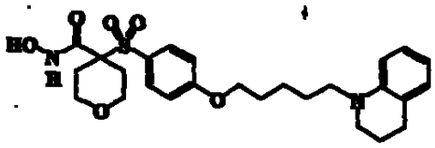
[372] In some preferred embodiments, B^5 is optionally-substituted tetrahydroisoquinolinyl . Such compounds include, for example:



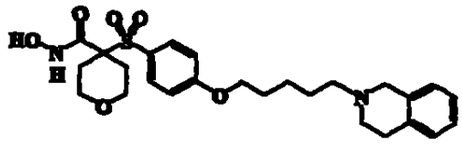
VIII-41



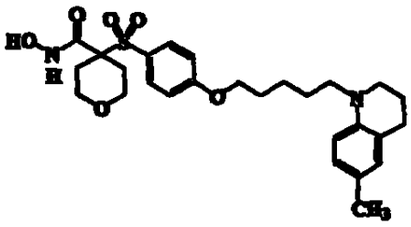
VIII-42



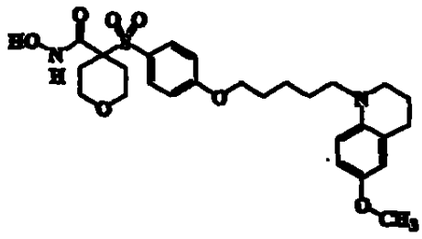
VIII-43



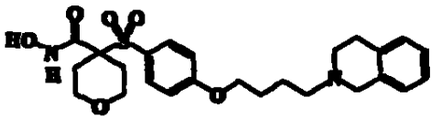
VIII-44



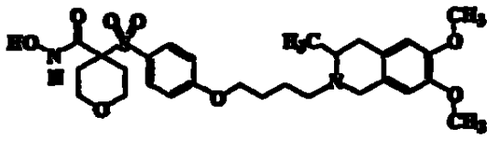
VIII-45



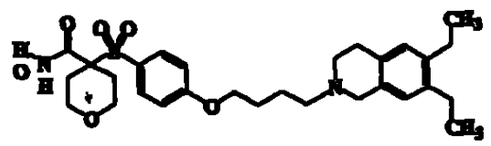
VIII-46



VIII-47

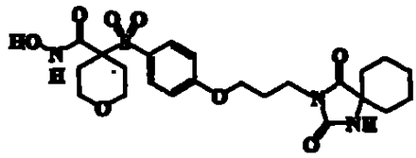


VIII-48



VIII-49

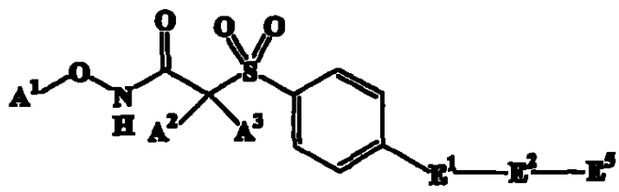
[373] In some preferred embodiments, R^5 is heterocyclyl that is substituted on the same atom with two substituents independently selected from the group consisting of alkyl and haloalkyl, the two substituents together forming C_3-C_6-cycloalkyl or halo-C_3-C_6-cycloalkyl. This heterocyclyl also optionally is substituted with one or more substituents independently selected from the group consisting of and halogen, -OH, -NO_2, -CN, keto, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl. The heterocyclyl that is substituted may be, for example, selected from the group consisting of dihydrofuranyl, tetrahydrofuranyl, dihydrothiophenyl, tetrahydrothiophenyl, pyrrolinyl, pyrrolidinyl, imidazolinyl, imidazolidinyl, pyrazolinyl, pyrazolidinyl, dithiolyl, oxathiolyl, thiazolinyl, isothiazolinyl, thiazolidinyl, isothiazolidinyl, oxathiolanyl, pyranyl, dihydropyranyl, piperidinyl, piperazinyl, and morpholinyl. Such compounds include, for example:



VIII-50

Preferred Embodiment No. 8

[374] In some embodiments of this invention, the compound has a structure corresponding to Formula IX:



IX

[375] A^1, A^2, and A^3 are as defined above for Formula I.

[376] E^1 is -O-, -$S(O)_2$-, -S(O)-, -$N(R^1)$-, -C(O)-$N(R^1)$-, -$N(R^1)$-C(O)-, or -$C(R^1)(R^2)$-.

[377] E^2 forms a link of at least 4 carbon atoms between E^1 and E^3. E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of this group optionally is substituted.

[378] In some preferred embodiments, E^2 is C_4-C_{20}-alkyl, cycloalkyl, C_1-C_{10}-alkyl-cycloalkyl, cycloalkyl-C_1-C_{10}-alkyl, or C_1-C_{10}-alkyl-cycloalkyl-C_1-C_{10}-alkyl. Any member of this group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, C_1-C_6-alkyl, and halo-C_1-C_6-alkyl.

[379] In some preferred embodiments, E^2 is C_4-C_6-alkyl optionally substituted with one or more halogen.

[380] In some preferred embodiments, E^2 is C_4-C_6-alkyl.

[381] E^3 is -OH or optionally-substituted carbocyclyl.

[382] In some preferred embodiments, E^3 is -OH or carbocyclyl wherein the carbocyclyl optionally is substituted with one or more substituents independently selected from the group consisting of and halogen, -OH, -NO_2, -CN, keto, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl. The carbocyclyl also optionally is substituted with two C_1-C_6-alkyl or halo-C_1-C_6-alkyl groups on the same atom that form a C_3-C_6-cycloalkyl or C_3-C_6-halocycloalkyl.

[383] In some preferred embodiments, E^3 is -OH or carbocyclyl wherein the carbocyclyl optionally is substituted with one or more substituents independently selected from the group consisting of and halogen, -OH, -NO_2, -CN, keto, C_1-C_6-alkyl,

halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl.

[384] R^1 and R^2 are independently selected from the group consisting of -H and alkyl. The alkyl optionally is substituted. Neither R^1 nor R^2 forms a ring structure with E^5.

[385] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_6-alkyl, and halo-C_1-C_6-alkyl.

[386] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_6-alkyl, and halo-C_1-C_6-alkyl.

[387] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H and C_1-C_6-alkyl.

[388] R^5 and R^6 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[389] In some preferred embodiments, R^5 and R^6 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

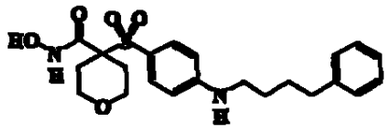
[390] R^7 is -H, C_1-C_6-alkyl, -O-R^8, -$N(R^8)(R^8)$, carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl. The C_1-C_6-alkyl, carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[391] In some preferred embodiments, R^7 is -H, C_1-C_6-alkyl, -O-R^8, -$N(R^8)(R^8)$, carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl. The C_1-C_6-alkyl, carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

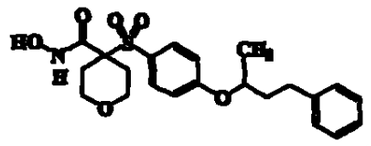
[392] R^8 and R^9 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[393] In some preferred embodiments, R^8 and R^9 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen. Such compounds include, for example:

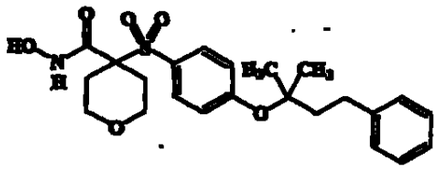
[394] In some preferred embodiments, R^5 is optionally-substituted carbocyclyl, often preferably optionally-substituted aryl, and more preferably optionally-substituted phenyl. Such compounds include, for example:



IX-1

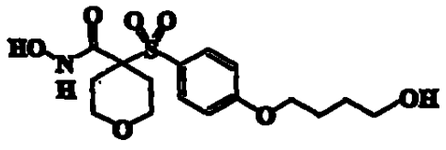


IX-2

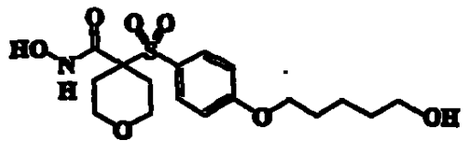


IX-3

[395] In some preferred embodiments, R^5 is -OH. Such compounds include, for example:



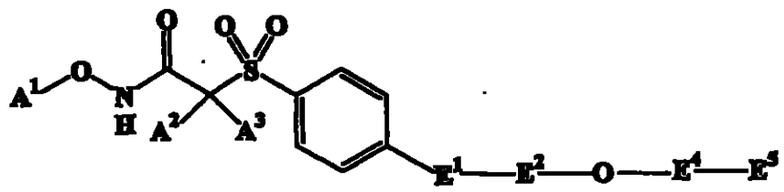
IX-4



IX-5

Preferred Embodiment No. 9

[396] In some embodiments of this invention, the compound has a structure corresponding to Formula X:



X

[397] A^1, A^2, and A^3 are as defined above for Formula I.

[398] E^1 is $-S(O)_2-$, $-S(O)-$, $-N(R^1)-$, $-C(O)-N(R^1)-$, $-N(R^1)-C(O)-$, or $-C(R^1)(R^2)-$.

[399] E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of this group optionally is substituted.

[400] In some preferred embodiments, E^2 is C_1-C_{20}-alkyl, cycloalkyl, C_1-C_{10}-alkylcycloalkyl, cycloalkyl-C_1-C_{10}-alkyl, or C_1-C_{10}-alkylcycloalkyl-C_1-C_{10}-alkyl. Any member of this group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, C_1-C_6-alkyl, C_1-C_6-halo-alkyl.

[401] In some preferred embodiments, E^2 is C_2-C_6-alkyl optionally substituted with one or more halogen.

[402] In some preferred embodiments, E^2 is C_2-C_6-alkyl.

[403] E^4 is a bond, alkyl, or alkenyl. The alkyl and alkenyl optionally are substituted.

[404] In some preferred embodiments, E^4 is a bond, C_1-C_{20}-alkyl, halo-C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, or halo-C_2-C_{20}-alkenyl.

[405] In some preferred embodiments, E^4 is a bond, C_1-C_3-alkyl, halo-C_1-C_3-alkyl, C_2-C_3-alkenyl, or halo-C_2-C_3-alkenyl.

[406] In some preferred embodiments, E^4 is a bond, C_1-C_3-alkyl, or C_2-C_3-alkenyl.

[407] E^5 is alkyl, alkenyl, alkynyl, alkoxy, alkoxyalkyl, carbocyclyl, or heterocyclyl. Any member of this group optionally is substituted.

[408] In some preferred embodiments, E^5 is C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, C_1-C_{20}-alkoxy, C_1-C_{20}-alkoxy-C_1-C_{20}-alkyl, carbocyclyl, or heterocyclyl.

The C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, C_1-C_{20}-alkoxy, and C_1-C_{20}-alkoxy-C_1-C_{20}-alkyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, and -CN. The carbocyclyl and heterocyclyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, keto, C_1-C_8-alkyl, halo-C_1-C_8-alkyl, C_1-C_8-alkoxy, halo-C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, halogen-substituted C_1-C_8-alkoxy-C_1-C_8-alkyl, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_8-alkyl, and halogen-substituted carbocyclyl-C_1-C_8-alkyl.

[409] In some preferred embodiments, E^5 is C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, carbocyclyl, or heterocyclyl. The C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, C_1-C_8-alkoxy, and C_1-C_8-alkoxy-C_1-C_8-alkyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, and -CN. The carbocyclyl and heterocyclyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, keto, C_1-C_8-alkyl, halo-C_1-C_8-alkyl, C_1-C_8-alkoxy, halo-C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, halogen-substituted C_1-C_8-alkoxy-C_1-C_8-alkyl, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_8-alkyl, and halogen-substituted carbocyclyl-C_1-C_8-alkyl.

[410] R^1 and R^2 are independently selected from the group consisting of -H and alkyl. The alkyl optionally is substituted. Neither R^1 nor R^2 forms a ring structure with E^2, E^4, or E^5.

[411] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_8-alkyl, and halo-C_1-C_8-alkyl.

[412] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_8-alkyl, and halo-C_1-C_8-alkyl.

[413] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H and C_1-C_8-alkyl.

[414] R^5 and R^6 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl. Except where the member is -H, any member of this group may

be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[415] In some preferred embodiments, R^5 and R^6 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[416] R^7 is -H, C_1-C_6-alkyl, -O-R^8, -N(R^8)(R^9), carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl. The C_1-C_6-alkyl, carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[417] In some preferred embodiments, R^7 is -H, C_1-C_6-alkyl, -O-R^8, -N(R^8)(R^9), carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl. The C_1-C_6-alkyl, carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

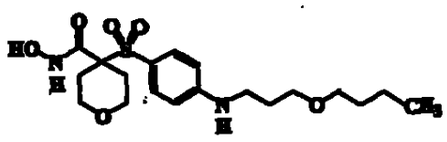
[418] R^8 and R^9 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[419] In some preferred embodiments, R^8 and R^9 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

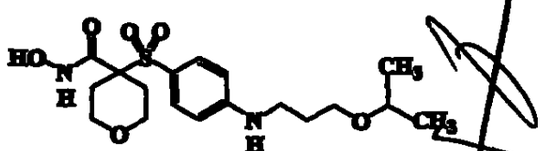
[420] In some preferred embodiments, E^5 is C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkoxy, or C_1-C_6-alkoxy-C_1-C_6-alkyl. The C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkoxy, and C_1-C_6-alkoxy-C_1-C_6-alkyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, and -CN.

[421] In some preferred embodiments, E^5 is C_1-C_6-alkyl. Such compounds include, for example:

183



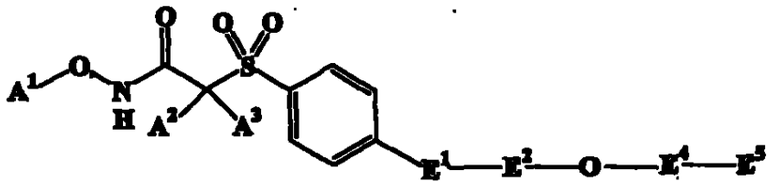
X-1



X-2

Preferred Embodiment No. 10

[422] In some embodiments of this invention, the compound has a structure corresponding to Formula XI:



XI

[423] A^1, A^2, and A^3 are as defined above for Formula I.

[424] E^2 comprises at least 3 carbon atoms. E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of this group optionally is substituted.

[425] In some preferred embodiments, E^2 is C_3-C_{20}-alkyl, cycloalkyl, C_1-C_{10}-alkylcycloalkyl, cycloalkyl-C_1-C_{10}-alkyl, or C_1-C_{10}-alkylcycloalkyl-C_1-C_{10}-alkyl. Any member of this group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, C_1-C_6-alkyl, and halo-C_1-C_6-alkyl.

[426] In some preferred embodiments, E^2 is C_3-C_{10}-alkyl optionally is substituted with one or more halogen.

[427] In some preferred embodiments, E^2 is C_3-C_{10}-alkyl.

[428] In some preferred embodiments, E^2 is C_3-C_5-alkyl.

[429] E^5 is -H, alkyl, alkenyl, alkynyl, alkoxyalkyl, carbocyclyl, carbocyclylalkoxyalkyl, heterocyclyl, heterocyclylalkyl, or heterocyclylalkoxyalkyl. The alkyl, alkenyl, alkynyl, and alkoxyalkyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, and -CN. The carbocyclyl, carbocyclylalkoxyalkyl, heterocyclyl, heterocyclylalkyl, and

heterocyclylalkoxyalkyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, alkyl, haloalkyl, alkoxy, haloalkoxy, alkoxyalkyl, halogen-substituted alkoxyalkyl, -$N(R^3)(R^4)$, -$C(O)(R^5)$, -S-R^3, -$S(O)_2$-R^3, carbocyclyl, halocarbocyclyl, carbocyclylalkyl, and halogen-substituted carbocyclylalkyl.

[430] In some preferred embodiments, E^5 is -H, C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, C_1-C_{20}-alkoxy-C_1-C_{20}-alkyl, carbocyclyl, carbocyclyl-C_1-C_{10}-alkoxy-C_1-C_{10}-alkyl, heterocyclyl, heterocyclyl-C_1-C_{10}-alkyl, or heterocyclyl-C_1-C_{10}-alkoxy-C_1-C_{10}-alkyl. The C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, and C_1-C_{20}-alkoxy-C_1-C_{20}-alkyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, and -CN. The carbocyclyl, carbocyclyl-C_1-C_{10}-alkoxy-C_1-C_{10}-alkyl, heterocyclyl, heterocyclyl-C_1-C_{10}-alkyl, and heterocyclyl-C_1-C_{10}-alkoxy-C_1-C_{10}-alkyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, keto, C_1-C_8-alkyl, halo-C_1-C_8-alkyl, C_1-C_8-alkoxy, halo-C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, halogen-substituted C_1-C_8-alkoxy-C_1-C_8-alkyl, -$N(R^3)(R^4)$, -$C(O)(R^5)$, -S-R^3, -$S(O)_2$-R^3, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_8-alkyl, and halogen-substituted carbocyclyl-C_1-C_8-alkyl.

[431] In some preferred embodiments, E^5 is -H, C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, C_1-C_8-alkoxy-C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkoxy-C_1-C_8-alkyl, heterocyclyl, heterocyclyl-C_1-C_8-alkyl, or heterocyclyl-C_1-C_8-alkoxy-C_1-C_8-alkyl. The C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, and C_1-C_8-alkoxy-C_1-C_8-alkyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, and -CN. The carbocyclyl, carbocyclyl-C_1-C_8-alkoxy-C_1-C_8-alkyl, heterocyclyl, heterocyclyl-C_1-C_8-alkyl, and heterocyclyl-C_1-C_8-alkoxy-C_1-C_8-alkyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, keto, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^3)(R^4)$, -$C(O)(R^5)$, -S-R^3, -$S(O)_2$-R^3, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl.

185

[432] R^1 and R^2 are independently selected from the group consisting of -H, alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, and heterocyclylalkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[433] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[434] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[435] R^3 is -H, alkyl, -O-R^4, -N(R^4)(R^5), carbocyclylalkyl, or heterocyclylalkyl. The alkyl, carbocyclylalkyl, or heterocyclylalkyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[436] In some preferred embodiments, R^3 is -H, C_1-C_8-alkyl, -O-R^4, -N(R^4)(R^5), carbocyclyl-C_1-C_8-alkyl, or heterocyclyl-C_1-C_8-alkyl. The C_1-C_8-alkyl, carbocyclyl-C_1-C_8-alkyl, or heterocyclyl-C_1-C_8-alkyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[437] In some preferred embodiments, R^3 is -H, C_1-C_6-alkyl, -O-R^4, -N(R^4)(R^5), carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl. The C_1-C_6-alkyl, carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

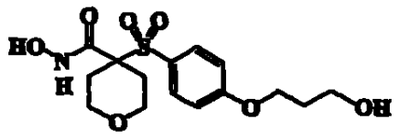
[438] R^4 and R^5 are independently selected from the group consisting of -H, alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, and heterocyclylalkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[439] In some preferred embodiments, R^4 and R^5 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl. Except where the member is -H, any member

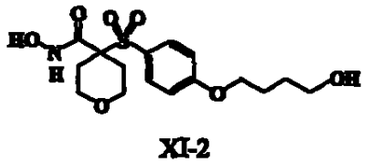
of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[440] In some preferred embodiments, R^4 and R^5 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

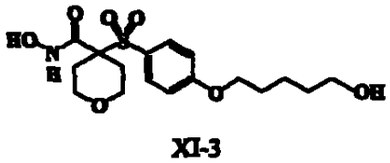
[441] In some preferred embodiments, E^5 is -H, C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, or C_1-C_8-alkoxy-C_1-C_8-alkyl. The C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, and C_1-C_8-alkoxy-C_1-C_8-alkyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, and -CN. Such compounds include, for example:



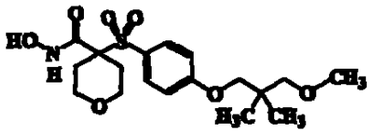
XI-1



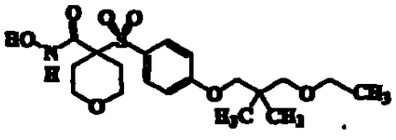
XI-2



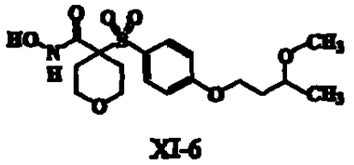
XI-3



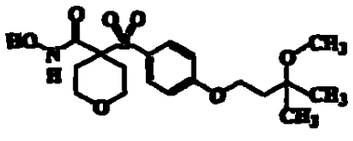
XI-4



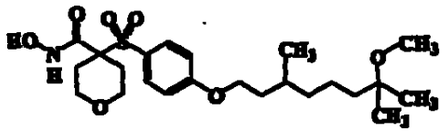
XI-5



XI-6



XI-7



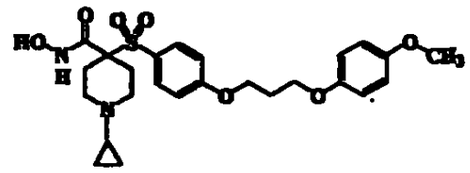
XI-8

[442] In some preferred embodiments, E^5 is carbocyclyl, carbocyclyl-C_1-C_8-alkoxy-C_1-C_8-alkyl, heterocyclyl, heterocyclyl-C_1-C_8-alkyl, or heterocyclyl-C_1-C_8-alkoxy-C_1-C_8-alkyl. the carbocyclyl,

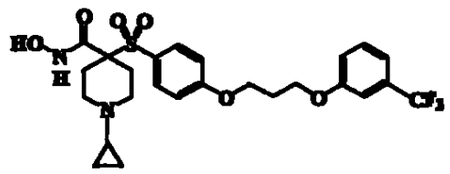
carbocyclyl-C_1-C_6-alkoxy-C_1-C_6-alkyl, heterocyclyl, heterocyclyl-C_1-C_6-alkyl, and heterocyclyl-C_1-C_6-alkoxy-C_1-C_6-alkyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, keto, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^3)(R^4)$, -$C(O)(R^5)$, -S-R^3, -$S(O)_2$-R^3, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl.

[443] In some preferred embodiments, E^5 is optionally-substituted carbocyclyl.

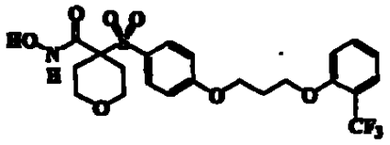
[444] In some preferred embodiments, E^5 is optionally-substituted phenyl. Such compounds include, for example:



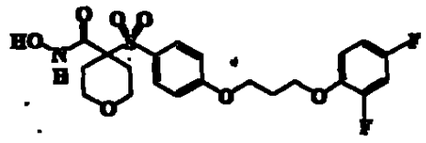
XI-9



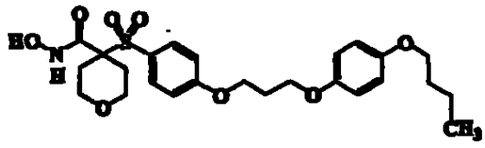
XI-10



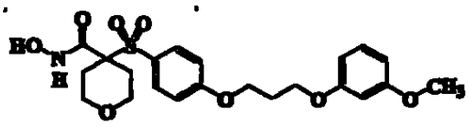
XI-11



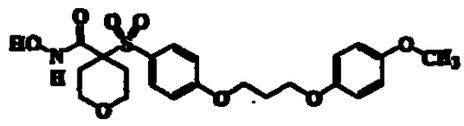
XI-12



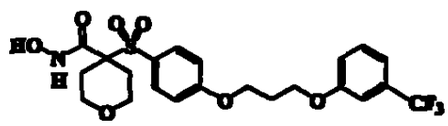
XI-13



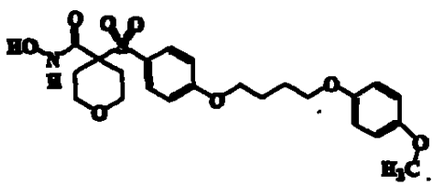
XI-14



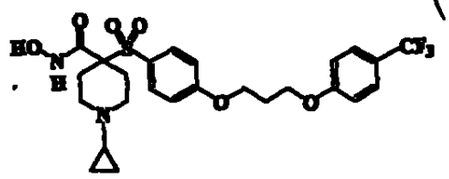
XI-15



XI-16

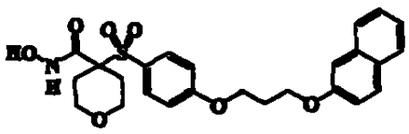


XI-17



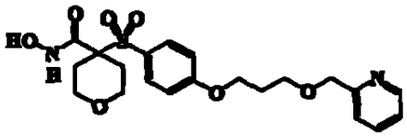
XI-18

[445] In some preferred embodiments, E^5 is optionally-substituted naphthalenyl. Such compounds include, for example:

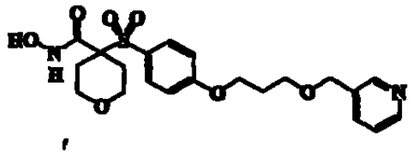


XI-19

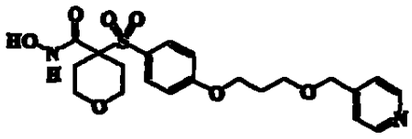
[446] In some preferred embodiments, E^5 is heterocyclyl or heterocyclyl-C_1-C_6-alkyl. Such compounds include, for example:



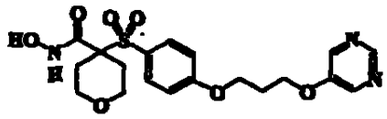
XI-20



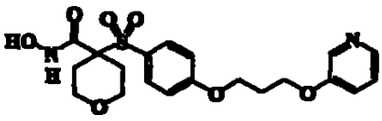
XI-21



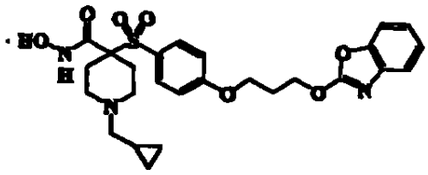
XI-22



XI-23



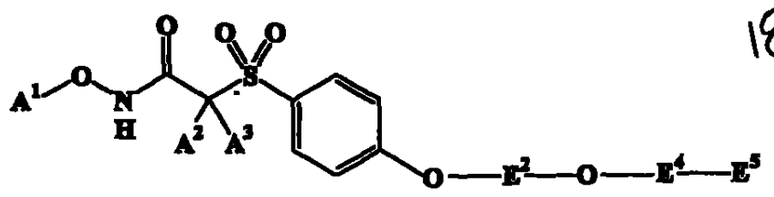
XI-24



XI-24

Preferred Embodiment No. 11

[447] In some embodiments of this invention, the compound has a structure corresponding to Formula XII:



XII

[448] A^1, A^2, and A^3 are as defined above for Formula I.

[449] E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of this group optionally is substituted. An atom in E^2 optionally is bound to an atom in E^5 to form a ring.

[450] In some preferred embodiments, E^2 is C_1-C_{20}-alkyl, cycloalkyl, C_1-C_{10}-alkylcycloalkyl, cycloalkyl-C_1-C_{10}-alkyl, or C_1-C_{10}-alkylcycloalkyl-C_1-C_{10}-alkyl. Any member of this group optionally is substituted with one or more substituents selected from the group consisting of halogen, C_1-C_6-alkyl, halo-C_1-C_6-alkyl.

[451] In some preferred embodiments, E^2 is C_2-C_6-alkyl optionally substituted with one or more halogen.

[452] In some preferred embodiments, E^2 is C_2-C_6-alkyl.

[453] E^4 is a bond, alkyl, or alkenyl. The alkyl and alkenyl optionally are substituted.

[454] In some preferred embodiments, E^4 is a bond, C_1-C_{20}-alkyl, halo-C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, or halo-C_2-C_{20}-alkenyl.

[455] In some preferred embodiments, E^4 is a bond, C_1-C_3-alkyl, halo-C_1-C_3-alkyl, C_2-C_3-alkenyl, or halo-C_2-C_3-alkenyl.

[456] In some preferred embodiments, E^4 is a bond, C_1-C_3-alkyl, or C_2-C_3-alkenyl.

[457] In some preferred embodiments, E^4 is methyl.

[458] In some preferred embodiments, E^4 is a bond.

[459] E^5 is:

an optionally-substituted radical selected from the group consisting of alkenyl, alkynyl, alkoxy, alkoxyalkyl, fused-ring carbocyclyl, and heterocyclyl; or

single-ring carbocyclyl substituted with one or more substituents independently selected from the group consisting of -OH, -NO_2, -CN, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbocyclyl, halocarbocyclyl, carbocyclylalkyl,

halogen-substituted carbocyclylalkyl, heterocyclyl, haloheterocyclyl, heterocyclylalkyl, and halogen-substituted heterocyclylalkyl; or

single-ring carbocyclyl having multiple substitutions.

[460] In some preferred embodiments, E^5 is C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, C_1-C_{20}-alkoxy, C_1-C_{20}-alkoxy-C_1-C_{20}-alkyl, heterocyclyl, single-ring carbocyclyl, or fused-ring carbocyclyl. The C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, C_1-C_{20}-alkoxy, and C_1-C_{20}-alkoxy-C_1-C_{20}-alkyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, and -CN. The heterocyclyl and fused-ring carbocyclyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_8-alkyl, halo-C_1-C_8-alkyl, C_1-C_8-alkoxy, halo-C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, halogen-substituted C_1-C_8-alkoxy-C_1-C_8-alkyl, $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_8-alkyl, halogen-substituted carbocyclyl-C_1-C_8-alkyl, heterocyclyl, haloheterocyclyl, heterocyclyl-C_1-C_8-alkyl, and halogen-substituted heterocyclyl-C_1-C_8-alkyl. The single-ring carbocyclyl is either:

substituted with one or more substituents independently selected from the group consisting of -OH, $-NO_2$, -CN, $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_8-alkyl, halogen-substituted carbocyclyl-C_1-C_8-alkyl, heterocyclyl, haloheterocyclyl, heterocyclyl-C_1-C_8-alkyl, and halogen-substituted heterocyclyl-C_1-C_8-alkyl, or

substituted with 2 or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_8-alkyl, halo-C_1-C_8-alkyl, C_1-C_8-alkoxy, halo-C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, halogen-substituted C_1-C_8-alkoxy-C_1-C_8-alkyl, $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_8-alkyl, halogen-substituted carbocyclyl-C_1-C_8-alkyl, heterocyclyl, haloheterocyclyl, heterocyclyl-C_1-C_8-alkyl, and halogen-substituted heterocyclyl-C_1-C_8-alkyl.

[461] In some preferred embodiments, E^5 is C_2-C_8-alkenyl, C_2-C_8-alkynyl, C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_2-C_8-alkyl, heterocyclyl, single-ring carbocyclyl, or fused-ring carbocyclyl. The C_2-C_8-alkenyl, C_2-C_8-alkynyl, C_1-C_8-alkoxy, and C_1-C_8-alkoxy-C_1-C_8-alkyl optionally are substituted with one or more substituents

independently selected from the group consisting of halogen, -OH, -NO_2, and -CN. The heterocyclyl and fused-ring carbocyclyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, halogen-substituted carbocyclyl-C_1-C_6-alkyl, heterocyclyl, haloheterocyclyl, heterocyclyl-C_1-C_6-alkyl, and halogen-substituted heterocyclyl-C_1-C_6-alkyl. The single-ring carbocyclyl is either:

substituted with one or more substituents independently selected from the group consisting of -OH, -NO_2, -CN, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, halogen-substituted carbocyclyl-C_1-C_6-alkyl, heterocyclyl, haloheterocyclyl, heterocyclyl-C_1-C_6-alkyl, and halogen-substituted heterocyclyl-C_1-C_6-alkyl; or

substituted with 2 or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, halogen-substituted carbocyclyl-C_1-C_6-alkyl, heterocyclyl, haloheterocyclyl, heterocyclyl-C_1-C_6-alkyl, and halogen-substituted heterocyclyl-C_1-C_6-alkyl.

[462] R^1 and R^2 are independently selected from the group consisting of -H, alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, and heterocyclylalkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[463] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[464] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl,

heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[465] R^3 is -H, alkyl, -O-R^4, -N(R^4)(R^5), carbocyclylalkyl, or heterocyclylalkyl. The alkyl, carbocyclylalkyl, or heterocyclylalkyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[466] In some preferred embodiments, R^3 is -H, C_1-C_8-alkyl, -O-R^4, -N(R^4)(R^5), carbocyclyl-C_1-C_8-alkyl, or heterocyclyl-C_1-C_8-alkyl. The C_1-C_8-alkyl, carbocyclyl-C_1-C_8-alkyl, or heterocyclyl-C_1-C_8-alkyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

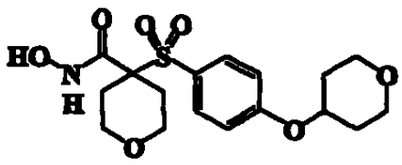
[467] In some preferred embodiments, R^3 is -H, C_1-C_6-alkyl, -O-R^4, -N(R^4)(R^5), carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl. The C_1-C_6-alkyl, carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[468] R^4 and R^5 are independently selected from the group consisting of -H, alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, and heterocyclylalkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[469] In some preferred embodiments, R^4 and R^5 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[470] In some preferred embodiments, R^4 and R^5 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

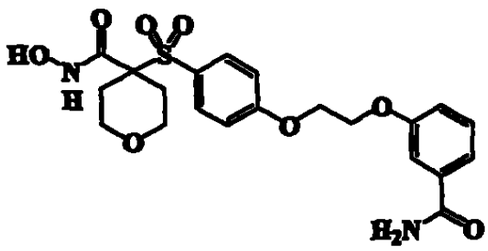
[471] In some preferred embodiments, E^2 is bound to an atom of E^5 to form a ring. Such compounds include, for example:



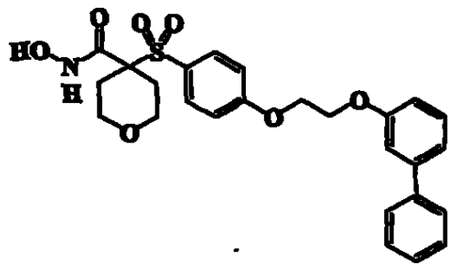
XII-1

[472] In some preferred embodiments, E^2 is not bound to an atom of E^5 to form a ring.

[473] In some such preferred embodiments, E^5 is a single-ring carbocyclyl (preferably phenyl) substituted with one or more substituents independently selected from the group consisting of -OH, $-NO_2$, -CN, $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, halogen-substituted carbocyclyl-C_1-C_6-alkyl, heterocyclyl, haloheterocyclyl, heterocyclyl-C_1-C_6-alkyl, and halogen-substituted heterocyclyl-C_1-C_6-alkyl. Such compounds include, for example:

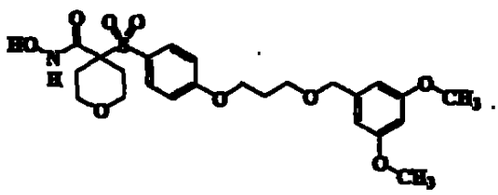


XII-2

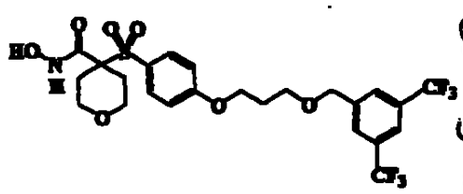


XII-3

[474] In some preferred embodiments, E^5 is single-ring carbocyclyl (preferably phenyl) substituted with 2 or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, halogen-substituted carbocyclyl-C_1-C_6-alkyl, heterocyclyl, haloheterocyclyl, heterocyclyl-C_1-C_6-alkyl, and halogen-substituted heterocyclyl-C_1-C_6-alkyl. Such compounds include, for example:

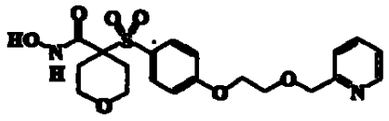


XII-4

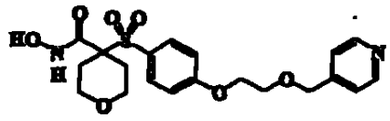


XII-5

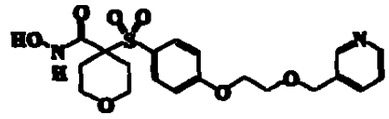
[475] In some preferred embodiments, E^5 is heterocyclyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, halogen-substituted carbocyclyl-C_1-C_6-alkyl, heterocyclyl, haloheterocyclyl, heterocyclyl-C_1-C_6-alkyl, and halogen-substituted heterocyclyl-C_1-C_6-alkyl. Such compounds include, for example:



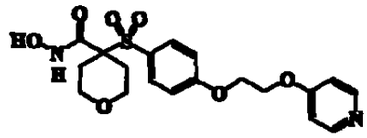
XII-6



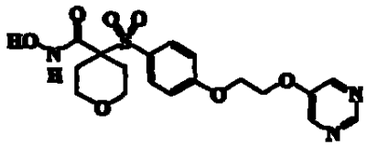
XII-7



XII-8



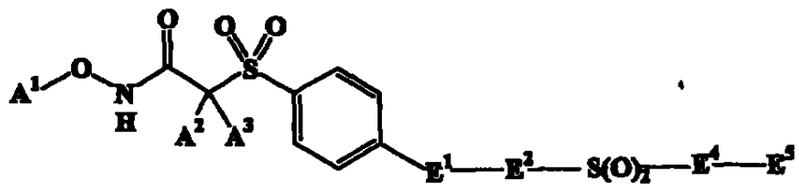
XII-9



XII-10

Preferred Embodiment No. 12

[476] In some embodiments of this invention, the compound has a structure corresponding to Formula XIII:



XIII

[477] A^1, A^2, and A^3 are as defined above for Formula I.

[478] E^1 is $-S(O)_2-$, $-S(O)-$, $-N(R^1)-$, $-C(O)-N(R^1)-$, $-N(R^1)-C(O)-$, or $-C(R^1)(R^2)-$.

[479] E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of this group optionally is substituted.

[480] In some preferred embodiments, E^2 is C_1-C_{20}-alkyl, cycloalkyl, C_1-C_{10}-alkylcycloalkyl, cycloalkyl-C_1-C_{10}-alkyl, or C_1-C_{10}-alkylcycloalkyl-C_1-C_{10}-alkyl. Any member of this group optionally is substituted with one or more substituents selected from the group consisting of halogen, C_1-C_6-alkyl, and halo-C_1-C_6-alkyl.

[481] In some preferred embodiments, E^2 is C_1-C_6-alkyl, cycloalkyl, C_1-C_6-alkylcycloalkyl, cycloalkyl-C_1-C_6-alkyl, or C_1-C_6-alkylcycloalkyl-C_1-C_6-alkyl. Any member of this group optionally is substituted with one or more halogen, although such substituent typically is preferably not substituted with halogen.

[482] E^4 is a bond, alkyl, or alkenyl. The alkyl and alkenyl optionally are substituted.

[483] In some preferred embodiments, E^4 is a bond, C_1-C_{20}-alkyl, halo-C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, or halo-C_2-C_{20}-alkenyl.

[484] In some preferred embodiments, E^4 is a bond, C_1-C_3-alkyl, halo-C_1-C_3-alkyl, C_2-C_3-alkenyl, or halo-C_2-C_3-alkenyl.

[485] In some preferred embodiments, E^4 is a bond, C_1-C_3-alkyl, or C_2-C_3-alkenyl.

[486] E^5 is alkyl, alkenyl, alkynyl, alkoxy, alkoxyalkyl, carbocyclyl, or heterocyclyl. Any member of this group optionally is substituted.

[487] In some preferred embodiments, E^5 is C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, C_1-C_{20}-alkoxy, C_1-C_{20}-alkoxy-C_1-C_{20}-alkyl, carbocyclyl, or heterocyclyl. The C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, C_1-C_{20}-alkoxy, and C_1-C_{20}-alkoxy-C_1-C_{20}-alkyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, $-OH$, $-NO_2$, and $-CN$. The

carbocyclyl and heterocyclyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl.

[488] In some preferred embodiments, E^5 is C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, carbocyclyl, or heterocyclyl. The C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkoxy, and C_1-C_6-alkoxy-C_1-C_6-alkyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, and -CN. The carbocyclyl and heterocyclyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl.

[489] R^1 and R^2 are independently selected from the group consisting of -H and alkyl. The alkyl optionally is substituted. Neither R^1 nor R^2 forms a ring structure with E^2, E^4, or E^5.

[490] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_6-alkyl, and halo-C_1-C_6-alkyl.

[491] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_6-alkyl, and halo-C_1-C_6-alkyl.

[492] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H and C_1-C_6-alkyl.

[493] R^5 and R^6 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[494] In some preferred embodiments, R^5 and R^6 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member

of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[495] R^7 is -H, C_1-C_8-alkyl, -O-R^8, -N(R^8)(R^9), carbocyclyl-C_1-C_8-alkyl, or heterocyclyl-C_1-C_8-alkyl. The C_1-C_8-alkyl, carbocyclyl-C_1-C_8-alkyl, or heterocyclyl-C_1-C_8-alkyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

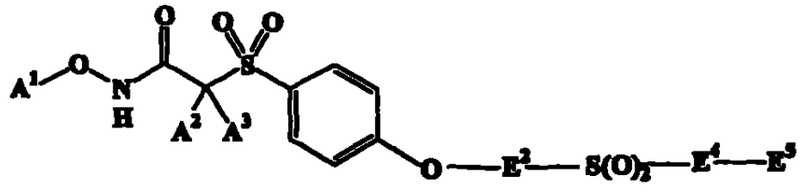
[496] In some preferred embodiments, R^7 is -H, C_1-C_6-alkyl, -O-R^8, -N(R^8)(R^9), carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl. The C_1-C_6-alkyl, carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[497] R^8 and R^9 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[498] In some preferred embodiments, R^8 and R^9 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

Preferred Embodiment No. 13

[499] In some embodiments of this invention, the compound has a structure corresponding to Formula XIV:



XIV

[500] A^1, A^2, and A^3 are as defined above for Formula I.

[501] E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of this group optionally is substituted.

[502] In some preferred embodiments, E^2 is C_1-C_{20}-alkyl, cycloalkyl, C_1-C_{10}-alkylcycloalkyl, cycloalkyl-C_1-C_{10}-alkyl, or C_1-C_{10}-alkylcycloalkyl-C_1-C_{10}-alkyl. Any member of this group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, C_1-C_6-alkyl, and halo-C_1-C_6-alkyl.

[503] In some preferred embodiments, E^2 is C_1-C_6-alkyl optionally substituted with one or more halogen.

[504] In some preferred embodiments, E^2 is C_1-C_6-alkyl.

[505] E^4 is alkyl or alkenyl. The alkyl and alkenyl optionally are substituted.

[506] In some preferred embodiments, E^4 is C_1-C_{20}-alkyl, halo-C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, or halo-C_2-C_{20}-alkenyl.

[507] In some preferred embodiments, E^4 is C_1-C_3-alkyl, halo-C_1-C_3-alkyl, C_2-C_3-alkenyl, or halo-C_2-C_3-alkenyl.

[508] In some preferred embodiments, E^4 is C_1-C_3-alkyl or C_2-C_3-alkenyl.

[509] E^5 is -H, alkyl, alkenyl, alkynyl, alkoxy, carbocyclyl, or heterocyclyl. Any member of this group optionally is substituted.

[510] In some preferred embodiments, E^5 is -H, C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, C_1-C_{20}-alkoxy, carbocyclyl, or heterocyclyl. The C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, and C_1-C_{20}-alkoxy optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, and -CN. The carbocyclyl and heterocyclyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_8-alkyl, halo-C_1-C_8-alkyl, C_1-C_8-alkoxy, halo-C_1-C_8-alkoxy, $-N(R^3)(R^4)$, $-C(O)(R^5)$, $-S-R^3$, $-S(O)_2-R^3$, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_8-alkyl, and halogen-substituted carbocyclyl-C_1-C_8-alkyl.

[511] In some preferred embodiments, E^5 is -H, C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, C_1-C_8-alkoxy, carbocyclyl, or heterocyclyl. The C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, and C_1-C_8-alkoxy optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, and -CN. The carbocyclyl and heterocyclyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_8-alkyl, halo-C_1-C_8-alkyl, C_1-C_8-alkoxy, halo-C_1-C_8-alkoxy, $-N(R^3)(R^4)$,

199

-C(O)(R^5), -S-R^3, -S(O)$_2$-R^3, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl.

[512] R^3 and R^4 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[513] In some preferred embodiments, R^3 and R^4 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[514] R^5 is -H, C_1-C_8-alkyl, -O-R^6, -N(R^6)(R^7), carbocyclyl-C_1-C_8-alkyl, or heterocyclyl-C_1-C_8-alkyl. The C_1-C_8-alkyl, carbocyclyl-C_1-C_8-alkyl, or heterocyclyl-C_1-C_8-alkyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[515] In some preferred embodiments, R^5 is -H, C_1-C_6-alkyl, -O-R^6, -N(R^6)(R^7), carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl. The C_1-C_6-alkyl, carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

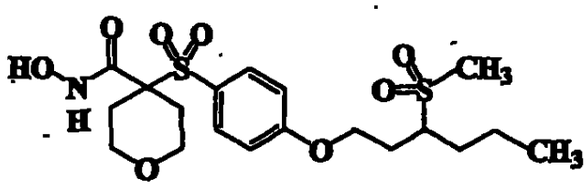
[516] R^6 and R^7 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[517] In some preferred embodiments, R^6 and R^7 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[518] In some preferred embodiments, E^3 is -H, C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, or C_1-C_8-alkoxy. The C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, and

200

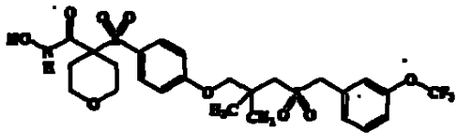
C_1-C_8-alkoxy optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, and -CN. In one such embodiment, E^5 is C_1-C_8-alkyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, and -CN. Such compounds include, for example:



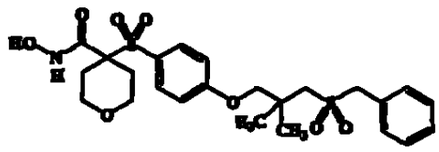
XIV-1

[519] In some preferred embodiments, E^5 is optionally-substituted carbocyclyl and optionally-substituted heterocyclyl.

[520] In some preferred embodiments, E^5 is optionally-substituted aryl, often preferably optionally-substituted phenyl. Such compounds include, for example:



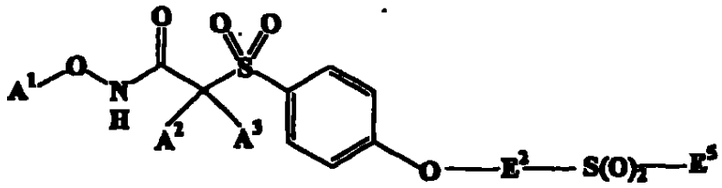
XIV-2



XIV-3

Preferred Embodiment No. 14

[521] In some embodiments of this invention, the compound has a structure corresponding to Formula XV:



XV

[522] A^1, A^2, and A^3 are as defined above for Formula I.

[523] E^2 comprises less than 5 carbon atoms. E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of this group optionally is substituted, but preferably is not substituted.

[524] E^5 is alkyl, alkenyl, alkynyl, alkoxyalkyl, carbocyclyl, or heterocyclyl. Any member of this group optionally is substituted.

[525] In some preferred embodiments, E^5 is C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, C_1-C_{20}-alkoxy-C_1-C_{20}-alkyl, carbocyclyl, or heterocyclyl. The C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, and C_1-C_{20}-alkoxy-C_1-C_{20}-alkyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, and -CN. The carbocyclyl and heterocyclyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, keto, C_1-C_8-alkyl, halo-C_1-C_8-alkyl, C_1-C_8-alkoxy, halo-C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, halogen-substituted C_1-C_8-alkoxy-C_1-C_8-alkyl, -$N(R^3)(R^4)$, -$C(O)(R^5)$, -S-R^3, -$S(O)_2$-R^3, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_8-alkyl, halogen-substituted carbocyclyl-C_1-C_8-alkyl, C_1-C_8-alkylcarbocyclyloxy, and halogen-substituted C_1-C_8-alkylcarbocyclyloxy.

[526] In some preferred embodiments, E^5 is C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, C_1-C_8-alkoxy-C_1-C_8-alkyl, carbocyclyl, or heterocyclyl. The C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, andC_1-C_8-alkoxy-C_1-C_8-alkyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, and -CN. The carbocyclyl and heterocyclyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, keto, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^3)(R^4)$, -$C(O)(R^5)$, -S-R^3, -$S(O)_2$-R^3, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, halogen-substituted carbocyclyl-C_1-C_6-alkyl, C_1-C_6-alkylcarbocyclyloxy, and halogen-substituted C_1-C_6-alkylcarbocyclyloxy.

[527] R^3 and R^4 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[528] In some preferred embodiments, R^3 and R^4 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl. Except where the member is -H, any member

of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[529] R^5 is -H, C_1-C_8-alkyl, -O-R^6, -N(R^6)(R^7), carbocyclyl-C_1-C_8-alkyl, or heterocyclyl-C_1-C_8-alkyl. The C_1-C_8-alkyl, carbocyclyl-C_1-C_8-alkyl, or heterocyclyl-C_1-C_8-alkyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[530] In some preferred embodiments, R^5 is -H, C_1-C_8-alkyl, -O-R^6, -N(R^6)(R^7), carbocyclyl-C_1-C_8-alkyl, or heterocyclyl-C_1-C_8-alkyl. The C_1-C_8-alkyl, carbocyclyl-C_1-C_8-alkyl, or heterocyclyl-C_1-C_8-alkyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

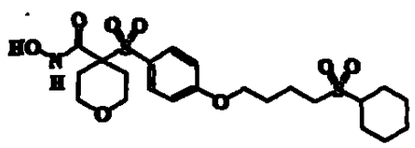
[531] R^6 and R^7 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[532] In some preferred embodiments, R^6 and R^7 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

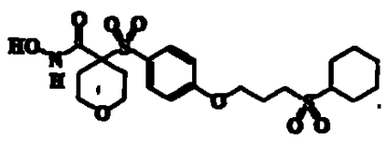
[533] In some preferred embodiments, E^5 is C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, or C_1-C_8-alkoxy-C_1-C_8-alkyl. The C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, and C_1-C_8-alkoxy-C_1-C_8-alkyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, and -CN.

[534] In some preferred embodiments, E^5 is optionally-substituted carbocyclyl.

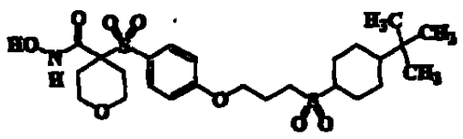
[535] In some preferred embodiments, E^5 is optionally-substituted C_3-C_6-cycloalkyl. Such compounds include, for example:



XV-1

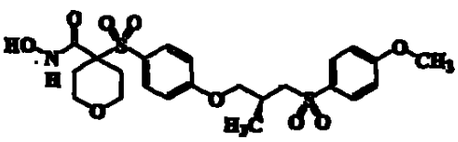


XV-2

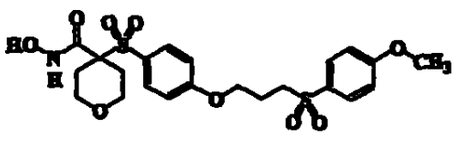


XV-3

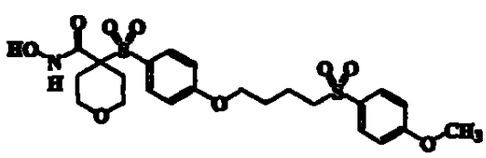
[536] In some preferred embodiments, E^5 is optionally-substituted phenyl. Such compounds include, for example:



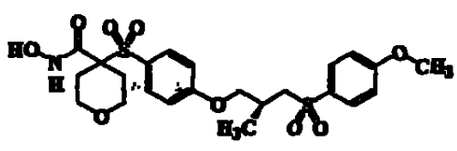
XV-4



XV-5



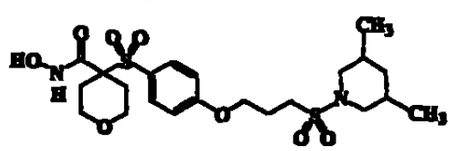
XV-6



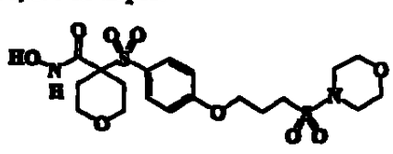
XV-7

[537] In some preferred embodiments, E^5 is optionally-substituted heterocyclyl.

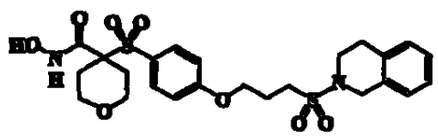
[538] In some preferred embodiments, E^5 is optionally-substituted heterocyclyl selected from the group consisting of piperidinyl, morpholinyl, and tetrahydroisoquinolinyl . Such compounds include, for example:



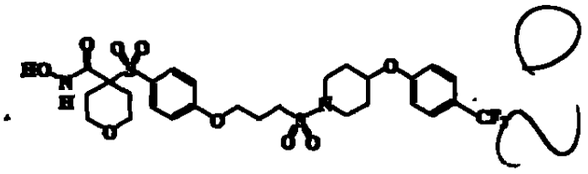
XV-8



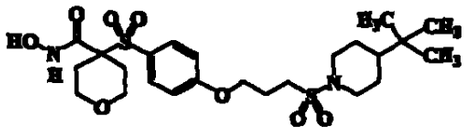
XV-9



XV-10



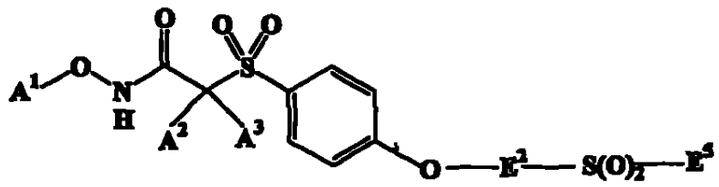
XV-11



XV-12

Preferred Embodiment No. 15

[539] In some embodiments of this invention, the compound has a structure corresponding to Formula XVI:



XVI

[540] A^1, A^2, and A^3 are as defined above for Formula I.

[541] E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of this group optionally is substituted.

[542] In some preferred embodiments, E^2 is C_1-C_{20}-alkyl, cycloalkyl, C_1-C_{10}-alkylcycloalkyl, cycloalkyl-C_1-C_{10}-alkyl, or C_1-C_{10}-alkylcycloalkyl-C_1-C_{10}-alkyl. Any member of this group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, C_1-C_6-alkyl, halo-C_1-C_6-alkyl.

[543] In some preferred embodiments, E^2 is C_1-C_6-alkyl optionally substituted with one or more halogen.

[544] In some preferred embodiments, E^2 is C_1-C_6-alkyl.

[545] E^5 is alkyl, alkenyl, alkynyl, alkoxyalkyl, saturated carbocyclyl, partially saturated carbocyclyl, or heterocyclyl. Any member of this group optionally is substituted.

[546] In some preferred embodiments, E^5 is C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, C_1-C_{20}-alkoxy-C_1-C_{20}-alkyl, saturated carbocyclyl, partially saturated carbocyclyl, or heterocyclyl. The C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, and C_1-C_{20}-alkoxy-C_1-C_{20}-alkyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, and -CN. The saturated carbocyclyl, partially saturated carbocyclyl, and heterocyclyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^3)(R^4)$, -$C(O)(R^5)$, -S-R^3, -$S(O)_2$-R^3, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, halogen-substituted carbocyclyl-C_1-C_6-alkyl, C_1-C_6-alkylcarbocyclyloxy, and halogen-substituted C_1-C_6-alkylcarbocyclyloxy.

[547] In some preferred embodiments, E^5 is C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkoxy-C_1-C_6-alkyl, saturated carbocyclyl, partially saturated carbocyclyl, or heterocyclyl. The C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, and C_1-C_6-alkoxy-C_1-C_6-alkyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, and -CN. The saturated carbocyclyl, partially saturated carbocyclyl, and heterocyclyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^3)(R^4)$, -$C(O)(R^5)$, -S-R^3, -$S(O)_2$-R^3, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, halogen-substituted carbocyclyl-C_1-C_6-alkyl, C_1-C_6-alkylcarbocyclyloxy, and halogen-substituted C_1-C_6-alkylcarbocyclyloxy.

[548] R^3 and R^4 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[549] In some preferred embodiments, R^3 and R^4 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[550] R^5 is a -H, C_1-C_8-alkyl, -O-R^6, -N(R^6)(R^7), carbocyclyl-C_1-C_8-alkyl, or heterocyclyl-C_1-C_8-alkyl. The C_1-C_8-alkyl, carbocyclyl-C_1-C_8-alkyl, or heterocyclyl-C_1-C_8-alkyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[551] In some preferred embodiments, R^5 is -H, C_1-C_6-alkyl, -O-R^6, -N(R^6)(R^7), carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl. The C_1-C_6-alkyl, carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[552] R^6 and R^7 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

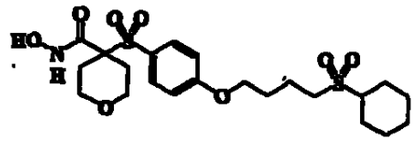
[553] In some preferred embodiments, R^6 and R^7 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[554] In some preferred embodiments, E^5 is C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, or C_1-C_8-alkoxy-C_1-C_8-alkyl. The C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, and C_1-C_8-alkoxy-C_1-C_8-alkyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, and -CN.

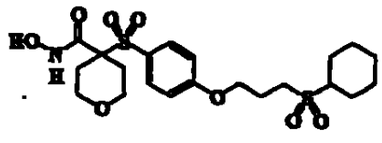
[555] In some preferred embodiments, E^5 is optionally-substituted, partially-saturated carbocyclyl.

207

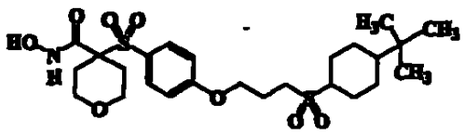
[556] In some preferred embodiments, E^5 is optionally-substituted, saturated carbocyclyl (preferably optionally-substituted C_5-C_6 cycloalkyl). Such compounds include, for example:



XVI-1

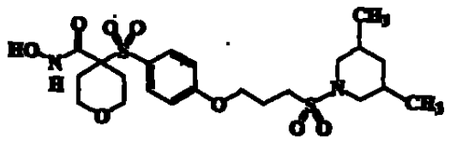


XVI-2

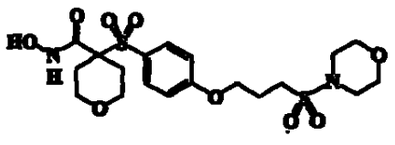


XVI-3

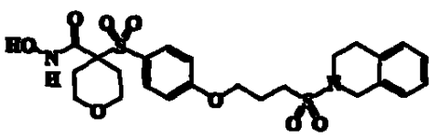
[557] In some preferred embodiments, E^5 is optionally-substituted heterocyclyl. Such compounds include, for example:



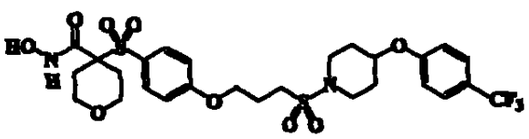
XVI-4



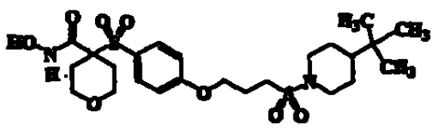
XVI-5



XVI-6



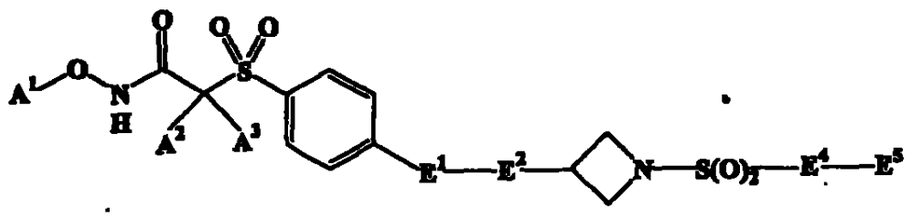
XVI-7



XVI-8

Preferred Embodiment No. 16

[558] In some embodiments of this invention, the compound has a structure corresponding to Formula XVII:



XVII

[559] A^1, A^2, and A^3 are as defined above for Formula I.

[560] E^1 is $-S(O)_2-$, $-S(O)-$, $-N(R^1)-$, $-C(O)-N(R^1)-$, $-N(R^1)-C(O)-$, or $-C(R^1)(R^2)-$.

[561] E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of this group optionally is substituted.

[562] In some preferred embodiments, E^2 is C_1-C_{20}-alkyl, cycloalkyl, C_1-C_{10}-alkylcycloalkyl, cycloalkyl-C_1-C_{10}-alkyl, or C_1-C_{10}-alkylcycloalkyl-C_1-C_{10}-alkyl. Any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[563] In some preferred embodiments, E^2 is C_1-C_6-alkyl optionally substituted with one or more halogen.

[564] In some preferred embodiments, E^2 is C_1-C_6-alkyl.

[565] E^4 is a bond, alkyl, or alkenyl, The alkyl and alkenyl optionally are substituted.

[566] In some preferred embodiments, E^4 is a bond, C_1-C_{20}-alkyl, halo-C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, or halo-C_2-C_{20}-alkenyl.

[567] In some preferred embodiments, E^4 is a bond, C_1-C_3-alkyl, halo-C_1-C_3-alkyl, C_2-C_3-alkenyl, or halo-C_2-C_3-alkenyl.

[568] In some preferred embodiments, E^4 is a bond, C_1-C_3-alkyl, or C_2-C_3-alkenyl.

[569] E^5 is alkyl, alkenyl, alkynyl, alkoxy, alkoxyalkyl, carbocyclyl, or heterocyclyl. Any member of this group optionally is substituted.

[570] In some preferred embodiments, E^5 is C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, C_1-C_{20}-alkoxy, C_1-C_{20}-alkoxy-C_1-C_{20}-alkyl, carbocyclyl, or heterocyclyl. The C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, C_1-C_{20}-alkoxy, and C_1-C_{20}-alkoxy-C_1-C_{20}-alkyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, and -CN. The

209

carbocyclyl and heterocyclyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl.

[571] In some preferred embodiments, E^5 is C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, carbocyclyl, or heterocyclyl. The C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkoxy, and C_1-C_6-alkoxy-C_1-C_6-alkyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, and -CN. The carbocyclyl and heterocyclyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl.

[572] R^1 and R^2 are independently selected from the group consisting of -H and alkyl. The alkyl optionally is substituted. Neither R^1 nor R^2 forms a ring structure with E^2, E^4, or E^5.

[573] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_6-alkyl, and halo-C_1-C_6-alkyl.

[574] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_6-alkyl, and halo-C_1-C_6-alkyl.

[575] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H and C_1-C_6-alkyl.

[576] R^5 and R^6 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[577] In some preferred embodiments, R^3 and R^6 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[578] R^7 is -H, C_1-C_6-alkyl, -O-R^8, -N(R^8)(R^9), carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl. The C_1-C_6-alkyl, carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

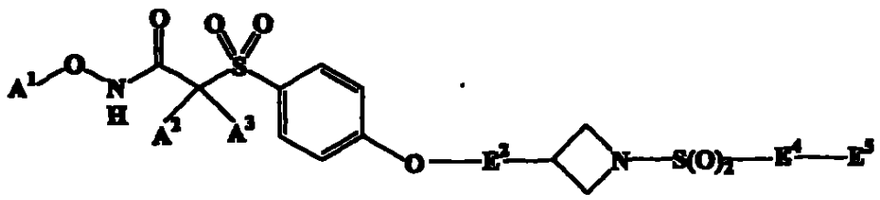
[579] In some preferred embodiments, R^7 is -H, C_1-C_6-alkyl, -O-R^8, -N(R^8)(R^9), carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl. The C_1-C_6-alkyl, carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[580] R^8 and R^9 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[581] In some preferred embodiments, R^8 and R^9 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

Preferred Embodiment No. 17

[582] In some embodiments of this invention, the compound has a structure corresponding to Formula XVII:



XVIII

[583] A^1, A^2, and A^3 are as defined above for Formula I.

[584] E^2 is a bond, alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of this group optionally is substituted.

[585] In some preferred embodiments, E^2 is a bond, C_1-C_{20}-alkyl, cycloalkyl, C_1-C_{10}-alkylcycloalkyl, cycloalkyl-C_1-C_{10}-alkyl, or C_1-C_{10}-alkylcycloalkyl-C_1-C_{10}-alkyl. Any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[586] In some preferred embodiments, E^2 is a bond, C_1-C_6-alkyl, or halo-C_1-C_6-alkyl.

[587] In some preferred embodiments, E^2 is a bond or C_1-C_6-alkyl.

[588] In some preferred embodiments, E^2 is a bond.

[589] E^4 is a bond, alkyl, or alkenyl. The alkyl and alkenyl optionally are substituted.

[590] In some preferred embodiments, E^4 is a bond, C_1-C_{20}-alkyl, halo-C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, or halo-C_2-C_{20}-alkenyl.

[591] In some preferred embodiments, E^4 is a bond, C_1-C_3-alkyl, halo-C_1-C_3-alkyl, C_2-C_3-alkenyl, or halo-C_2-C_3-alkenyl.

[592] In some preferred embodiments, E^4 is a bond, C_1-C_3-alkyl, or C_2-C_3-alkenyl.

[593] In some preferred embodiments, E^4 is a bond.

[594] E^5 is optionally-substituted heterocyclyl or substituted carbocyclyl.

[595] The E^5 heterocyclyl optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, alkyl, haloalkyl, alkoxy, haloalkoxy, alkoxyalkyl, halogen-substituted alkoxyalkyl, -$N(R^3)(R^4)$, -$C(O)(R^5)$, -S-R^3, -$S(O)_2$-R^3, carbocyclyl, halocarbocyclyl, carbocyclylalkyl, and halogen-substituted carbocyclylalkyl.

[596] In some preferred embodiments, E^5 is heterocyclyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^3)(R^4)$, -$C(O)(R^5)$, -S-R^3, -$S(O)_2$-R^3, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl.

[597] In some preferred embodiments, E^5 is heterocyclyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^3)(R^4)$, -$C(O)(R^5)$, -S-R^3, -$S(O)_2$-R^3, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl.

[598] The E^5 carbocyclyl is substituted with:

2 or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, alkyl, haloalkyl, alkoxy, haloalkoxy, alkoxyalkyl, halogen-substituted alkoxyalkyl, -$N(R^3)(R^4)$, -$C(O)(R^5)$, -S-R^3, -$S(O)_2$-R^3, carbocyclyl, halocarbocyclyl, carbocyclylalkyl, and halogen-substituted carbocyclylalkyl; or

a substituent selected from the group consisting of halogen, -OH, -NO_2, -CN, -C(O)-O-R^3, -S-R^3, -$S(O)_2$-R^3, carbocyclyl, halocarbocyclyl, carbocyclylalkyl, and halogen-substituted carbocyclylalkyl.

[599] In some preferred embodiments, E^5 is carbocyclyl substituted with:

2 or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^3)(R^4)$, -$C(O)(R^5)$, -S-R^3, -$S(O)_2$-R^3, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl, or

a substituent selected from the group consisting of halogen, -OH, $-NO_2$, -CN, $-C(O)-O-R^3$, $-S-R^3$, $-S(O)_2-R^3$, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl.

[600] In some preferred embodiments, E^3 is carbocyclyl substituted with:

2 or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^3)(R^4)$, $-C(O)(R^5)$, $-S-R^3$, $-S(O)_2-R^3$, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl, or

a substituent selected from the group consisting of halogen, -OH, $-NO_2$, -CN, $-C(O)-O-R^3$, $-S-R^3$, $-S(O)_2-R^3$, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl.

[601] R^3 and R^4 are independently selected from the group consisting of -H, alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, and heterocyclylalkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[602] In some preferred embodiments, R^3 and R^4 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[603] In some preferred embodiments, R^3 and R^4 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[604] R^5 is -H, alkyl, $-O-R^6$, $-N(R^6)(R^7)$, carbocyclylalkyl, or heterocyclylalkyl. The alkyl, carbocyclylalkyl, or heterocyclylalkyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[605] In some preferred embodiments, R^5 is -H, C_1-C_8-alkyl, $-O-R^6$, $-N(R^6)(R^7)$, carbocyclyl-C_1-C_8-alkyl, or heterocyclyl-C_1-C_8-alkyl. The C_1-C_8-alkyl,

carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[606] In some preferred embodiments, R^5 is -H, C_1-C_6-alkyl, -O-R^6, -N(R^6)(R^7), carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl. The C_1-C_6-alkyl, carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

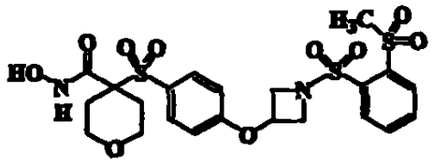
[607] R^6 and R^7 are independently selected from the group consisting of -H, alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, and heterocyclylalkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[608] In some preferred embodiments, R^6 and R^7 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

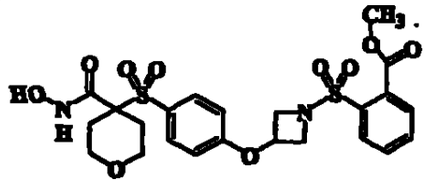
[609] In some preferred embodiments, R^6 and R^7 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group may be substituted with one or more halogen, but more typically is preferably not substituted with halogen.

[610] In some preferred embodiments, E^5 is optionally-substituted heterocyclyl.

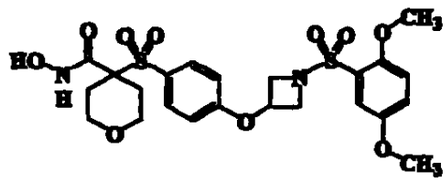
[611] In some preferred embodiments, E^5 is substituted carbocyclyl (preferably substituted phenyl). Such compounds include, for example:



XVIII-1



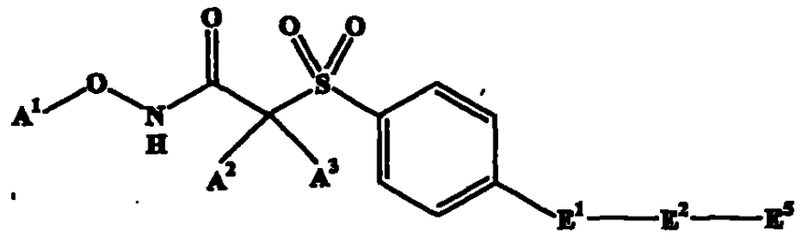
XVIII-2



XVIII-3

Preferred Embodiment No. 18

[612] In some embodiments of this invention, the compound has a structure corresponding to Formula XVIII:



XIX

[613] A^1, A^2 and A^3 are as defined above for Formula I.

[614] E^1 is -O-, -$S(O)_2$-, -S(O)-, -S-, -$N(R^1)$-, -C(O)-$N(R^1)$-, -$N(R^1)$-C(O)-, or -$C(R^1)(R^2)$-.

[615] E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of this group optionally is substituted.

[616] In some preferred embodiments, E^2 is C_1-C_{20}-alkyl, cycloalkyl, C_1-C_{10}-alkyl-cycloalkyl, cycloalkyl-C_1-C_{10}-alkyl, or C_1-C_{10}-alkyl-cycloalkyl-C_1-C_{10}-alkyl. Any member of this group optionally is substituted with one or more halogen.

[617] In some preferred embodiments, E^2 is C_1-C_8-alkyl. The alkyl optionally is substituted with one or more halogen.

[618] E^5 is substituted heterocyclyl.

[619] In some preferred embodiments, E^5 is heterocyclyl that is:

substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, keto, C_1-C_8-alkyl, halo-C_1-C_8-alkyl, C_1-C_8-alkoxy, halo-C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, halogen-substituted C_1-C_8-alkoxy-C_1-C_8-alkyl,

216

-$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbocyclyl, halocarbocyclyl, and carbocyclyl-C_1-C_6-alkyl, and/or

substituted on the same atom with two substituents independently selected from the group consisting of alkyl and haloalkyl, the two substituents together forming C_3-C_6-cycloalkyl or halo-C_3-C_6-cycloalkyl.

[620] In some preferred embodiments, B^5 is heterocyclyl that is:

substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, keto, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl, and/or

substituted on the same atom with two substituents independently selected from the group consisting of alkyl and haloalkyl, the two substituents together forming C_3-C_6-cycloalkyl or halo-C_3-C_6-cycloalkyl.

[621] R^1 and R^2 are independently selected from the group consisting of -H and alkyl. The alkyl optionally is substituted.

[622] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_6-alkyl, and halo-C_1-C_6-alkyl.

[623] R^3 and R^4 are independently selected from the group consisting of -H, C_1-C_6-alkyl, C_1-C_6-alkoxycarbonyl, C_1-C_6-alkylcarbonyl, carbocyclyl-C_1-C_6-alkyl, and carbocyclyl-C_1-C_6-alkoxycarbonyl.

[624] R^5 and R^6 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group optionally is substituted with one or more halogen.

[625] In some preferred embodiments, R^5 and R^6 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group optionally is substituted with one or more halogen.

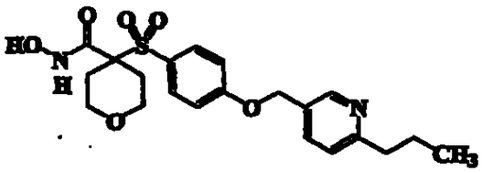
[626] R^7 is -H, C_1-C_6-alkyl, -O-R^8, -N(R^5)(R^5), carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl. The alkyl, carbocyclylalkyl, or heterocyclylalkyl may be substituted with one or more halogen.

[627] In some preferred embodiments, R^7 is -H, C_1-C_6-alkyl, -O-R^8, -N(R^5)(R^5), carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl. The alkyl, carbocyclylalkyl, and heterocyclylalkyl optionally are substituted with one or more halogen.

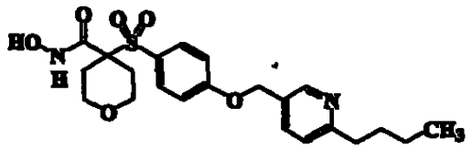
[628] R^8 and R^9 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group optionally is substituted with one or more halogen.

[629] In some preferred embodiments, R^8 and R^9 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is –H, any member of this group optionally is substituted with one or more halogen.

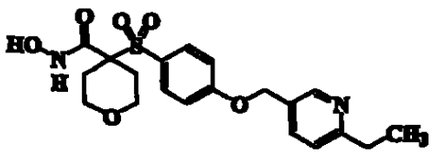
[630] Compounds of this embodiment include, for example:



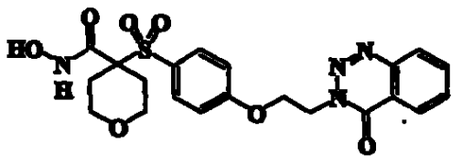
XIX-1



XIX-2



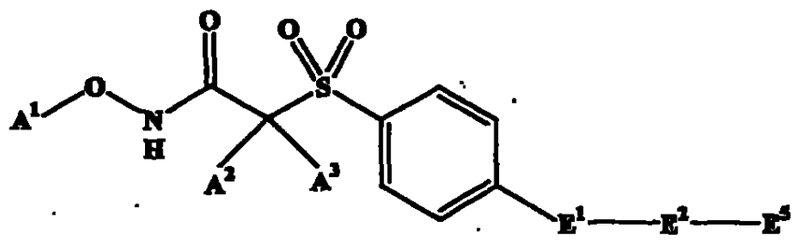
XIX-3



XIX-4

Preferred Embodiment No. 19

[631] In some embodiments of this invention, the compound has a structure corresponding to Formula XIX:



XX

[632] A^1, A^2, and A^3 are as defined above for Formula I.

[633] E^1 is -O-, -$S(O)_2$-, -S(O)-, -$N(R^1)$-, -C(O)-$N(R^1)$-, -$N(R^1)$-C(O)-, or -$C(R^1)(R^2)$-.

[634] E^2 comprises at least two carbon atoms. E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of this group optionally is substituted.

[635] In some preferred embodiments, E^2 is C_2-C_{20}-alkyl, cycloalkyl, C_1-C_{10}-alkyl-cycloalkyl, cycloalkyl-C_1-C_{10}-alkyl, or C_1-C_{10}-alkyl-cycloalkyl-C_1-C_{10}-alkyl. Any member of this group optionally is substituted with one or more halogen.

[636] In some preferred embodiments, E^2 is C_2-C_6-alkyl. The alkyl may optionally be substituted with one or more halogen.

[637] E^5 is optionally-substituted heterocyclyl.

[638] In some preferred embodiments, E^5 is heterocyclyl that is:

optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, keto, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbocyclyl, halocarbocyclyl, and carbocyclyl-C_1-C_6-alkyl, and/or

optionally substituted on the same atom with two substituents independently selected from the group consisting of alkyl and haloalkyl, the two substituents together forming C_3-C_6-cycloalkyl or halo-C_3-C_6-cycloalkyl.

[639] In some preferred embodiments, E^5 is heterocyclyl that is:

optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, keto, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl,

219

halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl, and

optionally substituted on the same atom with two substituents independently selected from the group consisting of alkyl and haloalkyl, the two substituents together forming C_3-C_6-cycloalkyl or halo-C_3-C_6-cycloalkyl.

[640] R^1 and R^2 are independently selected from the group consisting of -H and alkyl. The alkyl optionally is substituted.

[641] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_6-alkyl, and halo-C_1-C_6-alkyl.

[642] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_6-alkyl, and halo-C_1-C_6-alkyl.

[643] R^3 and R^4 are independently selected from the group consisting of -H, C_1-C_8-alkyl, C_1-C_8-alkoxycarbonyl, C_1-C_8-alkylcarbonyl, carbocyclyl-C_1-C_8-alkyl, and carbocyclyl-C_1-C_8-alkoxycarbonyl.

[644] R^5 and R^6 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl. Except where the member is –H, any member of this group optionally is substituted with one or more halogen.

[645] In some preferred embodiments, R^5 and R^6 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is –H, any member of this group optionally is substituted with one or more halogen.

[646] R^7 is -H, C_1-C_8-alkyl, -O-R^8, -$N(R^8)(R^9)$, carbocyclyl-C_1-C_8-alkyl, or heterocyclyl-C_1-C_8-alkyl. The alkyl, carbocyclylalkyl, and heterocyclylalkyl optionally are substituted with one or more halogen.

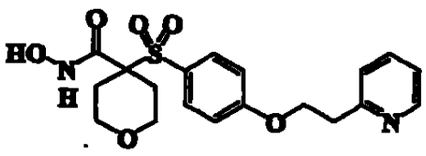
[647] In some preferred embodiments, R^7 is -H, C_1-C_6-alkyl, -O-R^8, -$N(R^8)(R^9)$, carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl. The alkyl, carbocyclylalkyl, and heterocyclylalkyl optionally are substituted with one or more halogen.

[648] R^8 and R^9 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and

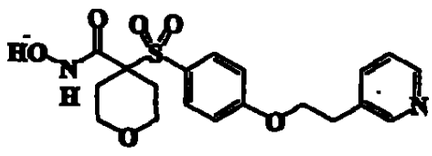
heterocyclyl-C_1-C_6-alkyl. Except where the member is –H, any member of this group optionally is substituted with one or more halogen.

[649] In some preferred embodiments, R^8 and R^9 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is –H, any member of this group optionally is substituted with one or more halogen.

[650] Some particularly preferred compounds include:



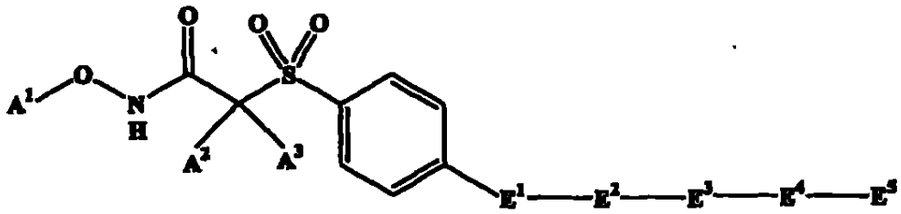
XX-1



XX-2

Preferred Embodiment No. 20

[651] In some embodiments of this invention, the compound has a structure corresponding to Formula XX:



XXI

[652] A^1, A^2, and A^3 are as defined above for Formula I.

[653] E^1 is -O-, -$S(O)_2$-, -S(O)-, -S-, -$N(R^1)$-, -C(O)-$N(R^1)$-, -$N(R^1)$-C(O)-, or -$C(R^1)(R^2)$-.

[654] E^2 is alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, or alkylcycloalkylalkyl. Any member of this group optionally is substituted.

[655] In some preferred embodiments, E^2 is C_2-C_{20}-alkyl, cycloalkyl, C_1-C_{10}-alkylcycloalkyl, cycloalkyl-C_1-C_{10}-alkyl, or C_1-C_{10}-alkylcycloalkyl-C_1-C_{10}-alkyl. Any member of this group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, C_1-C_6-alkyl, and halo-C_1-C_6-alkyl.

[656] In some preferred embodiments, E^2 is C_2-C_6-alkyl. The alkyl may optionally be substituted with one or more halogen.

[657] E^3 is -C(O)-, -O-(CO)-, -C(O)-O-, -C(NR^3)-, -N(R^4)-, -N(R^4)-C(NR^3)-, -C(NR^3)-N(R^4)-, -C(O)-N(R^4)-, -N(R^4)-C(O)-, -N(R^4)-C(O)-N(R^5)-, -S-, -S(O)-, -N(R^4)-S(O)$_2$-, -S(O)$_2$-N(R^4)-, -C(O)-N(R^4)-N(R^5)-C(O)-, -C(R^4)(R^6)-C(O)-, or -C(R^7)(R^8)-.

[658] E^4 is a bond, alkyl, or alkenyl. The alkyl and alkenyl optionally are substituted.

[659] In some preferred embodiments, E^4 is a bond, C_1-C_{20}-alkyl, or C_2-C_{20}-alkenyl. The alkyl and alkenyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, and carbocyclyl. The carbocyclyl, in turn, optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_8-alkyl, C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, halo-C_1-C_8-alkyl, halo-C_1-C_8-alkoxy, halogen-substituted C_1-C_8-alkoxy-C_1-C_8-alkyl, halocarbocyclyl, and halogen-substituted carbocyclyl-C_1-C_8-alkyl.

[660] In some preferred embodiments, E^4 is a bond, C_1-C_3-alkyl, or C_2-C_3-alkenyl. The alkyl and alkenyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen and carbocyclyl. The carbocyclyl, in turn, optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, halocarbocyclyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl.

[661] E^5 is carbocyclyl or heterocyclyl. The carbocyclyl and heterocyclyl are:

substituted with a substituent selected from the group consisting of optionally-substituted carbocyclyl, optionally-substituted carbocyclylalkyl, optionally-substituted heterocyclyl, and optionally-substituted heterocyclylalkyl, and

optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, alkyl, alkoxy, alkoxyalkyl, -$N(R^{11})(R^{12})$, -$C(O)(R^{13})$, -S-R^{11}, -$S(O)_2$-R^{11}, carbocyclyl, carbocyclylalkyl, haloalkyl, haloalkoxy, halogen-substituted alkoxyalkyl, halocarbocyclyl, halogen-substituted carbocyclylalkyl, hydroxycarbocyclyl, and heteroaryl.

[662] In some preferred embodiments, E^5 is carbocyclyl or heterocyclyl. The carbocyclyl and heterocyclyl are:

substituted with a substituent selected from the group consisting of optionally-substituted carbocyclyl, optionally-substituted carbocyclyl-C_1-C_6-alkyl, optionally-substituted heterocyclyl, and optionally-substituted heterocyclyl-C_1-C_6-alkyl, and

optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^{11})(R^{12})$, -$C(O)(R^{13})$, -S-R^{11}, -$S(O)_2$-R^{11}, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, halocarbocyclyl, halogen-substituted carbocyclyl-C_1-C_6-alkyl, hydroxycarbocyclyl, and heteroaryl.

[663] In some preferred embodiments, E^5 is carbocyclyl or heterocyclyl, wherein the carbocyclyl and heterocyclyl are:

substituted with a substituent selected from the group consisting of optionally-substituted carbocyclyl, optionally-substituted carbocyclyl-C_1-C_6-alkyl, optionally-substituted heterocyclyl, and optionally-substituted heterocyclyl-C_1-C_6-alkyl, and

optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^{11})(R^{12})$, -$C(O)(R^{13})$, -S-R^{11}, -$S(O)_2$-R^{11}, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, halocarbocyclyl, halogen-substituted carbocyclyl-C_1-C_6-alkyl, hydroxycarbocyclyl, and heteroaryl.

[664] R^1 and R^2 are independently selected from the group consisting of -H and alkyl. The alkyl optionally is substituted.

223

[665] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_8-alkyl, and halo-C_1-C_8-alkyl.

[666] In some preferred embodiments, R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_6-alkyl, and halo-C_1-C_6-alkyl.

[667] R^3 is -H or -OH.

[668] R^4 and R^5 are independently selected from the group consisting of -H, alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, and heterocyclylalkyl. Except where the member is -H, any member of this group optionally is substituted.

[669] In some preferred embodiments, R^4 and R^5 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is –H, any member of this group optionally is substituted with one or more halogen.

[670] In some preferred embodiments, R^4 and R^5 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group optionally is substituted with one or more halogen.

[671] R^6 is -CN or –OH.

[672] R^7 is -H, halogen, -OH, alkyl, alkoxy, or alkoxyalkyl. The alkyl, alkoxy, and alkoxyalkyl optionally are substituted.

[673] In some preferred embodiments, R^7 is -H, halogen, -OH, C_1-C_8-alkyl, C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, halo-C_1-C_8-alkyl, halo-C_1-C_8-alkoxy, or halogen-substituted C_1-C_8-alkoxy-C_1-C_8-alkyl.

[674] In some preferred embodiments, R^7 is -H, halogen, -OH, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, or halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl.

[675] R^8 is -OH or alkoxy. The alkoxy optionally is substituted.

[676] In some preferred embodiments, R^8 is -OH, C_1-C_8-alkoxy, or halo-C_1-C_8-alkoxy.

[677] In some preferred embodiments, R^8 is -OH, C_1-C_6-alkoxy, or halo-C_1-C_6-alkoxy.

224.

[678] R^9 and R^{10} are independently selected from the group consisting of -H, C_1-C_8-alkyl, C_1-C_8-alkoxycarbonyl, C_1-C_8-alkylcarbonyl, carbocyclyl-C_1-C_8-alkyl, and carbocyclyl-C_1-C_8-alkoxycarbonyl.

[679] R^{11} and R^{12} are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl. Except where the member is –H, any member of this group optionally is substituted with one or more halogen.

[680] In some preferred embodiments, R^{11} and R^{12} are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl. Except where the member is -H, any member of this group optionally is substituted with one or more halogen.

[681] In some preferred embodiments, R^{11} and R^{12} are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group optionally is substituted with one or more halogen.

[682] R^{13} is -H, C_1-C_8-alkyl, -O-R^{14}, -N(R^{14})(R^{15}), carbocyclyl-C_1-C_8-alkyl, heterocyclyl-C_1-C_8-alkyl, halo-C_1-C_8-alkyl, halogen-substituted carbocyclyl-C_1-C_8-alkyl, or halogen-substituted heterocyclyl-C_1-C_8-alkyl.

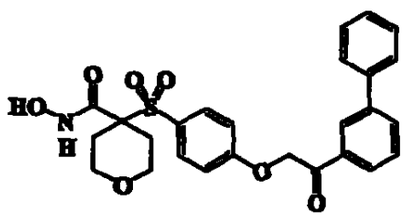
[683] In some preferred embodiments, R^{13} is of -H, C_1-C_6-alkyl, -O-R^{14}, -N(R^{14})(R^{15}), carbocyclyl-C_1-C_6-alkyl, heterocyclyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halogen-substituted carbocyclyl-C_1-C_6-alkyl, or halogen-substituted heterocyclyl-C_1-C_6-alkyl.

[684] R^{14} and R^{15} are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl. Except where the member is –H, any member of this group optionally is substituted with one or more halogen.

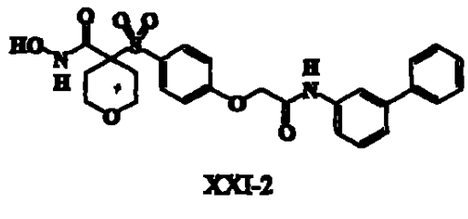
[685] In some preferred embodiments, R^{14} and R^{15} are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl. Except where the member is -H, any member of this group optionally is substituted with one or more halogen.

Some preferred compounds include, for example:

225



XXI-1



XXI-2

A-2. Preferred Selectivities

[686] The hydroxamate compound or salt preferably has an inhibitory activity against MMP-1 or MMP-14 that is substantially less than its inhibitory activity against MMP-2, MMP-9, or MMP-13. In other words, the hydroxamate compound or salt preferably has an in inhibition constant (K_i) against at least one of MMP-2, MMP-9, and MMP-13 that is no greater than about 0.1 times its inhibition constant(s) against at least one of MMP-1 and MMP-14. The inhibition constant of a compound or salt thereof may be determined using an *in vitro* inhibition assay, such as the K_i assay described below in Examples 55-89.

[687] In some particularly preferred embodiments, the hydroxamate compound or salt preferably has a K_i against MMP-2 that is no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its K_i(s) against one or both of MMP-1 and MMP-14.

[688] In some particularly preferred embodiments, the hydroxamate compound or salt preferably has a K_i against MMP-9 that is no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its K_i(s) against one or both of MMP-1 and MMP-14.

[689] In some particularly preferred embodiments, the hydroxamate compound or salt preferably has a K_i against MMP-13 that is no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its K_i(s) against one or both of MMP-1 and MMP-14. It is believed

that such a selectivity profile is often particularly preferred when preventing or treating, for example, a cardiovascular condition or arthritis.

[690] In some particularly preferred embodiments, the hydroxamate compound or salt preferably has K_i's against both MMP-2 and MMP-9 that are no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its K_i(s) against one or both of MMP-1 and MMP-14. It is believed that such a selectivity profile is often particularly preferred when preventing or treating, for example, cancer, a cardiovascular condition, or an ophthalmologic condition.

[691] In some particularly preferred embodiments, the hydroxamate compound or salt preferably has K_i's against all of MMP-2, MMP-9, and MMP-13 that are no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its K_i(s) against one or both of MMP-1 and MMP-14. It is believed that such a selectivity profile is often particularly preferred when preventing or treating, for example, cancer, a cardiovascular condition, arthritis, or an ophthalmologic condition.

[692] In some particularly preferred embodiments, the hydroxamate compound or salt preferably has a K_i against MMP-2 that is no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its K_i's against both MMP-1 and MMP-14.

[693] In some particularly preferred embodiments, the hydroxamate compound or salt preferably has a K_i against MMP-9 that is no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its K_i's against both MMP-1 and MMP-14.

[694] In some particularly preferred embodiments, the hydroxamate compound or salt preferably has a K_i against MMP-13 that is no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its K_i's against both MMP-1 and MMP-14. It is believed that such a

227

selectivity profile is often particularly preferred when preventing or treating, for example, a cardiovascular condition or arthritis.

[695] In some particularly preferred embodiments, the hydroxamate compound or salt preferably has K_i's against both MMP-2 and MMP-9 that are no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its K_i's against both of MMP-1 and MMP-14. It is believed that such a selectivity profile is often particularly preferred when preventing or treating, for example, cancer, a cardiovascular condition, or an ophthalmologic condition.

[696] In some particularly preferred embodiments, the hydroxamate compound or salt preferably has K_i's against all of MMP-2, MMP-9, and MMP-3 that are no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its K_i's against both of MMP-1 and MMP-14. It is believed that such a selectivity profile is often particularly preferred when preventing or treating, for example, cancer, a cardiovascular condition, arthritis, or an ophthalmologic condition.

[697] The activity and selectivity of a hydroxamate compound or salt may alternatively be determined using an *in vitro* IC_{50} assay, such as the IC_{50} assay described below in Examples 55-89. In that instance, the hydroxamate compound or salt preferably has an IC_{50} value against at least one of MMP-2, MMP-9, and MMP-13 that is no greater than about 0.1 times its IC_{50} value(s) against at least one of MMP-1 and MMP-14.

[698] In some particularly preferred embodiments, the hydroxamate compound or salt preferably has an IC_{50} value against MMP-2 that is no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its IC_{50} value(s) against one or both of MMP-1 and MMP-14.

[699] In some particularly preferred embodiments, the hydroxamate compound or salt preferably has an IC_{50} value against MMP-9 that is no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no

greater than about 0.00001) times its IC_{50} value(s) against one or both of MMP-1 and MMP-14.

[700] In some particularly preferred embodiments, the hydroxamate compound or salt preferably has an IC_{50} value against MMP-13 that is no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its IC_{50} value(s) against one or both of MMP-1 and MMP-14. It is believed that such a selectivity profile is often particularly preferred when preventing or treating, for example, a cardiovascular condition or arthritis.

[701] In some particularly preferred embodiments, the hydroxamate compound or salt preferably has IC_{50} values against both MMP-2 and MMP-9 that are no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its IC_{50} value(s) against one or both of MMP-1 and MMP-14. It is believed that such a selectivity profile is often particularly preferred when preventing or treating, for example, cancer, a cardiovascular condition, or an ophthalmologic condition.

[702] In some particularly preferred embodiments, the hydroxamate compound or salt preferably has IC_{50} values against all of MMP-2, MMP-9, and MMP-13 that are no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its IC_{50} value(s) against one or both of MMP-1 and MMP-14. It is believed that such a selectivity profile is often particularly preferred when preventing or treating, for example, cancer, a cardiovascular condition, arthritis, or an ophthalmologic condition.

[703] In some particularly preferred embodiments, the hydroxamate compound or salt preferably has an IC_{50} value against MMP-2 that is no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its IC_{50} values against both MMP-1 and MMP-14.

[704] In some particularly preferred embodiments, the hydroxamate compound or salt preferably has an IC_{50} value against MMP-9 that is no greater than about 0.1 (more

preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its IC_{50} values against both MMP-1 and MMP-14.

[705] In some particularly preferred embodiments, the hydroxamate compound or salt preferably has an IC_{50} value against MMP-13 that is no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its IC_{50} values against both MMP-1 and MMP-14. It is believed that such a selectivity profile is often particularly preferred when preventing or treating, for example, a cardiovascular condition or arthritis.

[706] In some particularly preferred embodiments, the hydroxamate compound or salt preferably has IC_{50} values against both MMP-2 and MMP-9 that are no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its IC_{50} values against both of MMP-1 and MMP-14. It is believed that such a selectivity profile is often particularly preferred when preventing or treating, for example, cancer, a cardiovascular condition, or an ophthalmologic condition.

[707] In some particularly preferred embodiments, the hydroxamate compound or salt preferably has IC_{50} values against all of MMP-2, MMP-9, and MMP-3 that are no greater than about 0.1 (more preferably no greater than about 0.01, even more preferably no greater than about 0.001, still more preferably no greater than about 0.0001, and still even more preferably no greater than about 0.00001) times its IC_{50} values against both of MMP-1 and MMP-14. It is believed that such a selectivity profile is often particularly preferred when preventing or treating, for example, cancer, a cardiovascular condition, arthritis, or an ophthalmologic condition.

B. Salts of the Compounds of this Invention

[708] The compounds of this invention can be used in the form of salts derived from inorganic or organic acids. Depending on the particular compound, a salt of the compound may be advantageous due to one or more of the salt's physical properties, such as enhanced pharmaceutical stability in differing temperatures and humidities, or a

desirable solubility in water or oil. In some instances, a salt of a compound also may be used as an aid in the isolation, purification, and/or resolution of the compound.

[709] Where a salt is intended to be administered to a patient (as opposed to, for example, being used in an *in vitro* context), the salt preferably is pharmaceutically acceptable. Pharmaceutically acceptable salts include salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. In general, these salts typically may be prepared by conventional means with a compound of this invention by reacting, for example, the appropriate acid or base with the compound.

[710] Pharmaceutically-acceptable acid addition salts of the compounds of this invention may be prepared from an inorganic or organic acid. Examples of suitable inorganic acids include hydrochloric, hydrobromic acid, hydroiodic, nitric, carbonic, sulfuric, and phosphoric acid. Suitable organic acids generally include, for example, aliphatic, cycloaliphatic, aromatic, araliphatic, heterocyclyl, carboxylic, and sulfonic classes of organic acids. Specific examples of suitable organic acids include acetate, trifluoroacetate, formate, propionate, succinate, glycolate, gluconate, digluconate, lactate, malate, tartaric acid, citrate, ascorbate, glucuronate, maleate, fumarate, pyruvate, aspartate, glutamate, benzoate, anthranilic acid, mesylate, stearate, salicylate, p-hydroxybenzoate, phenylacetate, mandelate, embonate (pamoate), methanesulfonate, ethanesulfonate, benzenesulfonate, pantothenate, toluenesulfonate, 2-hydroxyethanesulfonate, sulfanilate, cyclohexylaminosulfonate, algenic acid, b-hydroxybutyric acid, galactarate, galacturonate, adipate, alginate, bisulfate, butyrate, camphorate, camphorsulfonate, cyclopentanepropionate, dodecylsulfate, glycoheptanoate, glycerophosphate, hemisulfate, heptanoate, hexanoate, nicotinate, 2-naphthalesulfonate, oxalate, palmoate, pectinate, persulfate, 3-phenylpropionate, picrate, pivalate, thiocyanate, tosylate, and undecanoate.

[711] Pharmaceutically-acceptable base addition salts of the compounds of this invention include, for example, metallic salts and organic salts. Preferred metallic salts include alkali metal (group Ia) salts, alkaline earth metal (group IIa) salts, and other physiological acceptable metal salts. Such salts may be made from aluminum, calcium, lithium, magnesium, potassium, sodium, and zinc. Preferred organic salts can be made from tertiary amines and quaternary amine salts, such as tromethamine, diethylamine, N,N'-dibenzylethylenediamine, chloroprocaine, choline, diethanolamine, ethylenediamine, meglumine (N-methylglucamine), and procaine. Basic nitrogen-containing groups can be

231

quaternized with agents such as lower alkyl (C_1-C_6) halides *(e.g.,* methyl, ethyl, propyl, and butyl chlorides, bromides, and iodides), dialkyl sulfates *(e.g.,* dimethyl, diethyl, dibuyti, 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.

[712] Particularly preferred salts of the compounds of this invention include hydrochloric acid (HCl) salts and trifluoroacetate (CF_3COOH or TFA) salts.

C. Preventing or Treating Conditions Using the Compounds and Salts of this Invention

[713] One embodiment of this invention is directed to a process for preventing or treating a pathological condition associated with MMP activity in a mammal *(e.g.,* a human, companion animal, farm animal, laboratory animal, zoo animal, or wild animal) having or disposed to having such a condition. Such a condition may be, for example, tissue destruction, a fibrotic disease, pathological matrix weakening, defective injury repair, a cardiovascular disease, a pulmonary disease, a kidney disease, a liver disease, an ophthalmologic disease, or a central nervous system disease. Specific examples of such conditions include osteoarthritis, rheumatoid arthritis, septic arthritis, tumor invasion, tumor metastasis, tumor angiogenesis, a decubitis ulcer, a gastric ulcer, a corneal ulcer, periodontal disease, liver cirrhosis, fibrotic lung disease, otosclerosis, atherosclerosis, multiple sclerosis, dilated cardiomyopathy, epidermal ulceration, epidermolysis bullosa, aortic aneurysm, weak injury repair, an adhesion, scarring, congestive heart failure, post myocardial infarction, coronary thrombosis, emphysema, proteinuria, bone disease, chronic obstructive pulmonary diseases, and Alzheimer's disease.

[714] In some particularly preferred embodiments, the condition comprises arthritis.

[715] In some particularly preferred embodiments, the condition comprises tumor invasion, tumor metastasis, or tumor angiogenesis.

[716] In some particularly preferred embodiments, the condition comprises periodontal disease.

[717] In some particularly preferred embodiments, the condition comprises atherosclerosis.

[718] In some particularly preferred embodiments, the condition comprises multiple sclerosis.

[719] In some particularly preferred embodiments, the condition comprises dilated cardiomyopathy.

[720] In some particularly preferred embodiments, the condition comprises post myocardial infarction.

[721] In some particularly preferred embodiments, the condition comprises congestive heart failure.

[722] In some particularly preferred embodiments, the condition comprises chronic obstructive pulmonary disease.

[723] The condition may alternatively (or additionally) be associated with TNF-α convertase activity. Examples of such a condition include inflammation (*e.g.*, rheumatoid arthritis), autoimmune disease, graft rejection, multiple sclerosis, a fibrotic disease, cancer, an infectious disease (*e.g.*, malaria, mycobacterial infection, meningitis, etc.), fever, psoriasis, a cardiovascular disease (*e.g.*, post-ischemic reperfusion injury and congestive heart failure), a pulmonary disease, hemorrhage, coagulation, hyperoxic alveolar injury, radiation damage, acute phase responses like those seen with infections and sepsis and during shock (*e.g.*, septic shock, hemodynamic shock, etc.), cachexia, and anorexia.

[724] The condition may alternatively (or additionally) be associated with aggrecanase activity. Examples of such a condition include inflammation diseases (*e.g.*, osteoarthritis, rheumatoid arthritis, joint injury, reactive arthritis, acute pyrophosphate arthritis, and psoriatic arthritis) and cancer.

[725] In this patent, the phrase "preventing a condition" means reducing the risk of (or delaying) the onset of the condition in a mammal that does not have the condition, but is predisposed to having the condition. In contrast, the phrase "treating a condition" means ameliorating, suppressing, or eradicating an existing condition. The pathological condition may be (a) the result of pathological MMP activity itself, and/or (b) affected by MMP activity (*e.g.*, diseases associated with TNF-α).

[726] A wide variety of methods may be used alone or in combination to administer the hydroxamates and salt thereof described above. For example, the hydroxamates or salts thereof may be administered orally, parenterally, by inhalation spray, rectally, or topically.

[727] Typically, a compound (or pharmaceutically acceptable salt thereof) described in this patent is administered in an amount effective to inhibit a target MMP(s). The target MMP is/are typically MMP-2, MMP-9, and/or MMP-13, with MMP-13 often being a particularly preferred target. The preferred total daily dose of the hydroxamate or salt thereof (administered in single or divided doses) is typically from about 0.001 to about 100 mg/kg, more preferably from about 0.001 to about 30 mg/kg, and even more preferably from about 0.01 to about 10 mg/kg (*i.e.*, mg hydroxamate or salt thereof per kg body weight). Dosage unit compositions can contain such amounts or submultiples thereof to make up the daily dose. In many instances, the administration of the compound or salt will be repeated a plurality of times. Multiple doses per day typically may be used to increase the total daily dose, if desired.

[728] Factors affecting the preferred dosage regimen include the type, age, weight, sex, diet, and condition of the patient; the severity of the pathological condition; the route of administration; pharmacological considerations, such as the activity, efficacy, pharmacokinetic, and toxicology profiles of the particular hydroxamate or salt thereof employed; whether a drug delivery system is utilized; and whether the hydroxamate or salt thereof is administered as part of a drug combination. Thus, the dosage regimen actually employed can vary widely, and, therefore, can deviate from the preferred dosage regimen set forth above.

D. Pharmaceutical Compositions Containing the Compounds and Salts of this Invention

[729] This invention also is directed to pharmaceutical compositions comprising a hydroxamate or salt thereof described above, and to methods for making pharmaceutical compositions (or medicaments) comprising a hydroxamate or salt thereof described above.

[730] The preferred composition depends on the method of administration, and typically comprises one or more conventional pharmaceutically acceptable carriers, adjuvants, and/or vehicles. Formulation of drugs is generally discussed in, for example, Hoover, John E., *Remington's Pharmaceutical Sciences* (Mack Publishing Co., Easton, PA: 1975). See also, Liberman, H.A. *See also*, Lachman, L., eds., *Pharmaceutical Dosage Forms* (Marcel Decker, New York, N.Y., 1980).

[731] Solid dosage forms for oral administration include, for example, capsules, tablets, pills, powders, and granules. In such solid dosage forms, the hydroxamates or

salts thereof are ordinarily combined with one or more adjuvants. If administered *per os*, the hydroxamates or salts thereof can be mixed with lactose, sucrose, starch powder, cellulose esters of alkanoic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, and then tableted or encapsulated for convenient administration. Such capsules or tablets can contain a controlled-release formulation, as can be provided in a dispersion of the hydroxamate or salt thereof in hydroxypropylmethyl cellulose. In the case of capsules, tablets, and pills, the dosage forms also can comprise buffering agents, such as sodium citrate, or magnesium or calcium carbonate or bicarbonate. Tablets and pills additionally can be prepared with enteric coatings.

[732] Liquid dosage forms for oral administration include, for example, pharmaceutically acceptable emulsions, solutions, suspensions, syrups, and elixirs containing inert diluents commonly used in the art (*e.g.*, water). Such compositions also can comprise adjuvants, such as wetting, emulsifying, suspending, flavoring (*e.g.*, sweetening), and/or perfuming agents.

[733] "Parenteral administration" includes subcutaneous injections, intravenous injections, intramuscular injections, intrasternal injections, and infusion. Injectable preparations (*e.g.*, sterile injectable aqueous or oleaginous suspensions) can be formulated according to the known art using suitable dispersing, wetting agents, and/or suspending agents. Acceptable vehicles and solvents include, for example, water, 1,3-butanediol, Ringer's solution, isotonic sodium chloride solution, bland fixed oils (*e.g.*, synthetic mono- or diglycerides), fatty acids (*e.g.*, oleic acid), dimethyl acetamide, surfactants (*e.g.*, ionic and non-ionic detergents), and/or polyethylene glycols.

[734] Formulations for parenteral administration may, for example, be prepared from sterile powders or granules having one or more of the carriers or diluents mentioned for use in the formulations for oral administration. The hydroxamates or salts thereof can be dissolved in water, polyethylene glycol, propylene glycol, ethanol, corn oil, cottonseed oil, peanut oil, sesame oil, benzyl alcohol, sodium chloride, and/or various buffers.

[735] Suppositories for rectal administration can be prepared by, for example, mixing the drug with a suitable nonirritating excipient that is solid at ordinary temperatures, but liquid at the rectal temperature and will therefore melt in the rectum to

235

release the drug. Suitable excipients include, for example, such as cocoa butter; synthetic mono-, di-, or triglycerides; fatty acids; and/or polyethylene glycols

[736] "Topical administration" includes the use of transdermal administration, such as transdermal patches or iontophoresis devices.

[737] Other adjuvants and modes of administration well-known in the pharmaceutical art may also be used.

E. Definitions

[738] The term "alkyl" (alone or in combination with another term(s)) means a straight-or branched-chain saturated hydrocarbyl typically containing from 1 to about 20 carbon atoms, more typically from 1 to about 8 carbon atoms, and even more typically from 1 to about 6 carbon atoms. Examples of such substituents include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, iso-amyl, hexyl, octyl, and the like.

[739] The term "alkenyl" (alone or in combination with another term(s)) means a straight- or branched-chain hydrocarbyl containing one or more double bonds and typically from 2 to about 20 carbon atoms, more typically from about 2 to about 8 carbon atoms, and even more typically from about 2 to about 6 carbon atoms. Examples of such substituents include ethenyl (vinyl); 2-propenyl; 3-propenyl; 1,4-pentadienyl; 1,4-butadienyl; 1-butenyl; 2-butenyl; 3-butenyl; decenyl; and the like.

[740] The term "alkynyl" (alone or in combination with another term(s)) means a straight- or branched-chain hydrocarbyl containing one or more triple bonds and typically from 2 to about 20 carbon atoms, more typically from about 2 to about 8 carbon atoms, and even more typically from about 2 to about 6 carbon atoms. Examples of such substituents include ethynyl, 2-propynyl, 3-propynyl, decynyl, 1-butynyl, 2-butynyl, 3-butynyl, and the like.

[741] The term "carbocyclyl" (alone or in combination with another term(s)) means a saturated cyclic (*i.e.*, "cycloalkyl"), partially saturated cyclic, or aryl hydrocarbyl containing from 3 to 14 carbon ring atoms ("ring atoms" are the atoms bound together to form the ring or rings of a cyclic group). A carbocyclyl may be a single ring, which typically contains from 3 to 6 ring atoms. Examples of such single-ring carbocyclyls include cyclopropanyl, cyclobutanyl, cyclopentyl, cyclopentenyl, cyclopentadienyl,

cyclohexyl, cyclohexenyl, cyclohexadienyl, and phenyl. A carbocyclyl alternatively may be 2 or 3 rings fused together, such as naphthalenyl, tetrahydronaphthalenyl (also known as "tetralinyl"), indenyl, isoindenyl, indanyl, bicyclodecanyl, anthracenyl, phenanthrene, benzonaphthenyl (also known as "phenalenyl"), fluorenecyl, decalinyl, and norpinanyl.

[742] The term "cycloalkyl" (alone or in combination with another term(s)) means a saturated cyclic hydrocarbyl containing from 3 to 14 carbon ring atoms. A cycloalkyl may be a single carbon ring, which typically contains from 3 to 6 carbon ring atoms. Examples of single-ring cycloalkyls include cyclopropyl (or "cyclopropanyl"), cyclobutyl (or "cyclobutanyl"), cyclopentyl (or "cyclopentanyl"), and cyclohexyl (or "cyclohexanyl"). A cycloalkyl alternatively may be 2 or 3 carbon rings fused together, such as, decalinyl or norpinanyl.

[743] The term "aryl" (alone or in combination with another term(s)) means an aromatic carbocyclyl containing from 6 to 14 carbon ring atoms. Examples of aryls include phenyl, naphthalenyl, and indenyl.

[744] In some instances, the number of carbon atoms in a hydrocarbyl (*e.g.*, alkyl, alkenyl, alkynyl, or cycloalkyl) is indicated by the prefix "C_x-C_y-", wherein x is the minimum and y is the maximum number of carbon atoms in the substituent. Thus, for example, "C_1-C_6-alkyl" refers to an alkyl containing from 1 to 6 carbon atoms. Illustrating further, C_3-C_6-cycloalkyl means a saturated hydrocarbyl ring containing from 3 to 6 carbon ring atoms.

[745] The term "hydrogen" (alone or in combination with another term(s)) means a hydrogen radical, and may be depicted as -H.

[746] The term "hydroxy" (alone or in combination with another term(s)) means -OH.

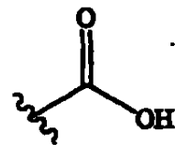
[747] The term "nitro" (alone or in combination with another term(s)) means $-NO_2$.

[748] The term "cyano" (alone or in combination with another term(s)) means -CN, which also may be depicted as:



[749] The term "keto" (alone or in combination with another term(s)) means an oxo radical, and may be depicted as =O.

[750] The term "carboxy" (alone or in combination with another term(s)) means -C(O)-OH, which also may be depicted as:



[751] The term "amino" (alone or in combination with another term(s)) means $-NH_2$. The term "monosubstituted amino" (alone or in combination with another term(s)) means an amino wherein one of the hydrogen radicals is replaced by a non-hydrogen substituent. The term "disubstituted amino" (alone or in combination with another term(s)) means an amino wherein both of the hydrogen atoms are replaced by non-hydrogen substituents, which may be identical or different.

[752] The term "halogen" (alone or in combination with another term(s)) means a fluorine radical (which may be depicted as -F), chlorine radical (which may be depicted as -Cl), bromine radical (which may be depicted as -Br), or iodine radical (which may be depicted as -I). Typically, a fluorine radical or chlorine radical is preferred, with a fluorine radical often being particularly preferred.

[753] If a substituent is described as being "substituted", a non-hydrogen radical is in the place of a hydrogen radical on a carbon or nitrogen of the substituent. Thus, for example, a substituted alkyl substituent is an alkyl substituent wherein at least one non-hydrogen radical is in the place of a hydrogen radical on the alkyl substituent. To illustrate, monofluoroalkyl is alkyl substituted with a fluoro radical, and difluoroalkyl is alkyl substituted with two fluoro radicals. It should be recognized that if there are more than one substitutions on a substituent, each non-hydrogen radical may be identical or different (unless otherwise stated).

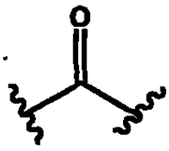
[754] If a substituent is described as being "optionally substituted", the substituent may be either (1) substituted, or (2) not substituted.

[755] This specification uses the terms "substituent" and "radical" interchangeably.

[756] The prefix "halo" indicates that the substituent to which the prefix is attached is substituted with one or more independently selected halogen radicals. For example, haloalkyl means an alkyl wherein at least one hydrogen radical is replaced with a halogen radical. Examples of haloalkyls include chloromethyl, 1-bromoethyl, fluoromethyl, difluoromethyl, trifluoromethyl, 1,1,1-trifluoroethyl, and the like. Illustrating further, "haloalkoxy" means an alkoxy wherein at least one hydrogen radical is replaced by a halogen radical. Examples of haloalkoxy substituents include chloromethoxy, 1-bromoethoxy, fluoromethoxy, difluoromethoxy, trifluoromethoxy (also known as "perfluoromethyoxy"), 1,1,1,-trifluoroethoxy, and the like. It should be recognized that if a substituent is substituted by more than one halogen radical, those halogen radicals may be identical or different (unless stated otherwise).

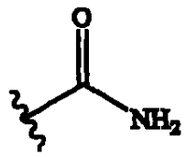
[757] The prefix "perhalo" indicates that every hydrogen radical on the substituent to which the prefix is attached is replaced with independently selected halogen radicals, *i.e.*, each hydrogen radical on the substituent is replaced with a halogen radical. If all the halogen radicals are identical, the prefix typically will identify the halogen radical. Thus, for example, the term "perfluoro" means that every hydrogen radical on the substituent to which the prefix is attached is substituted with a fluorine radical. To illustrate, the term "perfluoroalkyl" means an alkyl wherein a fluorine radical is in the place of each hydrogen radical. Examples of perfluoroalkyl substituents include trifluoromethyl ($-CF_3$), perfluorobutyl, perfluoroisopropyl, perfluorododecyl, perfluorodecyl, and the like. To illustrate further, the term "perfluoroalkoxy" means an alkoxy wherein each hydrogen radical is replaced with a fluorine radical. Examples of perfluoroalkoxy substituents include trifluoromethoxy ($-O-CF_3$), perfluorobutoxy, perfluoroisopropoxy, perfluorododecoxy, perfluorodecoxy, and the like.

[758] The term "carbonyl" (alone or in combination with another term(s)) means $-C(O)-$, which also may be depicted as:



This term also is intended to encompass a hydrated carbonyl substituent, *i.e.*, $-C(OH)_2-$.

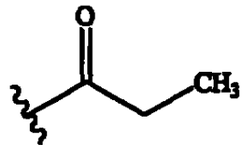
[759] The term "aminocarbonyl" (alone or in combination with another term(s)) means -C(O)-NH_2, which also may be depicted as:



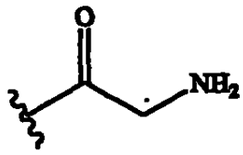
[760] The term "oxy" (alone or in combination with another term(s)) means an ether substituent, and may be depicted as -O-.

[761] The term "alkoxy" (alone or in combination with another term(s)) means an alkylether, *i.e.*, -O-alkyl. Examples of such a substituent include methoxy (-O-CH_3), ethoxy, n-propoxy, isopropoxy, n-butoxy, iso-butoxy, sec-butoxy, tert-butoxy, and the like.

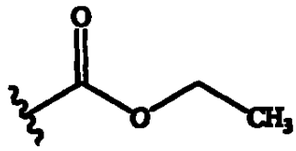
[762] The term "alkylcarbonyl" (alone or in combination with another term(s)) means -C(O)-alkyl. For example, "ethylcarbonyl" may be depicted as:



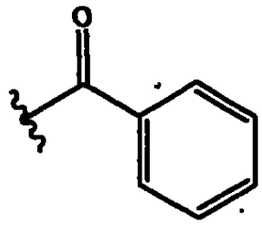
[763] The term "aminoalkylcarbonyl" (alone or in combination with another term(s)) means -C(O)-alkyl-NH_2. For example, "aminomethylcarbonyl" may be depicted as:



[764] The term "alkoxycarbonyl" (alone or in combination with another term(s)) means -C(O)-O-alkyl. For example, "ethoxycarbonyl" may be depicted as:

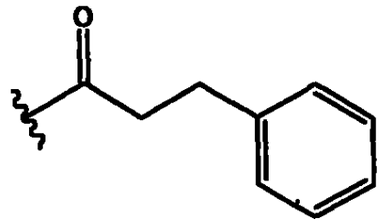


[765] The term "carbocyclylcarbonyl" (alone or in combination with another term(s)) means -C(O)-carbocyclyl. For example, "phenylcarbonyl" may be depicted as:



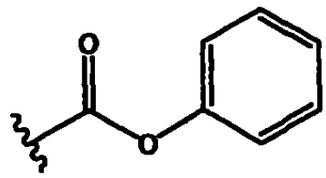
Similarly, the term "heterocyclylcarbonyl" (alone or in combination with another term(s)) means -C(O)-heterocyclyl.

[766] The term "carbocyclylalkylcarbonyl" (alone or in combination with another term(s)) means -C(O)-alkyl-carbocyclyl. For example, "phenylethylcarbonyl" may be depicted as:

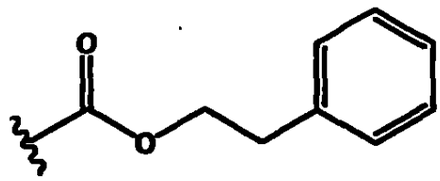


Similarly, the term "heterocyclylalkylcarbonyl" (alone or in combination with another term(s)) means -C(O)-alkyl-heterocyclyl.

[767] The term "carbocyclyloxycarbonyl" (alone or in combination with another term(s)) means -C(O)-O-carbocyclyl. For example, "phenyloxycarbonyl" may be depicted as:



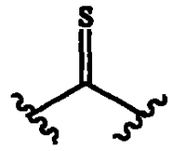
[768] The term "carbocyclylalkoxycarbonyl" (alone or in combination with another term(s)) means -C(O)-O-alkyl-carbocyclyl. For example, "phenylethoxycarbonyl" may be depicted as:



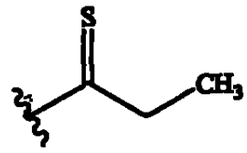
[769] The term "thio" or "thia" (alone or in combination with another term(s)) means a thiaether, *i.e.*, an ether substituent wherein a divalent sulfur atom is in the place of the ether oxygen atom. Such a substituent may be depicted as -S-. Thia, for example, "alkyl-thio-alkyl" means alkyl-S-alkyl.

[770] The term "thiol" or "sulfhydryl" (alone or in combination with another term(s)) means a sulfhydryl, and may be depicted as -SH.

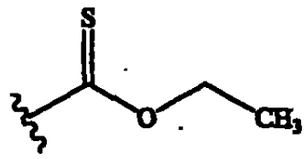
[771] The term "(thiocarbonyl)" (alone or in combination with another term(s)) means a carbonyl wherein the oxygen atom has been replaced with a sulfur. Such a substituent may be depicted as -C(S)-, and also may be depicted as:



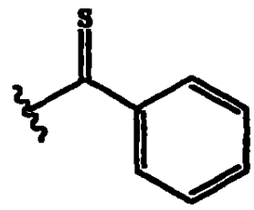
[772] The term "alkyl(thiocarbonyl)" (alone or in combination with another term(s)) means -C(S)-alkyl. For example, "ethyl(thiocarbonyl)" may be depicted as:



[773] The term "alkoxy(thiocarbonyl)" (alone or in combination with another term(s)) means -C(S)-O-alkyl. For example, "ethoxy(thiocarbonyl)" may be depicted as:

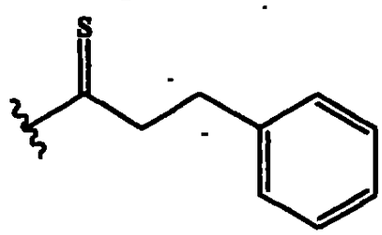


[774] The term "carbocyclyl(thiocarbonyl)" (alone or in combination with another term(s)) means -C(S)-carbocyclyl. For example, "phenyl(thiocarbonyl)" may be depicted as:



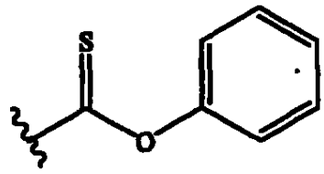
Similarly, the term "heterocyclyl(thiocarbonyl)" (alone or in combination with another term(s)) means -C(S)-heterocyclyl.

[775] The term "carbocyclylalkyl(thiocarbonyl)" (alone or in combination with another term(s)) means -C(S)-alkyl-carbocyclyl. For example, "phenylethyl(thiocarbonyl)" may be depicted as:

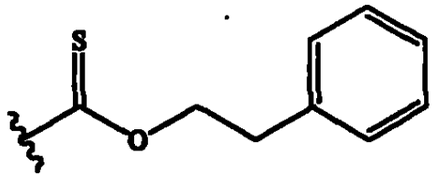


Similarly, the term "heterocyclylalkyl(thiocarbonyl)" (alone or in combination with another term(s)) means -C(S)-alkyl-heterocyclyl.

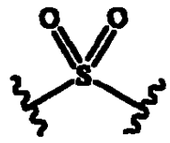
[776] The term "carbocyclyloxy(thiocarbonyl)" (alone or in combination with another term(s)) means -C(S)-O-carbocyclyl. For example, "phenyloxy(thiocarbonyl)" may be depicted as:



[777] The term "carbocyclylalkoxy(thiocarbonyl)" (alone or in combination with another term(s)) means -C(S)-O-alkyl-carbocyclyl. For example, "phenylethoxy(thiocarbonyl)" may be depicted as:

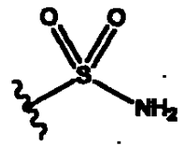


[778] The term "sulfonyl" (alone or in combination with another term(s)) means $-S(O)_2-$, which also may be depicted as:

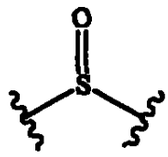


Thus, for example, "alkyl-sulfonyl-alkyl" means alkyl-$S(O)_2$-alkyl.

[779] The term "aminosulfonyl" (alone or in combination with another term(s)) means $-S(O)_2-NH_2$, which also may be depicted as:



[780] The term "sulfoxido" (alone or in combination with another term(s)) means -S(O)-, which also may be depicted as:



Thus, for example, "alkyl-sulfoxido-alkyl" means alkyl-S(O)-alkyl.

[781] The term "heterocyclyl" (alone or in combination with another term(s)) means a saturated (*i.e.*, "heterocycloalkyl"), partially saturated, or aryl (*i.e.*, "heteroaryl") ring structure containing a total of 3 to 14 ring atoms. At least one of the ring atoms is a heteroatom (*i.e.*, oxygen, nitrogen, or sulfur), with the remaining ring atoms being independently selected from the group consisting of carbon, oxygen, nitrogen, and sulfur.

[782] A heterocyclyl may be a single ring, which typically contains from 3 to 7 ring atoms, more typically from 3 to 6 ring atoms, and even more typically 5 to 6 ring atoms. Examples of single-ring heterocyclyls include furanyl, dihydrofurnayl, tetradydrofurnayl, thiophenyl (also known as "thiofuranyl"), dihydrothiophenyl, tetrahydrothiophenyl, pyrrolyl, isopyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, isoimidazolyl, imidazolinyl, imidazolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, triazolyl, tetrazolyl, dithiolyl, oxathiolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, thiazolinyl, isothiazolinyl, thiazolidinyl, isothiazolidinyl, thiodiazolyl, oxathiazolyl, oxadiazolyl (including 1,2,3-oxadiazolyl, 1,2,4-oxadiazolyl (also known as "azoximyl"), 1,2,5-oxadiazolyl (also known as "furazanyl"), or 1,3,4-oxadiazolyl), oxatriazolyl (including 1,2,3,4-oxatriazolyl or 1,2,3,5-oxatriazolyl), dioxazolyl (including 1,2,3-dioxazolyl, 1,2,4-dioxazolyl, 1,3,2-dioxazolyl, or 1,3,4-dioxazolyl), oxathiazolyl, oxathiolyl, oxathiolanyl, pyranyl (including 1,2-pyranyl or 1,4-pyranyl), dihydropyranyl, pyridinyl (also known as "azinyl"), piperidinyl, diazinyl (including pyridazinyl (also

244

known as "1,2-diazinyl"), pyrimidinyl (also known as "1,3-diazinyl"), or pyrazinyl (also known as "1,4-diazinyl")), piperazinyl, triazinyl (including s-triazinyl (also known as "1,3,5-triazinyl"), as-triazinyl (also known 1,2,4-triazinyl), and v-triazinyl (also known as "1,2,3-triazinyl")), oxazinyl (including 1,2,3-oxazinyl, 1,3,2-oxazinyl, 1,3,6-oxazinyl (also known as "pentoxazolyl"), 1,2,6-oxazinyl, or 1,4-oxazinyl), isoxazinyl (including o-isoxazinyl or p-isoxazinyl), oxazolidinyl, isoxazolidinyl, oxathiazinyl (including 1,2,5-oxathiazinyl or 1,2,6-oxathiazinyl), oxadiazinyl (including 1,4,2-oxadiazinyl or 1,3,5,2-oxadiazinyl), morpholinyl, azepinyl, oxepinyl, thiepinyl, and diazepinyl.

[783] A heterocyclyl alternatively may be 2 or 3 rings fused together, such as, for example, indolizinyl, pyrindinyl, pyranopyrrolyl, 4H-quinolizinyl, purinyl, naphthyridinyl, pyridopyridinyl (including pyrido[3,4-b]-pyridinyl, pyrido[3,2-b]-pyridinyl, or pyrido[4,3-b]-pyridinyl), and pteridinyl. Other examples of fused-ring heterocyclyls include benzo-fused heterocyclyls, such as indolyl, isoindolyl (also known as "isobenzazolyl" or "pseudoisoindolyl"), indoleninyl (also known as "pseudoindolyl"), isoindazolyl (also known as "benzpyrazolyl"), benzazinyl (including quinolinyl (also known as "1-benzazinyl") or isoquinolinyl (also known as "2-benzazinyl")), phthalazinyl, quinoxalinyl, quinazolinyl, benzodiazinyl (including cinnolinyl (also known as "1,2-benzodiazinyl") or quinazolinyl (also known as "1,3-benzodiazinyl")), benzopyranyl (including "chromanyl" or "isochromanyl"), benzothiopyranyl (also known as "thiochromanyl"), benzoxazolyl, indoxazinyl (also known as "benzisoxazolyl"), anthranilyl, benzodioxolyl, benzodioxanyl, benzoxadiazolyl, benzofuranyl (also known as "coumaronyl"), isobenzofuranyl, benzothienyl (also known as "benzothiophenyl", "thionaphthenyl", or "benzothiofuranyl"), isobenzothienyl (also known as "isobenzothiophenyl", "isothionaphthenyl", or "isobenzothiofuranyl"), benzothiazolyl, benzothiadiazolyl, benzimidazolyl, benzotriazolyl, benzoxazinyl (including 1,3,2-benzoxazinyl , 1,4,2-benzoxazinyl , 2,3,1-benzoxazinyl , or 3,1,4-benzoxazinyl), benzisoxazinyl (including 1,2-benzisoxazinyl or 1,4-benzisoxazinyl), tetrahydroisoquinolinyl , carbazolyl, xanthenyl, and acridinyl.

[784] The term "2-fused'ring" heterocyclyl (alone or in combination with another term(s)) means a saturated, partially saturated, or aryl heterocyclyl containing 2 fused rings. Examples of 2-fused-ring heterocyclyls include indolizinyl, pyrindinyl, pyranopyrrolyl, 4H-quinolizinyl, purinyl, naphthyridinyl, pyridopyridinyl, pteridinyl,

245

indolyl, isoindolyl, indolenimyl, isoindazolyl, benzazinyl, phthalazinyl, quinoxalinyl, quinazolinyl, benzodiazinyl, benzopyranyl, benzothiopyranyl, benzoxazolyl, indoxazinyl, anthranilyl, benzodioxolyl, benzodioxanyl, benzoxadiazolyl, benzofuranyl, isobenzofuranyl, benzothienyl, isobenzothienyl, benzothiazolyl, benzothiadiazolyl, benzimidazolyl, benzotriazolyl, benzoxazinyl, benzisoxazinyl, and tetrahydroisoquinolinyl.

[785] The term "heteroaryl" (alone or in combination with another term(s)) means an aromatic heterocyclyl containing from 5 to 14 ring atoms. A heteroaryl may be a single ring or 2 or 3 fused rings. Examples of heteroaryl substituents include 6-membered ring substituents such as pyridyl, pyrazyl, pyrimidinyl, and pyridazinyl; 5-membered ring substituents such as 1,3,5-, 1,2,4- or 1,2,3-tiiazinyl, imidazyl, furanyl, thiophenyl, pyrazolyl, oxazolyl, isoxazolyl, thiazolyl, 1,2,3-, 1,2,4-, 1,2,5-, or 1,3,4-oxadiazolyl and isothiazolyl; 6/5-membered fused ring substituents such as benzothiofuranyl, isobenzothiofuranyl, benzisoxazolyl, benzoxazolyl, purinyl, and anthranilyl; and 6/6-membered fused rings such as 1,2-, 1,4-, 2,3- and 2, 1-benzopyronyl, quinolinyl, isoquinolinyl, cinnolinyl, quinazolinyl, and 1,4-benzoxazinyl.

[786] A carbocyclyl or heterocyclyl can optionally be substituted with, for example, one or more substituents independently selected from the group consisting of halogen, hydroxy, carboxy, keto, alkyl, alkoxy, alkoxyalkyl, alkylcarbonyl (also known as "alkanoyl"), aryl, arylalkyl, arylalkoxy, arylalkoxyalkyl, arylalkoxycarbonyl, cycloalkyl, cycloalkylalkyl, cycloalkylalkoxy, cycloalkylalkoxyalkyl, and cycloalkylalkoxycarbonyl. More typically, a carbocyclyl or heterocyclyl may optionally be substituted with, for example, one or more substituents independently selected from the group consisting of halogen, -OH, -C(O)-OH, keto, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, C_1-C_6-alkylcarbonyl, aryl, aryl-C_1-C_6-alkyl, aryl-C_1-C_6-alkoxy, aryl-C_1-C_6-alkoxy-C_1-C_6-alkyl, aryl-C_1-C_6-alkoxycarbonyl, cycloalkyl, cycloalkyl-C_1-C_6-alkyl, cycloalkyl-C_1-C_6-alkoxy, cycloalkyl-C_1-C_6-alkoxy-C_1-C_6-alkyl, and cycloalkyl-C_1-C_6-alkoxycarbonyl. The alkyl, alkoxy, alkoxyalkyl, alkylcarbonyl, aryl, arylalkyl, arylalkoxy, arylalkoxyalkyl, or arylalkoxycarbonyl substituent(s) may further be substituted with, for example, one or more halogen. The aryls or cycloalkyls are typically single-ring substituents containing from 3 to 6 ring atoms, and more typically from 5 to 6 ring atoms.

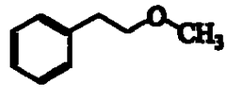
[787] An aryl or heteroaryl can optionally be substituted with, for example, one or more substituents independently selected from the group consisting of halogen, -OH, -CN, -NO_2, -SH, -C(O)-OH, amino, aminocarbonyl, aminoalkyl, alkyl, alkylthio, carboxyalkylthio, alkylcarbonyl, alkylcarbonyloxy, alkoxy, alkoxyalkyl, alkoxycarbonyl, alkoxycarbonylalkoxy, alkoxyalkylthio, alkoxycarbonylalkylthio, carboxyalkoxy, alkoxycarbonylalkoxy, carbocyclyl, carbocyclylalkyl, carbocyclyloxy, carbocyclylthio, carbocyclylalkylthio, carbocyclylamino, carbocyclylalkylamino, carbocyclylcarbonylamino, carbocyclylcarbonyl, carbocyclylalkyl, carbonyl, carbocyclylcarbonyloxy, carbocyclyloxycarbonyl, carbocyclylalkoxycarbonyl, carbocyclyloxyalkoxycarbocyclyl, carbocyclylthioalkylthiocarbocyclyl, carbocyclylthioalkoxycarbocyclyl, carbocyclyloxyalkylthiocarbocyclyl, heterocyclyl, heterocyclylalkyl, heterocyclyloxy, heterocyclylthio, heterocyclylalkylthio, heterocyclylamino, heterocyclylalkylamino, heterocyclylcarbonylamino, heterocyclylcarbonyl, heterocyclylalkylcarbonyl, heterocyclyloxycarbonyl, heterocyclylcarbonyloxy, heterocyclylalkoxycarbonyl, heterocyclyloxyalkoxyheterocyclyl, heterocyclylthioalkylthioheterocyclyl, heterocyclylthioalkoxyheterocyclyl, and heterocyclyloxyalkylthioheterocyclyl. More typically, an aryl or heteroaryl may, for example, optionally be substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -CN, -NO_2, -SH, -C(O)-OH, amino, aminocarbonyl, amino-C_1-C_6-alkyl, C_1-C_6-alkyl, C_1-C_6-alkylthio, carboxy-C_1-C_6-alkylthio, C_1-C_6-alkylcarbonyl, C_1-C_6-alkylcarbonyloxy, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, C_1-C_6-alkoxycarbonyl, C_1-C_6-alkoxycarbonyl-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkylthio, C_1-C_6-alkoxycarbonyl-C_1-C_6-alkylthio, carboxy-C_1-C_6-alkoxy, C_1-C_6-alkoxycarbonyl-C_1-C_6-alkoxy, aryl, aryl-C_1-C_6-alkyl, aryloxy, arylthio, aryl-C_1-C_6-alkylthio, arylamino, aryl-C_1-C_6-alkylamino, arylcarbonylamino, arylcarbonyl, aryl-C_1-C_6-alkylcarbonyl, arylcarbonyloxy, aryloxycarbonyl, aryl-C_1-C_6-alkoxycarbonyl, aryloxy-C_1-C_6-alkoxyaryl, arylthio-C_1-C_6-alkylthioaryl, arylthio-C_1-C_6-alkoxyaryl, aryloxy-C_1-C_6-alkylthioaryl, cycloalkyl, cycloalkyl-C_1-C_6-alkyl, cycloalkyloxy, cycloalkylthio, cycloalkyl-C_1-C_6-alkylthio, cycloalkylamino, cycloalkyl-C_1-C_6-alkylamino, cycloalkylcarbonylamino, cycloalkylcarbonyl, cycloalkyl-C_1-C_6-alkylcarbonyl, cycloalkylcarbonyloxy, cycloalkyloxycarbonyl,

cycloalkyl-C_1-C_6-alkoxycarbonyl, heteroaryl, heteroaryl-C_1-C_6-alkyl, heteroaryloxy, heteroarylthio, heteroaryl-C_1-C_6-alkylthio, heteroarylamino, heteroaryl-C_1-C_6-alkylamino, heteroarylcarbonylamino, heteroarylcarbonyl, heteroaryl-C_1-C_6-alkylcarbonyl, heteroaryloxycarbonyl, heteroarylcarbonyloxy, and heteroaryl-C_1-C_6-alkoxycarbonyl. Here, one or more hydrogen bound to a carbon in any such substituent may, for example, optionally be replaced with halogen. In addition, the cycloalkyl, aryl, and heteroaryl are typically single-ring substituents containing 3 to 6 ring atoms, and more typically 5 or 6 ring atoms.

[788] A prefix attached to a multi-component substituent only applies to the first component. To illustrate, the term "alkylcycloalkyl" contains two components: alkyl and cycloalkyl. Thus, the C_1-C_6- prefix on C_1-C_6-alkylcycloalkyl means that the alkyl component of the alkylcycloalkyl contains from 1 to 6 carbon atoms; the C_1-C_6- prefix does not describe the cycloalkyl component. To illustrate further, the prefix "halo" on haloalkoxyalkyl indicates that *only* the alkoxy component of the alkoxyalkyl substituent is substituted with one or more halogen radicals. If halogen substitution may *alternatively or additionally* occur on the alkyl component, the substituent would instead be described as "halogen-substituted alkoxyalkyl" rather than "haloalkoxyalkyl." And finally, if the halogen substitution may *only* occur on the alkyl component, the substituent would instead be described as "alkoxyhaloalkyl."

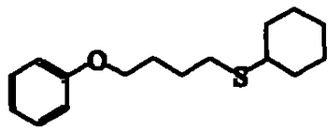
[789] If substituents are described as being "independently selected" from a group, each substituent is selected independent of the other. Each substituent therefore may be identical to or different from the other substituent(s).

[790] When words are used to describe a substituent, the rightmost-described component of the substituent is the component that has the free valence. To illustrate, benzene substituted with methoxyethyl has the following structure:



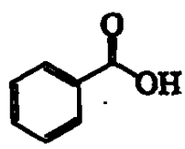
As can be seen, the ethyl is bound to the benzene, and the methoxy is the component of the substituent that is the component furthest from the benzene. As further illustration, benzene substituted with cyclohexanylthiobutoxy has the following structure:

248

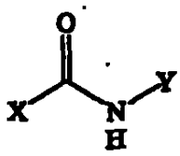


[791] When words are used to describe a linking element between two other elements of a depicted chemical structure, the rightmost-described component of the substituent is the component that is bound to the left element in the depicted structure. To illustrate, if the chemical structure is X-L-Y and L is described as methylcyclohexanylethyl, then the chemical would be X-ethyl-cyclohexanyl-methyl-Y.

[792] When a chemical formula is used to describe a substituent, the dash on the left side of the formula indicates the portion of the substituent that has the free valence. To illustrate, benzene substituted with -C(O)-OH has the following structure:



[793] When a chemical formula is used to describe a linking element between two other elements of a depicted chemical structure, the leftmost dash of the substituent indicates the portion of the substituent that is bound to the left element in the depicted structure. The rightmost dash, on the other hand, indicates the portion of the substituent that is bound to the right element in the depicted structure. To illustrate, if the depicted chemical structure is X-L-Y and L is described as -C(O)-N(H)-, then the chemical would be:



[794] The term "pharmaceutically acceptable" is used adjectivally in this patent to mean that the modified noun is appropriate for use as a pharmaceutical product or as a part of a pharmaceutical product.

[795] With reference to the use of the words "comprise" or "comprises" or "comprising" in this patent (including the claims), Applicants note that unless the context requires otherwise, those words are used on the basis and clear understanding that they are

249

to be interpreted inclusively, rather than exclusively, and that Applicants intend each of those words to be so interpreted in construing this patent, including the claims below.

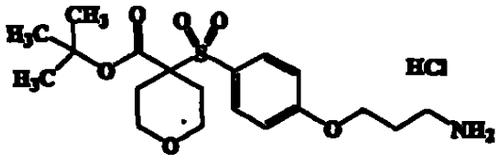
F. Compound Preparation

[796] The detailed examples below illustrate preparation of compounds and salts of this invention. Other compounds and salts of this invention may be prepared using the methods illustrated in these examples (either alone or in combination with techniques generally known in the art). Such known techniques include, for example, those disclosed in Int'l Publ. No. WO 99/25687 (PCT Patent Application No. PCT/US98/23242 published on May 27, 1999) (incorporated herein by reference). Such known techniques also include, for example, those disclosed in Int'l Publ. No. WO 00/50396 (PCT Patent Application No. PCT/US00/02518 published on August 31, 2000) (incorporated herein by reference). Such known techniques further include, for example, those disclosed in Int'l Publ. No. WO 00/69821 (PCT Patent Application No. PCT/US00/06719 published on November 23, 2000) (incorporated herein by reference).

EXAMPLES

[797] The following examples are merely illustrative, and not limiting to the remainder of this disclosure in any way.

[798] **Example 1. Preparation of 4-[[4-(3-aminopropoxy)-phenyl]sulfonyl]tetrahydro-2H-pyran-4-carboxylic acid 1,1-dimethylethyl ester, monohydrochloride.**



[799] **Part A.** To a solution of t-butylchloroacetate (67 g, 0.44 mol) and 4-fluorothiophenol (50 g, 0.40 mol) in N,N-dimethylformamide (1 L) was added potassium carbonate (62 g, 0.45 mol), followed by dimethylaminopyridine (2 g, 0.02 mol). The mixture was stirred at ambient temperature overnight under nitrogen. Once HPLC showed that the reaction was complete, the mixture was poured into stirring 10% aqueous HCl (1

250

L) and extracted with ethyl acetate (4x). The combined organic layers were washed with water (2x), dried over magnesium sulfate, filtered, and concentrated *in vacuo* to afford 112 g (100+% crude yield) of a brown oil. ^{1}H NMR confirmed the desired sulfide with no disulfide formation. This material was used without further purification.

[800] **Part B.** To a solution of the product from Part A (approximately 108 g, 0.45 mol) in tetrahydrofuran (400 ml) was added water (700 ml), followed by Oxone™ (600 g, 0.98 mol). The reaction mixture was stirred overnight. Once HPLC showed completion, the reaction mixture was filtered to remove excess Oxone™, and the mother liquor was then extracted with ethyl acetate (3x). The combined organic layers were washed with water (2x), dried over magnesium sulfate, filtered, and concentrated *in vacuo* to afford 78.3 g (64% crude yield) of a yellow oil. Both ^{19}F and ^{1}H NMR were consistent with the desired sulfone with no starting material remaining. This material was used without further purification.

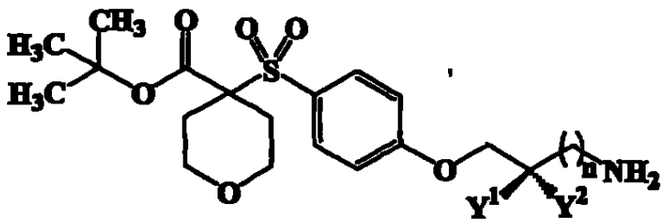
[801] **Part C.** To a solution of the product from Part B (78 g, 0.28 mol) in N,N-dimethylacetamide (300 ml) was added potassium carbonate (86 g, 0.62 mol). After stirring for 5 min, 2,2'- (dibromoethyl) ether (79 g, 0.34 mol) was added, followed by 4-dimethylaminopyridine (1.7 g, 0.014 mol) and tetrabutylammonium bromide (4.5 g, 0.14 mol). The reaction mixture was stirred overnight via a mechanical stirrer. Once HPLC showed completion, the reaction mixture was slowly dumped into stirring 10% aqueous HCl (1 L). The resulting yellow solid was collected and washed with hexanes to afford 84 g (86%) of a yellow solid. ^{1}H NMR confirmed the desired product.

[802] **Part D.** To a solution of the product from Part C (19.8 g, 57.5 mmol) and t-butyl-N-(3-hydroxypropyl) carbamate (11.1 g, 63.3 mmol) in anhydrous N,N-dimethylformamide (300 mL) at 0°C was added sodium hydride (2.8 g, 69.0 mmol; 60% dispersion in mineral oil). After 18 hr, the reaction was quenched with water and concentrated *in vacuo*. The oily residue was partitioned between ethyl acetate and saturated sodium bicarbonate solution. The layers were separated, and the organic layer was washed with brine (3X), dried over sodium sulfate, filtered, and concentrated *in vacuo*. The oily residue was taken up in acetonitrile and again concentrated *in vacuo*. The resulting solid was triturated with diethyl ether, and 15.3 g (53%) of the pure desired product was collected as a white powder. ESMS m/z = 522 $[M+Na]^+$. The filtrate

contained 11.6 g of material which was shown by HPLC to be 55% product. This material could be purified by flash chromatography to obtain more material if desired.

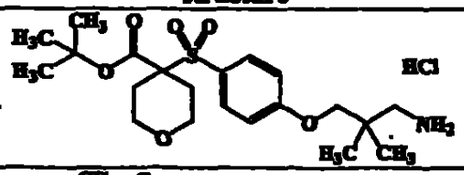
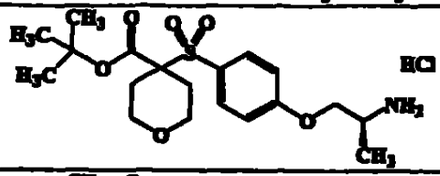
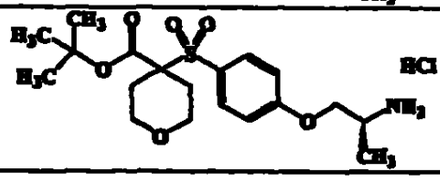
[883] Part E. The product from Part D (15.3 g, 30.6 mmol) was taken up in 4N HCl in dioxane (17 mL). After 1 hr, HPLC indicated incomplete reaction, so additional 4N HCl in dioxane (2 mL) was added. After 20 min, the reaction mixture was slowly added to rapidly stirring diethyl ether (400 mL). The resulting oily solid was rinsed with more diethyl ether then dissolved in acetonitrile and concentrated *in vacuo*. 12.3 g (92%) of the desired hydrochloride salt was obtained as a white solid. ESMS m/z = 400 $[M+H]^+$.

[884] Additional compounds can be prepared by one skilled in the art using similar methods. Examples of such compounds include those having a structure corresponding to generic formula EX-A. Such compounds include, for example, those summarized in Table 1.

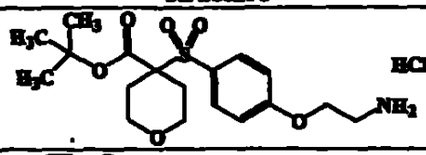
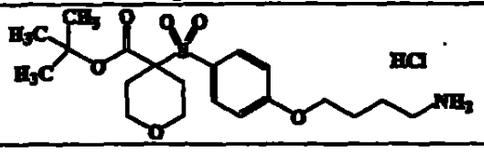


EX-A

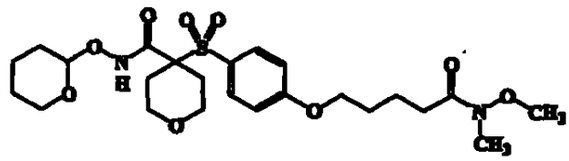
Table 1

Ex #	structure	n	Y^1	Y^2	ESMS m/z
2		1	CH_3	CH_3	428 $(M+H)^+$
3		0	CH_3	H	422 $[M+Na]^+$
4		0	H	CH_3	422 $[M+Na]^+$

252

Ex #	structure	n	Y^1	Y^2	ESMS m/z
5		0	H	H	408 $[M+Na]^+$
6		2	H	H	414 $(M+H)^+$

[805] **Example 7. Preparation of tetrahydro-4-[[4-[[5-(methoxy-methylamino)-5-oxopentyl]oxy] phenyl]sulfonyl]-N-(tetrahydro-2H-pyran-2-yl)oxy]-2H-pyran-4-carboxamide**



[806] **Part A.** To a solution of 5-benzyloxy-1-pentanol (32.6 g, 168 mmol) in anhydrous N,N-dimethylformamide (150 mL) at 0°C was added sodium hydride (7.7 g, 192 mmol, 60% dispersion in mineral oil). After 15 min, the reaction mixture was allowed to warm to 20°C, and then re-cooled to 0°C. A solution of 4-[(4-fluorophenyl)sulfonyl]tetrahydro-2H-pyran-4-carboxylic acid, 1,1-dimethylethyl ester (55.1 g, 160 mmol, as prepared in Example 1, Part C) in anhydrous N, N-dimethylformamide (100 mL) was added, and the cooling bath removed. After 4 hr, the reaction was concentrated *in vacuo*. The oily residue was partitioned between ethyl acetate and saturated sodium bicarbonate solution. The layers were separated, and the aqueous layer was back extracted with ethyl acetate (2X). The combined extracts were washed with 5% potassium hydrogensulfate, water, and brine (3X); dried over magnesium sulfate; filtered; and concentrated *in vacuo*. The resulting opaque oil solidified upon standing, and was subsequently purified by column chromatography using 10-20% ethyl acetate/ hexanes to afford 67.6 g (81%) of the desired product as a white solid. ESMS m/z = 541 $[M+Na]^+$.

[807] **Part B.** The product from Part A (20.0 g, 38.6 mmol) was dissolved in tetrahydrofuran (80 mL) in a small Fisher/Porter bottle. After purging with a stream of

253

nitrogen for 5 min, the reaction was charged with 5% palladium on carbon catalyst (4.0 g, Degussa E101 NO/W, 50% water) and pressurized to roughly ~80 psi with hydrogen. After 1.5 hr, hydrogen uptake had ceased and HPLC analysis indicated the reaction was complete. The reaction was filtered through a bed of celite and the filtrate was concentrated to yield 17.2 g (100%) of the desired alcohol as a viscous oil. This material was used without further purification.

[808] Part C. The product from Part B (16.5 g, 38.6 mmol) was dissolved in acetonitrile (80 mL). The reaction mixture was treated with carbon tetrachloride (80 mL), water (120 mL), then sodium periodate (24.7 g, 115.7 mmol), and finally ruthenium trichloride (180 mg, 0.9 mmol). After 1 hr, HPLC analysis indicated that the reaction was complete. The reaction mixture was diluted with methylene chloride (300 mL), and the solids were removed by gravity filtration. The layers were separated, and the aqueous layer was extracted with methylene chloride (3X). The combined organic extracts were dried over magnesium sulfate, filtered, and concentrated *in vacuo* to yield a blue solid. This was redissolved in tetrahydrofuran, slurried with activated carbon, filtered, and concentrated *in vacuo* to yield 17.1 g (100%) of an off-white solid. ^{1}HNMR was consistent with the desired product. This material was used without further purification.

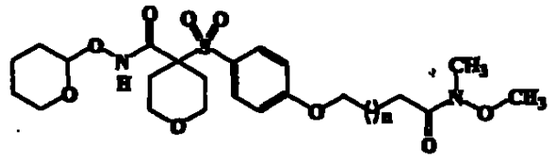
[809] Part D. To a solution of the product from Part C (17.1 g, 38.6 mmol) in N,N-dimethylformamide (160 ml) was added 1-hydroxybenzotriazole (7.8g, 57.9 mmol), and then 1-(3-dimethyaminopropyl)-3-ethylcarbodiimide hydrochloride (10.3 g, 54.0 mmol). After 1.5 hr, N,O-dimethylhydroxylamine HCl (11.3 g, 115.7 mmol) and triethylamine (32.2 ml, 231.4 mmol) were added. The reaction mixture was left stirring at ambient temperature overnight. The mixture was concentrated, and the residue partitioned between ethyl acetate and saturated sodium bicarbonate solution. The aqueous layer was back extracted with ethyl acetate (2X), and the combined organic layers were washed with 5% potassium hydrogensulfate solution, water, and brine (3X), then dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude solid was purified by column chromatography using 50% ethyl acetate/hexanes, and 14.7 g (79%) of the desired weinreb amide was obtained as an off-white solid. ESMS m/z = 508 $[M+Na]^+$.

[810] Part E. The product from Part D (6.24 g, 12.85 mmol) was taken up in neat trifluoroacetic acid (50 mL). After 1.5 hr, the trifluoroacetic acid was removed *in vacuo* at 50°C to give the free acid as a syrupy oil. ESMS m/z = 430 $[M+H]^+$. To a

254

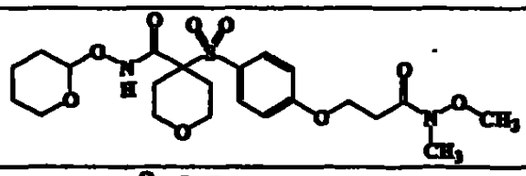
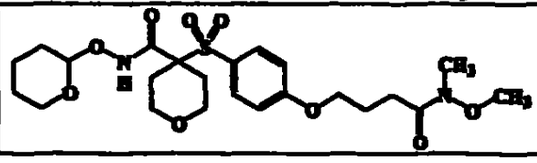
solution of this material in anhydrous N,N-dimethylformamide (25 mL) was added 1-hydroxybenzotriazole (2.14 g, 15.88 mmol), tetrahydropyranhydroxylamine (4.64 g, 39.72 mmol), and triethylamine (5.5 mL, 39.72 mmol), followed by 1-(3-dimethyaminopropyl)-3-ethylcarbodiimide hydrochloride (3.35 g, 15.83 mmol). The reaction mixture was heated at 40°C for 3.5 hr, and then cooled to ambient temperature and stirred overnight. The reaction mixture was concentrated *in vacuo* at 60°C. The residue was taken up in ethyl acetate, washed with saturated sodium bicarbonate solution (2X) and brine (3X), dried over sodium sulfate, filtered, and concentrated *in vacuo* to give 8 g of a syrup. The crude material was purified by flash chromatography using 50-100% ethyl acetate/hexanes to give the title compound as a white solid. ESMS m/z = 529 $[M+H]^+$. HRMS calculated for $C_{24}H_{36}N_2O_9S$: 529. 2220 $[M+H]^+$, found: 529.2210 .

[811] Additional compounds can be prepared by one skilled in the art using similar methods. Examples of such compounds include those having a structure corresponding to generic formula EX-B. Such compounds include, for example, the compound summarized in Table 2.



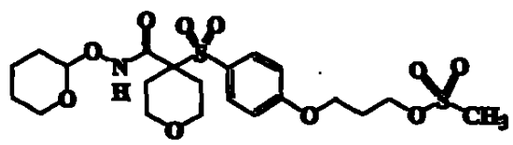
EX-B

Table 2

Ex #	structure	n	Calcd Mass	Observed Mass
8		0	518.2172	518.2176
9		1	532.2329	532.2307

255

[812] **Example 10: Preparation of tetrahydro-4-[[4-[3-[(methylsulfonyl)oxy]propoxy]phenyl]sulfonyl]-N-[(tetrahydro-2H pyran-2-yl)oxy]-2H-pyran-4-carboxamide**



[813] **Part A.** To a solution of 4-[(4-fluorophenyl)sulfonyl]-tetrahydro-2H-pyran-4-carboxylic acid, 1,1-dimethylethyl ester (5.0 g, 14.5 mmol, as prepared in **Example 1, Part C**) and 3-benzyloxy-1-propanol (2.3 mL, 14.5 mmol) in N,N-dimethylformamide (50 mL) at 0°C was added NaH (696 mg, 17.4 mmol, 60% dispersion in mineral oil). The solution was stirred at ambient temperature for 5 hr. The reaction was quenched with water, and then partitioned between ethyl acetate and water. The organic layer was washed with water and brine, dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford 7.89 g (quantitative yield) of the benzyl ether as a yellow oil. (ESMS m/z = 435 $[M- tBu]^+$.

[814] **Part B.** The benzyl ether of **Part A** (4.39 g, 8.94 mmol) was hydrolized in 1:1 trifluoroacetic acid:methylene chloride (50 mL). The solution was concentrated *in vacuo* to provide 3.69 g (950) of the free acid as a crude white solid. ESMS m/z = 452 $[M+NH4]^+$. This material was used without purification.

[815] **Part C.** To a solution of the crude acid of **Part B** (3.60 g, 8.29 mmol) in N,N-dimethylformamide (40 mL) was added 1-hydroxybenzotriazole (1.34 g, 9.95 mmol), triethylamine (3.5 mL, 24.9 mmol), and tetrahydropyranhydroxylamine (2.91 g, 24.9 mmol). After 30 min, 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (2.23 g, 11.6 mmol) was added. The solution was stirred for 18 hr at ambient temperature. The solution was partitioned between ethyl acetate and saturated sodium bicarbonate solution. The organic layer was washed with saturated sodium bicarbonate solution and brine, and then dried over sodium sulfate. Purification by flash chromatography using ethyl acetate/hexanes provided 3.71 g (84 0) of the protected hydroxamate as a crude oil. ESMS m/z = 551 $(M+NH4)^+$. HRMS calculated for $C_{27}H_{35}NO_9S\ NH_4$: 551.2427 $(M+NH4)^+$. Found: 551 .2418.

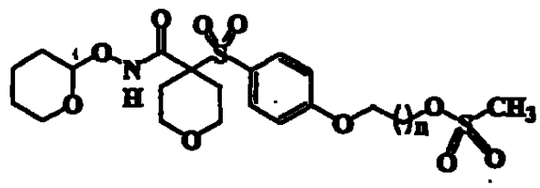
[816] **Part D.** The benzyl ether of **Part C** (3.52 g, 6.6 mmol) was hydrogenated over 10% palladium/carbon (3.31g) in methanol with ammonium formate (2.5 g, 39.6

256

mmol) as the hydrogen source added in 3 portions and heated at reflux. The solution was filtered through celite and concentrated *in vacuo* to provided 2.89 g (98 %) of the alcohol as a colorless oil. ESMS m/z = 442 $[M-H]^+$. This material was used without purification.

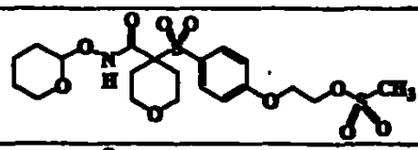
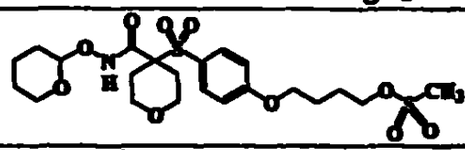
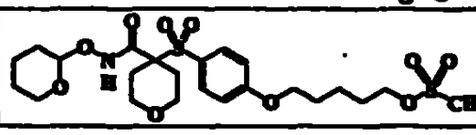
[817] **Part E.** To a solution of the protected hydroxamate of Part D (2.57 g, 5.8 mmol) in methylene chloride (25 mL) was added triethylamine (2.5 mL, 18.8 mmol). The solution was cooled to 0°C, and methylsulfonyl chloride (1.25 mL, 16.0 mmol) was added. After 18 hr, the reaction was washed with water, 10% citric acid, 5% sodium bicarbonate solution, and brine, and then dried over magnesium sulfate. Chromatography (on silica, ethyl acetate/hexanes) provided the title compound as a colorless oil (1.48 g, 49 0). ESMS m/z = 544 $(M+Na)^+$. HRMS calculated for $C_{21}H_{31}NO_{10}S_2\,NH_4$: 539. 1733 $(M+NH_4)^+$. Found: 539.1709.

[818] Additional compounds can be prepared by one skilled in the art using similar methods. Examples of such compounds include those having a structure corresponding to generic formula EX-C. Such compounds include, for example, the compounds summarized in Table 3.



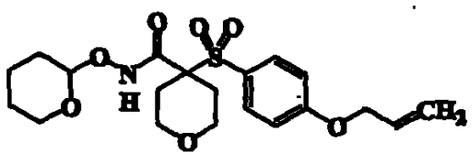
EX-C

Table 3

Ex #	structure	n	Calcd Mass	Observed Mass
11		1	525.1517	525.1561
12		3	558.1444	558.1429
13		4	572.16	572.1583

257

[819] **Example 14. Preparation of (tetrahydro-4-[[4-(2-propenyloxy)phenyl]sulfonyl]-N-[(tetrahydro-2H-pyran-2-yl)oxy]-2H-pyran-4-carboxamide**



[820] **Part A.** To a solution of sodium (8.97 g, 390 mmol) in methanol (1 L) at 0°C were added 4-fluorothiophenol (50 g, 390 mmol) and methyl chloroacetate (34.2 mL, 390 mmol). After stirring at ambient temperature for 4 hr, the solution was filtered to remove salts, and the filtrate was concentrated *in vacuo* to provide 75.85 g (970) for the desired sulfide as a colorless oil.

[821] **Part B.** To a solution of the product from Part A (75.85 g, 380 mmol) in methanol (1 L) and water (100 mL) was added Oxone™ (720 g, 1.17 mmol). After 2 hr, the reaction mixture was filtered to remove the excess salts, and the filtrate was concentrated *in vacuo*. The resulting residue was dissolved in ethyl acetate and washed with water, saturated sodium bicarbonate solution, and brine, and then dried over magnesium sulfate. Concentrating *in vacuo* provided 82.74 g (94%) of the desired sulfone as a white solid.

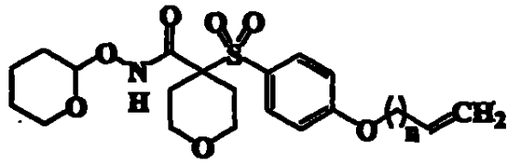
[822] **Part C.** To a solution of the product from Part B (28.5 g, 123 mmol) in N,N-dimethylacetamide (200 mL) were added potassium carbonate (37.3 g, 270 mmol), bis-(2-bromoethylether (19.3 mL, 147 mmol), 4-dimethylaminopyridine (750 mg, 6 mmol), and tetrabutylammonium bromide (1.98 g, 6 mmol). The resulting solution was stirred at ambient temperature for 72 hr, and then poured into 1 N HCl (300 mL). The resulting precipitate was collected by vacuum filtration. Recrystallization using ethyl acetate/hexanes provided 28.74 g (77%) of the tetrahydropyran product as a beige solid.

[823] **Part D.** To a solution of the product from Part C (8.0 g, 26.5 mmol) in tetrahydrofuran (250 mL) was added potassium trimethylsilonate (10.2 g, 79.5 mmol). After 1.5 hr, the reaction mixture was quenched with water, acidified to pH 2.5, and extracted with ethyl acetate. The organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford 5.78 g (76%) of the desired acid salt as a white solid.

[824] **Part E.** To a solution of the product from Part D (5.4 g, 18.7 mmol) in N,N-dimethylformamide (35 mL) were added 1-hydroxybenzotriazole (3.04 g, 22.5 mmol), N-methylmorpholine (6.2 mL, 56.2 mmol), tetrahydropyranhydroxylamine (6.8 g, 58.1 mmol) and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (5.0 g, 26.2 mmol). After stirring for 3 hr at ambient temperature, the solution was concentrated *in vacuo*, and the residue partitioned between ethyl acetate and water. The organic layer was washed with 5% aqueous potassium hydrogen sulfate, water, saturated sodium bicarbonate solution, and brine; dried over sodium sulfate; filtered; and concentrated *in vacuo* to provide 6.34 g (87%) of the THP protected hydroxamate as a white solid.

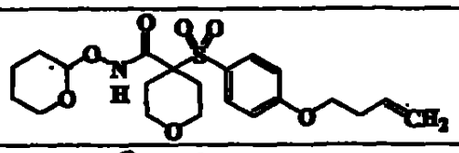
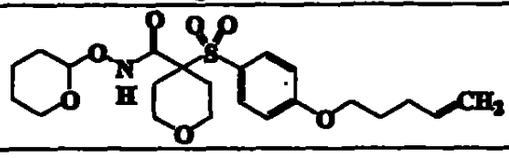
[825] **Part F.** To a solution of the product from Part E (1.0 g, 2.58 mmol) in dimethylsulfoxide (5 mL) was added potassium carbonate (0.89 g, 6.45 mmol) and allyl alcohol (0.35 mL, 12.9 mmol). The mixture was heated to 110°C for 72 hr. Additional allyl alcohol (0.88 mL, 13 mmol) and cesium carbonate (2.1 g, 6.45 mmol) were added, and the mixture heated at 120°C for 6 hr. After cooling to ambient temperature, the mixture was diluted with water (50 mL), and the pH adjusted to 8-9 with 1 N HCl. The aqueous layer was extracted with ethyl acetate. The organic layer was washed brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Purification via flash column chromatography with 15% ethyl acetate/hexanes yielded 0.67 g of pure title compound as a white solid. ESMS m/z = 426 $[M+H]^+$.

[826] Additional compounds can be prepared by one skilled in the art using similar methods. Examples of such compounds include those having a structure corresponding to generic formula EX-D. Such compounds include, for example, the compounds summarized in Table 4.

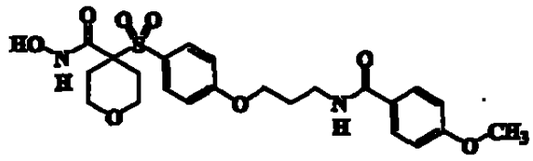


EX-D

Table 4

Ex. #	Structure	n	ESMS m/z
15		2	440 $[M+H]^+$
16		3	454 $[M+H]^+$

[827] **Example 17. Preparation of tetrahydro-N-hydroxy-4-[[4-[3-[(4-methoxybenzoyl) amino] propoxy]phenyl] sulfonyl]-2H-pyran-4-carboxamide**



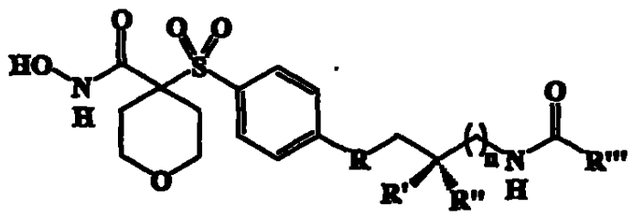
[828] **Part A.** To a solution of 4-[[4-(3-aminopropoxy)-phenyl] sulfonyl] tetrahydro-2H-pyran-4-carboxylic acid 1,1-dimethylethyl ester, monohydrochloride (507 mg, 1.27 mmol, prepared as in Example 1) in anhydrous N,N-dimethylformamide (5 mL) at ambient temperature was added triethylamine (215 uL, 1.54 mmol), followed immediately by panisoyl chloride (260 mg, 1.52 mmol). After 1 hr, the reaction mixture was quenched with water (~2 mL) and concentrated *in vacuo* at 60°C. The crude residue was partitioned between ethyl acetate and water. The layers were separated, and the organic layer was washed with brine (3X), dried over sodium sulfate, filtered, and concentrated *in vacuo* to give a pale yellow oil. The crude product was partially purified by flash chromatography using 80% ethyl acetate/hexanes to provide 225 mg (33%) of the desired acylated product as a clear, colorless oil. ESMS m/z = 556 $[M+Na]^+$. This material was used without further purification.

[829] **Part B.** The product from Part A (225 mg, 82% purity by HPLC) was taken up in neat trifluoroacetic acid (1 mL). After 3 hr, the trifluoroacetic acid was removed *in vacuo* at 50°C to give the free acid as a colorless oil. ESMS m/z = 478 $[M+H]^+$. To a solution of this material in anhydrous N,N dimethylformamide (2 mL) was added 1-hyrdoxybenzotriazole (72 mg, 0.53 mmol), N-methylmorpholine (100 uL, 0.91

mmol) and tetrahydropyranhydroxylamine (78 mg, 0.67 mmol), followed by 1-(3-dimethyaminopropyl)-3-ethylcarbodiimide hydrochloride (119 mg, 0.62 mmol). The reaction mixture was stirred at ambient temperature for 72 hr, and then concentrated *in vacuo* at 60°C. The residue was partitioned between ethyl acetate and water. The layers were separated, and the organic layer was washed with saturated sodium bicarbonate solution and brine (2X), dried over sodium sulfate, filtered, and concentrated *in vacuo* to give 255 mg of the desired THP protected hydroxamate as a colorless oil. ESMS m/z = 599 $[M+Na]^+$. HRMS calculated for $C_{28}H_{36}N_2O_9S$: 577.2220 $[M+H]^+$, found: 577.2215.

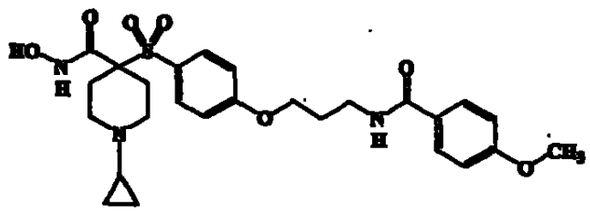
[830] Part C. The product from Part B (255 mg, 88% purity by HPLC) was dissolved in 4N HCl in dioxane (3 mL) and methanol (300 uL). After 1 hr at ambient temperature, the reaction mixture was poured into rapidly stirring diethyl ether (50 mL). A white solid was collected and dried over P_2O_5 under vacuum. The title compound was obtained as a faint pink solid. ESMS m/z = 493 $[M+H]^+$. HRMS calculated for $C_{23}H_{29}N_2O_9S$: 493.1645 $[M+H]^+$, found: 493.1636.

[831] Additional compounds (such as those having a structure corresponding to generic Formula EX-E) can be prepared by one skilled in the art using similar methods with either the t-butyl ester or free acid of 4-[[4-(3-aminopropoxy)-phenyl]sulfonyl]-tetrahydro-2H-pyran-4-carboxylic acid 1,1-dimethylethyl ester, monohydrochloride or similarly prepared starting materials. Also, one may use carboxylic acids as coupling agents in place of acid chlorides using standard peptide coupling conditions for formation of the amide bond.



EX-E

[832] **Example 18. Preparation of 1-cyclopropyl-N-hydroxy-4-[[4-[3[(4-methoxybenzoyl)amino]propoxy]phenyl]sulfonyl]-4-piperidinecarboxamide, monohydrochloride.**



[833] **Part A.** to a solution of ethyl isonipecotate (15.7 g, 0.1 mol) in tetrahydrofuran (100 mL) was added a solution of di-tert-butyl dicarbonate (21.8 g, 0.1 mol) in tetrahydrofuran (5 mL) dropwise over 20 min. The solution was stirred overnight at ambient temperature and concentrated *in vacuo* to yield a light oil. The oil was filtered through silica gel using ethyl acetate/hexanes then concentrated *in vacuo* to afford 26.2 g (100%) of the desired BOC-piperidine as a clear, colorless oil.

[834] **Part B.** A solution of 4-fluorothiophenol (50.29 g, 390 mmol) in dimethyl sulfoxide (500 mL) was heated to 65°C for 6 hr. The reaction was quenched by pouring into wet ice. The resulting solid was collected by vacuum filtration to afford 34.4 g (68.9%) of the desired disulfide as a white solid.

[835] **Part C.** To a solution of the product from Part A (16 g, 62 mmol) in tetrahydrofuran (300 mL) cooled to -50°C was added lithium diisopropylamide (41.33 mL, 74 mmol). After being at 0°C for 1.5 hr, the product from Part B (15.77 g, 62 mmol) was added. The reaction mixture was stirred at ambient temperature for 20 hr, and then quenched by the addition of water. The solution was concentrated *in vacuo*, and the resulting residue was partitioned between ethyl acetate and water. The organic layer was washed with 0.5 N KOH, water, and brine. Purification by column chromatography using ethyl acetate/hexanes provided 18.0 g (75%) of the desired sulfide as an oil.

[836] **Part D.** To a solution of the product from Part C (16.5 g, 43 mmol) in methylene chloride (500 mL) cooled to 0°C was added 3-chloroperbenzoic acid (18.0 g, 86 mmoL). After stirring for 20 hr, the reaction mixture was diluted with water and extracted with methylene chloride. The organic layer was washed with 10% aqueous sodium sulfite, water, and brine, dried over magnesium sulfate, filtered, and concentrated

262

in vacuo. The crude product was purified by column chromatography using ethyl acetate/hexanes to afford 10.7 g (60%) of the desired sulfone as a solid.

[837] **Part E.** Into a solution of the product from Part D (10 g, 24.0 mmol) in ethyl acetate (250 mL) was bubbled HCl gas for 10 min, followed by stirring at ambient temperature for 4 hr. Concentration *in vacuo* provided 7.27 g (86%) of the amine hydrochloride salt as a white solid.

[838] **Part F.** To a solution of the product from Part E (10.0 g, 28.4 mmol) in methanol (100 mL) was added acetic acid (16.2 mL, 284 mmol), powdered 4A molecular sieves (9.1 g), and [(1-ethoxycyclopropyl)oxyl trimethyl silane (17.1 mL, 85.2 mmol). Sodium cyanoborohydride (4,82 g, 76.7 mmol) was then added slowly. The reaction was heated at reflux with vigorous stirring for 4.5 hr. The reaction mixture was cooled to room temperature, filtered through celite, and concentrated *in vacuo*. The residue was partitioned between ethyl acetate and saturated sodium bicarbonate solution. The organic layer was washed with saturated sodium bicarbonate solution (3X) and brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo*. The crude material crystallized upon standing providing 10.9 g (100%) of the alkylated amine compound as a pale yellow oily crystal. ESMS m/z = 356 $(M+H)^+$. This material was used without purification.

[839] **Part G.** The product from Part F (28.4 mmol) was hydrolized in tetrahydrofuran (65 mL) with LiOH (3.58 g, 85.2 mmol) in 35 mL of water at 60°C over 3 days. The solution was concentrated *in vacuo*, diluted with water, and washed with diethyl ether. The aqueous layer was acidified with 1N HCl to a pH of ~4.5, causing a white precipitate to form. The solid was collected by filtration, washed with water, and washed with ethyl acetate. After drying over silica on a high vacuum, 8.06 g (78.2 %) of the acid was obtained as a crude white solid. ESMS m/z = 328 (M+H)+. HRMS calculated for $C_{15}H_{18}NO_4SF$: 328.1019 $(M+H)^+$, found: 328.1014. This material was used without purification.

[840] **Part H.** To a solution of the crude acid of Part G (7.92 g, 21.8 mmol) in N,N-dimethylformamide (48 mL) was added N-methylmorpholine (12.0 mL, 109 mmol) and PyBOP (12.5 g, 24.0 mmol). After stirring 15 min, tetrahydropyranhydroxylamine (3.07 g, 26.2 mmol) was added. The solution was stirred for 22 hr at ambient temperature. The solution was diluted with water (240 mL) and extracted with ethyl acetate (3X). The combined organics were washed with saturated aqueous sodium bicarbonate solution (2X)

263

and brine, dried over sodium sulfate, filtered, and concentrated *in vacuo* to a foamy oil. The crude material was filtered through a silica plug using 1% Et_3N in ethyl acetate/hexanes to afford 7.12 g (76.60) of the protected hydroxamate as a foamy oil. ESMS m/z = 427 $(M+H)^+$. HRMS calculated for $C_{20}H_{27}N_2O_3SF$: 427.1703 $(M+H)^+$. Found: 427.1693.

[841] **Part I.** To a solution of 3-(dibenzylamino)-1-propanol (4.3 g, 16.88 mmol) in anhydrous N,N-dimethylformamide (35 mL) was added sodium hydride (1.3 g, 32.35 mmol; 60% dispersion in mineral oil). The reaction mixture was stirred for 15 min, then cooled to 0°C in an ice bath and treated with a solution of the product from Part H (6.0 g, 14.07 mmol) in anhydrous N,N-dimethylformamide (15 mL). After the addition was completed, the ice bath was removed and the reaction was allowed to stir at ambient temperature for 18 hr. The reaction was quenched with water and concentrated *in vacuo*. The oily residue was partitioned between ethyl acetate and saturated sodium bicarbonate solution. The layers were separated and the aqueous layer was extracted with ethyl acetate (3X). The organic extracts were combined and washed with brine (3X), dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude yellow solid was re-crystallized from hot acetonitrile. 6.5 g (70%) of the pure desired product was collected as a white powder. ESMS m/z = 662 $[M+H]^+$.

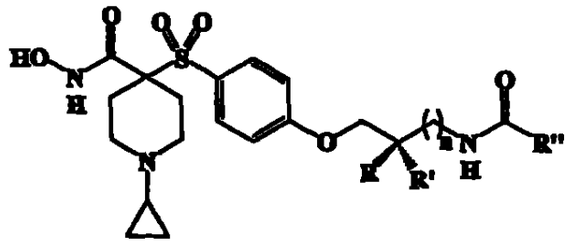
[842] **Part J.** The product from Part I (1.0 g, 1.51 mmol) and glacial acetic acid (0.2 g, 3.02 mmol) were slurried in methanol (15 mL) in a small Fisher/Porter bottle. After purging with a stream of nitrogen for 5 min, the reaction was charged with 20% palladium on carbon catalyst (0.5 g, Degussa E169X/W, 50% water) and pressurized to 50 psi with hydrogen. After 5 hr, hydrogen uptake had ceased, and HPLC analysis indicated the reaction was complete. The reaction was filtered through a bed of celite, and the filtrate was concentrated to yield 0.8 g (1000) of the desired mono-acetate salt as a dry, white foam. ESMS m/z = 481 $[M+H]^+$.

[843] **Part K.** To a solution of the product from Part J (0.7 g, 1.06 mmol) in anhydrous methylene chloride (11 mL) at ambient temperature was added triethylamine (0.73 mL, 6.35 mmol), followed by p-anisoyl chloride (0.3 g, 1.59 mmol). After 10 min, HPLC analysis showed the reaction to be complete. The reaction mixture was concentrated *in vacuo*, and the residue was partitioned between ethyl acetate and saturated sodium bicarbonate solution. The layers were separated, and the aqueous layer extracted

with ethyl acetate (3X). The organic extracts were combined and washed with brine (3X), dried over sodium sulfate, filtered, and concentrated *in vacuo* to yield a tan foam. The crude product was purified by flash chromatography using 60-100% [5% (2M ammonia in methanol) ethyl acetate]/hexanes to yield 0.2 g (34%) of the desired product as a dry white foam. ESMS m/z = 616 $[M+H]^+$.

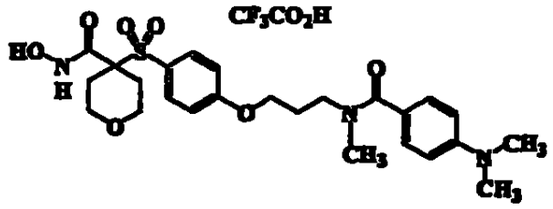
[844] **Part L.** The product from Part K (0.2 g, 0.34 mmol) was slurried in 4N HCl in dioxane (2 mL). After 5 min, methanol (0.2 mL) was added. After stirring for 10 min at ambient temperature, the reaction mixture was poured into rapidly stirring diethyl ether (50 mL). A white solid was collected and dried under vacuum. The title compound (as the HCl salt) was obtained as an off-white solid. ESMS m/z = 532 $[M+H]^+$. HRMS calculated for $C_{26}H_{33}N_3O_7S$: 532.2117 $[M+H]^+$, found: 532.2098.

[845] Additional compounds can be prepared by one skilled in the art using similar methods. Examples of such compounds include those having a structure corresponding to generic formula EX-F.



EX-F

[846] **Example 19. Preparation of 4-[[4-[3-[[4-(dimethylamino)benzoyl] methylamino] propoxy] phenyl] sulfonyl]-tetrahydro-N-hydroxy-2H-pyran-4-carboxamide.**

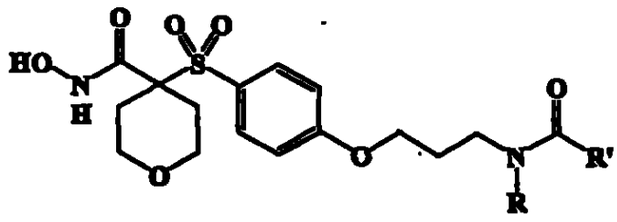


[847] **Part A.** To a solution of 4-[[4-[3-[[4(dimethylamino)-benzoyl]amino]propoxy]phenyl] sulfonyl] tetrahydro-2H-pyran-4carboxylic acid, 1,1-

dimethylethyl ester (prepared as in Example 17) in anhydrous N,N-dimethylformamide (3 mL) was added iodomethane (61 uL, 0.98 mmol), followed by sodium hydride (24 mg, 0.59 mmol; 60% dispersion in mineral oil). After 1 hr the reaction mixture was quenched with water, washed with brine (3X), dried over sodium sulfate, filtered, and concentrated *in vacuo* to yield the desired N-methylated product as a sticky solid. ESMS m/z = 561 $[M+H]^+$. HRMS calculated for $C_{28}H_{40}N_3O_7S$: 561.2634 $[M+H]^+$, found: 561.2628.

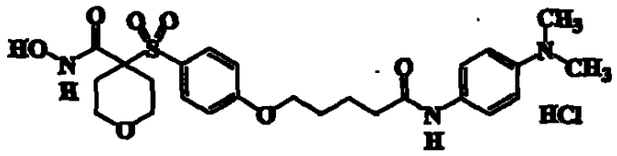
[848] **Part B.** The product from Part A (400 mg, 0.71 mmol) was taken up in neat trifluoroacetic acid (1 mL). After 1 hr, the trifluoroacetic acid was removed *in vacuo* at 60°C to give the free acid as a sticky solid. ESMS m/z = 505 $[M+H]^+$. To a solution of this material in anhydrous N,N-dimethylformamide (5 mL) was added 1-hydroxybenzotriazole (113 mg, 0.83 mmol), tetrahydropyranhydroxylamine (246 mg, 2.10 mmol), and triethylamine (390 uL, 2.8 mmol), followed by 1-(3dimethyaminopropyl)-3-ethylcarbodiimide hydrochloride (188 mg, 0.98 mmol). The reaction mixture was heated to 40°C for 4 hr, and then cooled to ambient temperature. The reaction mixture was diluted with ethyl acetate, washed with saturated sodium bicarbonate solution (2X) and brine (4X), dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was de-protected and simultaneously purified by reverse phase HPLC to give 59 mg of the title compound as an off-white solid. ESMS m/z = 520 $[M+H]^+$. HRMS calculated for $C_{25}H_{33}N_3O_7S$: 520.2117 $[M+H]^+$, found: 520.2120.

[849] Additional compounds can be prepared by one skilled in the art using similar methods. Examples of such compounds include those having a structure corresponding to generic formula EX-G.



EX-G

[850] **Example 20. Preparation of 4-[[4-[[5-[[4-(dimethylamino)-phenyl]amino]-5-oxopentyl] oxy]phenyl]sulfonyl]tetrahydro-N-hydroxy-2H-pyran-4-carboxamide, monohydrochloride.**

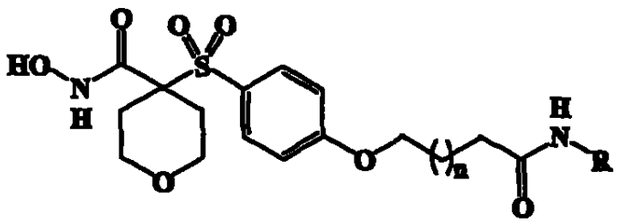


[851] **Part A.** To a solution of 4-[[4-(4-carboxybutoxy)phenyl-]sulfonyl]tetrahydro-2H-pyran-4-carboxylic acid, 1,1-dimethylethyl ester (446 mg, 0.91 mmol, prepared as in Example 7) in anhydrous N,N-dimethylformamide (6 mL) was added 1-hydroxybenzotriazole (150 mg, 1.11 mmol), triethylamine (400 uL, 2.87 mmol), N,N-dimethyl-1,4-phenylenediamine (188 mg, 1.38 mmol), and finally 1-(3-dimethyaminopropyl)-3-ethylcarbodiimide hydrochloride (300 mg, 1.56 mmol). The reaction mixture was stirred at ambient temperature for 18 hr, and then concentrated *in vacuo* at 60°C. The residue was partitioned between ethyl acetate and saturated sodium bicarbonate solution. The organic layer was washed with brine (2X), dried over sodium sulfate, filtered, and concentrated *in vacuo* to give the desired amide. ESMS m/z = 561 $[M+H]^+$. This material was taken up in neat trifluoroacetic acid (5 mL). After 3 hr the trifluoroacetic acid was removed *in vacuo* at 60°C to give the free acid. ESMS m/z = 505 $[M+H]^+$. To a solution of this material in anhydrous N,N-dimethylformamide (5 mL) was added 1-hydroxybenzotriazole (148 mg, 1.10 mmol), triethylamine (400 uL, 2.87 mmol), and tetrahydropyranhydroxylamine (320 mg, 2.73 mmol), followed by 1-(3-dimethyaminopropyl)-3-ethylcarbodiimide hydrochloride (262 mg, 1.37 mmol). The reaction mixture was stirred at ambient temperature overnight, and then partitioned between ethyl acetate and saturated sodium bicarbonate solution. The organic layer was washed with brine (3X), dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography using 80% ethyl acetate/hexanes as eluant to afford the desired THP hydroxamate. ESMS m/z = 604 $[M+H]^+$. HRMS calculated for $C_{30}H_{41}N_3O_8S$: 604.2693 $[M+H]^+$, found: 604.2709.

[852] **Part B.** The product from Part A was dissolved in 4N HCl in dioxane (5 mL) and methanol (500 uL). After 3 hr at ambient temperature the reaction mixture was poured into rapidly stirring diethyl ether (50 mL). A purplish-pink solid was collected and

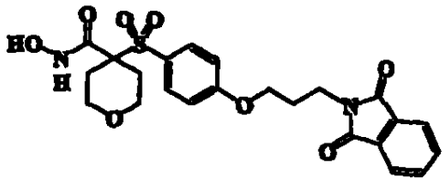
subsequently purified by reverse phase HPLC. The title compound was obtained as a faint pink solid 131 mg (28% from the starting acid in part A). ESMS m/z = 520 $[M+H]^+$. HRMS calculated for $C_{25}H_{33}N_3O_7SHCl$: 520.2117 $[M+H]^+$, found: 520.2127.

[853] Additional compounds can be prepared by one skilled in the art using similar methods. Examples of such compounds include those having a structure corresponding to generic formula EX-H.



EX-H

[854] **Example 21. Preparation of 4-[[4-[3-(1,3-dihydro-1,3-dioxo2H-isoindol-2-yl)propoxy] phenyl]sulfonyl]tetrahydro-N-hydroxy-2H-pyran-4-carboxamide**



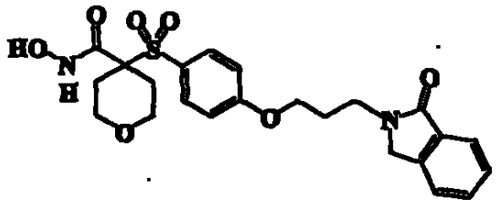
[855] **Part A.** To a solution of 4-[(4-fluorophenyl)sulfonyl]tetrahydro-2H-pyran-4-carboxylic acid, 1,1-di-methylethyl ester (6.7 g, 19 mmol, as prepared in Example 1, Part C) in anhydrous N,N-dimethylformamide (40 ml) at ambient temperature was added N-(3-hydroxypropyl)phthalimide (4 g, 19 mmol), followed immediately by NaH (700 mg, 20 mmol, 60% dispersion in mineral oil). After 1.5 hr, HPLC showed less than 1% of the starting electrophile. The reaction mixture was quenched with water (60 ml). The cloudy mixture was extracted with ethyl acetate (2x100 ml). The organic layers were combined, washed with brine (1x200 ml), dried over sodium sulfate, filtered, and concentrated *in vacuo* to give a tan, viscous oil that crystallized from methanol (3.2 g, 52%). ESMS m/z = 489 $[M+H]^+$. This material was used without further purification.

[856] Part B. The product from Part A (3 g, 6 mmol) was dissolved in methylene chloride (304 ml) and trifluoroacetic acid (6 ml). After 12 hr, the mixture was concentrated *in vacuo*, and the residue was triturated with diethyl ether to form a solid which was collected and dried to afford the carboxylic acid as a beige solid (3 g, 90%). ESMS m/z = 474 [M+H]+. This material was used without further purification.

[857] Part C. To a solution of the product from Part B (3 g, 6.2 mmol) in anhydrous N,N-dimethylformamide (25 ml) was added triethylamine (2 ml, 18 mmol), followed by tetrahydropyranhydroxylamine (1 g, 8 mmol), 1-hydroxybenzotriazole (0.5 g, 3 mmol), and 1-(3-dimethyaminopropyl)-3-ethylcarbodiimide hydrochloride (2 g, 8 mmol). The reaction mixture was heated at 40°C for 0.5 hr. The reaction was monitored by RPHPLC. After 2 hr, the mixture was concentrated *in vacuo*, the residue was flooded with water, and the product separated as a solid. The solid was filtered, and was of sufficient purity to carry on to the next step. Mass spectral data and NMR were consistent with the desired product.

[858] Part D. The solid from Part C (3 g) was slurried in methanol (1 mL) and diethyl ether (30 ml). To this was added 4N HCl in dioxane (10 ml) and stirred for 2 hr. RPHPLC showed complete reaction. The reaction mixture was concentrated by half, diethyl ether (100mL) was added, and the white solid (1.5 g, 70% yield) filtered and dried under vacuum. ^{1}H NMR was consistent with the desired product ESMS m/z $C_{23}H_{24}N_2O_8S$ = 489 $[M+H]^+$. HRMS calculated for $C_{23}H_{24}N_2O_8S$: 489.1332 $[M+H]^+$, found: 489.1298.

[859] Example 22. Preparation of 4-[[4-[3-(1,3-dihydro-1-oxo-2H-isoindol-2-yl)propoxy]phenyl]sulfonyl]tetrahydro-N-hydroxy-2H-pyran-4-carboxamide



[860] Part A. To a solution of 4-[(4-fluorophenyl)-sulfonyl]tetrahydro-2H-pyran-4-carboxylic acid, 1,1-dimethylethyl ester (5.2 g, 15 mmol, as prepared in Example 1, Part C) in dimethyl sulfoxide (40 ml) at ambient temperature was added N-(3-hydroxypropyl)phthalide (3 g, 15 mmol, prepared according to *J.Med.Chem.*, 146-157

269

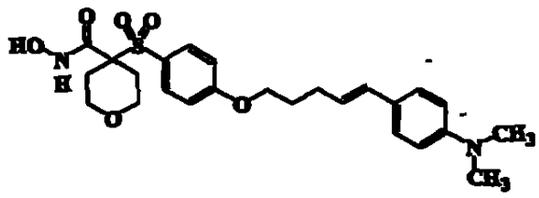
(1996)), followed by cesium carbonate (12 g, 45 mmol). After 15 hr at 80°C, HPLC indicated complete reaction. The reaction mixture was quenched with water (60 ml). The cloudy mixture was extracted with ethyl acetate (2x100 ml). The organic layers were combined, washed with brine (1x200 ml), dried over sodium sulfate, filtered, and concentrated *in vacuo* to give a tan, viscous oil that crystallized from methanol (7 g, 72%). ESMS m/z = 516 $[M+H]^+$, NMR was consistent with desired product. This material was used without further purification.

[861] Part B. The product from Part A (3 g, 6 mmol) was dissolved in methylene chloride (300 ml) and trifluoroacetic acid (6 ml). After 12 hr of stirring, the mixture was concentrated *in vacuo* and the residue was triturated with diethyl ether to form a solid which was collected and dried to afford the carboxylic acid as a beige solid (3 g, 91%). ESMS m/z = 474 $[M+H]^+$. This material was used without further purification.

[862] Part C. To a solution of the product from Part B (3 g, 6.2 mmol) in N,N-dimethylformamide (25 ml) was added triethylamine (2 ml, 18 mmol), followed by tetrahydropyranhydroxylamine (1.2 g, 8 mmol), 1-hydroxybenzotriazole (0.5 g, 3 mmol), and 1-(3-dimethyaminopropyl)-3-ethylcarbodiimide hydrochloride (1.5 g, 8 mmol). The reaction mixture was heated at 40°C for 0.5 hr. The reaction was monitored by RPHPLC. After completion the mixture was concentrated and the residue was flooded with water. The resulting solid was filtered, and was of sufficient purity to carry on to the next step. Mass spectral data and NMR were consistent with the desired product.

[863] Part D. The solid from Part C (3 g) was slurried in methanol (1 mL) and diethyl ether (30 ml). To this was added 4N HCl in dioxane (10 ml) and stirred for 2 hr. RPHPLC showed complete reaction. The reaction mixture was concentrated by half, diethyl ether (100 mL) was added, and the white solid (2.5 g, 90% yield) filtered and dried under vacuum. ^1H NMR was consistent with the desired product. HRMS calculated for $C_{23}H_{26}N_2O_7S$: 475.1525 $[M+H]^+$, found: 475.1510.

[864] **Example 23. Preparation of 4-[[4-[[4E)-5- [-4-(dimethylamino) phenyl]-4-pentenyl]oxy] phenyl] sulfonyl]tetrahydro-N-hydroxy-2H-pyran-4-carboxamide and 4-[[4-[[4Z)-5-[-4-(dimethyl-amino)phenyl]-4-pentenyl]oxy]phenyl]sulfonyl] tetrahydro-N-hydroxy-2H-pyran-4-carboxamide, monohydrochloride**



[865] **Part A.** To a solution of 4-[(4-fluorophenyl)sulfonyl]tetrahydro-2H-pyran-4-carboxylic acid, 1,1-di-methylethyl ester (10.0 g, 29.0 mmol, as prepared in Example 1, Part C) in N,N-dimethylformamide (60 ml) at ambient temperature was added 4-penten-1-ol (3.1 ml, 30.0 mmol), followed immediately by NaH (1.4 g, 34.8 mmol, 60% dispersion in mineral oil). After 1.5 hr, HPLC showed less than 1% of the starting material. The reaction mixture was quenched with water (60 ml). The cloudy mixture was extracted with ethyl acetate (3x-300 ml). The organic layers were combined; washed with 5% potassium hydrogensulfate (1x200 ml), saturated sodium bicarbonate solution (1x-200 ml), water (1x-200 ml), and brine (1x-200 ml); dried over sodium sulfate; filtered; and concentrated *in vacuo* to give a tan oil. The crude product was partially purified by flash chromatography using 15% ethylacetate/hexanes to provide 11.7 g (98%) of the desired ether product as a clear, colorless oil. ESMS m/z = 433 $[M+Na]^+$. This material was used without further purification.

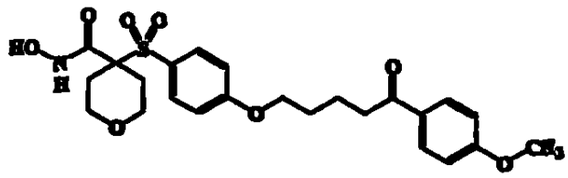
[866] **Part B.** To a solution of the product from Part A (2.0 g, 4.9 mmol) in N,N-dimethylformamide (3 ml) was added 4-bromo-N,N-dimethylaniline (1.2g, 5.8 mmol), followed by triethylamine (1.4 ml, 9.8 mmol), tri-ortho-tolylphosphine (34 mg, 0.10 mmol), and palladium(II) acetate (12 mg, 0.05 mmol). The reaction was heated at 100°C for 12 hr. The reaction was cooled and diluted with water (5 ml). The aqueous was extracted with ethyl acetate (3x15 ml). The organic extracts were dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford a black oil (3.2 g). The black crude product was partially purified by flash chromatography using 5% ethyl acetate/hexanes to

provide 1.2 g of the olefinic product as a tan oil (45% yield, trans:cis, 3:1). ESMS m/z = 552 $[M+Na]^+$. This material was used without further purification.

[867] Part C. The product from Part B (1.2 g, 2.3 mmol) was dissolved in methylene chloride (4 ml) and trifluoroacetic acid (4 ml). After 1 hr of stirring, the mixture was concentrated and the residue was triturated with diethyl ether to form a solid which was collected and dried to afford the carboxylic acid-TFA salt as a beige solid (0.73 g, 510). ESMS m/z = 474 $[M+H]^+$. This material was used without further purification.

[868] Part D. To a solution of the product from Part C (0.73 g, 1.2 mmol) in N,N-dimethylformamide (4 ml) was added triethylamine (0.9 ml, 6.2 mmol), followed by tetrahydropyranhydroxylamine (0.28 g, 2.4 mmol), 1-hydroxybenzotriazole (0.19 g, 1.4 mmol), and 1-(3-dimethyaminopropyl)-3-ethylcarbodiimide hydrochloride (0.32 g, 1.8 mmol). The reaction mixture was heated at 40°C for 24 hr. The mixture was concentrated and the residue was purified via reverse phase chromatography (C_{18}, acetonitrile/water/TFA). Fractions (10 ml) were collected to separate the isomers. While analyzing, the aqueous TFA mixtures de-protected the product affording the hydroxamic acid final products. 4-[[4-[[4E)-5-[-4-(dimethylamino) phenyl]-4-pentenyl] oxy]phenyl]sulfonyl]-tetrahydro-N-hydroxy-2H-pyran-4-carboxamide, (98% trans isomer by HPLC, 0.12 g, 17% yield). HRMS calculated for $C_{23}H_{28}N_2O_5S$: 489.2059 $[M+H]^+$, found: 489.2067. ^1H NMR confirmed trans isomerization (Job = 15.9 Hz). 4-[[4-[[4Z)-5-[-4-(dimethyl-amino)phenyl]-4-pentenyl]oxy]phenyl]sulfonyl]tetrahydro-N-hydroxy-2H-pyran-4-carboxamide, monohydrochloride, (79% cis/17% trans by HPLC, 15 mg tan solid, 2% yield). HRMS calculated for $C_{23}H_{28}N_2O_5S$: 489.2059 $[M+H]^+$, found: 489.2067.

[869] Example 24. Preparation of tetrahydro-N-hydroxy-4-[[4-[[5(4-methoxyphenyl)-5-oxopentyl]oxy]phenyl]sulfonyl]-2H-pyran-4-carboxamide

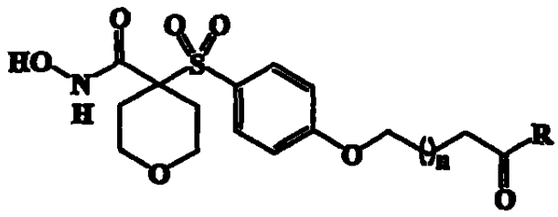


[870] Part A. To a mixture of magnesium turnings (344 mg, 14.18 mmol) etched with iodine in anhydrous tetrahydrofuran (4 mL) at reflux was added 4-bromoanisole (1.2 mL, 9.45 mmol) dropwise over 10 min. The reaction mixture was heated at reflux for 45

min, and then cooled to ambient temperature. The prepared grignard reagent was added to a mixture of tetrahydro-4-[[4-[[5-(methoxymethylamino)-5-oxopentyl]oxy]phenyl]sulfonyl]-N-[(tetrahydro-2H-pyran-2-yl)oxy]-2H-pyran-4-carboxamide (1.0 g, 1.9 mmol, as prepared in Example 7) in anhydrous tetrahydrofuran (10 mL) at 0°C. The reaction mixture was warmed to ambient temperature and left stirring overnight. The reaction was quenched with saturated ammonium chloride, and then partitioned between ethyl acetate and water. The layers were separated, and the organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude material was purified by flash chromatography using 50-100% ethyl acetate/hexanes to afford 320 mg (29%) of the desired ketone as a white powder. ESMS m/z = 593 $[M+NH_4]^+$. HRMS calculated for $C_{29}H_{37}NO_9S$: 593.2533 $[M+NH_4]^+$, found: 593.2555.

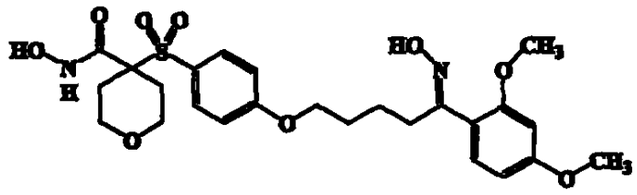
[871] **Part B.** The product from Part A (300 mg, 0.52 mmol) was dissolved in 4N HCl in dioxane (3 mL) and methanol (300 uL). After 10 min at ambient temperature, the reaction mixture was poured into hexanes (75 mL), and the product precipitated out as an oil. The solvent was decanted and additional hexanes was added. The resulting solid was triturated with diethyl ether, and the title compound was obtained as an off-white solid. ESMS m/z = 492 $[M+H]^+$. HRMS calculated for $C_{24}H_{29}NO_9S$: 492.1692 $[M+H]^+$, found: 492.1713.

[872] Additional compounds can be prepared by one skilled in the art using similar methods with either the t-butyl ester, THP protected hydroxamate, or resin bound hydroxamate of the weinreb amide. Examples of such compounds include those having a structure corresponding to generic formula EX-I.



EX-I

[873] **Example 25. Preparation of tetrahydro-N-hydroxy-4-[[4-[[5-(hydroxylimino)-5-(4-methoxyphenyl)pentyl]oxy]phenyl]-sulfonyl]-2H-pyran-4-carboxamide.**



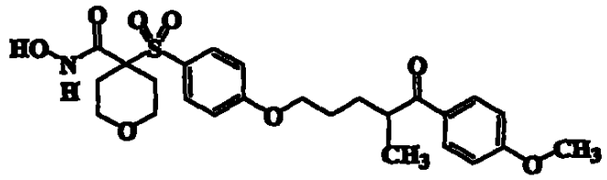
[874] **Part A.** To a mixture of magnesium turnings (1.2 g, 49.4 mmol) etched with iodine in anhydrous tetrahydrofuran (4 mL) at reflux was added 1-bromo-2,4-dimethyoxybenzene (6.0 mL, 41.7 mmol) dropwise over 10 min. The reaction mixture was heated at reflux for 30 min, and then cooled to ambient temperature. The prepared grignard reagent was added to a mixture of tetrahydro-4-[[4-[3-(methoxymethyl-amino)-3-oxopropoxy]phenyl]sulfonyl]-2H-pyran-4-carboxylic acid, 1,1-dimethylethyl ester (1.0 g, 1.9 mmol, prepared as in Example 7) in anhydrous THF (10 mL) at 0°C. The reaction mixture was warmed to ambient temperature, and, after 2 hr, was quenched with saturated ammonium chloride, and then partitioned between ethyl acetate and water. The layers were separated, and the organic layer was washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude material was covered with diethylether. The resulting green solid was triturated with diethyl ether. The final solid was collected to afford 2.2 g (94%) of the desired ketone as a pale green powder. ESMS m/z = 585 $[M+Na]^+$. HRMS calculated for $C_{29}H_{38}NO_9S$: 563 .2315 $[M+H]^+$, found: 563.2319.

[875] **Part B.** The product from Part A (2.2 g, 3.91 mmol) was taken up in neat trifluoroacetic acid (6 mL). After 2 hr, the trifluoroacetic acid was removed *in vacuo* at 50°C to give the free acid as a purple oil. ESMS m/z = 507 $[M+H]^+$. To a solution of this material in anhydrous N,N-dimethylformamide (20 mL) was added 1-hydroxybenzotriazole (670 mg, 4.96 mmol), triethylamine (1.8 mL, 12.91 mmol), tetrahydropyranhydroxylamine (1.48 g, 12.63 mmol), and 1-(3-dimethyaminopropyl)-3-ethylcarbodiimide hydrochloride (1.13 g, 5.89 mmol). After 16 hr, the reaction mixture was concentrated *in vacuo* at 60°C. The crude material was partitioned between ethyl acetate and saturated sodium bicarbonate solution. The organic layer was washed with

brine (2X), dried over sodium sulfate, filtered, and concentrated *in vacuo* to yield a yellow oil. Purification by flash chromatography using 80% ethyl acetate/hexanes afforded a mixture of THP hydroxamate/THP oxime (78%) and THP hydroxamate ketone (12%). ESMS m/z = 621 $[M+H]^+$ and ESMS m/z = 628 $[M+H]^+$ respectively. These products were not separated, and instead were carried forward as a mixture.

[876] Part C. The product from Part B (540 mg, 0.77 mmol) was dissolved in 4N HCl in dioxane (5 mL) and methanol (500 uL). After 2 hr at ambient temperature the reaction mixture was poured into rapidly stirring diethyl ether. A pale pinkish/purple solid was collected and purified by reverse phase HPLC. The title compound was obtained as a white solid. ESMS m/z = 537 $[M+H]^+$. HRMS calculated for $C_{25}H_{32}N_2O_9S$: 537.1907 $[M+H]^+$, found: 537.1921.

[877] **Example 26. Preparation of tetrahydro-N-hydroxy-4-[[4-[[5-(4-methyloxyphenyl)-4-methyl-5-oxopentyl] oxy]phenyl]sulfonyl]-2H-pyran-4-carboxamide**



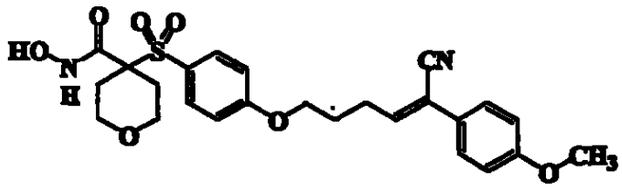
[878] Part A. To a solution of tetrahydro-4-[[4-[[5-(4methoxyphenyl)-5-oxopentyl]oxy]phenyl]sulfonyl]-2H-pyran-4-carboxylic acid, 1,1-dimethylethyl ester (532 mg, 1.0 mmol, prepared as in Example 24) and iodomethane (623 mg, 4.4 mmol) in 5 ml N,N-dimethylformamide was added sodium hydride (125 mg, 3.1 mmol, 60% dispersion in mineral oil). The reaction was stirred 40 min then quenched with 1N HCl_{aq}. The reaction mixture was partitioned between ethyl acetate and 5% aqueous potassium hydrogensulfate. The organic phase was dried over sodium sulfate, filtered, and concentrated *in vacuo* to give a crude oil. Purification by flash chromatography using 40% ethyl acetate/hexanes afforded 370 mg (68% yield) of the desired monomethyl ketoester. ESMS m/z = 547 $[M+H]^+$.

[879] Part B. The product from Part A (370 mg, 0.68 mmol) was taken up in neat trifluoroacetic acid. After 45 min, HPLC analysis indicated that the reaction was complete. The trifluoroacetic acid was removed *in vacuo*, and the residue chased with

acetonitrile (2x10 ml), and then vacuum dried to yield 335 mg of the free acid. ESMS m/z = 491 $[M+H]^+$. To a solution of this material in anhydrous N,N-dimethylformamide (4 mL) was added 1-hydroxybenzotriazole (138 mg, 0.68 mmol) and 1-(3-dimethyaminopropyl)-3-ethylcarbodiimide hydrochloride (150 mg, 0.78 mmol), followed by triethylamine (190 uL, 1.36 mmol) and tetrahydropyranhydroxylamine (160 mg, 1.37 mmol). After 16 hr, the reaction mixture was partitioned between ethyl acetate and 5% aqueous potassium hydrogensulfate. The combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo* to a crude oil. Purification by flash chromatography using 60% ethyl acetate/hexanes as eluant afforded 270 mg (67%) of the desired THP protected hydroxamate. ESMS m/z = 590 $[M+H]^+$.

[880] **Part C.** The product from Part B (270 mg, 0.46 mmol) was dissolved in 4N HCl in dioxane (2 mL) and methanol (500 uL). After 15 min at ambient temperature, the reaction mixture was partitioned between ethyl acetate and water. The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo* to yield 200 mg (86%) of the title compound. ESMS m/z = 406 $[M+H]^+$. HRMS calculated for $C_{25}H_{31}NO_5S$ 506.1849 $[M+H]^+$, found: 506.1828.

[881] **Example 27. Preparation of 4-[[4-[[(4Z)-5-cyano-5-(4-methoxyphenyl)-4-pentenyl]oxy]phenyl]sulfonyl] tetrahydro-N-hydroxy-2H-pyran-4-carboxamide**



Part A. To a solution of tetrahydro-4-[[4-[[5-(4-methoxyphenyl)-5-oxopentyl]oxy]phenyl]sulfonyl]-2H-pyran-4-carboxylic acid, 1,1-dimethylethyl ester (1.0 g, 1.9 mmol, prepared as in Example 24) in 15 ml methylene chloride was added trimethylsilyl cyanide (300 uL, 2.2 mmol) and zinc iodide (660 mg, 2.1 mmol). The reaction was stirred at ambient temperature for 3 hr, and then concentrated *in vacuo*. The residue was partitioned between ethyl acetate and 1 N HCl_{aq}. The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography using 25% ethyl acetate/hexanes to afford 950 mg (81%) of the

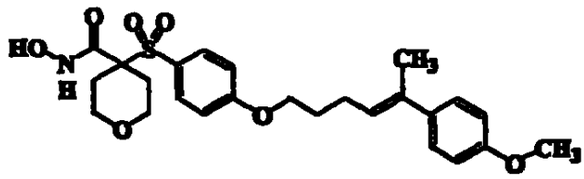
276

silylated cyanohydrin. This material was taken up in trifluoroacetic acid (15 mL). The dark red solution showed various peaks by HPLC analysis over the first 40 min. After 1 hr, HPLC analysis indicated 1 new peak at 93%. The reaction mixture was concentrated *in vacuo* and chased with acetonitrile (2x10 ml). The crude solid was dissolved in methanol and added to 40 ml diethyl ether. The resulting white solid was filtered and dried to yield 630 mg of the free acid/cyano olefin. ESMS m/z = 486 $[M+H]^+$.

[882] **Part B.** To a solution of the product from Part A (630 mg, 1.3 mmol) in anhydrous N,N-dimethylformamide (15 mL) was added 1-hydroxybenzotriazole (285 mg, 2.1 mmol) and 1-(3-dimethyaminopropyl)-3-ethylcarbodiimide hydrochloride (285 mg, 1.5 mmol), followed by N-methylmorpholine (545 uL, 5.0 mmol) and tetrahydropyranhydroxylamine (456 mg, 3.9 mmol). After 20 hr, the reaction mixture was concentrated *in vacuo*, and then partitioned between ethyl acetate and 5% aqueous potassium hydrogensulfate. The combined organic extracts were washed with brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification by flash chromatography using 80% ethyl acetate/hexanes to afford 530 mg (70%) of the desired THP protected hydroxamate. ESMS m/z = 585 $[M+H]^+$.

[883] **Part C.** The product from Part B (530 mg, 0.91 mmol) was dissolved in 4N HCl in dioxane (5 mL) and methanol (1 mL). After 15 min at ambient temperature, the reaction mixture was partitioned between ethyl acetate and water. The organic layer was dried over sodium sulfate, filtered, and concentrated *in vacuo* to yield 360 mg of the desired hydroxamate. Purification by reverse phase HPLC afforded 270 mg (59%) of the title compound. ESMS m/z = 504 $[M+H]^+$. HRMS calculated for $C_{25}H_{28}N_2O_7S$: 501.1695 $[M+H]^+$, found: 501.1689.

[884] **Example 28. Preparation of tetrahydro-N-hydroxy-4-[[4[[(4E)-5-(4-methoxyphenyl)-4-hexenyl]oxy]phenyl]sulfonyl]-2H-pyran-4-carboxamide**

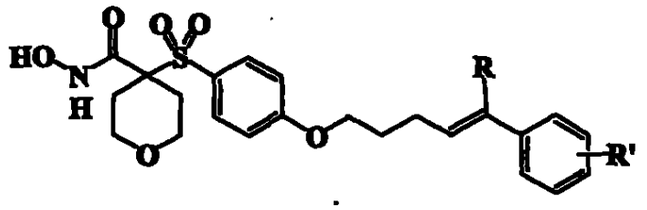


[885] **Part A.** To a cooled (0°C) solution of 4-[(4-{[5-(4-methoxyphenyl)-5-oxopentyl]oxy}phenylsulfonyl]-N-(tetrahydro-2H-pyran-2-yloxy)tetrahydro-2H-pyran-4-

carboxamide (0.2 g, 0.4 mmol, as prepared in Example 24) in tetrahydrofuran (2 ml) was added a 3.0 M solution of methylmagnesium bromide (1.2 ml, 3.6 mmol). The ice bath was removed, and the reaction stirred for 2 hr at room temperature. HPLC showed less than 1% of the ketone starting material. The reaction mixture was diluted with ethyl acetate and washed with saturated ammonium chloride solution, water, and brine. After drying over sodium sulfate and filtering, the organic layer was concentrated *in vacuo* to afford 0.25 g (100%) of a tan oil. ESMS m/z = 614 $[M+Na]^+$. This material was used without further purification.

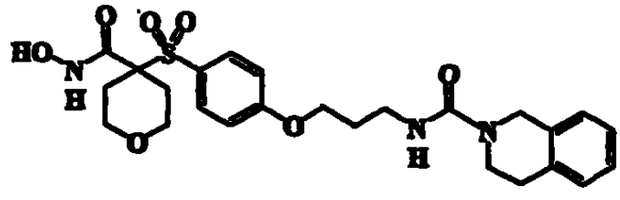
[886] Part B. To the product from Part A (0.24 g, 0.4 mmol) was added methanol (0.5 ml) and 4 N HCl in dioxane (4.0 ml). After stirring 2 hr, HPLC showed no remaining starting material. Diethyl ether was added to form a solid but a gummy residue developed. The mixture was concentrated and the oily residue was purified via reverse phase HPLC (C_{18}, acetonitrile/water/TFA) to afford 0.11 g (55%) of the desired product as a tan oil. ^{1}H NMR (N.O.E) confirmed the isomerized mixture as 70% trans:30% cis. HRMS calculated for $C_{25}H_{31}NO_7S$: 490.1899 [M+H], found: 490.1898.

[887] Additional compounds can be prepared by one skilled in the art using similar methods. Examples of such compounds include those having a structure corresponding to generic formula EX-J.



EX-J

[888] Example 29 Preparation of 3,4-dihydro-N-[3-[4-[[tetrahydro-4-[(hydroxyamino)carbonyl]-2H-pyran-4-yl]sulfonyl]-phenoxy] propyl]-2-(1H)-isoquinolinecarboxamide

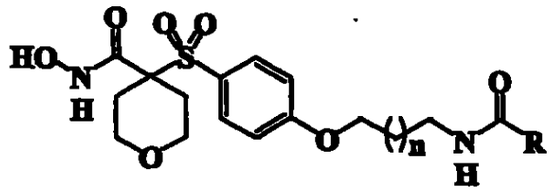


[889] **Part A.** To a solution of 4-[[4-(3-aminopropoxy)-phenyl]sulfonyl]tetrahydro-2H-pyran-4-carboxylic acid 1,1-dimethylethyl ester, monohydrochloride (467 mg, 1.07 mmol, prepared in Example 1) in anhydrous chloroform (3 mL) at ambient temperature was added triethylamine (170 uL, 1.22 mmol) and 1,1'-carbonyldiimidazole (180 mg, 1.11 mmol). After 1 hr at 50°C, 1,2,3,4-tetrahydroisoquinoline (162 mg, 1.22 mmol) was added neat. After an additional 2 hr at 50°C, HPLC indicated complete reaction. The reaction mixture was partitioned between ethyl acetate and 5% aqueous potassium hydrogen sulfate. The organic layer was washed with saturated sodium bicarbonate solution and brine, dried over sodium sulfate, filtered, and concentrated *in vacuo* to give a yellow oil. ESMS m/z = 559 $[M+H]^+$. This material was used without further purification.

[890] **Part B.** The product from Part A was taken up in neat trifluoroacetic acid (3 mL). After 13 hr, the trifluoroacetic acid was removed *in vacuo* at 50°C to give the free acid. ESMS m/z = 503 $[M+H]^+$. To a solution of this material in anhydrous N,N-dimethylformamide (5 mL) was added 1-hyrdoxybenzotriazole (176 mg, 1.30 mmol), triethylamine (500 uL, 3.59 mmol), and tetrahydropyranhydroxylamine (254 mg, 2.17 mmol), followed by 1-(3-dimethyaminopropyl)-3-ethylcarbodiimide hydrochloride (310 mg, 1.62 mmol). The reaction mixture was heated at 40°C for 4 hr, and then stirred at ambient temperature overnight. The reaction mixture was concentrated *in vacuo* at 60°C. The residue was partitioned between ethyl acetate and saturated sodium bicarbonate solution. The layers were separated, and the organic layer was washed with brine (3X), dried over sodium sulfate, filtered, and concentrated *in vacuo*. The crude product was purified by flash chromatography to give 260 mg (40% from the starting amine) of the desired THP protected hydroxamate as a white solid. ESMS m/z = 624 $[M+Na]^+$. HRMS calculated for $C_{30}H_{39}N_3O_8S$: 602 .2536 $[M+H]^+$, found: 602 .2546 .

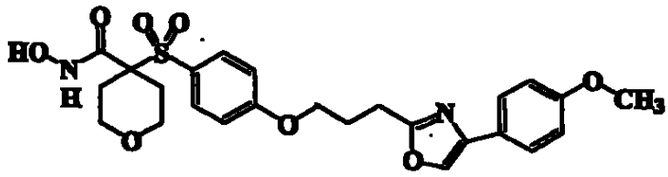
[891] **Part C.** The product from Part B (252 mg, 0.42 mmol) was dissolved in 4N HCl in dioxane (5 mL) and methanol (500 uL). After 1 hr at ambient temperature, the reaction mixture was poured into rapidly stirring diethyl ether. A white solid was collected and dried over P205 under vacumm. The title compound was obtained as a white solid. ESMS m/z = 518 $[M+H]^+$. HRMS calculated for $C_{25}H_{31}N_3O_7S$: 518. 1961 $[M+H]^+$, found: 518.1961.

[892] Additional compounds can be prepared by one skilled in the art using similar methods (urea formation also can be achieved by coupling the starting amine with and an isocyanate). Examples of such compounds include those having a structure corresponding to generic formula EX-K.



EX-K

[893] **Example 30. Preparation of tetrahydro-N-hydroxy-4-[[4-[3-[4-(4-methoxyphenyl)-2-oxazolyl]propoxy]phenyl]sulfonyl]-2Hpyran-4-carboxamide**



[894] **Part A.** To a solution of 4-[[4-(3-carboxypropoxy)phenyl]sulfonyl]tetrahydro-2H-pyran-4-carboxylic acid, 1,1-dimethylethyl ester (3.2 g, 7.5 mmol, prepared as in **Example 7**) in acetone (15 mL) was added 2-bromo-4-methoxyacetophenone (1.72 g, 7.5 mmol) and potassium carbonate (1.04 g, 7.5 mmol). The reaction mixture was stirred at ambient temperature for 3 hr. The reaction mixture was filtered, and the cake washed with acetone. The acetone solution was concentrated *in vacuo*. Purification by flash column chromatography using ethyl acetate/hexanes provided 3.68 g (85%) of the substituted ester as a white solid. ESMS m/z = 599 $[M+Na]^+$.

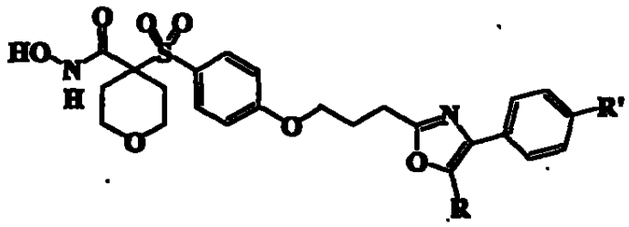
[895] **Part B.** The product from Part A (3.6 g, 6.25 mmol) was refluxed in acetic acid (12 mL) with ammonium acetate (2.41 g, 31.25 mmol) for 24 hr. The reaction was diluted with ethyl acetate (50 mL) and washed 2 times with water (25 mL) and filtered. The ethyl acetate filtrate was extracted with a 10% aqueous NaOH (50 mL). The basic solution was then acidified to a pH of 1, and then extracted with ethyl acetate (25 mL). The organic solution was then washed with water (25 mL), dried over sodium

sulfate, filtered, and concentrated *in vacuo* to give 1.5 g (48%) of the carboxylic acid of the oxazole as a brown solid. ESMS m/z = 502 $[M+H]^+$.

[896] **Part C.** In dry equipment under nitrogen, the carboxylic acid from Part B (1.3 g, 2.59 mmol) was dissolved in dry N,N-dimethylformamide (5 mL), and the remaining reagents were added to the solution in the following order: 1-hydroxybenzotriazole (490 mg, 3.63 mmol), triethylamine (0.43 mL, 3.11 mmol), tetrahydropyranhydroxylamine (364 mg, 3.11 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (746 mg, 3.89 mmol). After 12 hr at 40°C, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water, saturated sodium bicarbonate solution, and brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification by flash column chromatography using ethyl acetate/hexanes provided 0.70 g (450) of the THP hydroxamate as a white foam. ESMS m/z = 601 $[M+H]^+$.

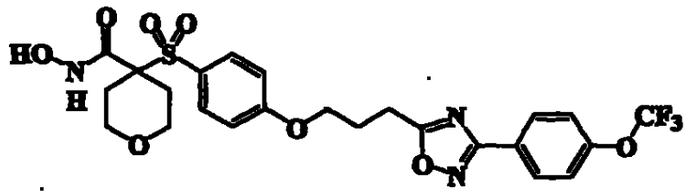
[897] **Part D.** To a solution of the product from Part C (0.6 g, 1.0 mmol) in 1,4-dioxane (1.0 mL) was added 4N HCl in dioxane (1.25 mL, 5 mmol) and methanol (0.13 mL). After 1 hr at ambient temperature, the reaction was diluted with ethyl acetate and washed with water, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Methylene chloride (20 mL) was added, and the solution was stripped to afford 0.29 g (56%) of the title compound as a light pink solid. HRMS calculated for $C_{25}H_{28}N_2O_6S$: 517.1645 $[M+H]^+$, found: 517.1651.

[898] Additional compounds can be prepared by one skilled in the art using similar methods. Examples of such compounds include those having a structure corresponding to generic formula EX-L.



EX-L

[899] **Example 31. Preparation of tetrahydro-N-hydroxy-4-[[4-[3-[3[4-(trifluoromethoxy)phenyl]-1,2,4-oxadiazol-5-yl]propoxy]phenyl]sulfonyl]-2H-pyran-4-carboxamide**



[900] **Part A.** In dry equipment under nitrogen, 4-[[4-(3-carboxypropoxy)phenyl]sulfonyl]tetrahydro-2H-pyran-4-carboxylic acid, 1,1-dimethylethyl ester (2.57 g, 6.0 mmol, prepared as in Example 7) was dissolved in dry N,N-dimethylformamide (12 mL), and the remaining reagents were added to the solution in the following order: 1-hydroxybenzotriazole hydrate (1.13 g, 8.4 mmol), triethylamine (1.0 mL, 7.2 mmol), 4-(trifluoromethoxy)benzamidoxime (1.58 g, 7.2 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.73 g, 9.0 mmol). After 2 hr at 35°C, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water, saturated sodium bicarbonate solution, and brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification by flash column chromatography using ethyl acetate/hexanes afforded 3.05 g (81%) of the desired product as a clear glass. ESMS m/z = 631 $[M+Na]^+$.

[901] **Part B.** The product from Part A (2.9 g, 4.60 mmol) was heated at 90°C in toluene (15 mL) for 30 hr. The reaction was concentrated *in vacuo*. Purification by column chromatography using ethyl acetate/hexanes afforded 2.06 g (73%) of the oxadiazole as a white solid. ESMS m/z = 635 $[M+Na]^+$.

[902] **Part C.** The product from Part B (2.0 g, 3.27 mmol) was dissolved in trifluoroacetic acid (8 mL) and stirred at ambient temperature for 2 hr. The reaction was diluted with methylene chloride (10 mL) and concentrated *in vacuo*. Methylene chloride (10 mL) was added to the residue and concentrated *in vacuo* again to provide 1.8 g (99%) of the free acid as an off- white solid. ESMS m/z = 557 $[M+H]^+$.

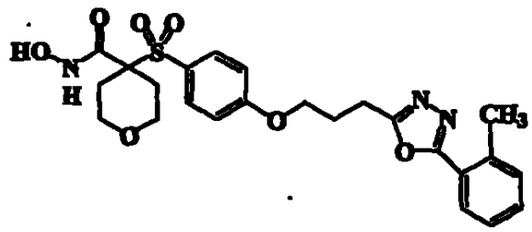
[903] **Part D.** In dry equipment under nitrogen, the product from Part C (1.7 g, 3.06 mmol) was dissolved in dry N,N-dimethylformamide (6 mL), and the remaining reagents were added to the solution in the following order: 1-hydroxybenzotriazole

282

hydrate (578 mg, 4.28 mmol), triethylamine (0.51 mL, 3.67 mmol), tetrahydropyranhydroxylamine (429 mg, 3.67 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (879 mg, 4.59 mmol). After 90 min at 40°C, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water, saturated sodium bicarbonate solution, and brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Purification by flash column chromatography using ethyl acetate/hexanes provided 1.9 g (95%) of the THP hydroxamate as a white foam. ESMS m/z = 678 $[M+Na]^+$.

[904] **Part E.** To a solution of the product from Part D (1.8 g, 2.75 mmol) in 1,4-dioxane (1.0 mL) was added 4N HCl in dioxane (3.5 mL, 13.7 mmol) and methanol (0.35 mL). After 2 hr at ambient temperature, the reaction was diluted with ethyl acetate and washed with water, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Reverse phase chromatography provided 1.12 g (71%) of the title compound as a white solid. HRMS calculated for $C_{24}H_{24}N_3O_8S_1F_3$: 572.1314 $[M+H]^+$, found: 572.1290.

[905] **Example 32. Preparation of tetrahydro-N-hydroxy-4-[[4-[3-[5-(2-methylphenyl)-1,3,4-oxadiazol-2-yl]propoxy]phenyl]sulfonyl]-2H-pyran-4-carboxamide**



[906] **Part A.** In dry equipment under nitrogen, 4-[[4-(3-carboxypropoxy)phenyl]sulfonyl]tetrahydro-2H-pyran-4-carboxylic acid, 1,1-dimethylethyl ester (2.14 g, 5.0 mmol, prepared as in Example 7) was dissolved in dry N,N-dimethylformamide (10 mL), and the remaining reagents were added to the solution in the following order: 1-hydroxybenzotriazole hydrate (945 mg, 7.0 mmol), triethylamine (0.84 mL, 6.0 mmol), o-toluic hydrazide (901 mg, 6.0 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.44 g, 7.5 mmol). After 2 hr at 35°C, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl

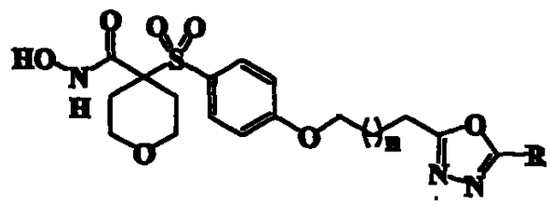
acetate; washed with water, saturated sodium bicarbonate solution, and brine; dried over sodium sulfate; filtered; and concentrated *in vacuo*. Purification by flash column chromatography using ethyl acetate/hexanes provided 2.32 g (83%) of the desired product as a white foam. ESMS m/z = 583 $[M+Na]^+$.

[907] **Part B.** The product from Part A (2.1 g, 3.75 mmol) was heated to reflux in toluene (25 mL) with p-toluenesulfonic acid (100 mg) for 4 hr. The reaction was concentrated *in vacuo*. Recrystalization from hot methanol provided 1.6 g (88%) of the free acid of the oxadiazole as a white solid. ESMS m/z = 487 $[M+Na]^+$.

[908] **Part C.** In dry equipment under nitrogen, the product from Part B (1.5 g, 3.09 mmol) was dissolved in dry N,N-dimethylformamide (6 mL), and the remaining reagents were added to the solution in the following order: 1-hydroxybenzotriazole hydrate (578 mg, 4.28 mmol), triethylamine (0.51 mL, 3.67 mmol), tetrahydropyranhydroxylamine (429 mg, 3.67 mmol), and 1-(3 dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (879 mg, 4.59 mmol). After 6 hr at 40°C, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate; washed with water, saturated sodium bicarbonate solution, and brine; dried over sodium sulfate; filtered; and concentrated *in vacuo*. Purification by flash column chromatography using ethyl acetate/hexanes provided 1.53 g (85%) of the THP hydroxamate as a white foam. ESMS m/z = 608 $[M+Na]^+$.

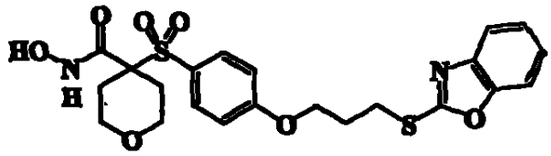
[909] **Part D.** To a solution of the product from Part C (1.4 g, 2.39 mmol) in 1,4-dioxane (1.0 mL) was added 4N HCl in dioxane (6 mL, 23.9 mmol) and methanol (0.6 mL). After 2 hr at ambient temperature, the reaction was diluted with ethyl acetate and washed with water, dried over sodium sulfate, filtered, and concentrated *in vacuo*. Reverse phase chromatography provided 1.02 g (85%) of the title compound as a white solid. HRMS calculated for $C_{24}H_{37}N_3O_7S_1$: 502.1648 $[M+H]^+$, found: 502.1652.

[910] Additional compounds can be prepared by one skilled in the art using similar methods. Examples of such compounds include those having a structure corresponding to generic formula EX-M..



EX-M

[911] **Example 33. Preparation of 4-[[4-[3-(2-benzoxazolylthio)propoxy]phenyl]sulfonyl]tetrahydro-N-N-hydroxy-2H-pyran-4-carboxamide.**

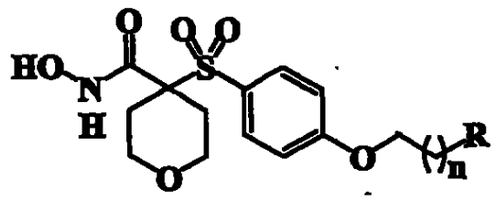


[912] **Part A.** To a solution of 2-mercaptobenzoxazole (290 mg, 1.92 mmol) in N,N-dimethylformamide (5 mL) at 0°C was added NaH (128 mg, 1.92 mmol, 60% dispersion in mineral oil). After 30 min, tetrahydro-4-[[4-[3-[(methylsulfonyl-)oxy]propoxy]phenyl]sulfonyl]-N-[(tetrahydro-2H-pyran-2-yl)oxy]-2H-pyran-4-carboxamide (1.0 g, 1.92 mmol, prepared as in Example 29) was added, and the solution was stirred for 2 hr at 65°C. The solution was partitioned between ethyl acetate and water. The organic layer was washed with water and brine, dried over sodium sulfate, filtered, and concentrated *in vacuo* to afford 510 mg (46%) of the thiobenzoxazole as a crude dark oil. ESMS m/z = 577 $[M+H]^+$.

[913] **Part B.** To a solution of the crude thiobenzoxazole of Part A (505 mg, 0.88 mmol) in 1,4-dioxane (5 mL) was added 4 N HCl in dioxane (5 mL), and was stirred for 2 hr. Purification by reverse phase HPLC (C_{18}, acetonitrile/water) provided 257 mg (60%) of the title compound as a white solid. ESMS m/z = 493 $[M+H]^+$. HRMS calculated for $C_{22}H_{24}N_2O_7S_2$: 493.1103, found 493.1122. Analytical calculation for $C_{22}H_{24}N_2O_7S_2 \cdot 0.3H_2O$: C, 53.06; H, 4.98; N, 5.63; S, 12.88. Found: C, 53.08; H, 5.03; N, 5.62; S 12.69.

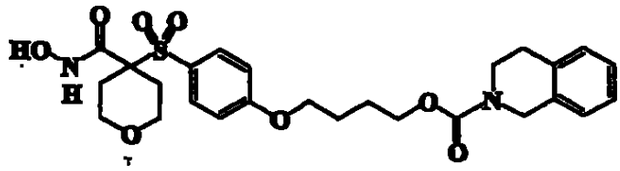
285

[914] Additional compounds can be prepared by one skilled in the art using similar methods. Examples of such compounds include those having a structure corresponding to generic formula EX-N.



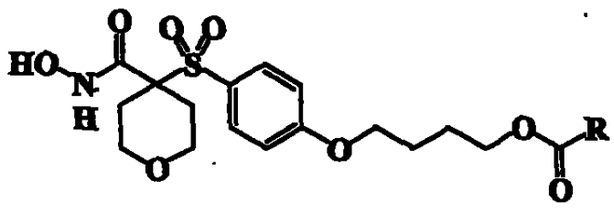
EX-N

[915] **Example 34. Preparation of 4-[[4-[[tetrahydro-4-[(hydroxyamino)carbonyl]-2H-pyran-4-yl]sulfonyl]cyclohexyl]oxy]butyl ester 3,4-dihydro-2(1H)-isoquinolinecarboxylic acid**



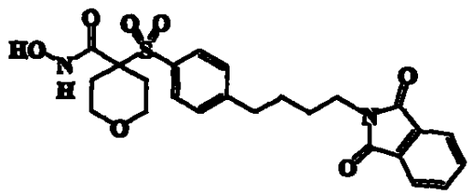
[916] **Part A.** To a solution of tetrahydro-4-[[4-[4-[(methylsulfonyl)oxy]butoxy]phenyl] sulfonyl]-N-[(tetrahydro-2H-pyran-2-yl)oxy]-2H-pyran-4-carboxamide (200 mg, 0.37 mmol, synthesized in a fashion similar to Example 29) in anhydrous N,N-dimethylformamide (2 mL) was added to 1,2,3,4-tetrahydroisoquinoline (0.24 mL, 1.9 mmol) and cesium carbonate (0.62 g, 1.9 mmol). The reaction mixture was stirred at ambient temperature overnight. The crude reaction mix was poured onto a 20 mL ChemElut tube (celite) prewetted with 15 mL of water, and eluted with 1:1 ethyl acetate:methylene chloride. Purification by reverse phase HPLC (C18, acetonitrile/water), followed by treatment with 2 mL of 4N HCl in dioxane, provided 12.2 mg (6.2 %) of the desired product as an amorphous solid after lyophilization. ESMS m/z = 531 $[M+H]^+$. HRMS calculated for $C_{26}H_{31}N_2O_9S$: 533.1958 $[M+H]^+$, found: 533.1943.

[917] Additional compounds can be prepared by one skilled in the art using similar methods. Examples of such compounds include those having a structure corresponding to generic formula EX-O.



EX-O

[918] **Example 35. Preparation of 4-[[4-[4-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)butyl]phenyl]sulfonyl]tetrahydro-N-hydroxy-2H-pyran-4-carboxamide**



[919] **Part A.** A solution of 4-bromobenzenethiol (28.5 g, 151 mmol) in N,N-dimethylformamide (250 mL) was purged with nitrogen for 10 min and then potassium carbonate (22.9 g, 166 mmol) was added. After purging for another 10 min with nitrogen, t-butyl bromoacetate (24.5 g, 166 mmol) was added, and the reaction was stirred at ambient temperature for 1 hr. The reaction was chilled to 0°C and diluted with water (250 mL). The slurry was extracted with ethyl acetate. The organic layer was washed with water, saturated sodium bicarbonate solution, and brine; dried over sodium sulfate; filtered; and concentrated *in vacuo* to provide 49.8g (100%) of the sulfide as a light yellow oil. ESMS m/z = 3 2 0 $[M+NH4]^+$.

[920] **Part B.** To a solution of the product from Part A (45.67 g, 151 mmol) in tetrahydrofuran (300 mL) was added water (75 mL) and Oxone™ (278.5 g, 453 mmol) at 20°C. An exotherm to 43°C was observed. After 3 hr, the reaction was filtered, and the cake was washed well with tetrahydrofuran. The filtrate was concentrated *in vacuo* to 1 third the volume. The residue was taken up in ethyl acetate, washed with brine, dried over magnesium sulfate, filtered, and concentrated *in vacuo* to give 51.0 g (100%) of the sulfone as a crystalline solid. ESMS m/z = 335 $[M+H]^+$.

[921] **Part C.** To a solution of the product from Part B (23.45 g, 16 mmol) in N,N-dimethylformamide (140 mL) was added potassium carbonate (19.3 g, 140 mmol),

bis-(2-bromoethyl)ether (9.1 mL, 70 mmol), and 18-Crown-6 (1 g). The slurry was stirred at 60°C. After 16 hr, the reaction was filtered, and the filtrate was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water (3X) and brine, dried over sodium sulfate, filtered, and concentrated *in vacuo*. The product was recrystallized from methanol to provide 19.79 g (70%) of the desired compound as a white solid. (ESMS m/z = 405 $[M+H]^+$.

[922] **Part D.** To a solution of N-(3-buten-1-yl)phthalimide (1.2 g, 5.97 mmol) in anhydrous tetrahydrofuran (3 mL) at 0°C was added 0.5 M 9-borobicyclononane in tetrahydrofuran (11.9 mL, 5.97 mmol) dropwise. The resultant solution was stirred with cooling for 10 min, and then the ice bath was removed. After 18 hr, the product from Part C (1 g, 2.98 mmol), tetrakis(triphenyl-phosphine)palladium(0) (172 mg, 0.15 mmol) and 2 M sodium carbonate (3 mL, 6 mmol) were added, and the reaction mixture was heated to 65°C for 2 hr. After cooling to ambient temperature, the solution was concentrated *in vacuo*. The residue was partitioned between ethyl acetate (50 mL) and water (50 mL). The layers were separated, and the organic layer was washed with water (50 mL) and brine (50 mL), dried over magnesium sulfate, filtered, and concentrated *in vacuo*. Purification by flash column chromatography using 25-50% ethyl acetate/hexanes yielded 1.21 g of the desired compound as an off-white solid. HRMS calculated for $C_{28}H_{37}N_2O_7S$: 545.2321 $[M+H]^+$, found: 545.2311.

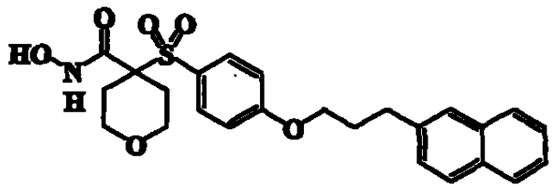
[923] **Part E.** To a solution of the product from Part D (1.16 g, 2.2 mmol) in anhydrous methylene chloride (20 mL) at ambient temperature was added trifluoroacetic acid (20 mL). The solution was stirred for 2 hr, and then concentrated *in vacuo*. The resulting residue was dissolved in methanol (50 mL) and concentrated *in vacuo*, and subsequently dissolved in methylene chloride (50 mL) and concentrated *in vacuo*. Trituration with hexanes yielded 0.98 g of the carboxylic acid as an off-white solid. HRMS calculated for $C_{28}H_{37}N_2O_7S$: 489.1695 $[M+NH_4]$, found: 489.1702.

[924] **Part F.** To a solution of the product from Part E (0.95 g, 2.01 mmol) in a mixture of methylene chloride (4 mL) and N,N-dimethylformamide (4 mL) was added triethylamine (0.28 mL, 2.01 mmol), 1-hydroxybenzotriazole (0.407 g, 3.015 mmol), and 1-[3-(dimethylamino)propyl]-3-ethylcarbodiimide hydrochloride (0.538 g, 2.814 mmol). After 10 min, additional triethylamine (0.56 mL, 4.02 mmol) and tetrahydropyranhydroxylamine (0.706 g, 6.03 mmol) were added. The solution was

warmed to 38°C and stirred for 20 hr. The mixture was partitioned between ethyl acetate (50 mL) and water (50 mL). The organic layer was washed with 1 M HCl (50 mL), water, brine. After drying over magnesium sulfate, the organic layer was concentrated to give 1.31 g of an off white solid. Purification by flash column chromatography using 25-50% ethyl acetate/hexanes yielded 1.05 g of the pure product as a white solid. HRMS calculated for $C_{29}H_{34}N_2O_8SNa$: 593.1934 [M+Na], found: 593.1967.

[925] Part G. To a solution of the product from Part F above (0.255 g, 0.446 mmol) in a mixture of methanol (3 mL) and dioxane (3 mL) was added 4 N HCl in dioxane (3 mL). The mixture was stirred at ambient temperature for 10 min, and then concentrated *in vacuo*. Trituration with diethyl ether/hexanes yielded 224 mg of the title compound as a white solid. HRMS calculated for $C_{24}H_{27}N_2O_7S$: 487.1539 [M+H], found: 487.1559.

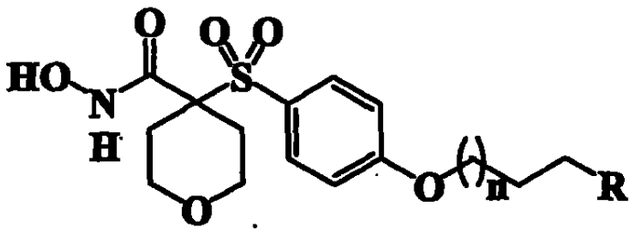
[926] **Example 36. Preparation of 2H-pyran-4-carboxamide, tetrahydro-N-hydroxy-4[[4-[3-(2-naphthalenyl)propoxy]-phenyl]sulfonyl]**



[927] To a solution of (tetrahydro-4-[[4-(2propenyloxy)phenyl]sulfonyl]-N-[(tetrahydro-2H-pyran-2-yl)oxy]-2H-pyran-4-carboxamide (200 mg, 0.47 mmol, prepared as in Example 35) in tetrahydrofuran (1 mL) was added 0.5 M 9-borobicyclononane (0.94 mL, 0.47 mmol). The solution was stirred at ambient temperature for 16 hr. To this solution was added 2 M sodium carbonate (0.5 mL, 1 mmol), 2-bromonaphthalenylene (108 mg, 0.52 mmol), and tetrakis(triphenylphosphine)palladium(0) (54 mg, 0.047 mmol). The mixture was heated to 65°C for 4 hr, and then cooled to ambient temperature. Saturated ammonium chloride solution (3 mL) was added to the reaction mixture. The resulting mixture was filtered through a small column of celite. The column was washed with ethyl acetate (35 mL). The eluant was concentrated *in vacuo*, and the residue was dissolved in methanol (3 mL), dioxane (3 mL), and 4 N HCl in dioxane. After 10 min, the solution was concentrated *in vacuo*, and the residue purified by preparative reverse

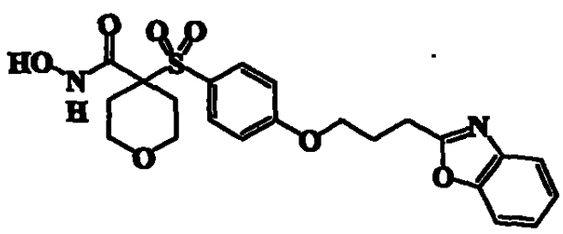
phase HPLC (10-90% acetonitrile/0.05% TFA in water) yielding 20 mg of the title compound as a white solid. HRMS calculated for $C_{15}H_{28}NO_6S$: 470.1670 [M+H], found: 470.1614.

[928] Additional compounds can be prepared by one skilled in the art using similar methods. Examples of such compounds include those having a structure corresponding to generic formula EX-P.



EX-P.

[929] Example 37. Preparation of 4-[[4-[3-(2-benzoxazolyl)propoxy]phenyl]sulfonyl]tetrahydro-N-hydroxy-2H-pyran-4-carboxamide



[930] Part A. To a solution of 4-[[4-(3-carboxypropoxy)phenyl]sulfonyl]tetrahydro-2H-pyran-4-carboxylic acid, 1,1-dimethylethyl ester (3.0 g, 7.0 mmol) in N,N-dimethylformamide (14 mL) was added 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride (1.88 g, 9.8 mmol) and 1-hydroxybenzotriazole (1.32 g, 9.8 mmol). The resulting suspension became a clear amber solution after stirring at 50°C for 1.5 hr. The reaction was then treated with 2-aminophenol (0.76 g, 7.0 mmol), followed by N-methylmorpholine (2.3 mL, 21.0 mmol). The reaction was stirred at 50°C overnight. After 21 hr, the reaction was partitioned between ethyl acetate (50 mL) and water (50 mL). The aqueous layer was extracted with ethyl acetate. The organic layers were combined and washed with saturated sodium

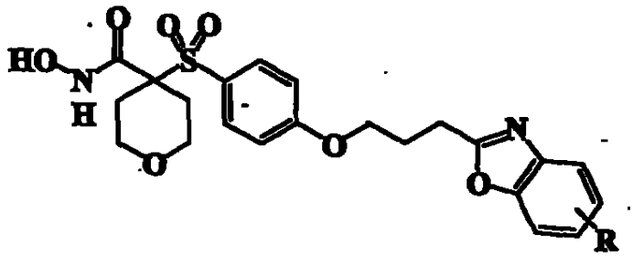
bicarbonate solution, water, 1:1 solution of water:brine, and brine; dried over sodium sulfate; filtered; and concentrated *in vacuo*. The resulting oil was purified on silica gel using ethyl acetate/hexanes to afford 2.98 g (82%) of the amide as an amber oil. ESMS m/z = 542 $[M+Na]^+$.

[931] Part B. To a suspension of the product from Part A the (1.59 g, 3.1 mmol) toluene (50.0 mL) was added p-toluenesulfonic acid (0.12 g, 0.6 mmol), and the resulting mixture heated at reflux under Dean-Stark conditions. After 39 hr, the reaction was concentrated *in vacuo*, and the resulting residue was partitioned between ethyl acetate and 1 M aqueous hydrochloric acid. The organic layer was washed with 1 M aqueous hydrochloric acid, water, and brine; dried over sodium sulfate; filtered; and concentrated *in vacuo* to afford 1.25 g (92%) of the crude carboxylic acid benzoxazole as a tan, white solid. ESMS m/z = 446 $[M+H]^+$.

[932] Part C. To a solution of the product from Part B (0.98 g, 2.2 mmol) in N,N-dimethylformamide (10.0 mL) was added 1-(3-dimethylamino-propyl)-3-ethylcarbodiimide hydrochloride (0.59 g, 3.1 mmol) and 1-hydroxybenzotriazole (0.42 g, 3.1 mmol). The resulting suspension became a clear amber solution after stirring at 50°C for 0.5 hr. The reaction was then treated with tetrahydropyranhydroxylamine (0.36 g, 3.1 mmol), followed by N-methylmorpholine (0.73 mL, 6.6 mmol). The reaction was stirred at 50°C overnight. After 12 hr, the reaction was partitioned between ethyl acetate and water. The aqueous layer was extracted with ethyl acetate. The organic layers were combined and washed with saturated sodium bicarbonate solution, water, 1:1 solution of water:brine, and brine; dried over sodium sulfate; filtered; and concentrated *in vacuo*. The resulting oil was purified on silica gel using ethyl acetate/hexanes as eluant to afford 1.2 g (98%) of the THP hydroxamate benzoxazole as an amber oil. ESMS m/z = 545 $[M+H]^+$.

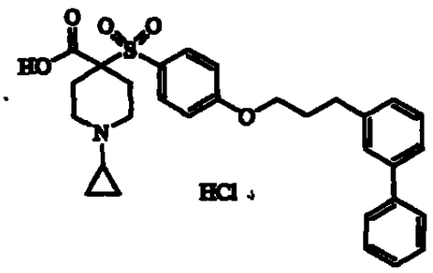
[933] Part D. To a solution of the product from Part C (0.104 g, 0.19 mmol) in a mixture of methanol (0.3 mL) and dioxane (2 mL) was added 4 N HCl in dioxane (0.5 mL). The mixture was stirred at ambient temperature for 30 min, concentrated in half *in vacuo*, and diluted with diethyl ether. Filtration afforded 17 mg (20%) of the title compound as a tan solid. HRMS calculated for $C_{22}H_{24}N_2O_7S$: 461.1382 [M+H], found: 461.1374.

[934] Additional compounds can be prepared by one skilled in the art using similar methods. Examples of such compounds include those having a structure corresponding to generic formula EX-Q.

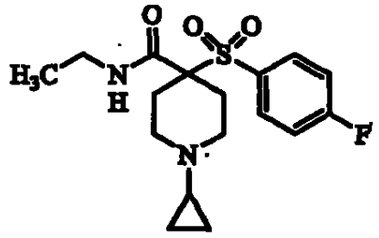


EX-Q.

[935] Example 38. Preparation of:



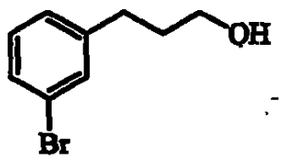
[936] Part A. Preparation of:



To a solution of ethyl 4-[(4-fluorophenyl)sulfonyl]piperidine-4-carboxylate hydrochloride (60.0 g, 170 mmol) in methanol (600 mL), were added acetic acid (97 mL, 1.7 mole), [(1-ethoxycyclopropyl)oxy]trimethylsilane (102 mL, 510 mmol) and 4A molecular sieves (55 g) followed by sodium cyanoborohydride (28.8 g, 459 mmol). The solution was stirred at ambient temperature overnight, then refluxed for 6 hr. The reaction mixture was filtered through celite and concentrated to solid/oil mix. Ethyl acetate and saturated sodium bicarbonate were added very carefully. When aqueous layer stayed basic, the layers were

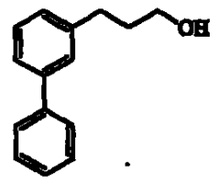
separated and the organic layer was washed 3 times with saturated sodium bicarbonate, then with brine and then dried over sodium sulfate. Concentration *in vacuo* and crystallization from ethyl acetate/hexane provided the n-cyclopropyl compound as an off white solid (53.8 g, 88.8%). ESMS $_{mh}$ = 356 (M+H).

[937] Part B. Preparation of:



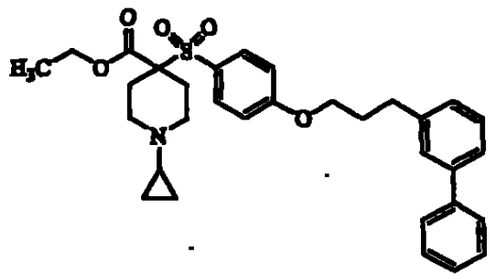
To a solution of 3-(3-bromophenyl)propionic acid (10.0 g, 43.7 mmol) in anhydrous THF (150 mL) was added 1.0 M BH_3·THF (150 mL, 150 mmol) via addition funnel. After BH_3·THF was added, the reaction was refluxed for 18 hrs. The reaction was quenched with water (100 mL) and 1N HCl (300 mL). The solution was saturated with sodium chloride and extracted with ethyl acetate. The organic extract was washed with brine and dried over magnesium sulfate. The organic material was purified by chromatography on silica gel eluting with ethyl acetate in hexane to produce 9.39 g (100 %) of the desired alcohol as a colorless oil. NMR ($CDCl_3$) δ 1.82-1.89 (m, 2H), 2.67 (t, 2H) , 3.64 (t, 2H), 7.11 7.15 (m, 1H), 7.29-7.31 (m, 1H), 7.34 (s, 1H).

[938] Part C. Preparation of:



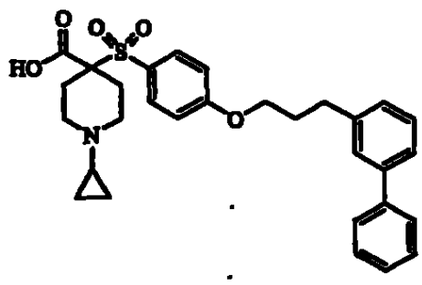
In a flask were combined the alcohol from Part B (3.43 g, 16.0 mmol), phenyl boronic acid (2.93 g, 24.0 mmol), palladium tetrakistriphenylphosphine (0.92 g, 0.8 mmol), 2M cesium carbonate (24 mL, 48 mmol) and dimethoxyethylether (48 mL). The mixture was stirred vigorously under nitrogen at reflux. After 1.5 hr the reaction was cooled to ambient temperature, diluted with water and extracted with ether 3 times. The combined organic extracts were washed with brine and dried over magnesium sulfate. 2.74 g (81% yield) purified product was obtained as a crystalline solid by chromatography (on silica, ethyl acetate/hexane). NMR ($CDCl_3$) δ 1.91-1.98 (m, 2H) , 2.77 (t, 2H), 3.71 (t, 2H), 7.19 (d, 1H), 7.31-7.38 (m, 2H), 7.41-7.45 (m, 4H), 7.58 (d, 2H).

[939] Part D. Preparation of:



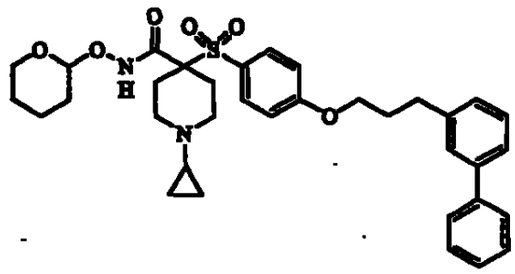
To a solution of the alcohol from Part C (2.7 g, 12.7 mmol) in anhydrous dimethylformamide (12 mL) at 0°C was added 60 % sodium hydride (0.58 g, 14.5 mmol) in portions. After that the reaction was stirred at 0°C for 15 min and then at ambient temperature for 15 min. The reaction mixture was cooled to 0°C and the cyclopropyl compound from Part A (4.3 g, 12.4 mmol) in anhydrous dimethylformamide (10 mL) was added slowly. Upon completion of addition, ice bath was removed and the reaction stirred at ambient temperature for 1 hr the reaction, then diluted with water and extracted with ethyl acetate 3 times. The combined organic extracts were washed with saturated $NaHCO_3$ and brine and dried over sodium sulfate. After concentration 4.63 g of material was obtained. This material was used without purification.

[940] Part E. Preparation of:



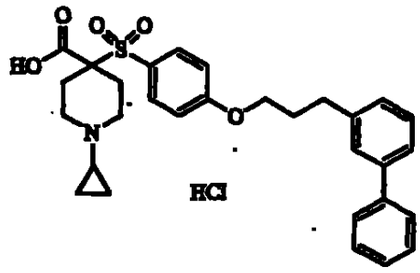
The ester of Part D (4.61 g, 8.4 mmol) was hydrolyzed in 1:1:0.56 mixture of ethanol:1,4-dioxane:6N NaOH (25.6 mL) at 60°C. The solution was concentrated *in vacuo*, diluted with water and extracted with ether to remove color. Acidification with 1N HCl caused precipitation of the acid which was collected by filtration, washed with water and hexane and dried under high vacuum yielding the acid as an off white solid (3.45 g, 79 % yield). ESMS $_{m/z}$ = 520 $(M+H)^+$. This material was used without purification.

[941] Part F. Preparation of:



To a suspension of the crude acid of Part E (3.44 g, 6.62 mmol) in DMF (27 mL) were added HOBt (1.52 g, 9.93 mmol), N-methylmorpholine (2.2 mL, 19.9 mmol) and EDC (1.77 g, 9.27 mmol). After heating at 40°C, acid slowly went into solution. When reaction was clear, it was cooled to ambient temperature and THP-hydroxylamine (1.16 g, 9.93 mmol) was added. The solution was stirred for 18 hr at ambient temperature. The solution was partitioned between ethyl acetate and water. The organic layer was washed with water and brine and dried over magnesium sulfate. Chromatography (on silica, ethyl acetate/hexanes) provided the protected hydroxamate as a crystalline solid (3.20 g, 74 %). NMR δ 0.36 (d, 4H), 1.50-1.92 (m, 8H), 2.05-2.21 (m, 3H), 2.32 (s, 2H), 2.86 (t, 2H), 2.98 (s, 2H), 3.69 (d, 1H), 3.96-4.07 (m, 3H), 5.00 (s, 1H), 6.95 (d, 2H), 7.17 (d, 1H), 7.30-7.43 (m, 6H), 7.54 (d, 2H), 7.73 (d, 2H), 9.41 (s, 1H).

[942] Part G. Preparation of:

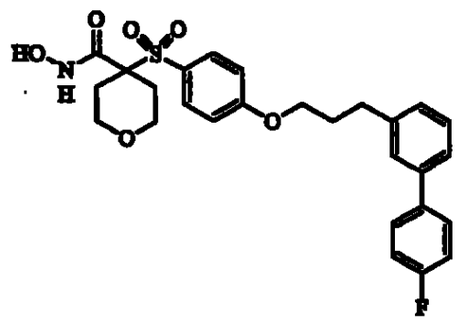


To the semi pure product from Part F (3.03 g, 4.89 mmol) in methanol (10 mL) and 1,4-dioxane (10 mL) was added 4M hydrochloric acid in 1,4-dioxane (10 mL) and after stirring 20-30 min the product began to crystallize out. Reverse phase chromatography (on C_{18}, acetonitrile/water) to remove color followed by conversion to HCl salt with methanol and 4N HCl/dioxane then recrystallization from methanol/iso propanol provided 1.95 g (70 %) of the title compound as a hydrochloric acid salt that was colorless. ESMS

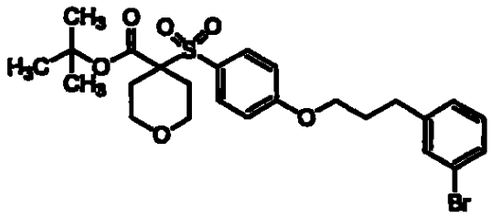
295

$_{m/z}$ = 535 $(M+H)^+$. HRMS calcd. for $C_{30}H_{35}N_2O_5S$ H: 535.2261 $(M+H)^+$. Found: 535.2270.

[943] **Example 39. Preparation of:**

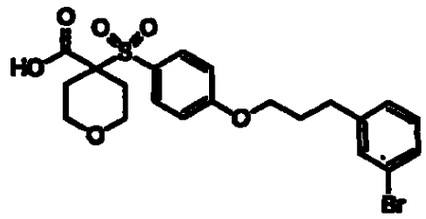


[944] **Part A. Preparation of:**



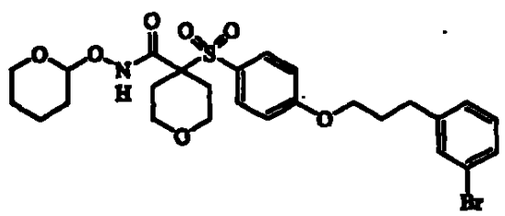
A solution of the alcohol from Part B, Example 38 (4.4 g, 20.4 mmol), tert-butyl 4-[(4-fluorophenyl)sulfonyl]tetrahydro-2H-pyran-4-carboxylate (5.0 g, 14.6 mmol) and Cs_2CO_3 (9.5 g, 29.2 mmol) in anhydrous dimethylformamide (30 mL) was stirred at 80°C for 30 hr. The reaction was diluted with water (300 mL) and extracted with ethyl acetate (3 times). The combined organic extracts were washed with brine and dried over magnesium sulfate. Crystallization from methylene chloride/hexane gave 6.95 g (88%) of the product as a colorless solid. ESMS $_{m/z}$ = 556 $(M+NH_4)^+$. HRMS calcd. for $C_{25}H_{35}BrNO_6S$ H: 556.1368 $(M+NH_4)^+$. Found: 556.1318.

[945] **Part B. Preparation of:**



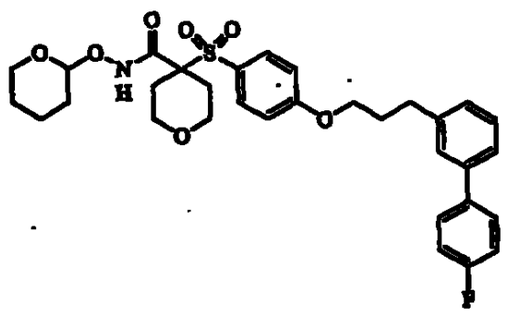
The ester of Part A (6.81 g, 12.6 mmol) was hydrolyzed in 1:1 TFA:methylene chloride (50 mL) at ambient temperature for 1.5 hr. The solution was concentrated *in vacuo*, taken up in toluene, concentrated to a colorless solid and dried under high vacuum yielding the acid as an impure white solid (6.28 g, 100 % yield). ESMS $_{m/z}$ = 500 $(M+NH_4)^+$. HRMS calcd. for $C_{21}H_{29}BrO_6SNH_4$: 500.0742 $(M+NH_4)^+$. Found: 500.0761.

[946] Part C. Preparation of:



To a suspension of the impure acid of Part B (theoretically 12.5 mmol) in anhydrous DMF (25 mL) were added HOBt (2.0 g, 15 mmol), triethylamine (5.2 mL, 37.5 mmol) and EDC (3.4 g, 17.5 mmol). After heating at 40°C for 1 hr, THP hydroxylamine (4.4 g, 37.5 mmol) was added. The solution was stirred for 18 hr at ambient temperature, then at 40°C for 3 hr. The reaction was diluted with water (150 mL) and extracted with ethyl acetate (3 times). The combined organic extracts were washed with brine and dried over magnesium sulfate. Chromatography (on silica, ethyl acetate/hexanes) provided the protected hydroxamate as a viscous oil (4.32 g, 60 %). ESMS $_{m/z}$ = 601 $(M+NH_4)^+$. HRMS calcd. for $C_{26}H_{32}BrNO_7SNH_4$: 601.1410 $(M+NH_4)^+$. Found: 601.1448.

[947] Part D. Preparation of:

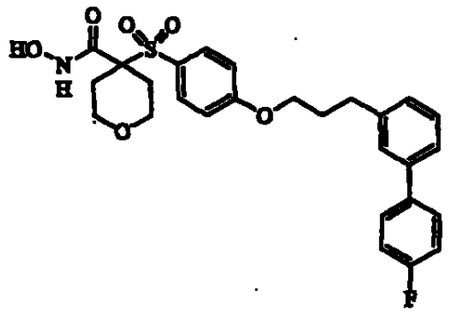


In a vial were combined the aryl bromide from Part C (0.20 g, 0.34 mmol) in 1 mL of dimethoxyethyl ether, 4-fluorobenzeneboronic acid (74 mg, 0.53 mmol), palladium tetrakistriphenylphosphine (23 mg, 0.02 mmol) in 0.5 mL of dimethoxyethyl ether and 2M cesium carbonate (0.51 mL, 1.02 mmol). The mixture stirred vigorously at 65°C for 18 hr.

297

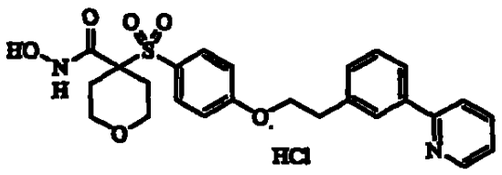
The eaction mixture was poured onto 5 mL Chem-Elut tube pre-wetted with 3 mL of water and eluted with 10% ethyl acetate/methylene chloride. Concentration under nitrogen gave 254 mg of crude product that was carried on as is.

[948] Part E. Preparation of:

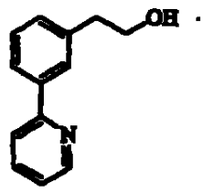


The crude product from Part D (254 mg) was taken up in 4M hydrochloric acid in 1,4-dioxane (2 mL) and methanol (1-2 mL) and stirred for 2 hr then concentrated. Material purified by reverse phase chromatography (on C_{18}, acetonitrile/water). Product crystallized upon concentration yielding 108.5 mg (62%) of the title compound as colorless solid. ESMS $_{m/z}$ = 514 $(M+H)^+$. HRMS calcd. for $C_{27}H_{29}FNOS$: 514.1700 $(M+H)^+$. Found: 514.1694 .

[949] Example 40. Preparation of:



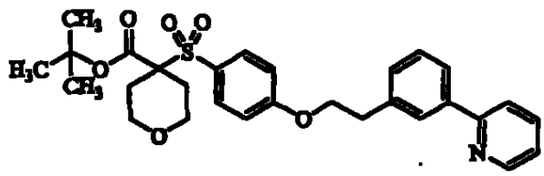
[950] Part A. Preparation of:



3-bromophenethyl alcohol (5.0 g, 24.9 mmol) and 2-(tributylstannyl)pyridine (13.6 g, 37.4 mmol) were combined in a round bottom flask with $PdCl_2(PPh_3)_2$ (0.84 g, 1.2 mmol), CuI

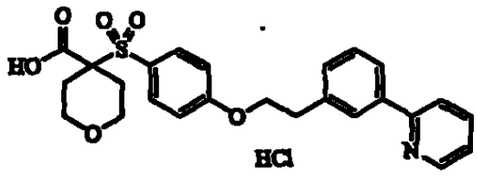
(0.23 g, 1.2 mmol) and anhydrous THF (100 mL) and heated to reflux. After refluxing overnight, additional $PdCl_2(PPh_3)_2$ (0.84 g, 1.2 mmol) and CuI (0.23 g, 1.2 mmol) were added and the reaction refluxed overnight. The reaction was cooled to ambient temperature, Norit A charcoal added, the mixture stirred and then filtered through a bed of celite. Chromatography (on silica, ethyl acetate/hexanes) provided the alcohol as an orange oil (2.76 g, 55.8%). ESMS $_{m/z}$ = 200 $(M+H)^+$.

[951] Part B. Preparation of:



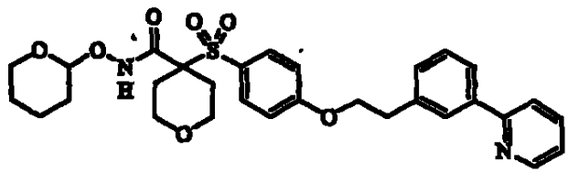
To a solution of the alcohol from Part A (2.75 g, 13.8 mmol) in anhydrous dimethylformamide (13 mL) at 0°C was added 60 % sodium hydride (0.58 g, 14.4 mmol) in portions. After completion of the addition, the reaction was stirred at 0°C for 30 min. tert-butyl 4-[(4-fluorophenyl)sulfonyl]tetrahydro-2H-pyran-4-carboxylate (4.51 g, 13.1 mmol) in anhydrous dimethylformamide (10 mL) was added over 15 min. Upon completion of addition, the ice bath was removed and the reaction stirred at ambient temperature. After 1.5 hr the reaction was diluted with water and extracted with ethyl acetate 3 times. The combined organics were washed with saturated NaCl and dried over magnesium sulfate. Chromatography (on silica, ethyl acetate/hexanes) provided the product as an off white solid (5.44 g, 79 %). ESMS $_{m/z}$ = 524 $(M+H)^+$.

[952] Part C. Preparation of:



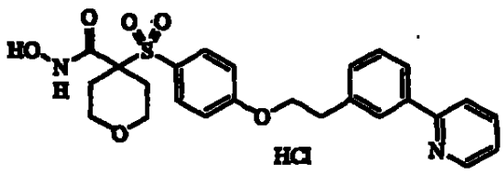
The ester of Part B (5.45 g, 10.4 mmol) was hydrolyzed in 1:1 mixture of TFA:methylene chloride (30 mL) at ambient temperature for 8 hr. The solution was concentrated *in vacuo*, taken up in methanol and 4N HCl in dioxane and concentrated. This was repeated to give a viscous oil (6.25 g, > 100 % yield). This material was used without further purification.

[953] Part D. Preparation of:



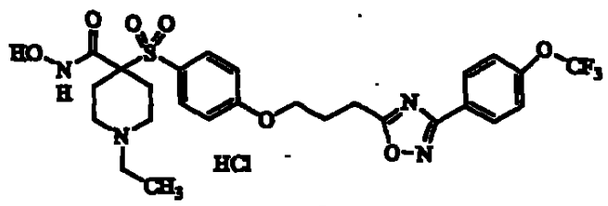
To a suspension of the crude acid of Part C (assume 10.4 mmol) in NMP (40 mL) were added HOBt (2.39 g, 15.6 mmol), N-methylmorpholine (3.4 mL, 31.2 mmol) and EDC (2.79 g, 14.6 mmol). After heating at 40°C overnight, HPLC still showed acid to be present so additional added HOBt (2.39 g, 15.6 mmol), N-methylmorpholine (3.4 mL, 31.2 mmol) and EDC (2.79 g, 14.6 mmol) were added. After 1 hr at 40°C, THP hydroxylamine (3.66 g, 31.2 mmol) was added. After 1 hr, the solution was diluted with water and extracted with ethyl acetate 3 times. The combined organic layers were washed with brine and dried over magnesium sulfate. Chromatography (on silica, ethyl acetate/hexanes) provided the protected hydroxamate as a colorless foam (5.05 g, 85.7). ESMS $_{m/z}$ = 567 $(M+H)^+$.

[954] Part E. Preparation of:



To the product from Part D (5.05 g, 8.91 mmol) in methanol (15 mL) and 1,4-dioxane (15 mL) was added 4M hydrochloric acid in 1,4-dioxane (15 mL) and after stirring 1 hr reaction was complete. Concentration followed by crystallization from methanol/iso-propanol provided 3.88 g (84 %) of the title compound as a hydrochloric acid salt that was colorless. ESMS $_{m/z}$ = 483 $(M+H)^+$. HRMS calcd. for $C_{25}H_{27}N_2O_6S$ H: 483.1584 $(M+H)^+$. Found: 483.1585.

[955] **Example 41. Preparation of 1-ethyl-N-hydroxy 4-{[4-(3-{3-[4-(trifluoromethoxy)phenyl]-1,2,4-oxadiazol-5-yl}propoxy)phenyl]sulfonyl}piperidine-4-carboxamide hydrochloride.**



[956] **Part A.** To a slurry of ethyl 4-[(4-fluorophenyl)sulfonyl]-4-piperidinecarboxylate, monohydrochloride (14.06 g, 40 mmol) in dimethylacetamide (80 mL) were added potassium carbonate (13.82 g, 100 mmol) and iodoethane (3.36 mL, 42 mmol). The slurry was stirred at ambient temperature. After 3 hr the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water three times, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Chromatography (on silica, methylene chloride/hexanes) provided the N-ethyl piperidine as a white solid (13.05 g, 95%).

[957] **Part B.** In dry equipment under nitrogen, potassium trimethylsilanolate (10.52 g, 73.8 mmol) was dissolved in dimethylsulfoxide (40 mL) and gamma-butyrolactone (4.26 mL, 55.4 mmol) was added over 5 min while the reaction temperature rose to 49 C. After stirring at ambient temperature for 90 min, sodium hydride (2.2 g of a 60% oil dispersion, 55.4 mmol) was added portion wise over 20 min and the reaction temperature rose to 38°C. Gas evolution was also observed. After stirring at ambient temperature for 40 min, a solution of the N-ethyl piperidine from Part A (12.66 g, 36.9 mmol) in dimethylsulfoxide (10 mL) was added over 10 min as the reaction rose to 8°C. The reaction was stirred at ambient temperature for t30 min. The slurry was slowly poured into ice water (400 mL) and then extracted with hexanes (100 mL) two times followed by a diethyl ether extraction (100 mL). The aqueous layer was chilled to 5°C and the pH adjusted to 7 with concentrated hydrochloric acid. The aqueous solution was extracted with methylene chloride (150 mL) until there was no UV activity in the extract. The combined methylene chloride extracts were washed with saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The solid was

recrystallized from isopropanol (65 mL) to give the butyric acid as a white solid (8.2 g, 52%). LCMS $_{m/z}$ = 428 $[M+H]^+$.

[958] Part C. In dry equipment under nitrogen, the butyric acid from Part B (5.12 g, 12.0 mmol) was dissolved in dry dimethylacetamide (20 mL) and the remaining reagents were added to the solution in the following order: N-hydroxybenzotriazole hydrate (2.43 g, 18.0 mmol), triethylamine (3.34 mL, 24.0 mmol), 4-(trifluoromethoxy)benzamidoxime (3.96 g, 18.0 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (4.6 g, 24.0 mmol). After 24 hr at 70°C, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water, saturated $NaHCO_3$, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/methanol/hexanes) provided the oxadiazole as a light yellow solid (5.05 g, 69%). LCMS $_{m/z}$ = 612 $[M+H]^+$.

[959] Part D. A slurry of the oxadiazole from Part C (4.9 g, 8.02 mmol), 2.5N sodium hydroxide (9.6 mL, 24.06 mmol) and sodium hydroxide (1.28 g, 32.08 mmol) in isopropanol (40 ml) were stirred at 70°C for 7 hr. The heat was removed and the reaction diluted with water (100 ml) and chilled to 5°C. The pH was adjusted to 7 with concentrated hydrochloric acid. The solids were filtered, washed with hexanes, and dried *in vacuo* to give the carboxylic acid as a white solid (4.54 g, 97%). LCMS $_{m/z}$ = 584 $[M+H]^+$.

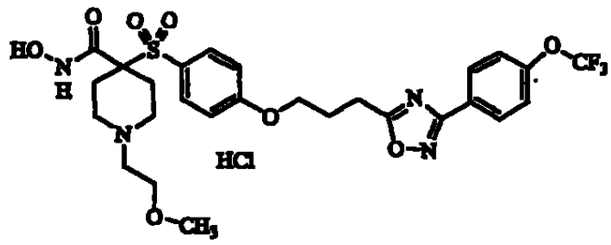
[960] Part E. In dry equipment under nitrogen, the carboxylic acid from Part D (4.5 g, 7.72 mmol) was dissolved in dry dimethylacetamide (15 ml) and the remaining reagents were added to the solution in the following order: N-hydroxybenzotriazole hydrate (1.56 g, 11.6 mmol), triethylamine (3.22 mL, 23.2 mmol), O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (1.35 g, 11.6 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.96 g, 15.4 mmol). After 29 hr at 50°C, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water, saturated $NaHCO_3$, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/methanol/hexanes) provided the THP hydroxamate as a light yellow solid (2.4 g, 46%). LCMS $_{m/z}$ = 683 $[M+H]^+$.

[961] Part F. To the THP hydroxamate from Part E (2.3 g, 3.37 mmol) was added 4N HCl dioxane solution (8.4 mL, 33.7 mmol) and methanol (0.84 mL). The slurry

302

became very thick. Diethyl ether (50 ml) was added to and after 1 hr at ambient temperature the reaction was filtered under nitrogen. The solids were washed with diethyl ether (150 ml) under nitrogen and dried *in vacuo* over phoshorus pentoxide to give the title compound as a white solid (1.92 g, 91%). HRMS (ES+) $M+H^+$ calculated for $C_{26}H_{28}N_4O_7S_1F_3$: 599.1787, found 599.1766.

[962] **Example 42. Preparation of:**



[963] **Part A.** In dry equipment under nitrogen, potassium trimethylsilanolate (42.76 g, 0.3 mol) was dissolved in dimethylsulfoxide (170 mL) and gamma-butyrolactone (17.31 mL, 0.225 mol) was added over 5 min while the reaction temperature rose to 49 C. After stirring at ambient temperature for 90 min, sodium hydride (9.0 g of a 60% oil dispersion, 0.225 mol) was added portion wise over 20 min and the reaction temperature rose to 38°C. Gas evolution was also observed. After stirring at ambient temperature for 40 min, a solution of ethyl 4-[(4-fluorophenyl)sulfonyl]-1-(2-methoxyethyl)piperidine-4-carboxylate (56 g, 0.15 mol) in dimethylsulfoxide (20 mL) was added over 10 mins as the reaction rose to 38°C. The reaction was stirred at ambient temperature for 30 min. The slurry was slowly poured into ice water (1.1 L) and then extracted with hexanes (300 mL) two times followed by a diethyl ether extraction (200 mL). The aqueous layer was chilled to 5°C and the pH adjusted to 7 with concentrated hydrochloric acid. The aqueous solution was extracted with methylene chloride (150 mL) until there was no UV activity in the extract. The combined methylene chloride extracts were washed with saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The solid was recrystallized from methanol (200 mL) to give the butyric acid as a white solid (34.8 g, 51%). LCMS $_{m/z}$ = 458 $[M+H]^+$.

[964] **Part B.** In dry equipment under nitrogen, the butyric acid from Part A (19.19 g, 42.0 mmol) was dissolved in dry dimethylformamide (100 mL) and the

remaining reagents were added to the solution in the following order: N-hydroxybenzotriazole hydrate (8.5 g, 63.0 mmol), triethylamine (11.7 mL, 84.0 mmol), 4-(trifluoromethoxy)benzamidoxime (13.9 g, 63.0 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (16.1 g, 84.0 mmol). After 24 hr at 70°C, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water, saturated $NaHCO_3$, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. The solid was recrystallized from methanol (35 mL) to give the oxadiazole as an off white solid (17.86 g, 66%). *LCMS* $_{m/z}$ = 642 $[M+H]^+$.

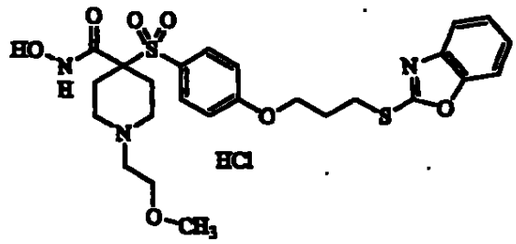
[965] Part C. A slurry of the oxaziazole from Part B (16.9 g, 26.4 mmol), 2.5N sodium hydroxide (31.6 mL, 79.1 mmol) and sodium hydroxide (4.22 g, 105.5 mmol) in isopropanol (30 mL) were stirred at 70°C for 7 hr. The heat was removed and the reaction diluted with water (150 mL) and chilled to 5°C. The pH was adjusted to 7 with concentrated hydrochloric acid. The solids were filtered, washed with hexanes, and dried *in vacuo* to give the carboxylic acid as a white solid (15.78 g, 98%). LCMS $_{m/z}$ = 614 $[M+H]^+$.

[966] Part D. In dry equipment under nitrogen, the carboxylic acid from Part C (15.7 g, 25.6 mmol) was dissolved in dry dimethylformamide (70 mL) and the remaining reagents were added to the solution in the following order: N-hydroxybenzotriazole hydrate (5.19 g, 38.4 mmol), triethylamine (10.7 mL, 76.8 mmol), O-(tetrahydro-2H-pyran2-yl)hydroxylamine (5.99, 51.2 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (10.8 g, 56.3 mmol). After 12 hr at 40°C, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water, saturated $NaHCO_3$, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/hexanes) provided the THP hydroxamate as a white foam (14.94 g, 82%). LCMS $_{m/z}$ = 713 $[M+H]^+$.

[967] Part E. To the THP hydroxamate from Part D (14.88 g, 20.9mmol) was added 4N HCl dioxane solution (52 mL, 209.0 mmol) and methanol (5.2 mL). The slurry became very thick. Dioxanes (50 mL) and diethyl ether (100 mL) were added to facilitate stirring. After 1 hr at ambient temperature the reaction was filtered under nitrogen. The solids were washed with acetonitrile (100 mL) under nitrogen and dried *in vacuo* over

phosphorus pentoxide to give the title compound as a white solid (13.25 g, 95%). HRMS (ES+) M+ H^+ calculated for $C_{27}H_{31}N_4O_8S_1F_3$: 629.1893, found 629.1913.

[968] **Example 43. Preparation of 4-({4-[3-(1,3-benzoxazol-2-ylthio)propoxy]phenyl}sulfonyl)-N-hydroxy-1-(2-methoxyethyl)piperidine-4-carboxamide hydrochloride.**



[969] **Part A.** A solution of 1-benzyl 4-tert-butyl 4-[(4-fluorophenyl)sulfonyl]piperidine-1,4-dicarboxylate (16.0 g, 33.5 mmol) in methanol/tetrahydropyran was hydrogenated for 1 hr at 5 psi in the presence of 5% Pd/C. The solution was filtred to remove the catalyst and concentrated *in vacuo*. 11.0 g (95% yield) of the amine was obtained as a white solid.

[970] **Part B.** The solution of the amine of Part A (11.0 g, 32.1 mmol) in N,N-dimethylformamide (100 mL) was cooled to 0°C on an ice bath. Potassium carbonate (13.3 g, 96.4 mmol) and 2-bromoethylmethyl ether (7.54 mL, 80.2 mmol) were added to the chilled solution. The solution was stirred for 72 hr at ambient temperature and partitioned between ethyl acetate and water. The organic layer was washed with water and saturated sodium chloride and dried over sodium sulfate. 14.5 g of the desired alkylated amine was obtained as an orange oil by concentration *in vacuo*.

[971] **Part C.** To a solution of propanediol (10.44 mL, 144 mmol) in 1-methyl-2-pyrrolidinone (40 mL) cooled to 0°C was added sodium hydride (60% suspension in mineral oil, 3.85 g, 96.3 mmol). The alkylated amine from Part B (14.5 g, 32.1 mmol) was dissolved into 1-methyl-2-pyrrolidinone (50 mL) and added dropwise to the cooled solution. The solution was stirred at ambient temperature for 1 hr. The reaction was quenched by adding water and partitioned between ethyl acetate and water. The organic layer was washed with water and saturated sodium chloride and dried over sodium sulfate.

305

The desired alcohol was obtained as an orange oil by concentration *in vacuo*. MS(CI) MH^+ calculated for $C_{22}H_{35}NO_7S$: 457, found 457.

[972] **Part D.** To a solution of the alcohol of Part C (32.1 mmol) in methylene chloride (100 mL) was added triethylamine (4.92 mL, 35.3 mmol). The solution was cooled to 0°C and methanesulfonyl choride (2.56 mL, 33.0 mmol) was added dropwise. After 1 hr the reaction was concentrated *in vacuo*. The residue was dissolved into ethyl actate and washed with water, saturated sodium bicarbonate and saturated sodium chloride and dried over sodium sulfate. The solution was concentrated *in vacuo* to provide 17.5 g of the desired mesylate. MS(CI) MH^+ calculated for $C_{23}H_{37}NO_9S_2$: 536, found 536.

[973] **Part E.** To a solution of 2-mercaptobenzoxazole (4.86 g, 32.1 mmol) in N,N-dimethylformamide (30 mL) cooled to 0°C was added sodium hydride (60% suspension in mineral oil, 1.54 g, 38.5 mmol). After 30 min the mesylate of Part D (17.5 g, 32.1 mmol) in N,N-dimethylformamide (30 mL) was added dropwise. The solution was heated at 60°C for 4 hr and at 45°C for 18 hr. The solution was returned to ambient temperature and partitioned between ethyl acetate and water. The organic layer was washed with water and saturated sodium chloride and dried over sodium sulfate. Chromotography (ethyl acetate, on silica) provided the mercaptobenzoxazole as a colorless oil (7.3 g, 39% yield over four steps). MS(CI) MH^+ calculated for $C_{29}H_{38}N_2O_7S_2$: 591, found 591.

[974] **Part F.** To a solution of the mercaptobenzoxazole of Part E (7.3 g, 12.4 mmol) was added trifluoroacetic acid (20 mL) and the solution stirred for 3 hr. The solution was concentrated *in vacuo* and azotroped with toluene to provide the acid as an oil. The material was carried on without additional purification. MS(CI) MH^+ calculated for $C_{25}H_{30}N_2O_7S_2$: 535, found 535.

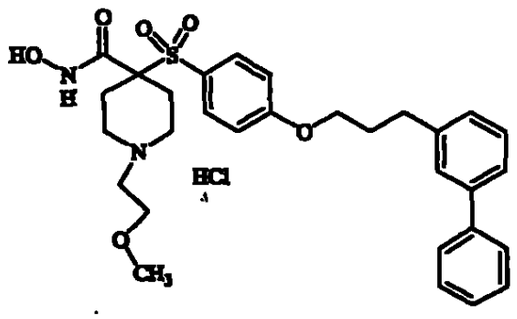
[975] **Part G.** To a solution of the acid of Part F (12.4 mmol) in N,N-dimethylformamide (50 mL) were added 1-hydroxybenztriazole (2.01 g, 14.9 mmol), 4-methylmorpholine (6.82 mL, 62 mmol) and tetrahydropyranylamine (2.18 g, 18.6 mmol). After30 min 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (3.33 g, 17.4 mmol) was added. The solution was heated to 65°C for 2 hr. The solution was partitioned between ethyl acetate and water. The organic layer was washed with water and saturated sodium chloride and dried over sodium sulfate. Chromotography (ethyl acetate/methanol,

306

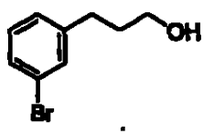
on silica) provided the protected hydroxamate as a colorless oil (3.9 g, 50 % yield). MS(CI) MH^+ calculated for $C_{30}H_{39}N_3O_8S_2$: 634, found 634.

[976] **Part H.** To a solution of the protected hydroxamate of Part G (3.9 g, 6.2 mmol) in 1,4-dioxane (10 mL) was added 4M hydrochloric acid in 1,4-dioxane (10 mL). The reaction was complete after 1 hr. The solution was concentrated *in vacuo*. The residue was purified via reverse phase chromatography (acetonitrile/water, on silica) to provide the title compound as a white solid (1.49 g, 41% yield). MS(CI) MH^+ calculated for $C_{25}H_{31}N_3O_7S_2$: 550, found 550. HRMS calculated for $C_{25}H_{31}N_3O_7S_2$: 550.1682, found 550.1668. Analytical calculation for $C_{25}H_{31}N_3O_7S_2.HCl.H_2O$: C, 49.70; H, 5.67; N, 6.96; S, 10.62; Cl, 5.87. Found: C, 49.91; H, 6.03; N, 6.74; S, 10.75; Cl, 6.35.

[977] **Example 44. Preparation of:**



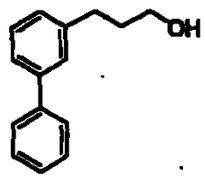
[978] **Part A.** Preparation of:



To a solution of 3-(3-bromophenyl)propionic acid (15.0 g, 65.5 mmol) in anhydrous THF (200 mL) at 5°C was added, via addition funnel, 1.0 M BH_3·THF (200 mL, 200 mmol). The reaction temperature was kept below 14°C during the addition of the BH_3·THF. After all the BH_3·THF was added, the reaction was refluxed for 22 hr and then quenched with water (100 mL) and 1N HCl (300 mL). The solution was saturated with sodium chloride and extracted with ethyl acetate (3x300 mL). The organic extract was washed with brine, dried over magnesium sulfate, and concentrated providing 14.4 g (100%) of crude alcohol as a colorless oil. NMR($CDCl_3$) δ 1.82-1.89 (m, 2H), 2.67 (t, 2H), 3.64 (t, 2H), 7.11-7.15 (m, 1H), 7.29-7.31 (m, 1H), 7.34 (s, 1H).

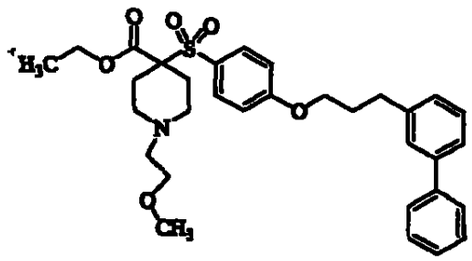
307

[979] Part B. Preparation of:



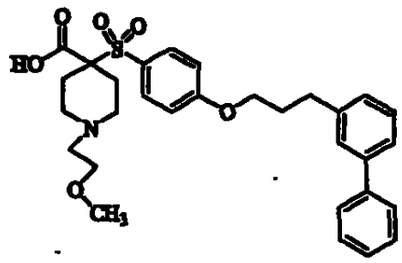
In a flask were combined the alcohol from Part A (65.5 mmol), phenyl boronic acid (12.0 g, 98.2 mmol), palladium tetrakistriphenylphosphine (3.8 g, 3.3 mmol), 2*M* cesium carbonate (98 mL, 196 mmol) and dimethoxyethylether (100 mL). The mixture was stirred vigorously under nitrogen at reflux overnight. The reaction was cooled to ambient temperature, poured into water (300 mL) and extracted 3 times with ethyl acetate. The combined organic extracts were washed with brine and dried over magnesium sulfate. Chromatography (on silica, ethyl acetate / hexane) provided the coupled product as a golden oil (11.95 g, 86.0 %). NMR($CDCl_3$) δ 1.91-1.98 (m, 2H), 2.77 (t, 2H), 3.71 (t, 2H), 7.19 (d, 1H), 7.31-7.38 (m, 2H), 7.41-7.45 (m, 4H), 7.58 (d, 2H).

[980] Part C. Preparation of:



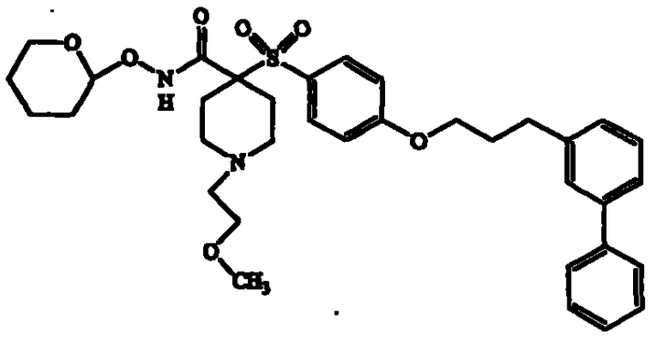
To a solution of the alcohol from Part B (11.9 g, 56.1 mmol) in anhydrous dimethylformamide (56 mL) at 0°C was added 60% sodium hydride (2.55 g, 63.8 mmol) in portions. After completion of the addition, the reaction was stirred at 0°C for 15 min then ambient temperature for 15 min. The reaction was cooled to 0°C and ethyl 4-[(4-fluorophenyl)sulfonyl]-1-(2-methoxyethyl)piperidine-4-carboxylate (19.0 g, 51 mmol) in anhydrous dimethylformamide (60 mL) was added slowly. Upon completion of addition, the ice bath was removed and the reaction stirred at ambient temperature overnight. Reaction was poured into water (1 L) and extracted with ethyl acetate (800 mL). The combined organics were washed with water (2x500 mL) and brine and dried over magnesium sulfate. Concentration gave 34.4 g of crude material. This material was used without purification.

[981] Part D. Preparation of:



The impure ester of Part C (34.4 g, 51 mmol theoretical) was hydrolyzed in 41 mL of ethanol, 41 mL of 1,4-dioxane and 26.5 mL of 6 N NaOH at 60°C. The solution was poured into water and extracted with ether to remove color. Acidification with 1N HCl caused precipitation of the acid which was collected by filtration and washed with water, ethyl acetate and hexane then dried under high vacuum yielding the acid as an off white solid (18.8 g, 68.6% yield). NMR (CD_3OD w/ K_2CO_3) δ 1.98 (t, 2H), 2.07-2.19 (m, 4H), 2.32 (d, 2H), 2.48 (t, 2H), 2.85-2.95 (m, 4H), 3.25 (s, 3H), 4.06 (t, 2H), 7.04 (d, 2H), 7.20 (d, 1H), 7.27-7.48 (m, 5H), 7.54 (d, 2H), 7.78 (d, 2H). ESMS m/z = 538 $(M+H)^+$.

[982] Part E. Preparation of:

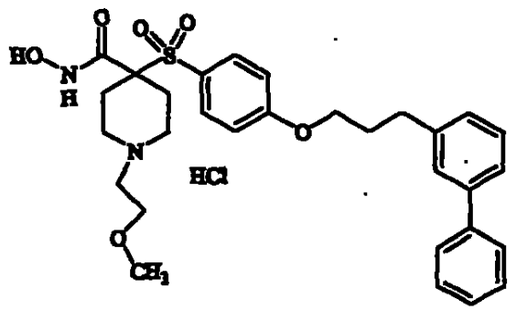


To the acid of Part D (12.7 g, 23.6 mmol), HOBt (5.42 g, 35.4 mmol), EDC (6.30 g, 3.30 mmol) in a flask under N_2 was added 70 mL anhydrous DMF. The mixture was heated to 60°C and triethylamine (9.85 mL, 70.8 mmol) was added. After heating at 60°C for 1 hr, THP-hydroxylamine (4.14 g, 35.4 mmol) was added. The solution was stirred for 16.5 hr at 60°C. The solution was partitioned between ethyl acetate (300 mL) and water (500 mL). The organic layer was washed with brine and dried over magnesium sulfate. Concentration provided the protected hydroxamate as an oil (14.86 g, 98.7 %).

NMR($CDCl_3$) δ 1.55-1.90 (m, 6H), 2.09-2.27 (m, 8H), 2.50 (t, 2H), 2.87 (t, 2H), 2.90-2.98

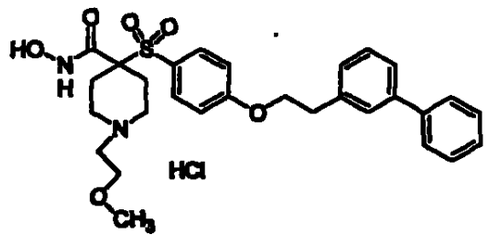
(m, 2H), 3.32 (s, 3H), 3.42 (t, 2H), 3.7.1 (d, 1H), 3.98 (d, 1H), 4.03 (t, 2H), 4.99 (s, 1H), 6.97 (d, 2H), 7.19 (d, 1H), 7.30-7.46 (m, 6H), 7.57 (d, 2H), 7.77 (d, 2H), 9.42 (s, 1H). ESMS m/z = 637 $(M+H)^+$.

[963] Part F. Preparation of:

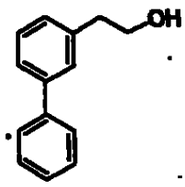


To the product from Part E (14.7 g, 23.1 mmol) in methanol (23 mL) and 1,4-dioxane (23 mL) was added 4M hydrochloric acid in 1,4-dioxane (23 mL) and after stirring 1 hr, material dripped in to stirring IPA, let stand overnight. Collection of solid under N_2 followed by washing with IPA and hexane then drying on high vacuum over P_2O_5 provided 12.5 g (91.8 %) of the title compound as a hydrochloric acid salt that was colorless. NMR(DMSO) δ 2.05-2.25 (m, 4H), 2.74, (t, 2H), 2.81 (t, 2H), 3.18-3.26 (m, 4H), 3.39 (s, 3H), 3.51-3.61 (m, 4H), 4.09 (t, 2H), 7.15 (d, 2H), 7.22 (d, 1H), 7.29-7.49 (m, 6H), 7.58 (d, 2H), 7.45 (d, 2H). ESMS m/z = 553 $(M+H)^+$. HRMS calcd. for $C_{30}H_{33}N_2O_5S$ H: 553.2369 $(M+H)^+$. Found: 553.2372.

[964] Example 45. Preparation of:

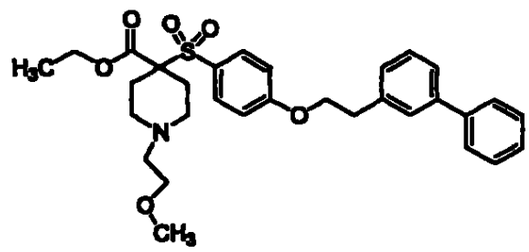


[985] Part A. Preparation of:



In a flask were combined the 3-bromophenethyl alcohol (17.5 g, 87.1 mmol), phenyl boronic acid (12.7 g, 104.5 mmol), palladium tetrakistriphenylphosphine (2.0 g, 1.74 mmol), 2M cesium carbonate (105 mL, 210 mmol) and dimethoxyethylether (105 mL). Mixture stirred vigorously under nitrogen at reflux overnight. After cooling to ambient temperature, poured mixture into water (400 mL) and extracted with ethyl acetate (2x400 mL). Combined organics were washed with brine and dried over magnesium sulfate. Silica gel chromotography (ethyl acetate / hexane) provided the coupled product as a crystalline solid (15.04 g, 87.3 %). NMR($CDCl_3$) δ 2.95 (t, 2H), 3.93 (q, 2H), 7.19-18 (m, 2H), 7.31-7.51 (m, 5H), 7.58 (d, 2H). GCMS EI+ 198 (M+).

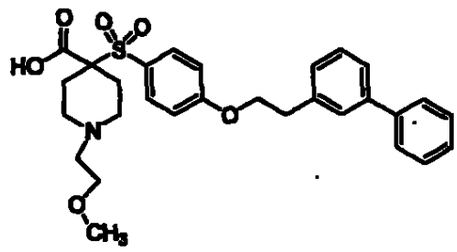
[986] Part B. Preparation of:



To a solution of the alcohol from Part A (14.9 g, 75.2 mmol) in anhydrous dimethylformamide (70 mL) at 0°C was added 60 % sodium hydride (3.0 g, 75.2 mmol) in portions. After completion of the addition, the reaction was stirred at 0°C for 30 min. ethyl 4-[(4-fluorophenyl)sulfonyl]-1-(2-methoxyethyl)piperidine-4-carboxylate (33.6 g, 90.2 mmol) in anhydrous dimethylformamide (50 mL) at 5°C was added slowly. Upon completion of addition let reaction slowly warm up overnight. Reaction was poured into water (700 mL) and extracted with ethyl acetate (3x500 mL). The combined organics were washed with brine and dried over sodium sulfate. Concentration gave 50.6 g of crude material. This material was used without purification. ESMS *m/z* = 552 $(M+H)^+$.

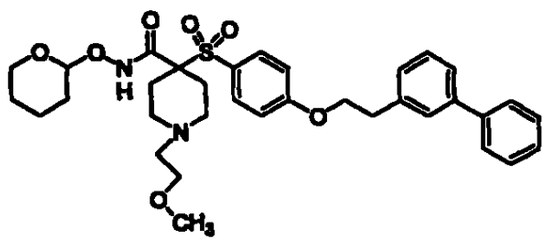
311

[987] Part C. Preparation of:



The impure ester of Part B (75.2 mmol theoretical) was hydrolyzed in 75 mL of ethanol, 75 mL of 1,4-dioxane and 50 mL of 6 N NaOH at 60 C for 2.5 hr. The solution was poured into water and extracted with ether to remove color. Acidification with 1N HCl caused precipitation of the acid which was collected by filtration and washed with water, ethyl acetate and diethyl ether then dried under high vacuum yielding the acid as a white solid (31.7 g, 80.6% yield). ESMS m/z = 524 $(M+H)^+$. HRMS calcd. for $C_{29}H_{34}NO_6S$: 524.2101 $(M+H)^+$. Found: 524.2075.

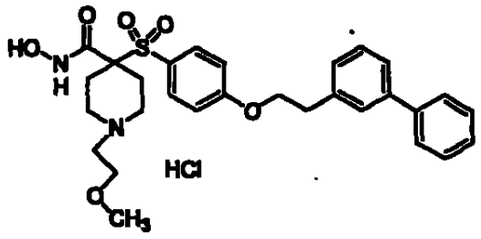
[988] Part D. Preparation of:



The acid of Part C (31.6 g, 60.4 mmol), HOBt (13.9 g, 90.6 mmol), EDC (16.2 g, 84.6 mmol), triethylamine (25.2 mL, 181 mmol) and THP-hydroxylamine (10.6 g, 90.6 mmol) were stirred in anhydrous dimethylformamide (200 mL) under N_2 at 60°C overnight. After cooling to room temperature solution was poured into 1.6 L of ice water and extracted with ethyl acetate (2x1 L). The organic layer was washed with brine and dried over sodium sulfate. Silica gel chromatography (2.0M NH_3 in MeOH/ethyl acetate/hexane) gave the desired product as a colorless foam (30.89 g, 82%). ESMS m/z = 623 $(M+H)^+$. HRMS calcd. for $C_{34}H_{43}N_2O_7S$: 623.2786 $(M+H)^+$. Found: 623.2793.

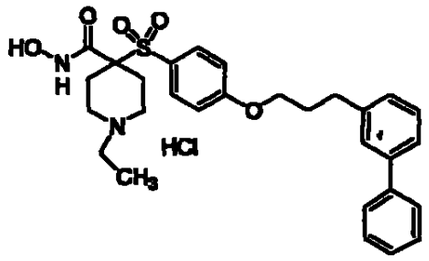
312

[989] Part E. Preparation of:

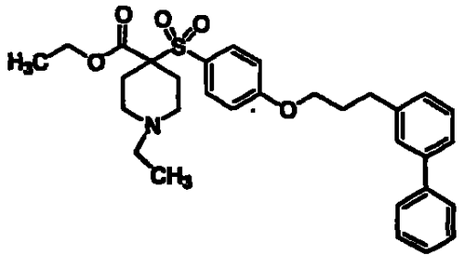


To the product from Part D (30.7 g, 49.3 mmol) in methanol (49 mL) and 1,4-dioxane (49 mL) was added 4N HCl in dioxane (50 mL). Material concentrated after 1 hr and crystallized from methanol providing the desired product as a colorless crystalline solid (25.6 g, 90.2%). ESMS *m/z* = 539 $(M+H)^+$. HRMS calcd. for $C_{29}H_{35}N_2O_6S$: 539.2210 $(M+H)^+$. Found: 539.2187.

[990] Example 46. Preparation of:



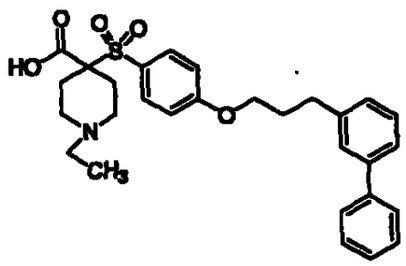
[991] Part A. Preparation of:



To a solution of the alcohol from Example 38, Part B (12.0 g, 56.1 mmol) in anhydrous dimethylformamide (50 mL) at 0°C was added 60 % sodium hydride (2.58 g, 64.5 mmol) in portions. After completion of the addition, the reaction was stirred at 0°C for 15 min then ambient temperature for 15 min. The reaction was cooled to 0°C and ethyl 1-ethyl-4-[(4-fluorophenyl)sulfonyl]piperidine-4-carboxylate (17.7 g, 51.6 mmol) in anhydrous dimethylformamide (60 mL) was added slowly. Upon completion of addition, ice bath

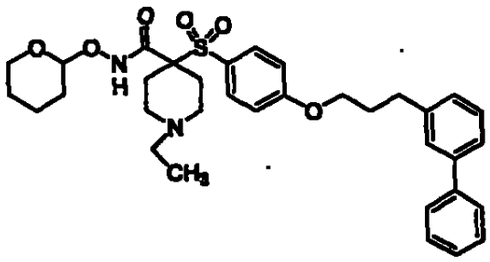
was removed and reaction stirred at ambient temperature overnight. Reaction was poured into water and extracted with ethyl acetate 2 times. The combined organics were washed with water 2 times and brine and dried over sodium sulfate. Concentration gave 34.4 g of crude material. This material was used without purification. ESMS *m/z* = 536 $(M+H)^+$.

[992] Part B. Preparation of:



The impure ester of Part A (51.6 mmol theoretical) was hydrolyzed in 50 mL of ethanol, 50 mL of 1,4-dioxane and 34.4 mL of 6 N NaOH at 60°C. After cooling to room temperature, the solution was poured into water (500 mL) and extracted with ether (2x250 mL) to remove color. Acidification with 1N HCl caused precipitation of the acid which was collected by filtration and washed with water, ethyl acetate and hexane then dried under high vacuum yielding the acid as an off white solid (18.4 g, 70% yield). ESMS *m/z* = 508 $(M+H)^+$. HRMS calcd. for $C_{29}H_{34}NO_5S$ H: 508.2152 $(M+H)^+$. Found: 508.2176.

[993] Part C. Preparation of:

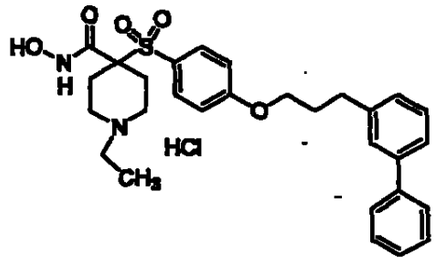


The acid of Part B (18.0g, 35.4 mmol), HOBt (8.12 g, 53.1 mmol), EDC (9.47 g, 49.6 mmol), triethylamine (14.8 mL, 106.2 mmol) and THP-hydroxylamine (6.21g, 53.1 mmol) were stirred in anhydrous dimethylformamide (110 mL) under N_2 at 60°C overnight. After cooling to room temperature, the solution was poured into water (600 mL) and extracted with ethyl acetate. The organic layer was washed with water and brine and dried over sodium sulfate. Silica gel chromatography (2.0M NH_3 in MeOH/ethyl

314

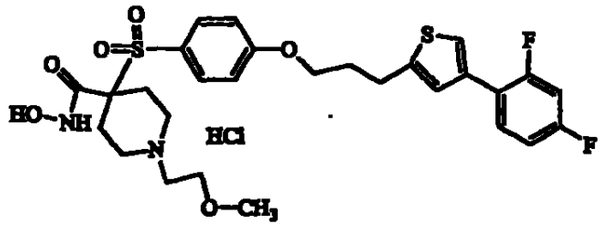
acetate/hexane) gave the desired product as a colorless foam (11.0 g, 51%). ESMS *m/z* = 607 $(M+H)^+$. HRMS calcd. for $C_{34}H_{43}N_2O_6S$: 607.2836 $(M+H)^+$. Found: 607.2829

[994] Part D. Preparation of:



To the product from Part C (10.8 g, 17.8 mmol) in methanol (18 mL) and 1,4-dioxane (18 mL) was added 4M hydrochloric acid in 1,4-dioxane (18 mL) and after stirring 1 hr, material concentrated. Co-crystallized with another batch from MeOH/4N HCl/dioxane. Collection of solid followed by washing with methanol then drying on high vac provided 11.51 g (88 %) of the title compound as a hydrochloric acid salt that was colorless. ESMS *m/z* = 523 $(M+H)^+$. HRMS calcd. for $C_{29}H_{35}N_2O_5S$ H: 523.2261 $(M+H)^+$. Found: 523.2224.

[995] Example 47. Preparation of 4-[(4-{3-[4-(2,4-difluorophenyl)thien-2-yl]propoxy}phenyl) sulfonyl]-N-hydroxy-1-(2-methoxyethyl)piperidine-4-carboxamide hydrochloride.



[996] Part A. A round bottom flask was charged with 4-bromo-2-thiophene carboxaldehyde (Aldrich, 55.8 g, 292 mmol), 2,4-difluorophenyl boronic acid (Aldrich, 60.0 g, 380 mmol), tetrakis-triphenylphosphine palladium (Aldrich, 16.9 g, 14.6 mmol), 2 M $Na_2CO_{3(aq)}$ (190 ml, 380 mmol), and ethylene glycol-dimethyl ether (Aldrich, 500 ml). The reaction was heated to 80°C and stirred for 5 hr. The reaction suspension was then poured into a mixture of methylene chloride (500 ml) and ice water (500ml). The organic layer was separated and washed with water (2x-200 ml) and brine (1x-300 ml) then dried

315

over Na_2SO_4 and concentrated to afford the thiophene phenyl adduct as a brown oil. Silica gel purification (hexanes/ethyl acetate) yielded a white solid (34.2 g, 52 % yield). ^1H NMR showed the desired compound.

[997] **Part B.** A solution of triethyl phosphonoacetate (Aldrich, 24.2 g, 108 mmol) in tetrahydrofuran (100 ml) was cooled to –78°C. A 1.6 M *n*-butyllithium solution in hexanes (68 ml, 108 mmol) was slowly dripped in then the reaction stirred for 30 min at –78°C. A solution of the thiophene phenyl carboxaldehyde product from Part A in tetrahydrofuran (100 ml) was slowly dripped in. The dry ice bath was removed and the reaction stirred as it came to ambient temperature overnight. The mixture was diluted with water (200 ml) to quench. The organic layer was separated and washed with water (2x- 200 ml) and brine (1x- 300 ml) then dried over Na_2SO_4 and concentrated to afford a tan solid. This solid was recrystallized from warm methanol to yield a light yellow solid (16.1 g, 56 % yield). ^1H NMR showed the desired compound.

[998] **Part C.** A solution of the ethyl ester olefin of Part B (16 g, 54.4 mmol) in methylene chloride was cooled to 0°C. A 1.0 M solution of lithium aluminum hydride was dripped in slowly, then the reaction continued stirring for 45 min at 0°C. A saturated solution of NH_4Cl_{aq} was dripped in to quench, followed by a solution of sodium, potassium tartrate $_{aq}$ (10 ml). After stirring for 30 min, Na_2SO_4 (40 g) was added. The mixture was filtered and concentrated to afford a yellow oil (16.8 g, 100$^+$ % yield). ^1H NMR showed the desired compound along with impurities.

[999] **Part D.** A hydrogenation flask was charged with the crude hydroxy olefin residue from Part C (~54.4 mmol) was dissolved in tetrahydrofuran (125 ml) and methanol (20 ml). Nitrogen gas was bubbled through for 15 min then 10% Pd/C catalyst (Aldrich, 50% water, 2.7 g) was added. A hydrogenation head was attached and the vessel was purged with nitrogen (3x), followed by hydrogen (3x). The vessel was left at 50 psi of hydrogen. After 1 hr of stirring, the reaction was complete by LCMS. The mixture was filtered through a Celite pad and concentrated to afford a black oil that was purified on silica gel (hexanes/ethyl acetate). Collected fractions gave the product as a clear oil (8.6 g, 62% yield).). ^1H NMR showed the desired compound.

[1000] **Part E.** The saturated alcohol from Part D (7.6 g, 30.0 mmol) was dissolved in dimethylsulfoxide (60 ml). Sodium hydride (Aldrich, 60 % in oil dispersion, 1.3 g, 32.6 mmol) was added portion wise over 30 min. After stirring for 1 hr, the aryl-

fluoride, SC 84087, was added and the reaction was stirred overnight at ambient temperature. The reaction was quenched with saturated NH_4Cl_{aq} (100 ml) then extracted with ethyl acetate (3x-125 ml). The combined organics were washed with water (2x-200 ml) and brine (1x-200 ml) then dried over Na_2SO_4 filtered and concentrated to a brown oil. The residue was purified on silica gel (hexanes/ethyl acetate) to afford the product as a tan solid (14.0 g, 81% yield).). ^{1}H NMR showed the desired compound at 90% purity.

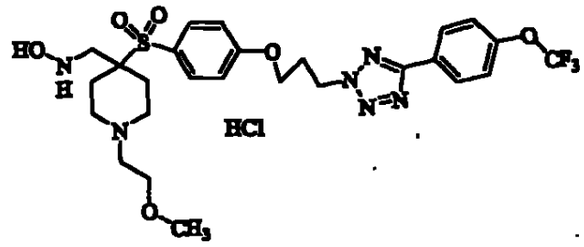
[1001] Part F. The *t*-butyl ester from Part E (9.5 g, 15.0 mmol) was dissolved in methylene chloride (30 ml) after which, trilfluoroacetic acid (Aldrich, 30 ml) was added. The reaction stirred for 4 hr then was concentrated to one-third volume via a nitrogen stream. The slightly viscous residue was then dripped into stirring diethyl ether to form a solid that was filtered and dried to give the product as a tan solid (6.9 g, 66 % yield).). ^{1}H NMR showed the desired compound.

[1002] Part G. To a solution of the carboxylic acid of Part F (6.9 g, 9.9 mmol) in N,N-dimethylformamide (20 ml) was added triethylamine (Aldrich, 4.2 ml, 30.0 mmol) followed by N-hydroxybenzotriazole hydrate (Aldrich, 2.7 g, 20.0 mmol), O- (tetrahydro-2H-pyran-2-yl) hydroxylamine (2.34 g, 20.0 mmol), and, lastly, 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (Sigma, 4.18 g, 21.8 mmol). The reaction stirred at room temperature for 18 hr. The mixture was diluted with water (30ml) then extracted with ethyl acetate (3x- 100 ml). The organics were combined and washed with saturated $NaHCO_{3\ aq}$ (3x-100 ml), water (2x- 100ml), and brine (1x- 150 ml). After drying over Na_2SO_4, the mixture was filtered and concentrated for a tan oil. The oil was tritiated with ethanol (3x) and methanol (3x) to afford a tan oil (8.1 g, 100$^+$ % yield). ^{1}H NMR showed the desired compound with trace impurities.

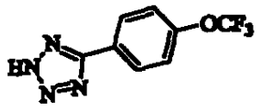
[1003] Part H. The crude protected hydroxamic acid of Part G (~ 9.9 mmol) was slurried in methanol (4 ml) and stirred with 4 N HCl in dioxane (20 ml) for 1 hr. The solvent volume was reduced in half then diethylether was added, providing a gummy solid that was purified by Reverse Phase LC (C_{18}, acetonitrile/water). The resulting partial TFA salt was dissolved in 4 N HCl in dioxane (20 ml) and stirred for 1 hr. The solvent volume was again reduced in half then diethyl ether was added, providing a white solid. The solid was collected and dried to afford the desired hydrochloride salt as a white powder (3.35g, 54% yield). ^{1}H NMR showed the desired compound.

317

[1004] Example 48: Preparation of:

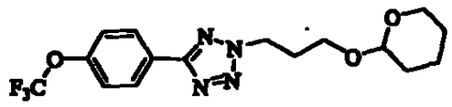


[1005] Part A. Preparation of:



A mixture of lithium chloride (1.71 g, 40.3 mmol), trifluoromethoxy-benzonitrile (5.00 g, 26.7 mmol), and sodium azide (1.75 g, 26.7 mmol) in 2-methoxyethanol (26 mL) under an N_2 atmosphere was refluxed for 4 hr. The ambient mixture was poured into a mixture of ice (84 g) and concentrated HCl (8.4 mL) and stirred until the ice melted. The white solid was collected by filtration, washed with water, and dried for 2 hr in a 40°C vacuum oven to produce the tetrazole in the form of an off white solid (4.86 g, 79% yield). MS MH^+ calcd. for $C_8H_6N_4OF_3$ 231, found 231.

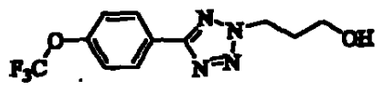
[1006] Part B. Preparation of:



A solution of the tetrazole of Part A (2.00 g, 8.69 mmol) in NMP (12 mL) was added dropwise to an ambient mixture of 95% sodium hydride (0.438 g, 18.2 mmol) in NMP (12 mL) under an N_2 atmosphere. After an 1 hr of stirring, 2-(3-chloropropoxy)tetrahydro-2H-pyran (1.58 mL, 9.56 mmol) was added dropwise. The mixture was stirred at ambient temperature for 18 hr and then at 70°C for 2 hr. The mixture was diluted with a solution of water (200 mL) and saturated $NaHCO_3$ (100 mL), and extracted with ethyl acetate (3x100 mL). The organic layer was washed with water (2x100 mL) and brine (100 mL), dried over $MgSO_4$, and concentrated *in vacuo* to produce a yellow liquid. Flash chromatography purification (ethyl acetate-hexane/silica gel) provided the pyran in the form of a white solid (1.46 g, 45% yield). Anal. Calcd. for $C_{16}H_{19}N_4O_2F_3$: C,56.34; H, 5.98; N, 7.73; S, 4.42. Found C,56.13; H, 6.08; N, 7.65; S, 4.75.

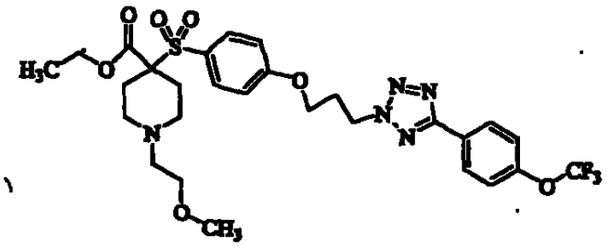
318

[1007] Part C. Preparation of:



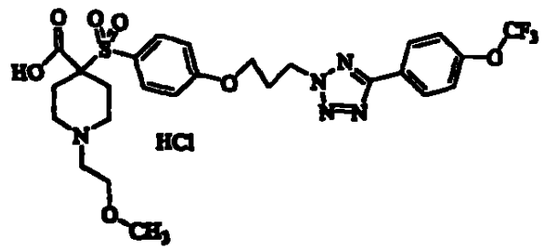
To an ambient solution of the pyran of Part B (1.40 g, 3.76 mmol) in MeOH (13.5 mL) was added a solution of acetyl chloride (0.896 mL, 13.1 mmol) in MeOH (13.5 mL). After 15 min, the solution was concentrated *in vacuo* to provide the alcohol in the form of a solid (1.02 g, 94% yield). MS MH^+ calcd. for $C_{11}H_{12}N_4O_2F_3$ 289, found 289.

[1008] Part D. Preparation of:



To an ambient mixture of 95% sodium hydride (0.110g, 3.58 mmol) in NMP (2.5 mL) under an N_2 atmosphere was added dropwise a solution of the alcohol of Part C (1.00 g, 3.47 mmol) in NMP (3.2 mL), and then the mixture was heated at 55°C for 30 min. A solution of ethyl 4-[(4-fluorophenyl)sulfonyl]-1-(2-methoxyethyl)piperidine-4-carboxylate (1.22 g, 3.27 mmol) in NMP (3.2 mL) was added dropwise to the 55°C reaction mixture. After 1 hr at 55°C, the ambient mixture was diluted with a solution of water (600 mL) and $NaHCO_3$ (100 mL), and extracted with ethyl acetate (3x200 mL). The organic layer was washed with water (2x150 mL) and brine (150 mL), dried over $MgSO_4$, and concentrated *in vacuo* to form a yellow oil (1.96 g). Flash chromatography purification (MeOH-EA/silica gel) provided the sulfone in the form of a yellow oil (1.48 g, 70% yield). MS MH^+ calcd. for $C_{28}H_{33}N_5O_7SF_3$ 642, found 642.

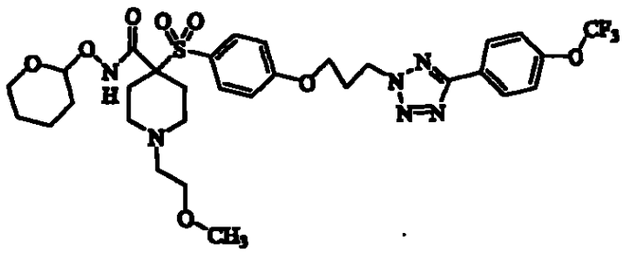
[1009] Part E. Preparation of:



319

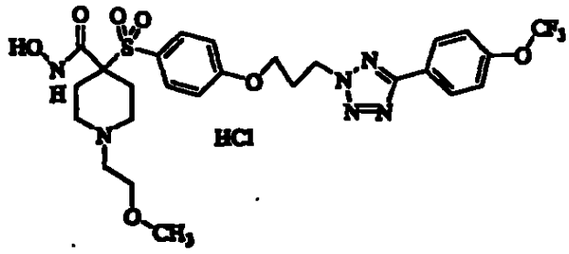
A mixture of the sulfone of Part D (1.44 g, 2.24 mmol) and 50% aqueous NaOH (1.08 g, 22.4 mmol) in a solution of THF (23 mL) and EtOH (11 mL) was stirred at ambient temperature for 3 hr and then 60°C for 15 min. The mixture was concentrated *in vacuo*, diluted with a solution of acetonitrile and water, acidified to a pH of approximately 2 with concentrated HCl, and concentrated *in vacuo* to provide the acid (containing NaCl) as a crude tan foam (2.77 g). MS MH^+ calcd. for $C_{26}H_{31}N_5O_7SF_3$ 614, found 614.

[1010] Part F. Preparation of:



A mixture of the crude acid of Part E (2.24 mmol), 1-hydroybenzotriazole hydrate (0,534 g, 3.95 mmol), triethylamine (3.62mL, 25.9 mmol), O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (0.542 g, 4.63 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (0.888 g, 4.63 mmol) in DMF (23 mL) under an N_2 atmosphere was stirred at ambient temperature for 40 hr. The mixture was diluted with water (400 mL) and extracted with ethyl acetate (3x100 mL). The organic layer was washed with water (2x100 mL) and brine (100 mL), dried over $MgSO_4$, and concentrated *in vacuo* to form a white foam (1.37 g). Chromatography purification (MeOH-EA/silica gel) produced the O-protected hydroxamate in the form of a white foam (1.04 g, 65% based on the ester of Part 1D). MS MH^+ calcd. for $C_{31}H_{40}N_6O_8F_3S$ 713, found 713. Anal. Calcd. for $C_{31}H_{39}N_6O_8F_3S$: C,52.24; H, 5.52; N,11.79. Found C,52.47; H, 5.73; N, 11.64.

[1011] Part G. Preparation of:

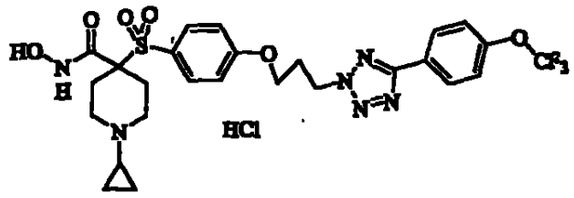


A solution of the O-protected hydroxamate of Part F (0.960 g, 1.35 mmol) and acetyl chloride (0.493 g, 6.53 mmol) in methanol (15 mL) was stirred at ambient temperature for

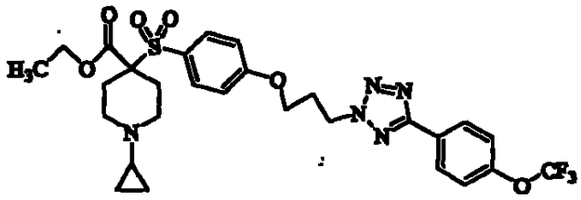
320

1 hr. The solution was concentrated *in vacuo* to a white solid. The solid was triturated with ether and concentrated *in vacuo* to provide the title compound in the form of a white solid (0.66 g, 74% yield). Anal. Calcd. for $C_{26}H_{31}N_6O_7F_3S$·HCl: C, 46.95; H, 4.85; N, 12.64; Cl, 5.33; S, 4.82. Found C, 46.59; H, 5.07; N, 12.64; Cl, 5.36; S, 5.20. MS MH^+ calcd. for $C_{26}H_{32}N_6O_7F_3S$ 629, found 629.

[1012] **Example 49. Preparation of:**



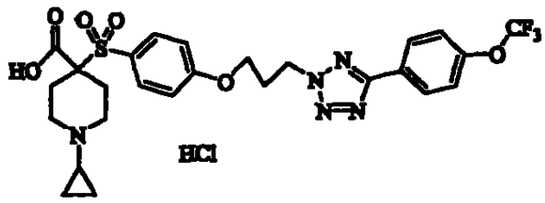
[1013] **Part A. Preparation of:**



To an ambient mixture of 95% sodium hydride (0.397g, 16.5 mmol) in NMP (7 mL) under an N_2 atmosphere was added dropwise a solution of the alcohol of Part C of Example 48 (3.44 g, 11.9 mmol) in NMP (7 mL). The mixture was then stirred at ambient temperature for 45 min. The ethyl 1-cyclopropyl-4-[(4-fluorophenyl)sulfonyl]piperidine-4-carboxylate (4.00 g, 11.3 mmol) was added in one portion, and the mixture was heated to 60°C. After heating for 24 hr at 60°C and adding 2 more portions of 95% sodium hydride (0.10 g, 4.0 mmol and 0.08 g, 3.0 mmol), the mixture was diluted with water (300 mL) and extracted with ethyl acetate (3x100 mL). The organic layer was washed with water (2x100 mL) and brine (100 mL), dried over $MgSO_4$, and concentrated *in vacuo* to form a yellow oil (5.81 g). Flash chromatography purification (Hexane-EA/silica gel) produced the sulfone in the form of a yellow oil (3.10 g, 44% yield). The proton NMR ($CDCl_3$) spectrum was consistent with the desired sulfone product.

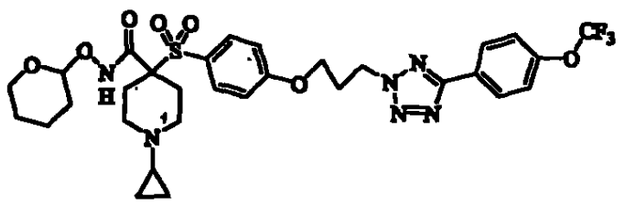
321

[1014] Part B. Preparation of:



A mixture of the sulfone of Part A (3.00 g, 4.81 mmol) and 50% aqueous NaOH (3.85 g, 48.1 mmol) in a solution of THF (50 mL) and EtOH (24 mL) was stirred for 2.5 hr at 60°C. The mixture was concentrated *in vacuo*, diluted with a solution of acetonitrile and water, acidified to a pH of approximately 2 with concentrated HCl, and concentrated *in vacuo*. The crude acid was purified by reverse phase HPLC (H_2O-CH_3CN) to produce the acid in the form of a white solid (1.86 g, 55% yield). MS MH^+ calcd. for $C_{26}H_{29}N_5O_6F_3S$ 596, found 596.

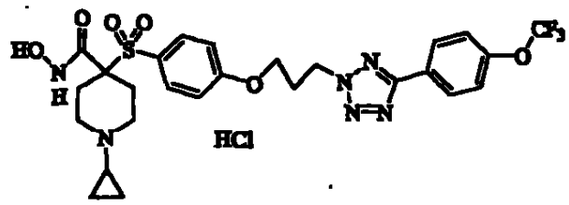
[1015] Part C. Preparation of:



A mixture of the acid of Part B (1.80 g, 2.85 mmol), 1-hydroybenzotriazole hydrate (0.679 g, 5.02 mmol), triethylamine (4.61mL, 33.1 mmol), O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (0.692 g, 5.91 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.13 g, 5.91 mmol) in DMF (29 mL) under an N_2 atmosphere was stirred at ambient temperature for 24 hr and 57°C for 6.5 hr. The mixture was concentrated *in vacuo*, diluted with water (300 mL), and extracted with ethyl acetate (3x100 mL). The organic layer was washed with water (2x100 mL) and brine (100 mL), dried over $MgSO_4$, and concentrated *in vacuo* to form a yellow oil (1.80 g). Flash chromatography purification (*MeOH*-CH_2Cl_2/silica gel) produced the O-protected hydroxamate in the form of a white foam (0.89 g, 45% yield). MS MH^+ calcd. for $C_{31}H_{38}N_6O_7F_3S$ 695, found 695. Anal. Calcd. for $C_{31}H_{37}N_6O_7F_3S$: C,53.59; H, 5.37; N,12.10; S, 4.62. Found C,53.30; H, 5.43; N, 12.05; S, 4.73.

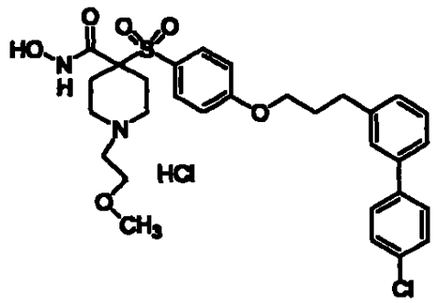
322

[1016] Part D. Preparation of:

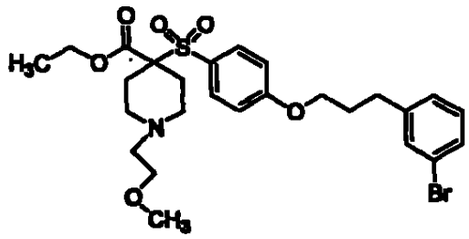


A solution of the O-protected hydroxamate of Part C (0.870 g, 1.25 mmol) and acetyl chloride (0.456 g, 6.04 mmol) in methanol (14 mL) was stirred at ambient temperature for 30 min. The mixture was poured into diethyl ether (250 mL). The white solid was isolate by filtration and dried in a 40°C vacuum oven to produce the title compound in the form of a white solid (0.56 g, 69% yield). MS MH^+ calcd. for $C_{26}H_{30}N_6O_6F_3S$ 611, found 611.

[1017] Example 50. Preparation of:



[1018] Part A. Preparation of:

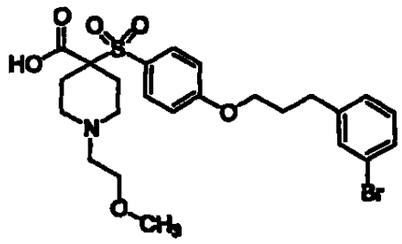


To a solution of the alcohol from Part B of Example 38 (3.65 g, 17.0 mmol) in anhydrous dimethylformamide (17 mL) at 5°C was added 60% sodium hydride (0.77 g, 19.3 mmol) in portions. After completion of the addition, the reaction was stirred at 5°C for 15 min and then at ambient temperature for 15 min. The reaction was cooled to 5°C and ethyl 4-[(4-fluorophenyl)sulfonyl]-1-(2-methoxyethyl)piperidine-4-carboxylate (6.0 g, 16.1 mmol) in anhydrous dimethylformamide (15 mL) was added slowly. Reaction stirred at room

323

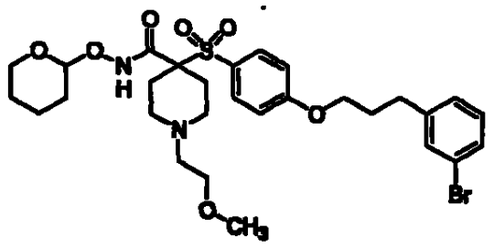
temperature for 2 hr, then was diluted with water (250 mL) and extracted with ethyl acetate (3x150 mL). The combined organics were washed with brine and dried over magnesium sulfate. Silica Gel chromatography (ethyl acetate/hexane) gave the product as a colorless oil (8.06 g, 88%). NMR($CDCl_3$) δ 1.20-1.26 (m, 3H), 1.88-2.02 (m, 2H), 2.06-2.27 (m, 4H), 2.43 (d, 2H), 2.53 (bs, 2H), 2.78 (t, 2H), 2.97-3.08 (m, 2H), 3.32 (s, 3H), 3.47 (bs, 2H), 4.00 (t, 2H), 4.18 (q, 2H), 6.95 (d, 2H), 709-7.18 (m, 2H), 7.34 (d, 2H), 7.68 (d, 2H).

[1019] Part B. Preparation of:



The impure ester of Part A (8.06 g, 14.2 mmol theoretical) was hydrolyzed in 15 mL of ethanol, 15 mL of 1,4-dioxane and 9.5 mL of 6 N NaOH at 60°C. The solution was poured into water and extracted with ether to remove color. Acidification with 1N HCl caused precipitation of the acid which was collected by filtration and washed with water and hexane then dried under high vacuum yielding the acid as an off white solid (5.90 g, 76.8 % yield). NMR (CD_3OD w/ K_2CO_3) δ 2.00 (q, 2H), 2.07-2.19 (m, 4H), 2.32 (d, 2H), 2.48 (t, 2H), 2.79 (d, 2H), 2.91 (d, 2H), 3.45 (t, 2H), 4.06 (t, 2H), 7.04 (d, 2H), 7.20 (d, 2H), 7.29-7.35 (m, 1H), 7.40 (s, 1H), 7.78 (d, 2H).

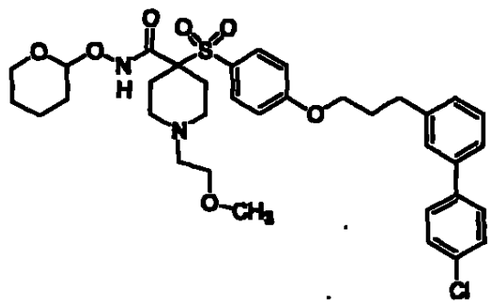
[1020] Part C. Preparation of:



To the acid of Part B (5.90, 10.9 mmol), EDC (2.9 g, 15.3 mmol), and HOBt (2.5g, 16.4 mmol) in anhydrous NMP (33 mL) was added triethylamine (4.5 mL, 32.7 mmol). After heating at 60°C for 1 hr, THP-hydroxylamine (1.9 g, 16.4 mmol) was added. The solution was stirred for 18 hr at 60°C, additional EDC (2.9 g, 15.3 mmol), HOBt (2.5g, 16.4

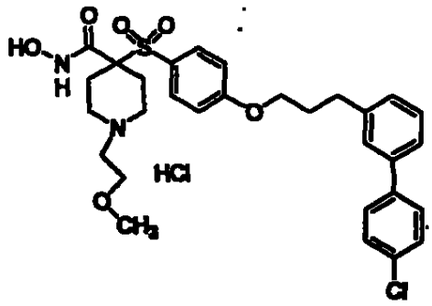
mmol), triethylamine (4.5 mL, 32.7 mmol) and THP-hydroxylamine (1.9 g, 16.4 mmol) were added. After 2 hr, the reaction was diluted with water (300 mL) and extracted with ethyl acetate (3x150 mL). The combined organics were washed with brine and dried over magnesium sulfate. Silica gel Chromatography (ethyl acetate/hexanes) provided the protected hydroxamate as a viscous impure colorless oil (5.70 g). ESMS $m/z = 641$ $(M+H)^+$.

[1021] Part D. Preparation of:



In a vial were combined the aryl bromide from Part C (0.50 g, 0.78 mmol) in 3 mL of dimethoxyethyl ether, 4-chlorobenzeneboronic acid (185 mg, 1.17 mmol), palladium tetrakistriphenylphosphine (~45 mg, 0.04 mmol) and 2M cesium carbonate (1.17 mL, 2.34 mmol). Mixture stirred vigorously at 80°C for 18 hr. Reaction poured onto 2 mL Chem-Elut tube prewetted with 3 mL of water and eluted with ethyl acetate and methylene chloride. Purification by reverse phase chromatography (acetonitrile/water/0.05% TFA) gave the TFA salt of the deprotected material (239.6 mg) which was carried on as is.

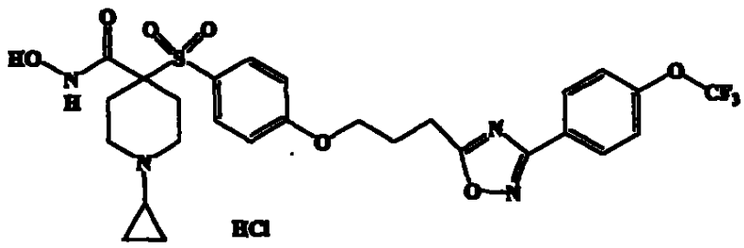
[1022] Part E. Preparation of:



The product from Part D (239.6 mg) was taken up in 4M hydrochloric acid in 1,4-dioxane (2 mL) and methanol (1-2 mL) and stirred for 0.5 hr then concentrated. This was repeated. Product crashed out of solution, was collected by filtration, washed with diethyl ether and

dried under high vacuum yielding the title compound as colorless solid (170.5 mg, 35% over two steps). ESMS $m/z = 587$ $(M+H)^+$. HRMS calcd. for $C_{30}H_{36}ClN_7O_6S$: 587.1977 $(M+H)^+$. Found: 587.1979.

[1023] **Example 51. Preparation of 1-cyclopropyl-N-hydroxy-4-{[4-(3-{3-[4-(trifluoromethoxy) phenyl]-1,2,4-oxadiazol-5-yl}propoxy)phenyl]sulfonyl}piperidine-4-carboxamide hydrochloride.**



[1024] **Part A.** In dry equipment under nitrogen, potassium trimethylsilanolate (35.9 g, 0.28 mol) was dissolved in dimethylsulfoxide (250 mL) and gamma-butyrolactone (16.14 mL, 0.21 mol) was added over 10 min while the reaction temperature rose to 38°C. After stirring at ambient temperature for 40 min, sodium hydride (8.4 g of a 60% oil dispersion, 0.21 mol) was added portion wise over 20 min and the reaction temperature rose to 43°C. Gas evolution was also observed. After stirring at ambient temperature for 50 min, a solution of ethyl 1-cyclopropyl-4-[(4-fluorophenyl)sulfonyl]-4-piperidinecarboxylate (49.7g, 0.14 mol) in dimethylsulfoxide (50 mL) was added over 10 min as the reaction temperature rose to 38°C. The reaction was stirred at ambient temperature for 30 min. The slurry was slowly poured into ice water (1.5 L) and then extracted with hexanes (150 mL) 3 times followed by a diethyl ether extraction (300 mL). The aqueous layer was chilled to 5°C and the pH adjusted to 6 with concentrated hydrochloric acid. The slurry was filtered and the cake washed with 500 mL water two times. The solid was dried *in vacuo* to give the butyric acid as a white solid (47.5 g, 77%). LCMS $m/z = 440$ $[M+H]^+$.

[1025] **Part B.** In dry equipment under nitrogen, the butyric acid from Part A (3.07 g, 7.0 mmol) was dissolved in dry dimethylacetamide (15 mL) and the remaining reagents were added to the solution in the following order: N-hydroxybenzotriazole hydrate (1.42 g, 10.5 mmol), triethylamine (1.95 mL, 14.0 mmol), 4-

(trifluoromethoxy)benzamidoxime (2.31 g, 10.5 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (2.68 g, 14.0 mmol). Additional dry dimethylacetamide (5 mL) was added. After 24 hr at 70°C, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water, saturated $NaHCO_3$, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/methanol/hexanes) provided the oxadiazole as a light white solid (3.38 g, 78%). LCMS *m/z* = 624$[M+H]^+$.

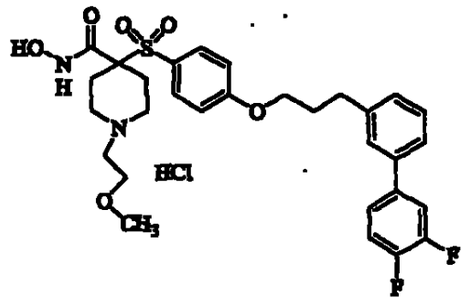
[1026] **Part C.** A slurry of the oxadiazole from Part B (3.36 g, 5.39 mmol), 2.5N sodium hydroxide (6.5 mL, 16.2 mmol) and sodium hydroxide (0.86 g, 21.6 mmol) in isopropanol (27 mL) was stirred at 75°C for 5 hr. The heat was removed and the reaction diluted with water (50 mL) and chilled to5°C. The pH was adjusted to 7 with concentrated hydrochloric acid. The solids were filtered, washed with hexanes, and dried *in vacuo* to give the carboxylic acid as a white solid (3.1 g, 97%). LCMS *m/z* = 596 $[M+H]^+$.

[1027] **Part D.** In dry equipment under nitrogen, the carboxylic acid from Part C (2.9 g, 4.87 mmol) was dissolved in dry dimethylacetamide (10 mL) and the remaining reagents were added to the solution in the following order: N-hydroxybenzotriazole hydrate (0.99 g, 7.3 mmol), triethylamine (2.03 mL, 14.6 mmol), O-(tetrahydro-2H-pyran-2-yl)hydroxylamine (0.86 g, 7.31 mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.87 g, 9.75 mmol). Additional dry dimethylacetamide (5 mL) was added. After 29 hr at 40°C, the reaction was concentrated *in vacuo*. The residue was taken up in ethyl acetate, washed with water, saturated $NaHCO_3$, saturated sodium chloride solution, dried over Na_2SO_4, filtered, and concentrated *in vacuo*. Chromatography (on silica, ethyl acetate/methanol/hexanes) provided the THP hydroxamate as a white foam (1.48 g, 44%). LCMS *m/z* = 695 $[M+H]^+$.

[1028] **Part E.** To the THP hydroxamate from Part D (1.4 g, 2.02 mmol) was added 4N HCl dioxane solution (5 mL, 20.2 mmol) and methanol (0.5 mL). The slurry became very thick. Diethyl ether (50 mL) was added to and after 1 hr at ambient temperature the reaction was filtered under nitrogen. The solids were washed with diethyl ether (150 mL) under nitrogen and dried *in vacuo* over phosphorus pentoxide to give the title compound as a white solid (1.4 g, 100%). HRMS (ES+) $M+H^+$ calculated for $C_{27}H_{29}N_4O_7S_1F_3$ 611.1787, found 611.1773.

327

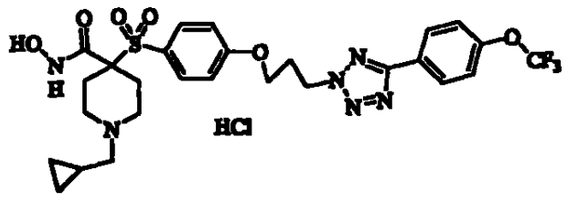
[1629] **Example 52. Preparation of:**



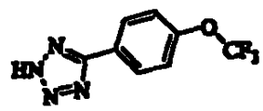
[1630] **Part A.** In a vial were combined the aryl bromide from Part C of Example 50 (0.50 g, 0.78 mmol) in 3 mL of dimethoxyethyl ether, 3,4-difluorobenzeneboronic acid (185 mg, 1.17 mmol), palladium tetrakistriphenylphosphine (~45 mg, 0.04 mmol) and 2M cesium carbonate (1.17 mL, 2.34 mmol). Mixture stirred vigorously at 80°C for 18 hr. Reaction poured onto 2 mL Chem-Elut tube prewetted with 3 mL of water and eluted with ethyl acetate and methylene chloride. Purification by reverse phase chromatography (acetonitrile/water/0.05% TFA) gave the TFA salt of the deprotected material (354.8 mg) which was carried on as is.

[1631] **Part B.** The product from Part D (354.8 mg) was taken up in 4M hydrochloric acid in 1,4-dioxane (2 mL) and methanol (1-2 mL) and stirred for 30 min and then concentrated. This was repeated. Product crashed out of solution, was collected by filtration, washed with diethyl ether and dried under high vacuum yielding the title compound as a colorless solid (298.0 mg, 61% over two steps). ESMS m/z = 589 $(M+H)^+$. HRMS calcd. for $C_{30}H_{35}F_2N_2O_6S$: 589.2178 $(M+H)^+$. Found: 589.2192.

[1632] **Example 53. Preparation of:**



[1633] **Part A.** Preparation of:



328

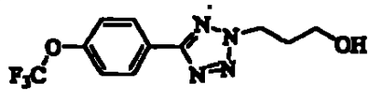
A mixture of lithium chloride (1.71 g, 40.3 mmol), trifluoromethoxy-benzonitrile(5.00 g, 26.7 mmol), and sodium azide(1.75 g, 26.7 mmol) in 2-methoxyethanol(26 mL) under an N_2 atmosphere was refluxed for 4 hr. The ambient mixture was poured into a mixture of ice (84 g) and concentrated hydrochloric acid (8.4 mL), and then stirred until the ice melted. The resulting white solid was collected by filtration, washed with water, and dried for 2 hr in a 40°C vacuum oven to provide the tetrazole in the form of an off white solid (4.86 g, 79% yield). MS MH^+ calcd. for $C_8H_6N_4OF_3$ 231, found 231.

[1034] Part B. Preparation of:



A solution of the tetrazole of Part A (2.00 g, 8.69 mmol) in NMP (12 mL) was added dropwise to an ambient mixture of 95% sodium hydride (0.438 g, 18.2 mmol) in NMP (12 mL) under an N_2 atmosphere. After an 1 hr of stirring, 2-(3-chloropropoxy)tetrahydro-2H-pyran(1.58 mL, 9.56 mmol) was added dropwise. The mixture was stirred at ambient temperature for 18 hr and then at 70°C for 2 hr. The mixture was diluted with a solution of water (200 mL) and saturated $NaHCO_3$ (100 mL), and extracted with ethyl acetate (3x100 mL). The organic layer was washed with water (2x100 mL) and brine(100 mL), dried over $MgSO_4$, and concentrated *in vacuo* to give a yellow liquid. Flash chromatography purification (ethyl acetate-hexane/silica gel) provided the pyran in the form of a white solid (1.46 g, 45% yield). Anal. Calcd. for $C_{16}H_{19}N_4O_3F_3$: C,56.34; H, 5.98; N, 7.73; S, 4.42. Found C,56.13; H, 6.08; N, 7.65; S, 4.75.

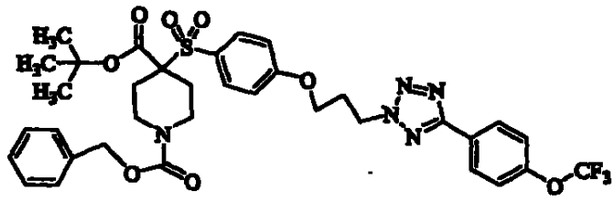
[1035] Part C. Preparation of:



To an ambient solution of the pyran of Part B (1.40 g, 3.76 mmol) in MeOH (13.5 mL) was added a solution of acetyl chloride (0.896 mL, 13.1 mmol) in MeOH (13.5 mL). After 15 min, the solution was concentrated *in vacuo* to provide the alcohol in the form of a solid (1.02 g, 94% yield). MS MH^+ calcd. for $C_{11}H_{12}N_4O_2F_3$ 289, found 289.

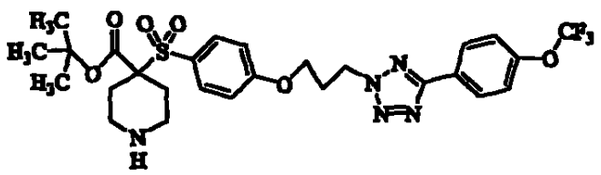
329

[1036] **Part D.** Preparation of:



To an ambient mixture of 95% sodium hydride (0.923g, 38.5 mmol) in NMP (16 mL) under an N_2 atmosphere was added dropwise a solution of the alcohol of Part C (8.00 g, 27.7 mmol) in NMP(16 mL), and the mixture was stirred at ambient temperture for 35 minutes. A solution of 1-benzyl 4-tert-butyl 4-[(4-fluorophenyl)sulfonyl]piperidine-1,4-dicarboxylate (12.5 g, 26.3 mmol) in NMP (16 mL) was added dropwise to the reaction mixture. After 3 hr at 55°C, the ambient mixture was diluted with water (700 mL) and extracted with ethyl acetate (3x150 mL). The organic layer was washed with water (2x100 mL) and brine (100 mL), dried over $MgSO_4$, and concentrated *in vacuo* to produce a yellow oil (18.6 g). Chromatography purification (hexane-EA/silica gel) provided the sulfone as a yellow oil (10.1 g, 52% yield). MS MH^+ calcd. for $C_{35}H_{39}N_5O_8SF_3$ 746, found 746. Anal. Calcd. for $C_{35}H_{38}N_5O_8SF_3$ C,56.37; H, 5.14; N, 9.39; S, 4.30. Found C,56.22; H, 4.96; N, 9.22; S, 4.37.

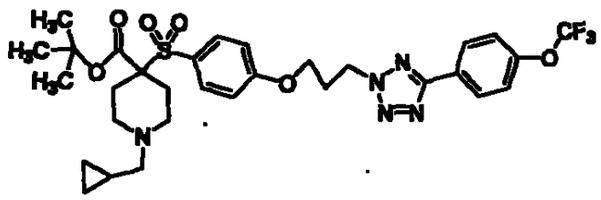
[1037] **Part E.** Preparation of:



A mixture of the sulfone of Part D (10.0 g, 13.4 mmol) and 10% palladium on carbon (1.43g, 1.34 mmol) in methanol (50 mL) was placed under an H_2 atmosphere with a balloon at ambient temperature for 20 hr. The mixture was filtered through a bed of celite and concentrated *in vacuo* to provide the piperidine in the form of a pale yellow oil (7.57 g, 92%). The proton NMR spectrum was consistent for the desired compound.

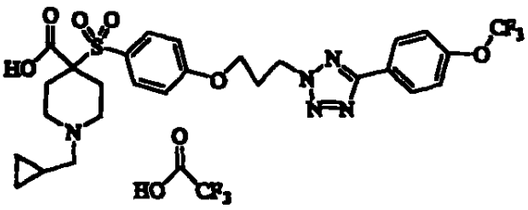
330

[1038] Part F. Preparation of:



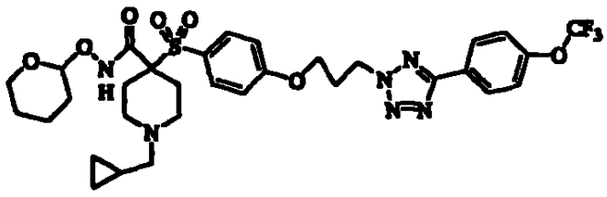
A mixture of the piperidine of Part E (3.50 g, 5.72 mmol), (bromomethyl)cyclopropane (0.67 mL,6.87 mmol), and potassium carbonate (2.38 g, 17.2 mmol) in DMF (15 mL) was stirred at ambient temperature for 20 hr under an N_2 atmosphere. The mixture was diluted with water (700 mL) and extracted with ethyl acetate (3x100 mL). The organic layer was washed with water (2x75 mL) and brine (75 mL), dried over $MgSO_4$, and concentrated *in vacuo* to produce a yellow oil. Flash chromatography purification (hexane-EA/silica gel) provided the alkylpiperidine in the form of a colorless oil(2.08 g, 55% yield): MS MH^+ calcd. for $C_{31}H_{39}N_5O_6SF_3$ 666, found 666. Anal. Calcd. for $C_{31}H_{38}N_5O_6SF_3$: C,55.93; H, 5.75; N, 10.52; S, 4.82. Found C,55.85; H, 5.91; N, 10.25; S, 4.99.

[1039] Part G. Preparation of:



A solution of the alkylpiperidine of Part F (2.00 g, 3.00 mmol) in trifluoroacetic acid (10 mL, 130 mmol) was stirred at ambient temperature for 1.7 hr. The mixture was concentrated *in vacuo*, triturated twice with ether, and dried in a 40°C vacuum to provide the acid as a white solid (2.21 g, 102%). MS MH^+ calcd. for $C_{27}H_{31}N_5O_6SF_3$ 610, found 610.

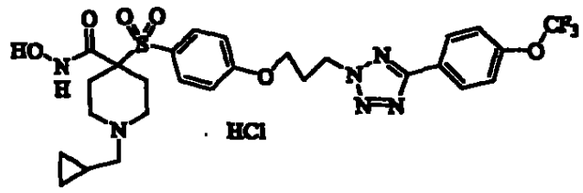
[1040] Part H. Preparation of:



331

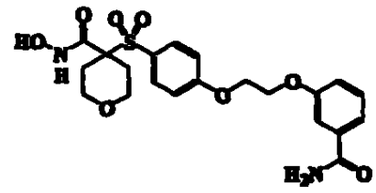
A mixture of the crude acid of Part G (2.10 g, 3.44 mmol), 1-hydroybenzotriazole hydrate(0.820 g, 6.07 mmol), triethylamine(5.57mL, 39.9 mmol), O-(tetrahydro-2H-pyran-2-yl)hydroxylamine(0.835 g, 7.13mmol), and 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (1.37 g, 7.13 mmol) in DMF (35 mL) under an N_2 atmosphere was stirred at ambient temperature for 20 hr. The mixture was diluted with water (700 mL) and extracted with ethyl acetate (3x200 mL). The organic layer was washed with water (2x100 mL) and brine (100 mL), dried over $MgSO_4$, and concentrated *in vacuo* to produce a yellow foam. Chromatography purification ($MeOH-CH_2Cl_2$/silica gel) produced the O-protected hydroxamate in the form of a white foam (1.60 g, 66%). MS MH^+ calcd. for $C_{32}H_{40}N_6O_7F_3S$ 709, found 709.

[1041] Part I. Preparation of:

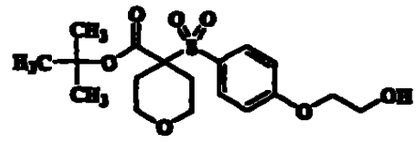


A solution of the O-protected hydroxamate of Part H (1.50 g, 2.12 mmol) and acetyl chloride(0.677 mL, 10.2 mmol) in methanol (23 mL) was stirred at ambient temperature for 1 hr. The solution was diluted with ether and a solid formed. The solid was isolated by filtration, washed with ether, and dried in a 40°C vacuum oven to produce the title compound as a white solid (1.55 g, 82% yield). Anal. Calcd. for $C_{27}H_{31}N_6O_6F_3S \cdot HCl$: C, 49.05; H, 4.88; N, 12.71; Cl, 5.36; S, 4.85. Found C, 48.94; H, 4.72; N, 12.71; Cl, 5.29; S, 4.94

[1042] Example 54. Preparation of:



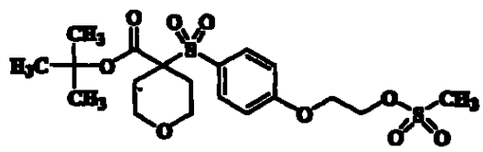
[1043] Part A. Preparation of:



332

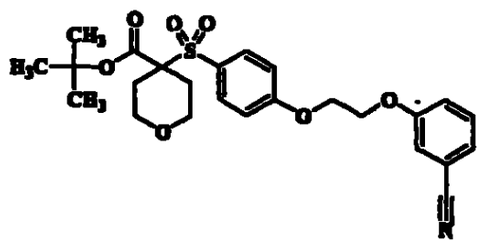
To a solution of tert-butyl 4-[(4-fluorophenyl)sulfonyl]tetrahydro-2H-pyran-4-carboxylate (5.0 g, 14.6 mmol) and cesium carbonate (14.3 g, 43.8 mmol) in anhydrous DMSO (30 mL) was added ethylene glycol (8.1 mL, 146 mmol). The resulting reaction mixture was stirred at 80°C for 3 hr. After cooling to room temperature, the mixture was poured into water (350 mL) and extracted with ethyl acetate (3x). The organics were washed with brine and dried over magnesium sulfate. Silica gel chromatography (ethyl acetate/methylene chloride) provided the alcohol as a colorless solid (2.33 g, 41%). NMR($CDCl_3$) δ 1.45 (s, 9H), 2.13-2.20 (m, 4H), 3.22-3.33 (m, 2H), 3.94-4.03 (m, 4H), 4.16 (q, 2H), 7.02 (d, 2H), 7.73 (d, 2H). ESMS *m/z* = 404 $(M+NH4)^+$. HRMS calcd. for $C_{18}H_{26}O_7S\ NH_4$: 404.1743 $(M+NH_4)^+$. Found: 404.1734.

[1644] Part B. Preparation of:



To a solution of the alcohol from Part A (0.50 g, 1.3 mmol) in CH_2Cl_2 (2.5 mL) was added triethylamine (0.24 mL g, 1.7 mmol), followed by mesyl chloride. The resulting mixture was stirred at room temperature for 1.5 hr. The mixture was diluted with methylene chloride and washed with 10% citric acid, washed with 5% sodium bicarbonate, washed with brine, and dried over $MgSO_4$. Concentration produced the desired compound in the form of a tan solid (0.62 g, 100%). NMR($CDCl_3$) 1.45 (s, 9H), 2.13-2.22 (m, 4H), 3.07 (s, 3H), 3.22-3.37 (m, 2H), 4.00 (dt, 2H), 4.32-4.37 (m, 2H), 4.58-4.62 (m, 2H), 7.02 (d, 2H), 7.75 (d, 2H). ESMS *m/z* = 482 $(M+NH4)^+$.

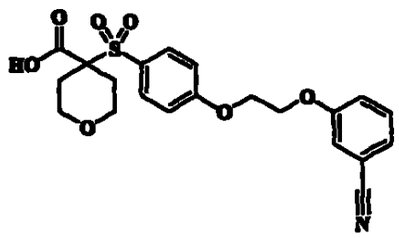
[1645] Part C. Preparation of:



To a solution of 60% sodium hydride (39 mg, 0.98 mmol) in anhydrous dimethylformamide (2.5 mL) was added 3-cyanophenol (108 mg, 0.91 mmol). After stirring for 15 min, solution was clear. The mesylate from Part B (0.30 g, 0.65 mmol) in

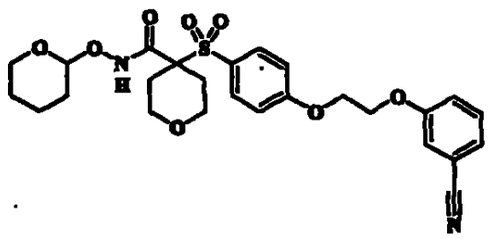
anhydrous dimethylformamide (1 mL) was added. After completion of the addition, the mixture as stirred at ambient temperature overnight. The next morning, the mixture was poured onto a 10 mL Chem-Elut tube, prewetted with 5 mL of water, and eluted with ethyl acetate and CH_2Cl_2. Chromatography (silica gel with ethyl acetate/hexane) produced the desired ester (0.27 g, 85%). NMR ($CDCl_3$) δ1.46 (s, 9H), 2.17-2.21 (m, 4H), 3.22-3.36 (m, 2H), 3.98 (dt, 2H), 4.35-4.43 (m, 4H), 7.04 (d, 2H), 7.15-7.20 (m, 2H), 7.28 (dt, 1H), 7.39 (t, 1H), 7.74 (d, 2H). ESMS *m/z* = 505 $(M+NH4)^+$. HRMS calcd. for $C_{25}H_{33}N_2O_7S$: 505.2008 $(M+NH_4)^+$. Found: 505.2019.

[1046] Part D. Preparation of:



The ester of Part C (0.24 g, 0.49 mmol) was hydrolyzed in 5 mL of methylene chloride and 5 mL of trifluoroacetic acid. Concentration and drying under high vacuum produced the desired acid (0.21 g, 100%). NMR (CD_3OD w/ K_2CO_3) δ 2.01-2.11 (m, 2H), 2.20 (d, 2H), 3.32-3.42 (m, 2H), 3.95 (dt, 2H), 4.38-4.45 (m, 4H), 7.13 (d, 2H), 7.26-7.34 (m, 3H), 7.45 (t, 1H), 7.76 (d, 2H). ESMS *m/z* = 449 $(M+NH4)^+$. HRMS calcd. for $C_{21}H_{21}NO_7S$ NH_4: 449.1382 $(M+NH_4)^+$. Found: 449.1407.

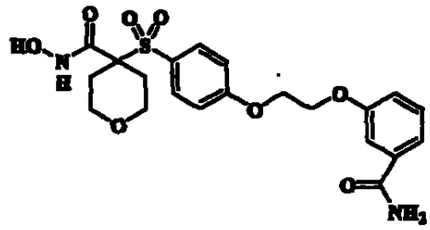
[1047] Part E. Preparation of:



To a slurry of the acid of Part D (0.20 g, 0.46 mmol), HOBt (76 mg, 0.55 mmol), and EDC (130 mg, 0.68 mmol) was added triethylamine (1.4 mmol) and THP-hydroxylamine (167 mg, 1.4 mmol) in a flask under N_2 in 2 mL anhydrous DMF. The resulting mixture was stirred at 40°C overnight. The next morning, the mixture was poured onto 10 mL Chem-Elut tube prewetted with 6 mL of water and eluted with ethyl acetate and CH_2Cl_2.

Chromatography (silica gel, ethyl acetate/hexane) produced the product as a colorless oil (0.18 g, 74%).

[1048] Part F. Preparation of:



To the product from Part E (0.18 g, 0.34 mmol) in methanol (1-2 mL) was added 4M HCl in 1,4-dioxane (2.5 mL). The resulting mixture was stirred overnight. Reverse phase chromatography (water/acetonitrile/0.05% TFA) produced the desired compound as a colorless crystalline solid (25.0 mg 16 %). NMR(DMSO) δ 1.82-1.98 (m, 2H),2.15-2.30 (m, 2H), 3.15, (t, 2H), 3.86 (d, 2H), 4.44 (d, 4H), 7.10-7.25 (m, 3H), 7.38 (t, 1H), 7.44-7.52 (m, 2H), 7.68 (d, 2H).ESMS *m/z* = 465 $(M+H)^+$. HRMS calcd. for $C_{21}H_{25}N_2O_8S$: 465.1332 $(M+H)^+$. Found: 465.1354.

[1049] **Examples 55-89. *In Vitro* MMP Inhibition Analysis**

[1050] Several hydroxamates and salts thereof were analyzed in *in vitro* assays to determine their ability to inhibit the MMP cleavage of peptide substrates. Inhibition (K_i) and IC_{50} constants were calculated from the assayed hydroxamate-MMP interactions.

[1051] Human recombinant MMP-1, MMP-2, MMP-9, MMP-13, and MMP-14 were used in this assay. All enzymes were prepared in Assignee's laboratories following usual laboratory procedures. Protocols for the preparation and use of these enzymes are available in the scientific literature. *See, e.g., Enzyme Nomenclature* (Academic Press, San Diego, CA, 1992) (and the citations therein). *See also*, Frije et al., *J Biol. Chem.*, 26(24), 16766-73 (1994).

[1052] The MMP-1 proenzyme was purified from the spent media of MMP-1-transfected HT-1080 cells provided by Dr. Harold Welgus of Washington University (St. Louis, MO). The protein was purified on a zinc chelating column.

[1053] The MMP-2 proenzyme was purified by gelatin Sepharose chromatography from MMP-2- transfected p2AHT2 cells provided by Dr. Gregory Goldberg of Washington University (St. Louis, MO).

[1054] The MMP-9 proenzyme was purified by gelatin Sepharose chromatography from spent media of MMP-9- transfected HT1080 cells provided by Dr. Howard Welgus of Washington University (St. Louis, MO).

[1055] The MMP-13 was obtained as a proenzyme from a full-length cDNA clone using baculovirus, as described by V.A. Luckow, "Insect Cell Expression Technology," *Protein Engineering: Principles and Practice*, pp. 183-218 (edited by J.L. Cleland et al., Wiley-Liss, Inc., 1996). The expressed proenzyme was first purified over a heparin agarose column, and then over a chelating zinc chloride column. The proenzyme was then activated by APMA for use in the assay. Further details on baculovirus expression systems may be found in, for example, Luckow et al., *J. Virol.*, 67, 4566-79 (1993). *See also*, O'Reilly et al, *Baculovirus Expression Vectors: A Laboratory Manual* (W.H. Freeman and Co., New York, NY, 1992). *See also*, King et al., *The Baculovirus Expression System: A Laboratory Guide* (Chapman & Hall, London, England, 1992).

[1056] The MMP-14 full length cDNA was provided by Dr. Gregory Goldberg of Washington University (St. Louis, MO). The catalytic domain enzyme was expressed in *E. coli* inclusion bodies, solubilized in urea, purified on a preparative C-14 reverse phase HPLC column, and then refolded in the presence of zinc acetate and purified for use.

[1057] All MMPs were activated using 4-aminophenylmercuric acetate ("APMA", Sigma Chemical, St. Louis, MO) or trypsin. MMP-9 also was activated using human recombinant MMP-3 (purified in Assignee's laboratory following standard cloning and purification techniques).

[1058] Two fluorogenic, methoxycoumarin-containing polypeptide substrates were used in the MMP inhibition assays:

MCA-ProLeuGlyLeuDpaAlaArgNH$_2$

(I)

MCA-ArgProLeuGlyLeuDpaAlaArgGluArgNH$_2$

(II)

Here, "Dpa" is 3-(2,4-dinitrophenyl)-L-2,3-diaminopropionyl group, and "MCA" is 7-methoxycoumarin-4-yl acetyl. Substrate (I) was purchased from Bachem (Redwood City, CA), and substrate II was prepared Assignee's laboratory. Substrate I was used in the IC_{50} determination assays, while substrate II was used in the K_i determination assays. In the absence of MMP inhibitory activity, either substrate is cleaved at the Gly-Leu

peptide bond. This cleavage separates the highly fluorogenic peptide from the 2,4-dinitrophenyl quencher, thus resulting in increase of fluorescent intensity.

[1059] The stock solutions of the assayed hydroxamates (or salts thereof) were prepared in 1% dimethyl sulfoxide (DMSO). These stock solutions were diluted in Buffer A (100 mM Tris-HCl, 100 mM NaCl, 10 mM $CaCl_2$, 0.05% polyoxyethylene 23 lauryl ether, pH 7.5) to obtain solutions with different hydroxamate concentrations, *i.e.*, assay solutions with different concentrations of the assayed MMP inhibitory compound. The experiment controls contained the same amount of Buffer A/DMSO as the assayed sample, but contained no hydroxamate (or salt thereof).

[1060] The assays from which the IC_{50} determinations were made were performed as follows. The MMPs were activated with either trypsin or APMA (4-aminophenylmercuric acetate, Sigma Chemical, St. Louis, MO). The assayed hydroxamate samples were incubated in Microfluor™ White Plates (Dynatech, Chantilly, VA) and analyzed on a Perkin Elmer L550 plate reader (Norwalk, CT). The excitation wavelength was 328 nm, and the emission wavelength – 415 nm. All samples (assayed hydroxamates and controls) were incubated in separate plates at room temperature in the presence of 4 μM of MMP substrate (I). As stated in the previous paragraph, samples containing varying concentrations of the same assayed hydroxamate were prepared. Inhibition was measured as a reduction in fluorescent intensity as a function of MMP inhibitor concentration.

[1061] The assays from which the K_i determinations were made were performed as follows. The assayed hydroxamate samples were incubated in separate wells of untreated white polystyrene plates (Nunc Nalgene International, Rochester, NY), and analyzed on a Tecan SpectraFlour Plus plate reader. The excitation wavelength was 330 nm, and the emission wavelength – 420 nm. All samples (assayed hydroxamates and controls) were incubated in separate plate wells at room temperature for 1 hr in the presence of 4 μM of MMP substrate (II). In the absence of MMP inhibitory activity, substrate II was cleaved at the Gly-Leu bond resulting in an increase of relative fluorescence. Inhibition was observed as a reduced rate of this increase in relative fluorescence. The various hydroxamates were analyzed using a single low enzyme concentration with a single substrate concentration fixed at or below the K_m. This protocol is a modification of method by Knight et al., *FEBS Lett.*, 296(3), 263-266 (1992). Apparent inhibitory

constants were determined by non-linear regression of reaction velocity as a function of inhibitor and enzyme concentration using Morrison's equation, as described by Kuzmic, Anal. Biochem. 286, 45-50 (2000). Modifications were made in the non-linear regression method to allow a common control reaction rate and effective enzyme concentration to be shared between all dose-response relationships on a given assay plate. Since the substrate concentration was chosen to be at or below the K_m, the apparent K_i's from this analysis were reported as K_i's without correction for the influence of substrate.

[1062] The above protocols were used to determine IC50 constants and K_i values values for several of the compounds in Examples 1-52 above. The results are shown in Table 5. All values in Table 5 are given in nM units. The K_i measurements are in parenthesis.

Table 5

Ex. #	Compound	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
55	Example 17		550		1.6	
56	Example 18	>10000	537	6000	1.8	>10000
57	Example 19	>10000	9000	5190	15	>10000
58	Example 20	>10000	1.8	498	1.8	>10000
59	Example 21	>10000	450	>10000	3.5	>10000
60	Example 22	>10000	1000	>10000	4.9	>10000
61	Example 25	>10000	247.2	8498	1.8	>10000
62	Example 26	>10000	52.0	4429	3.4	>10000
63	Example 27	>10000	83.9	9366	0.2	>10000
64	Example 28	>10000	76.4	3710	7.0	>10000
65	Example 30	>10000	22.6	809	1.3	>10000
66	Example 31	>10000 (>10000)	346.3 (412.93)	5651 (1596.8)	2.1 (1.503)	>10000 (>10000)
67	Example 32	>10000	217.7	4076	0.8	>10000
68	Example 33	>10000	16	7.9	1	4936
69	Example 34	429	36.6	>10000	3.0	>10000
70	Example 35	>10000	600	>10000	3	>10000
71	Example 36		95		2.4	
72	Example 37	8708	30.3	449	1.4	>10000
73	Example 38	>10000 (>10000)	157.5	1026.3 (369.98)	0.9 (6.55)	>10000 (4451.2)
74	Example 39	(>10000)	1299 (1640)	(2360)	0.9 (3.04)	(>10000)
75	Example 40	>10000 (>10000)	112.4 (215.98)	413 (585.44)	0.5 0.58)	>10000 (>10000)

Ex. #	Compound	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
76	Example 41	>10000 (>10000)	357.5 (414.99)	1597 (1465.7)	2.0 (1.056)	>10000 (>10000)
77	Example 42	>10000 (>10000)	100.3 (186.28)	382.5 (661.7)	0.3 (0.486)	>10000 (>10000)
78	Example 43	>10000	4.8	1.0	1.0	2084
79	Example 44	>10000	133.2	154.5	1.4	4976
80	Example 45	(>10000)	(224.78)	(499.18)	(0.62)	(>10000)
81	Example 46	>10000 (>10000)	320.9 (786.36)	1966 (417.51)	3.1 (2.29)	>10000 (>10000)
82	Example 47	(>10000)	18.2 (19.15) (46.49)	(118.75) (308.77)	0.2 (0.304) (0.423)	(3317.66) (5293)
83	Example 48	>10000 (>10000)	104.6 (227.54)	4450.3 (159.2)	0.2 (0.127)	>10000 (>10000)
84	Example 49	>10000 (>10000)	273.9 (439.76)	4056 (1947.90)	0.3 (0.439)	>10000 (>10000)
85	Example 50	(>10000)	(1127.89)	(304.41)	(0.60)	(>10000)
86	Example 51	>10000 (5160.20)	251.6 (93.68)	7983 (98.72)	0.2 (1.697)	>10000 (687.93)
87	Example 52	(>10000)	(542.89)	(617.14)	(0.81)	(>10000)
88	Example 53	>10000 (>10000)	383.5 (697)	75.5 (2900)	1.0 (0.662)	>10000 - (>10000)
89	Example 54	(>10000)	35.5 (64.8)	(388)	10.5	(4120)

[1863] **Example 90.** ***In Vivo*** **Angiogenesis Assay**

[1864] The study of angiogenesis depends on a reliable and reproducible model for the stimulation and inhibition of a neovascular response. The corneal micropocket assay provides such a model of angiogenesis in the cornea of a mouse. *See, A Model of Angiogenesis in the Mouse Cornea*; Kenyon,BM, et al., Investigative Ophthalmology & Visual Science, July 1996, Vol. 37, No. 8.

[1865] In this assay, uniformLy sized Hydron™ pellets containing bFGF and sucralfate are prepared and surgically implanted into the stroma mouse cornea adjacent to the temporal limbus. The pellets are formed by making a suspension of 20 μL sterile saline containing 10 μg recombinant bFGF, 10 mg of sucralfate and 10 μL of 12 percent Hydron™ in ethanol. The slurry is then deposited on a 10 x 10 mm piece of sterile nylon mesh. After drying, the nylon fibers of the mesh are separated to release the pellets.

[1066] The corneal pocket is made by anesthetizing a 7 week old C57Bl/6 female mouse, then proptosing the eye with a jeweler's forceps. Using a dissecting microscope, a central, intrastromal linear keratotomy of approximately 0.6 mm in length is performed with a #15 surgical blade, parallel to the insertion of the lateral rectus muscle. Using a modified cataract knife, a lamellar micropocket is dissected toward the temporal limbus. The pocket is extended to within 1.0 mm of the temporal limbus. A single pellet is placed on the corneal surface at the base of the pocket with a jeweler's forceps. The pellet is then advanced to the temporal end of the pocket. Antibiotic ointment is then applied to the eye.

[1067] Mice are dosed on a daily basis for the duration of the assay. Dosing of the animals is based on bioavailability and overall potency of the compound. An exemplary dose is 10 or 50 mg/kg (mpk) bid, po. Neovascularization of the corneal stroma is permitted to continue under the influence of the assayed compound for 2 days. At that point, the degree of angiogenic inhibition is scored by viewing the neovascular progression with a slit lamp microscope.

[1068] The mice are anesthetized and the studied eye is once again proptosed. The maximum vessel length of neovascularization, extending from the limbal vascular plexus toward the pellet is measured. In addition, the contiguous circumferential zone of neovascularization is measured as clock hours, where 30 degrees of arc equals one clock hour. The area of angiogenesis is calculated as follows.

$$\text{area} = \frac{(0.4 \times \text{clock hours} \times 3.14 \times \text{vessel length (in mm)})}{2}$$

[1069] Five to six mice should be utilized for each compound in each study. The studied mice are thereafter compared to control mice and the difference in the area of neovascularization is recorded as an averaged value. Each group of mice so studied constitutes an "n" value of one, so that "n" values greater than one represent multiple studies whose averaged result is provided in the table. A contemplated compound typically exhibits about 25 to about 75 percent inhibition, whereas the vehicle control exhibits zero percent inhibition.

[1070] **Example 91. Tumor Necrosis Factor Assays**

[1071] **Cell Culture.**

[1072] The cells used in the assay are the human monocytic line U-937 (ATCC CRL-1593). The cells are grown in RPMI w/10% FCS and PSG supplement (R-10) and are not permitted to overgrow. The assay is carried out as follows:

[1073] 1. Count, then harvest cells by centrifugation. Resuspend the pellet in R-10 supplement to a concentration of 1.540×10^6 cells/mL.

[1074] 2. Add test compound in 65 uL R-10 to the appropriate wells of a 96-well flat bottom tissue culture plate. The initial dilution from a DMSO stock (100 mM compound) provides a 400 uM solution, from which five additional three-fold serial dilutions are made. Each dilution of 65 ul (in triplicate) yields final compound test concentrations of 100 μM, 33.3 μM, 11.1 μM, 3.7 μM, 1.2 μM and 0.4 μM.

[1075] 3. The counted, washed and resuspended cells (200,000 cells/well) in 130 μL are added to the wells.

[1076] 4. Incubation is for 45 min to 1 hr at 37°C in 5% CO_2 in a water saturated container.

[1077] 5. R-10 (65 uL)containing 160 ng/mL PMA (Sigma) is added to each well.

[1078] 6. The test system is incubated at 37°C in 5% CO2 overnight (18-20 hr) under 100% humidity.

[1079] 7. Supernatant, 150 μL, is carefully removed from each well for use in the ELISA assay.

[1080] 8. For toxicity, a 50 μL aliquot of working solution containg 5 mL R-10, 5 mL MTS solution [CellTiter 96 AQueous One Solution Cell Proliferation Assay Cat.#G358/0,1 (Promega Biotech)] and 250 ul PMS solution are added to each well containing the remaining supernatant and cells and the cells incubated at 37°C in 5% CO_2 until the color develops. The system is excited at 570 nm and read at 630 nm.

[1081] TNF Receptor II ELISA Assay

[1082] 1. Plate 100 μL/well 2 ug/mL mouse anti-human TNFrII antibody (R&D Systems #MAB226) in 1 x PBS (pH 7.1, Gibco) on NUNC-Immuno Maxisorb plate. Incubate the plate at 4°C overnight (about 18-20 hr).

[1083] 2. Wash the plate with PBS-Tween (1 x PBS w/ 0.05% Tween).

[1084] 3. Add 200 µL 5% BSA in PBS and block at 37°C in a water saturated atmosphere for 2 hr.

[1085] 4. Wash the plate with PBS-Tween.

[1086] 5. Add sample and controls (100 ul of each) to each well. The standards are 0, 50, 100, 200, 300 and 500 pg recombinant human TNFrII (R&D Systems #226-B2) in 100 µL 0.5% BSA in PBS. The assay is linear to between 400-500 pg of standard.

[1087] 6. Incubate at 37°C in a saturated atmosphere for 1.5 hr.

[1088] 7. Wash the plate with PBS-Tween.

[1089] 8. Add 100 µL goat anti-human TNFrII polyclonal (1.5 µg/mL R&D Systems #AB226-PB in 0.5% BSA in PBS).

[1090] 9. Incubate at 37°C in a saturated atmosphere for 1 hr.

[1091] 10. Wash the plate with PBS-Tween.

[1092] 11. Add 100 µL anti-goat IgG-peroxidase (1:50,000 in 0.5% BSA in PBS, Sigma #A5420).

[1093] 12. Incubate at 37°C in a saturated atmosphere for 1 hr.

[1094] 13. Wash the plate with PBS-Tween.

[1095] 14. Add 10 µL KPL TMB developer, develop at room temperature (usually about 10 min), then terminate with phosphoric acid and excite at 450 nm and read at 570 nm.

[1096] TNFα ELISA Assay.

[1097] Coat Immulon® 2 plates with 0.1 mL/well of 1ug/mL Genzyme mAb in 0.1 M NaHCO3 pH 8.0 buffer overnight (about 18-20 hr) at 4°C, wrapped tightly in Saran® wrap.

[1098] Flick out coating solution and block plates with 0.3 mL/well blocking buffer overnight at 4°C, wrapped in Saran® wrap.

[1099] Wash wells thoroughly 4X with wash buffer and completely remove all wash buffer. Add 0.1 mL/well of either samples or rhTNFα standards. Dilute samples if necessary in appropriate diluent (e.g. tissue culture medium). Dilute standard in same diluent. Standards and samples should be in triplicates.

[1100] Incubate at 37°C for 1 hr in humified container.

[1101] Wash plates as above. Add 0.1 mL/well of 1:200 dilution of Genzyme rabbit anti-hTNFa.

[1102] Repeat incubation.

[1103] Repeat wash. Add 0.1 mL/well of 1 μg/mL Jackson goat anti-rabbit IgG (H+L)-peroxidase.

[1104] Incubate at 37°C for 30 min.

[1105] Repeat wash. Add 0.1 mL/well of peroxide-ABTS solution.

[1106] Incubate at room temperature for 5-20 min.

[1107] Read OD at 405 nm.

[1108] 12 Reagents are:

Genzyme mouse anti-human TNF monoclonal (Cat.# 80-3399-01)

Genzyme rabbit anti-human TNF polyclonal (Cat.#IP-300)

Genzyme recombinant human TNF (Cat.#TNF-H).

Jackson Immunoresearch peroxide-conjugated goat anti-rabbit IgG (H+L) (Cat.#111-035-144).

Kirkegaard/Perry peroxide ABTS solution (Cat#50-66-01).

Immulon 2 96-well microtiter plates.

Blocking solution is 1 mg/mL gelatin in PBS with 1X thimerasol.

Wash buffer is 0.5 mL Tween® 20 in 1 liter ofPBS.

[1109] **Example 92.** ***In Vitro*** **Aggrecanase Inhibition Analysis**

[1110] Assays for measuring the potency (IC_{50}) of a compound toward inhibiting aggrecanase are known in the art.

[1111] One such assay, for example, is reported in European Patent Application Publ. No. EP 1 081 137 A1. In that assay, primary porcine chondrocytes from articular joint cartilage are isolated by sequential trypsin and collagenase digestion followed by collagenase digestion overnight and are plated at $2x10^5$ cells per well into 48 well plates with 5 μCi/ml ^{35}S (1000 Ci/mmol) sulphur in type 1 collagen coated plates. Cells are allowed to incorporate label into their proteoglycan matrix (approximately 1 week) at 37°C under an atmosphere of 5% CO_2. The night before initiating the assay, chondrocyte monolayers are washed 2 times in DMEM/1% PSF/G and then allowed to incubate in

fresh DMEM/1% FBS overnight. The next morning, chondrocytes are washed once in DMEM/1% PSF/G. The final wash is allowed to sit on the plates in the incubator while making dilutions. Media and dilutions are made as described in the following Table 6:

Table 6

control media	DMEM alone
IL-1 media	DMEM + IL-1 (5ng/ml)
drug dilutions	Make all compound stocks at 10 mM in DMSO. Make a 100 μM stock of each compound in DMEM in 96-well plate. Store in freezer overnight. The next day, perform serial dilutions in DMEM with IL-1 to 5 μM, 500 nM, and 50 nM. Aspirate final wash from wells and add 50 μM of compound from above dilutions to 450 μL of IL-1 media in appropriate wells of the 48 well plates. Final compound concentrations equal 500 nM, 50 nM, and 5 nM. All samples completed in triplicate with control and IL-1 alone on each plate.

Plates are labeled and only the interior 24 wells of the plate are used. On one of the plates, several columns are designated as IL-1 (no drug) and control (no IL-1, no drug). These control columns are periodically counted to monitor 35S-proteoglycan release. Control and IL-1 media are added to wells (450 μL) followed by compound (50 μL) so as to initiate the assay. Plates are incubated at 37°C with 5% CO_2 atmosphere. At 40-50% release (when CPM from IL-1 media is 4-5 times control media) as assessed by liquid scintillation counting (LSC) of media samples, the assay is terminated (about 9 to about 12 hours). Media is removed from all wells and placed into scintillation tubes. Scintillate is added and radioactive counts are acquired (LSC). To solubilize cell layers, 500 μL of papain digestion buffer (0.2 M Tris, pH 7.0, 5 mM DTT, and 1 mg/ml papain) is added to each well. Plates with digestion solution are incubated at 60°C overnight. The cell layer is removed from the plates the next day and placed in scintillation tubes. Scintillate is then added, and samples counted (LSC). The percent of released counts from the total present in each well is determined. Averages of the triplicates are made with control background

subtracted from each well. The percent of compound inhibition is based on IL-1 samples as 0% inhibition (100% of total counts).

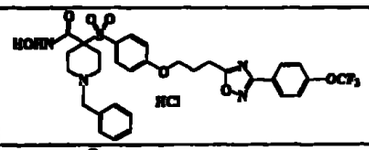
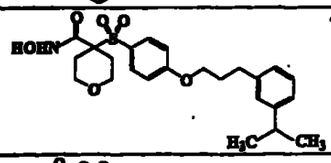
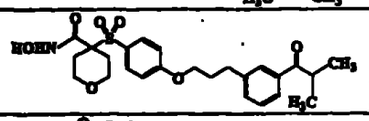
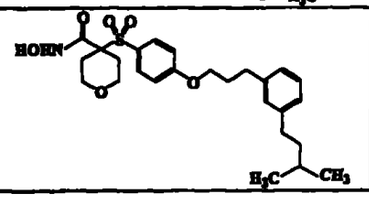
[111] Another assay for measuring aggrecanase inhibition is reported in WIPO Int'l Publ. No. WO 00/59874. That assay reportedly uses active aggrecanase accumulated in media from stimulated bovine cartilage (BNC) or related cartilage sources and purified cartilage aggrecan monomer or a fragment thereof as a substrate. Aggrecanase is generated by stimulation of cartilage slices with interleukin-1 (IL-1), tumor necrosis factor alpha (TNF-α), or other stimuli. To accumulate BNC aggrecanase in culture media, cartilage reportedly is first depleted of endogenous aggrecan by stimulation with 500 ng/ml human recombinant IL-β for 6 days with media changes every 2 days. Cartilage is then stimulated for an additional 8 days without media change to allow accumulation of soluble, active aggrecanase in the culture media. To decrease the amounts of matrix metalloproteinases released into the media during aggrecanase accumulation, agents which inhibit MMP-1, -2, -3, and -9 biosynthesis are included during stimulation. This BNC conditioned media containing aggrecanase activity is then used as the source of aggrecanase for the assay. Aggrecanase enzymatic activity is detected by monitoring production of aggrecan fragments produced exclusively by cleavage at the Glu373-Ala374 bond within the aggrecan core protein by Western analysis using the monoclonal antibody, BC-3 (Hughes, et al., *Biochem J*, 306:799-804 (1995)). This antibody reportedly recognizes aggrecan fragments with the N-terminus, 374ARGSVIL, generated upon cleavage by aggrecanase. The BC-3 antibody reportedly recognizes this neoepitope only when it is at the N-terminus and not when it is present internally within aggrecan fragments or within the aggrecan protein core. Only products produced upon cleavage by aggrecanase reportedly are detected. Kinetic studies using this assay reportedly yield a Km of 1.5+/-0.35 μM for aggrecanase. To evaluate inhibition of aggrecanase, compounds are prepared as 10 mM stocks in DMSO, water, or other solvents and diluted to appropriate concentrations in water. Drug (50 μL) is added to 50 μL of aggrecanase-containing media and 50 μL of 2 mg/ml aggrecan substrate and brought to a final volume of 200 μL in 0.2 M Tris, pH 7.6, containing 0.4 M NaCl and 40 mM $CaCl_2$. The assay is run for 4 hr at 37°C, quenched with 20 mM EDTA, and analyzed for aggrecanase-generated products. A sample containing enzyme and substrate without drug is included as a positive control and enzyme incubated in the absence of substrate serves as a measure of background.

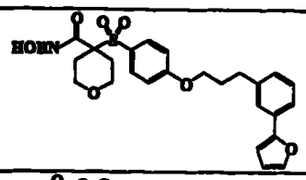
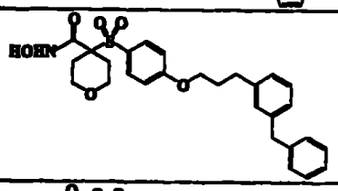
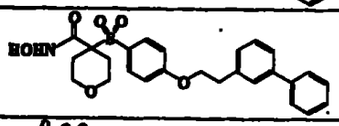
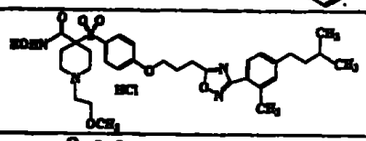
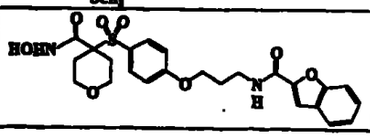
Removal of the glycosaminoglycan side chains from aggrecan reportedly is necessary for the BC-3 antibody to recognize the ARGSVIL epitope on the core protein. Therefore, for analysis of aggrecan fragments generated by cleavage at the Glu373-Ala374 site, proteoglycans and proteoglycan fragments are enzymatically deglycosylated with chondroitinase ABC (0.1 units/10 μg GAG) for 2 hr at 37°C and then with keratanase (0.1 units/10 μg GAG) and keratanase II (0.002 units/10 μg GAG) for 2 hr at 37°C in buffer containing 50 mM sodium acetate, 0.1 M Tris/HCl, pH 6.5. After digestion, aggrecan in the samples is precipitated with 5 volumes of acetone and resuspended in 30 μL of Tris glycine SDS sample buffer (Novex) containing 2.5% beta mercaptoethanol. Samples are loaded and then separated by SDS-PAGE under reducing conditions with 4-12% gradient gels, transferred to nitrocellulose and immunolocated with 1:500 dilution of antibody BC3. Subsequently, membranes are incubated with a 1:5000 dilution of goat anti-mouse IgG alkaline phosphatase second antibody and aggrecan catabolites visualized by incubation with appropriate substrate for 10-30 minutes to achieve optimal color development. Blots are quantitated by scanning densitometry and inhibition of aggrecanase determined by comparing the amount of product produced in the presence versus absence of compound.

[1113] **Examples 93-645.**

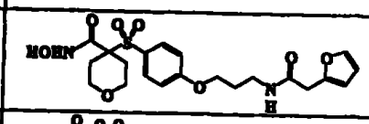
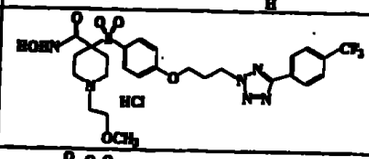
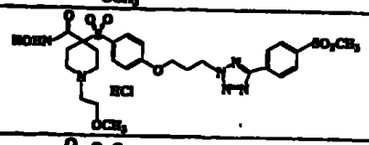
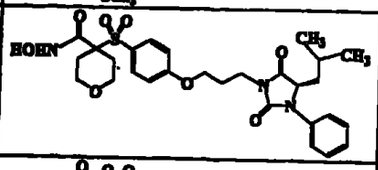
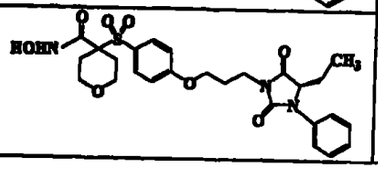
[1114] Additional hydroxamate compounds (and salts thereof) can be prepared by one skilled in the art using methods similar to those described in Examples 1-54 alone or in combination with techniques well known in the art. Such compounds include, for example, the compounds summarized in the following Table 7. Table 7 also summarizes *in vitro* MMP inhibition results obtained by Applicants with the listed hydroxamates. As with Table 5, all *in vitro* K_i and IC_{50} results in Table 7 are given in nM units. The Ki measurements are in parenthesis.

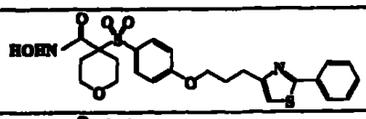
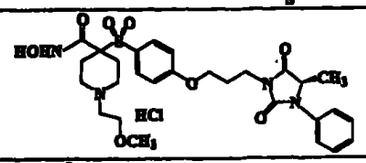
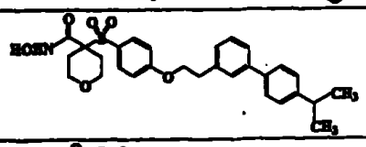
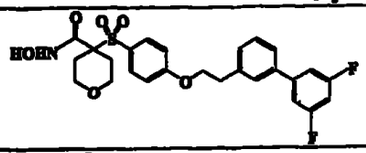
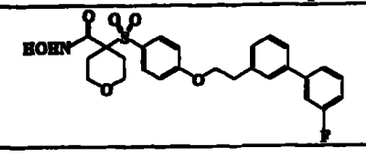
Table 7

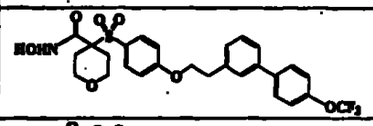
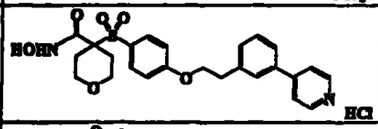
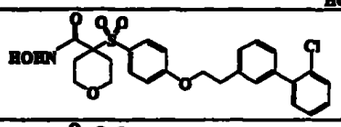
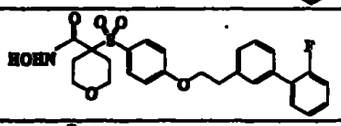
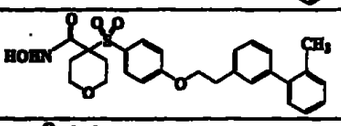
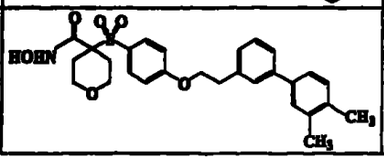
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
93				(>10000)	746.6 (676)	(1120)	15.5 (9.29)	(>10000)
94					17.8		3.7	
95				>10000 (>10000)	91.4 (149)	1204.6 (788)	2.7	>10000 (5410)
96					39.1		15.3	

Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
97		486.1586	486.1602	(7360)	185.0 (295)	(473)	3.3 (5.57)	(>10000)
98		510.1950	510.1947	>10000 (>10000)	316.2 (625)	2418 (1450)	1.8 (9.15)	>10000 (>10000)
99		482.1637	482.1661	>10000	245.8	3435	0.4	>10000
100					1691.4		152.6	
101		503.1480	503.1465		18.2		0.2	

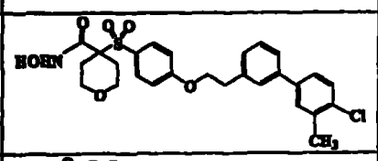
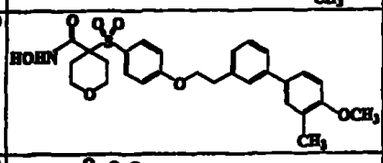
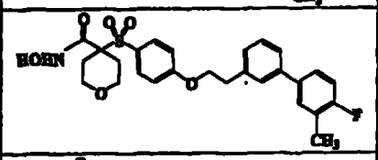
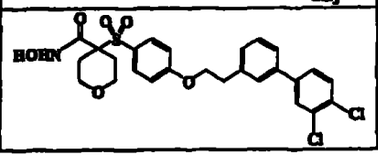
WO 02/092588 PCT/US02/15257

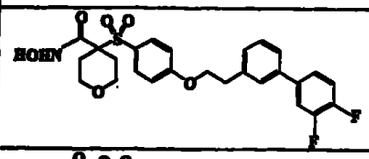
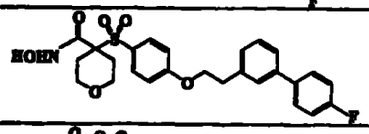
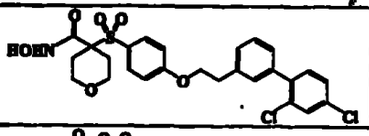
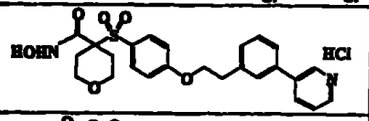
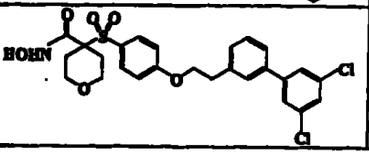
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
102		483.1260	483.1264		12.4		1.2	
103		613	613	>10000	85.8	1134	0.4	>10000
104					44.2		0.8	
105				>10000	1368.8	7694	9.7	>10000
106				>10000	1046.6	>10000	3.5	>10000

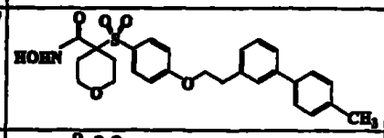
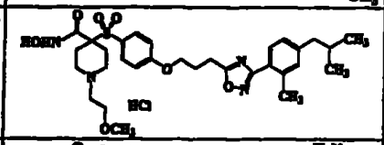
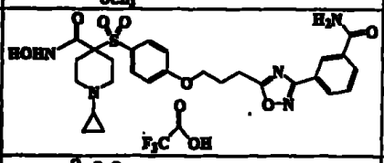
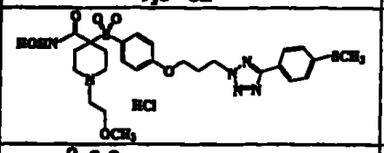
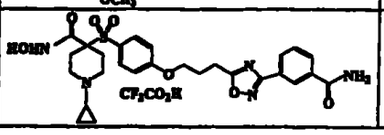
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
107					34.0		5.5	
108					433.7		20.0	
109		524.2107	524.2136	(>10000)	5410.3 (8100)	(>10000)	152.1 (93.1)	(>10000)
110		518.1449	518.1505	(>10000)	1198.5 (1120)	(4340)	7.6 (11.4)	(>10000)
111		500.1543	500.1561	(>10000)	559.4 (769)	(2680)	2.0 (6.39)	(>10000)

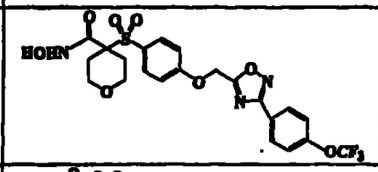
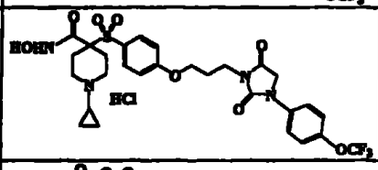
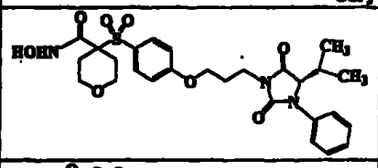
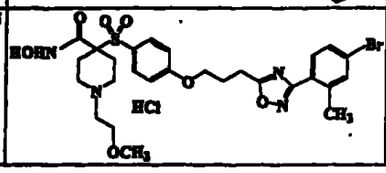
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
112		566.1460	566.1500	(>10000)	66.4 (3970)	(8850)	37.9 (51.2)	(>10000)
113		483.1590	483.1597	>10000 (>10000)	20.3 (42.30)	1980.5 (161.22)	0.2 (0.312)	7725 (3481.8)
114		516.1248	516.1259	(>10000)	1010.6 (1500)	(4870)	5.2 (4.2)	(>10000)
115		500.1543	500.1550	>10000 (>10000)	311.9 (807)	>10000 (1980)	0.9 (2.24)	>10000 (>10000)
116		496.1794	496.1811	(>10000)	1053.2 (1250)	(5550)	11.2 (5.1)	(>10000)
117		510.1950	510.1965	(>10000)	1744.7 (3640)	(9910)	16.0 (21)	(>10000)

WO 02/092588 PCT/US02/15357

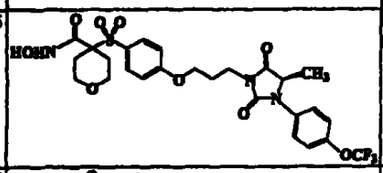
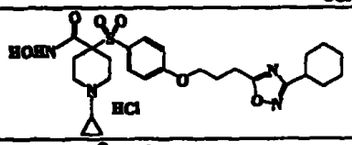
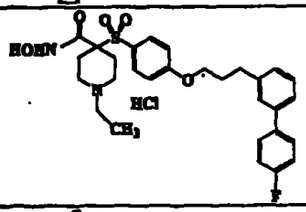
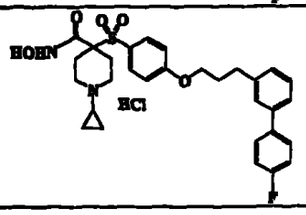
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
118		530.1404	530.1418	(>10000)	1862.0 (2650)	(>10000)	29.8 (18.8)	(>10000)
119		526.1899	526.1920	(>10000)	1187.6 (1680)	(3950)	18.3 (31.4)	(>10000)
120		514.1700	514.1724	>10000	1171.6	>10000	5.8	>10000
121		550.0858	550.0846	(>10000)	2469.3 (4620)	(>10000)	21.6 (26.9)	(>10000)

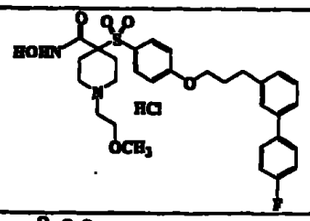
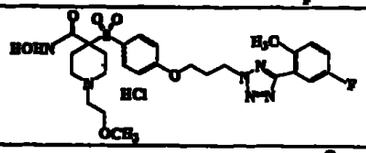
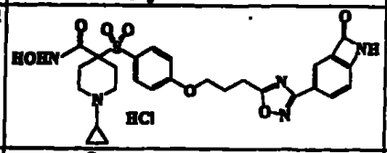
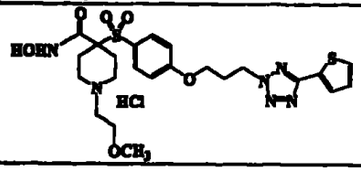
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
122		518.1449	518.1470	>10000	759.7	7668	1.9	>10000
123		500.1543	500.1545	>10000 (>10000)	383.0 (793)	>10000 (2130)	1.4 (7.35)	>10000 (>10000)
124		550.0858	550.0896	(>10000)	2151.5 (5730)	(>10000)	21.9 (20.1)	(>10000)
125				2937 (3584.24)	27.3 (51.34)	962.9 (146.43)	0.2 (0.17)	5825 (1666.65)
126		550.0858	550.0881	(>10000)	3260.4 (6360)	(>10000)	349.0 (81.3)	(>10000)

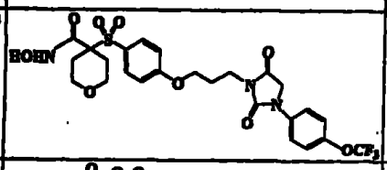
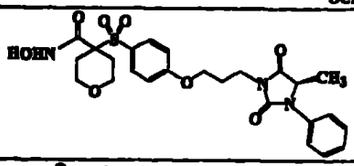
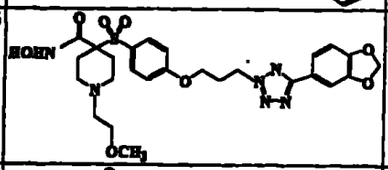
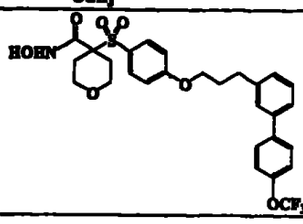
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
127		496.1794	496.1800	>10000 (>10000)	1380.0 (2160)	>10000 (4230)	5.5 (16.2)	>10000 (>10000)
128		615.2902	615.2852	(>10000)	658.7 (1130)	(3550)	23.7 (13.8)	(>10000)
129				(>10000)	41.4 (50)	(110)	1.9 (0.27)	(>10000)
130				4611	4.7	50.2	0.3	499.8
131					107.9		4.5	

Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
132					61.7		3.7	
133					84.4		4.3	
134				>10000	2382	>10000	7.7	>10000
135		637.1332	637.1315	(>10000)	24.3 (58.5)	(457)	2.9 (0.761)	(9510)

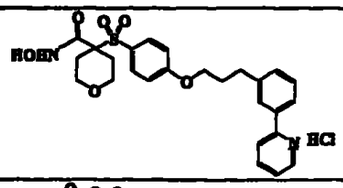
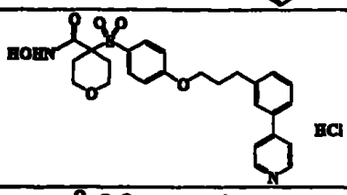
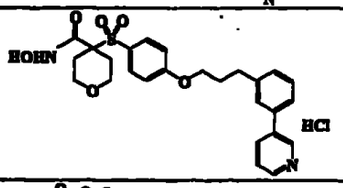
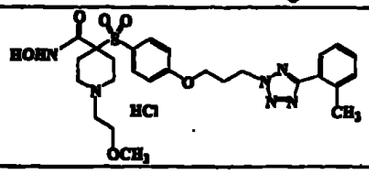
WO 03/053388 PCT/US02/15757

Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
136					229.4		4.4	
137				(>10000)	20.4 (36.6)	(604)	7.0 (0.976)	(>10000)
138				>10000	247.3	1896	2.1	>10000
139		553.2172	553.2176	>10000 (>10000)	207.7 (1410)	4514 (1390)	0.4 (2.89)	>10000 (>10000)

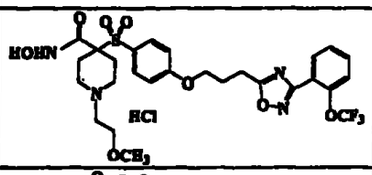
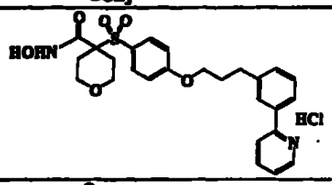
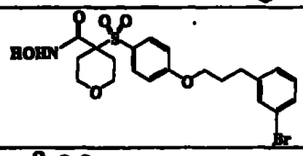
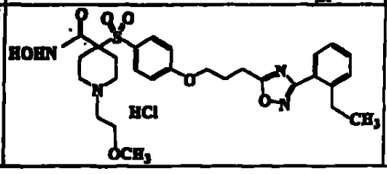
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
140				>10000 (>10000)	48.0 (708)	1692 (754)	0.5 (0.895)	>10000 (>10000)
141		577	577		32.5		3.6	
142				(>10000)	58.6 (96.4)	(310)	7.5 (1.34)	(>10000)
143					4.9		1.4	

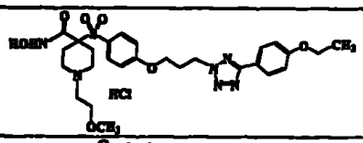
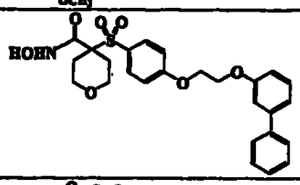
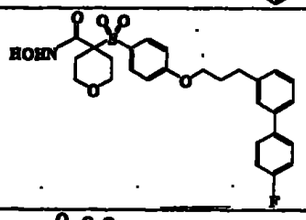
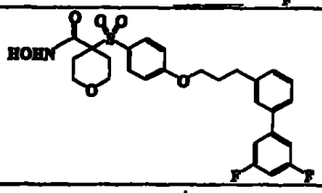
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
144				>10000	238.6	5989	2.5	>10000
145				>10000	816.9	9438	2.0	>10000
146					11.1		0.4	
147		580.1617	580.1620	(>10000)	4746.8 (>10000)	(7970)	28.3 (23.9)	(>10000)

357

Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
148				(8790)	272.0 (213)	(427)	3.1 (1.72)	(5150)
149				(>10000)	77.1 (84.1)	(94.5)	1.3 (1.18)	(2530)
150				>10000 (>10000)	135.5 (159)	529.9 (125)	0.6 (0.587)	6630 (5510)
151		559	559		38.4		2.6	

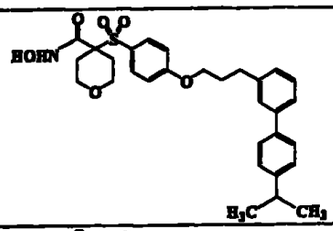
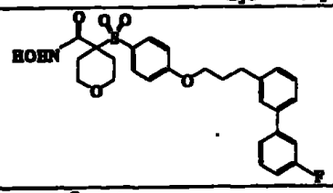
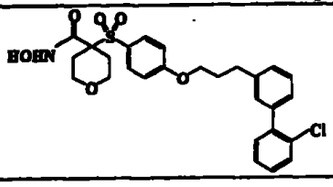
WO 02/074288 PCT/US02/13257

Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
152		629.1893	629.1885	>10000 (>10000)	58.8 (149)	72.3 (44.5)	11.8 (2.66)	>10000 (>10000)
153					192.5		7.6	
154		498.0586	498.0591	>10000 (>10000)	10.9 (33.9)	111 (151)	0.8 (0.95)	9123 (3910)
155		573.2383	573.2413	>10000 (>10000)	13.8 (37.9)	1173.7 (172)	9.7 (1.58)	>10000 (9370)

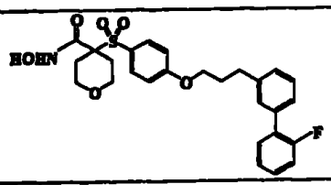
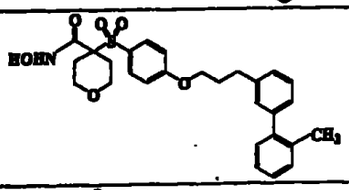
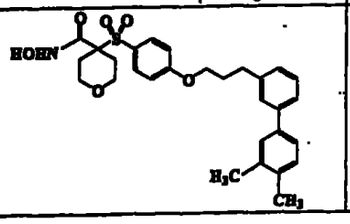
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
156					32.1		1.0	
157				>10000 (>10000)	182.1 (419)	2473 (1390)	3.5 (4.01)	>10000 (>10000)
158		530.1404	530.1446	>10000 (>10000)	2184 (2730)	5630 (3950)	3.6 (5.1)	>10000 (>10000)
159		532.1605	532.1632		1368.6		24.4	

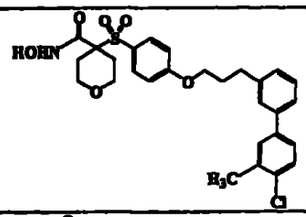
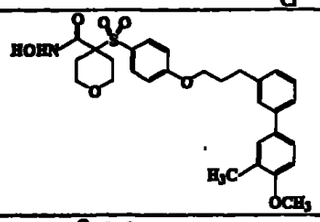
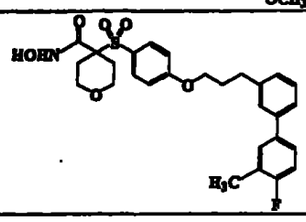
WO 02/092588 PCT/US02/15257

364

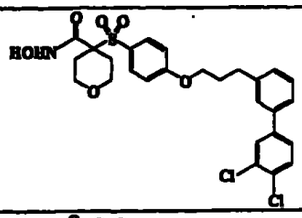
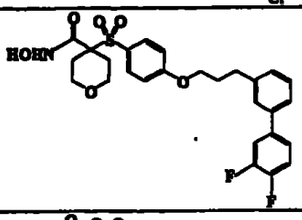
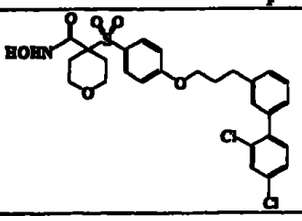
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
160		538.2263	538.2275	>10000 (>10000)	>10000 (>10000)	(>10000)	505.1	(>10000)
161		514.1700	514.1708	>10000 (>10000)	1001.1 (1760)	2625 (1730)	2.6 (20.3)	>10000
162		530.1404	530.1428	(>10000)	1596.6 (2370)	(3150)	15.6 (12)	(>10000)

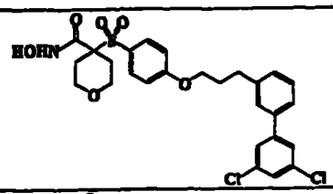
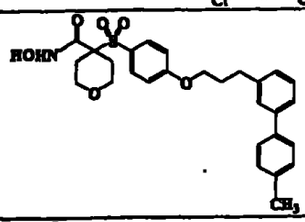
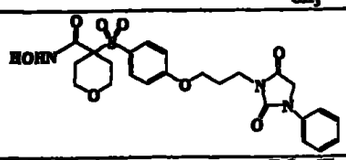
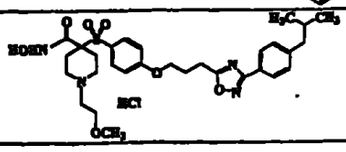
WO 02/092588 PCT/US02/15257

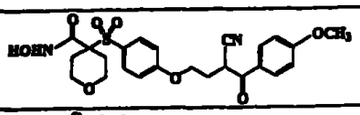
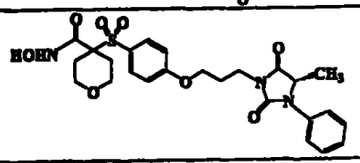
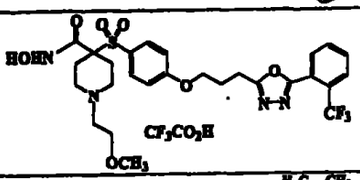
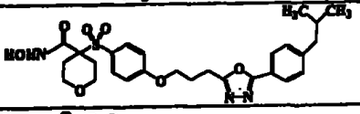
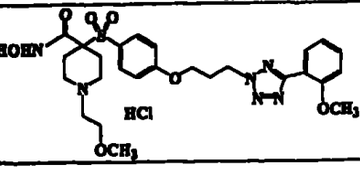
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
163		514.1700	514.1680	>10000 (>10000)	1370.7 (1010)	2880 (2500)	2.5 (11.6)	>10000 (>10000)
164		510.1950	510.1940	(>10000)	1073.2 (978)	(2720)	20.0 (6.85)	(>10000)
165		524.2107	524.2112	(>10000)	3396.2 (>10000)	(9750)	146.9 (144)	(>10000)

Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
166		544.1561	644.1606	(>10000)	3081.7 (8090)	(8690)	135.9 (63.4)	(>10000)
167		540.2056	540.2029	(>10000)	3739.4 (128)	(68.1)	147.0 (78.9)	(>10000)
168		528.1856	528.1863	(>10000)	3428.2 (5500)	(6500)	34.3 (27.3)	(>10000)

WO 02/092588 PCT/US02/15257

Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
169		564.1014	564.1026	(>10000)	4363.5 (5360)	(6500)	70.7 (20.4)	(>10000)
170		532.1605	532.1618	(>10000)	1608.7 (1410)	(1500)	3.3 (6.79)	(>10000)
171		564.1014	564.1028	(>10000)	2288.8 (3190)	(6600)	62.8 (12.5)	(>10000)

Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
172		564.1014	564.1032	(>10000)	5163.1 (>10000)	(9440)	377.0 (71.1)	(>10000)
173		509.1950	509.1954	(>10000)	2120.4 (4090)	(3480)	12.2 (11.5)	(>10000)
174				>10000	708.6	4017	5.2	>10000
175		601.2696	601.2657	>10000 (>10000)	438.0 (872)	7296.6 (1390)	1.4 (2.01)	>10000 (>10000)

Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
176					108.9		7.8	
177					333.2		17.0	
178				>10000 (>10000)	28.4 (39.3)	1166.4 (306)	7.8 (1.71)	>10000 (>10000)
179					246.9		1.1	
180					443.0		17.0	

WO 02/092588 PCT/US02/15257

PATENTE [X] MODELO DE UTILIDAD [ ] DISEÑO INDUSTRIAL [ ]

SALICITANTE/S. RAZON SOCIAL O APELLIDOS Y NOMBRES Pharmacia y Corporation.

DOMICILIO Estados Unidos de America.

APODERADO Ramiro Castro Duque

TITULO Sulfona-hidroxamatos Aromaticos y su uso como Inhibidores de proteasas

CLASIFICACION A61K31/351

EXPEDIENTE No. 03-99304 FECHA DE SOLICITUD 10/11/03 ROLLO MICROFILM

CERTIFICADO No. FECHA DE CONCESION VIGENCIA DESDE HASTA

PRORROGA CAMBIO DE NOMBRE

TRASPASO A

INVENTOR Borta; Becker; Bendall; Bogan; Carroll; Decarsenzo; Fabian y

OTROS 11 inventores Más PCT/US02/15257 16/05/02 Capitulo II

EN

PCT/US02/15259

21 03-99304

22 10/11/2003

31 60/296,395

32 11/05/2001

33 US

51 A61K 31/551

74 Ramiro Cortes Dague

72 Barta; Becker, Bradill; Bachm; Carroll
Decrescenzo; Fabian y Himebaugh Mary

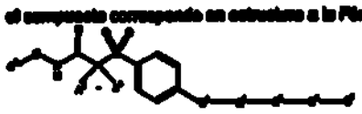
CONTINUA AL RESPALDO

71 Pharmacia Corporation

54 TITULO Sulfona-hidroxamatos Aromaticos y su uso como inhibidores de Proteasas.

PCT/US02/15257
21 03-99304
22 10/11/2003
31 60/290,395
32 11/05/2001
33 US
51 A61K 31/551
74 Ramiro Garza J
72 Barta; Becker, B
Decrescenzo; Fabia
71 Pharmacia Corpo
54 TITULO Sulfona-hid

1 Un compuesto o sal del mismo en el cual el compuesto corresponde en estructura a la Fórmula 1-1:



(1-1), y

A¹ se selecciona del grupo formado por -H, alquilcarbonilo, alcoxicarbonilo, carbocicliloxicarbonilo, carbociclilalquiloxicarbonilo, heterociclooxicarbonilo, heterociclilalquiloxicarbonilo, carbociclilaminocarbonilo, carbociclilalcoxicarbonilo, carbociclilalquilcarbonilo, alquiltiocarbonilo, alcoxi(tiocarbonilo), carbociclil(tiocarbonilo), carbociclilalquil(tiocarbonilo), heterociclil(tiocarbonilo), heterociclilalquil(tiocarbonilo), carbociclotio(carbonilo), carbociclilalcox(tiocarbonilo), y arilalquil(tiocarbonilo), donde cualquier miembro (excepto -H) de dicho grupo es opcionalmente sustituido; y

A^2 y A^3, junto con el átomo de carbono al cual ambos están unidos, forman un heterociclo opcionalmente sustituido que contiene entre 5 y 6 miembros en el anillo, y

E^1 se selecciona del grupo formado por -O-, -S(O)$_m$-, -S(O)$_2$-O-, -N(R^1)-, -C(O)-N(R^1)-, -N(R^1)-C(O)-, y -C(R^1)(R^2)-, y

E^2 se selecciona del grupo formado por alquilo, cicloalquilo, alquilcicloalquilo, cicloalquilalquilo, y alquilcicloalquilalquilo donde cualquier miembro de dicho grupo es opcionalmente sustituido, y

E^3 forma un enlace de al menos 2 átomos de carbono entre E^1 y E^2; y

VIENE AL RESPALDO

E^4 se selecciona del grupo formado por -C(O)-, -O-(CO)-, -C(O)-O-, -C(NR^1)-, -N(R^1)-, -N(R^1)-C(NR^1)-, -C(NR^1)-N(R^1)-, -C(O)-N(R^1)-, -N(R^1)-C(O)-, -N(R^1)-C(O)-N(R^1)-, -S-, -S(O)-, -N(R^1)-S(O)$_2$-, -S(O)$_2$-N(R^1)-, -C(O)-N(R^1)-N(R^1)-C(O)-, -O-N(R^1)-C(O)-, -C(R^1)(R^1)-, y

E^5 se selecciona del grupo formado por un enlace, alquilo, y alquenilo donde el alquilo o alquenilo es opcionalmente sustituido, y

E^6 se selecciona del grupo formado por -H, -OH, alquilo, alquenilo, alquinilo, alcoxi, cicloalquilo, carbocíclico, y heterocíclico donde cualquier miembro (excepto -H o -OH) de dicho grupo es opcionalmente sustituido, y

R^1 y R^2 se seleccionan independientemente del grupo formado por -H y alquilo donde el alquilo es opcionalmente sustituido, y

R^3 se selecciona del grupo formado por -H y -OH, y

R^4 y R^5 se seleccionan independientemente del grupo formado por -H, alquilo, carbocíclico, carbociclilalquilo, heterocíclico, y heterociclilalquilo donde cualquier miembro (excepto -H) de dicho grupo es opcionalmente sustituido, y

R^6 se selecciona del grupo formado por -OH y -OH, y

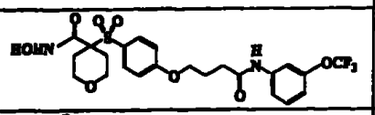
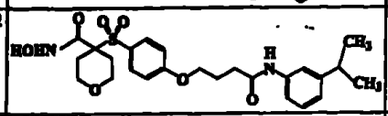
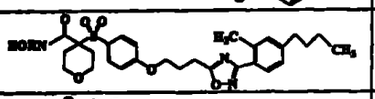
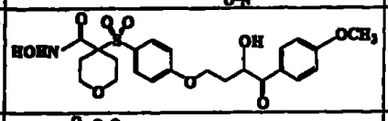
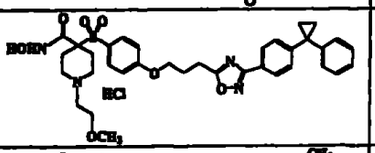
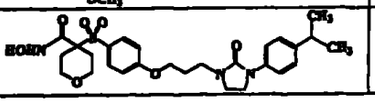
R^7 se selecciona del grupo formado por -H, halógeno, -OH, alquilo, alcoxi, y cicloalquilo donde el alquilo , alcoxi, o cicloalquilo es opcionalmente sustituido, y

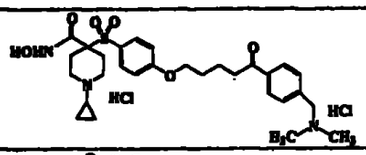
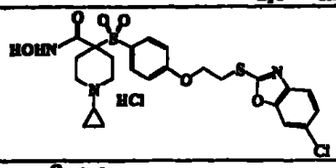
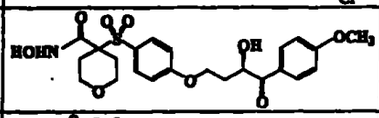
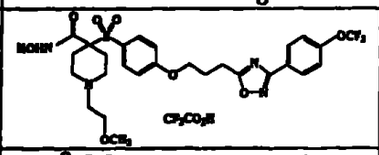
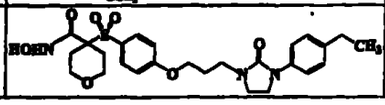
R^8 se selecciona del grupo formado por -OH y alcoxi donde el alcoxi es opcionalmente sustituido, y

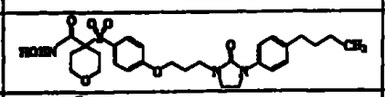
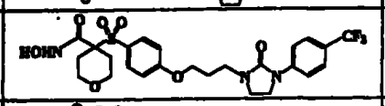
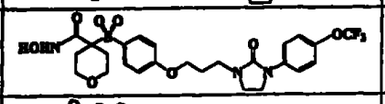
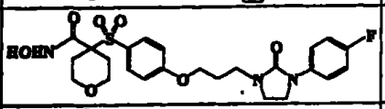
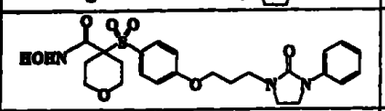
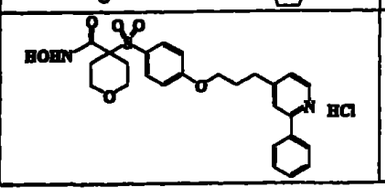
ni R^1 ni R^2 forman una estructura de anillo con E^2, E^3, E^4, o E^5; y

ni R^4 ni R^5 forman una estructura de anillo con E^2, E^3, o E^5; y

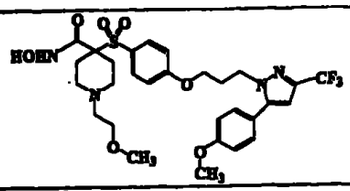
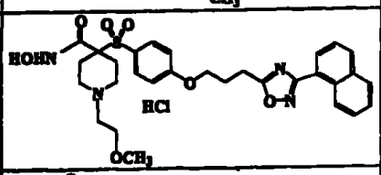
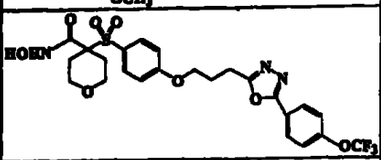
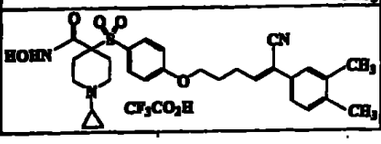
E^2 no es -H cuando E^3 es -C(R^1)(R^2)- y E^4 es un enlace.

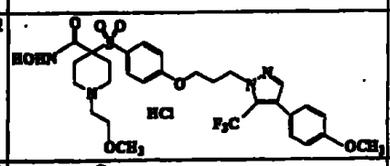
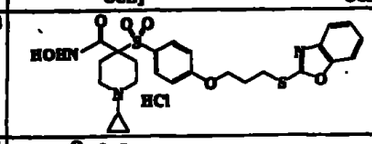
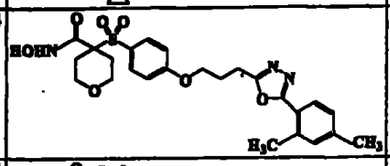
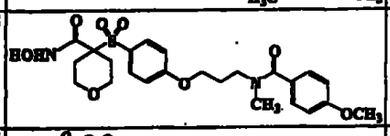
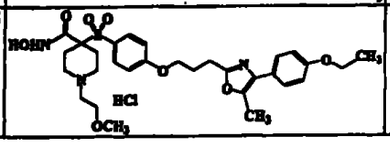
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
181				>10000 (1850)	13.9 (15.8)	26.4 (40.5)	0.3 (0.27)	8059 (4830)
182				>10000 (6540)	33.1 (34.3)	62.1 (85.4)	0.5 (0.212)	>10000 (5850)
183				(>10000)	708.0 (643)	(2510)	21.0 (15.1)	(>10000)
184				1528.7	30.4	103.5	3.9	2715.4
185				(>10000)	84.7 (116)	(220)	12.4 (3.73)	(>10000)
186					609.9		13.5	

Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
187				3868	3.6	11.2	1.8	1425
188				>10000	4.7	48.2	0.3	3537.7
189				1070	19.3	24.1	1.9	4316
190				>10000 (>10000)	165.9 (283)	1742.6 (669)	0.5 (0.6)	>10000 (>10000)
191				6956	341.2	383.4	9.5	>10000

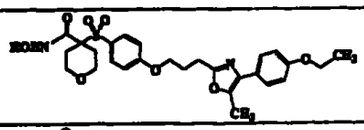
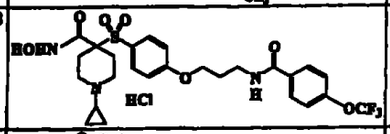
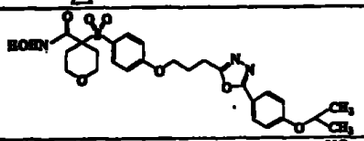
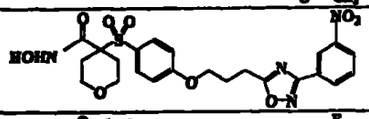
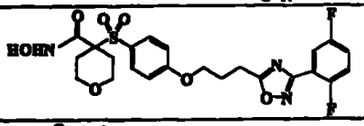
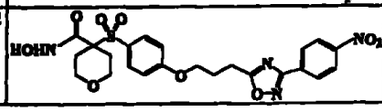
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
192					1256.4		15.4	
193				5931.6	312.3	272.5	6.8	>10000
194				>10000	221.6	515.7	6.2	>10000
195				4381.7	20.6	45.8	7.5	2741.5
196					32.2		11.4	
197				>10000 (>10000)	13.2 (30.7)	432.2 (334)	0.5 (0.37)	>10000 (>10000)

370

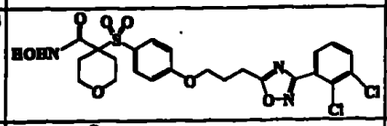
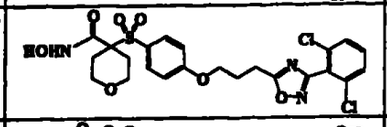
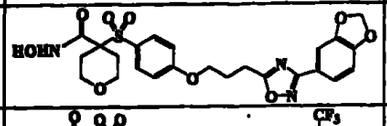
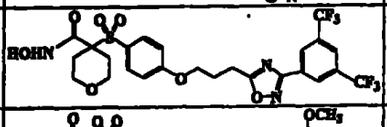
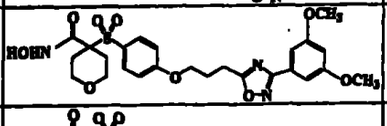
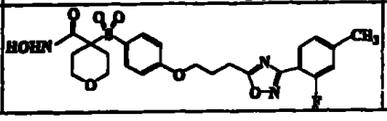
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
198					4527.4		834.9	
199				(>10000)	133.2 (228)	(59.5)	7.4 (3.09)	(>10000)
200				7498	84.0	1207.2	0.6	>10000
201		538.2376	538.2362	>10000	127.7	4509.5	0.7	>10000

Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
202					1604.4		41.9	
203				>10000	4.2	6.0	1.0	>10000
204				>10000	145.7	1824.8	0.6	>10000
205					4780.2		17.6	
206				>10000	92.6	59.4	15.8	3112

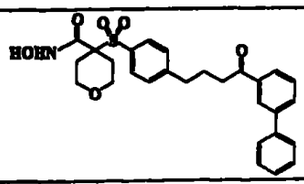
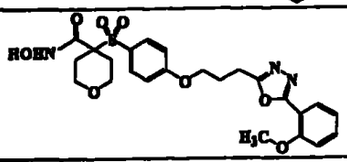
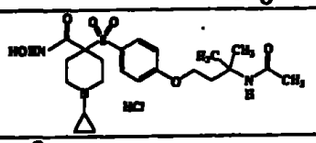
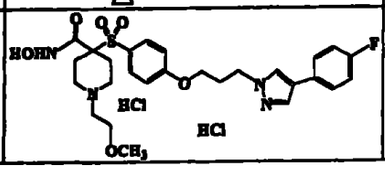
WO 02/075368 PCT/US02/08257

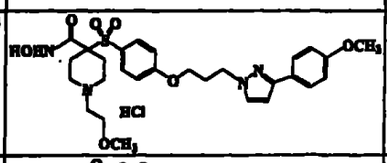
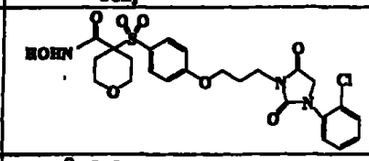
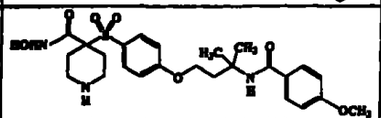
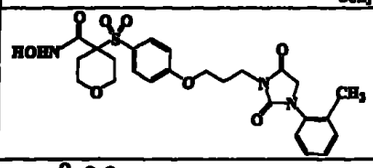
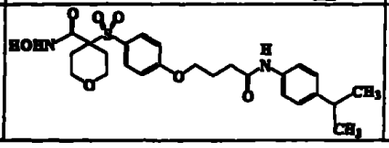
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
207				>10000	114.3	126.7	3.7	>10000
208				>10000	230.2	6587.6	0.6	>10000
209				>10000	172.5	905.6	1.4	>10000
210				>10000	6.9	284.6	1.3	>10000
211				9653	26.2	863.5	0.4	>10000
212				1408	4.1	212.2	0.3	>10000

WO 01/97828
PCT/US01/15571

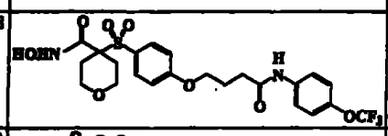
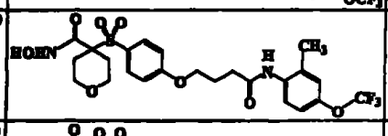
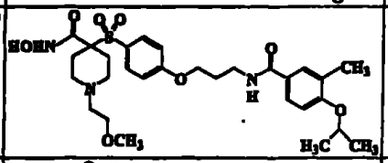
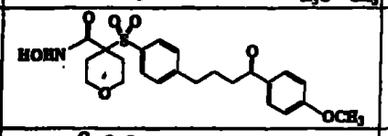
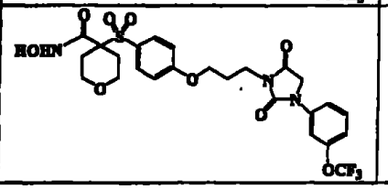
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
213				>10000	54.8	2204	2.2	>10000
214				>10000	15.8	4239	3.3	>10000
215				>10000	20.3	767.9	0.3	>10000
216					1952.2		51.2	
217				>10000	48.9	5179	4.6	>10000
218				>10000	40.4	2973	1.4	>10000

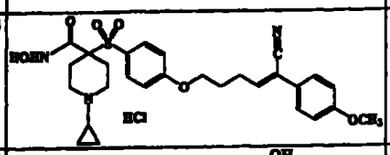
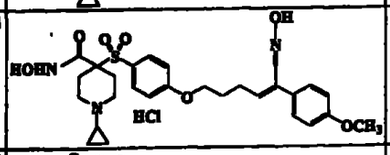
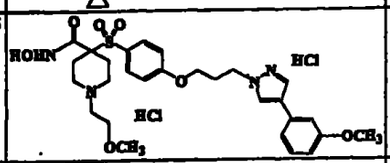
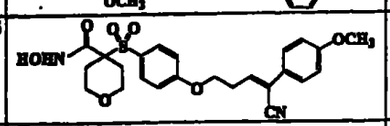
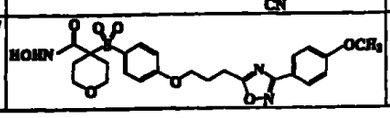
WO 02/092588
PCT/US02/15257

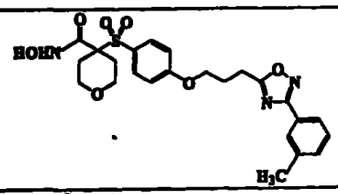
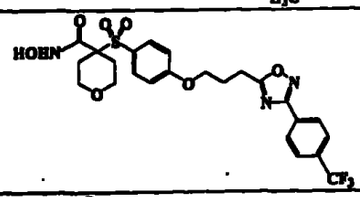
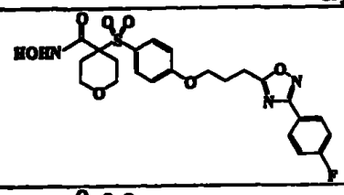
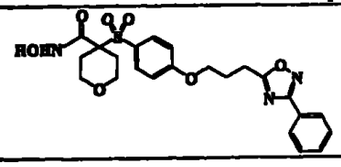
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
219				>10000 (5600)	60.8 (105)	77.7 (59.5)	0.4 (0.355)	>10000 (7940)
220				>10000	409.7	1466.8	5.7	>10000
221					8796.4		243.8	
222					138.1		13.3	

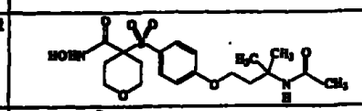
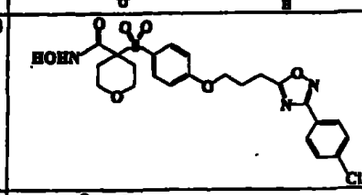
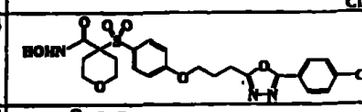
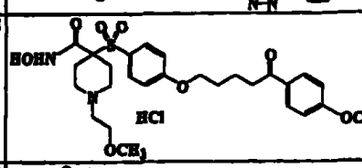
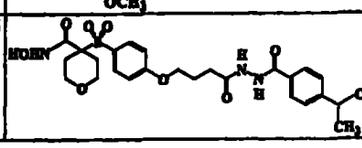
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
223					69.7		11.9	
224				>10000	193.5	1466.8	4.7	>10000
225					2332.3		17.8	
226				>10000	222.0	2144.0	4.3	>10000
227					2.7		0.2	

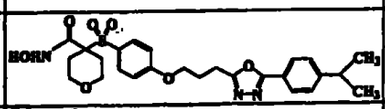
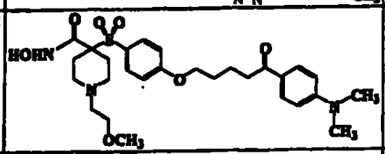
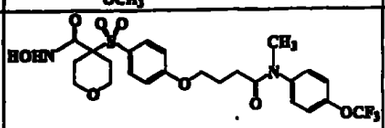
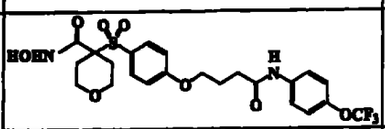
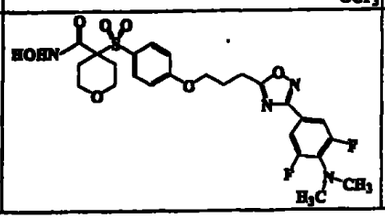
376

Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
228				6871 (3940)	11.4 (22.4)	180.4 (247)	0.2 (0.324)	>10000 (6290)
229				5033 (955)	12.2 (10.4)	293.7 (281)	1.7 (0.27)	>10000 (7870)
230				>10000	555.2	1017.7	1.1	>10000
231				>10000	1.6	10.2	0.2	641.7
232				>10000	74.2	877.7	5.6	>10000

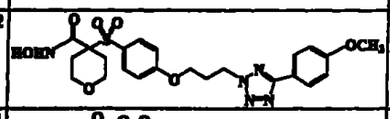
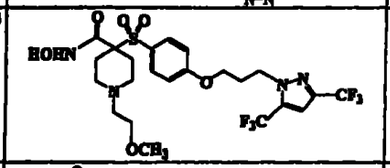
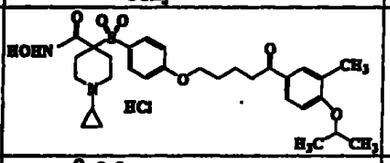
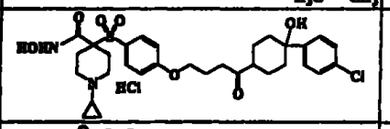
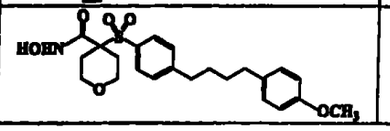
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
233				>10000 (>10000)	25.5 (60.18)	831.8 (509.42)	0.1 (0.137)	>10000 (>10000)
234		596.2430	596.2441		213.4		10.3	
235					421.7		26.0	
236					7.6		3.4	
237				>10000	42.5	1111	0.7	>10000

Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
238				>10000	78.7	1186.1	1.2	>10000
239					236.9		2.5	
240				≥10000	84.0	1428.4	0.7	>10000
241				>10000	60.2	944.2	1.3	>10000

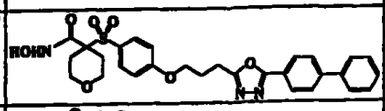
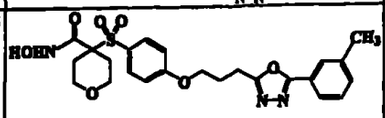
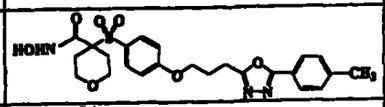
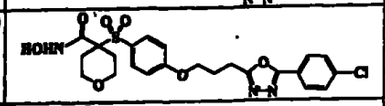
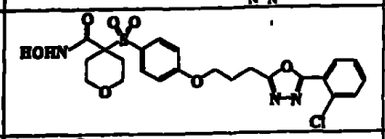
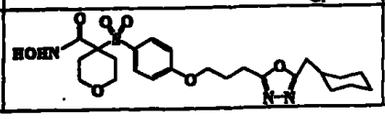
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
242					2720.2		203.0	
243				9313.6	49.4	2101.9	0.5	>10000
244				3250.6	18.8	108.2	0.7	>10000
245				>10000	8.6	61.1	0.2	>10000
246				1166.7	7.5	104.7	3.0	>10000

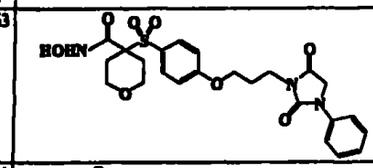
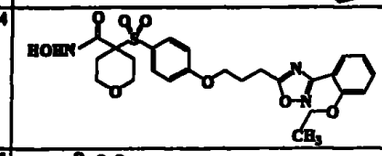
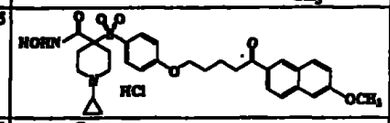
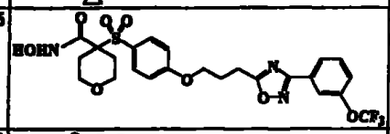
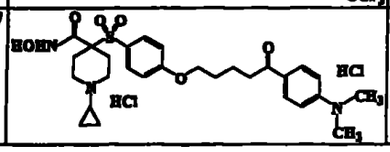
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
247				3610.8	445.1	341.1	1.1	>10000
248				>10000	15.7	105.6	0.2	1704.1
249				>10000 (>10000)	226 (333)	3628.6 (1490)	5.09 (1.49)	>10000 (>10000)
250				4406.1 (1440)	2.5 (3.12)	22.5 (12.5)	0.3 (0.127)	7630.2 (1700)
251					182.4		5.4	

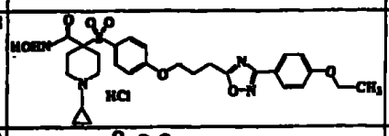
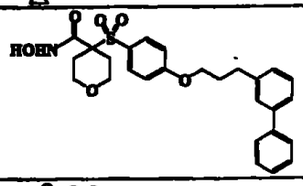
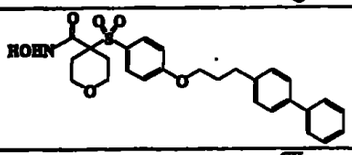
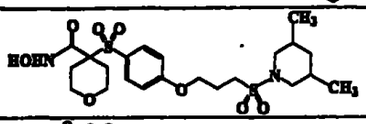
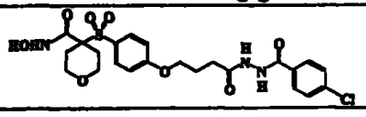
WO 02/055488 PCT/US02/15257

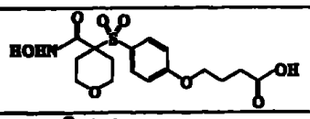
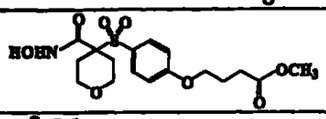
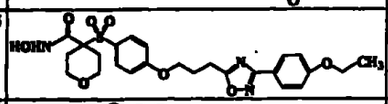
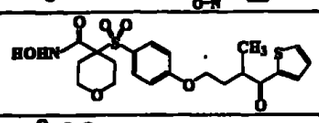
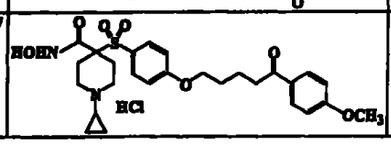
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
252				5602.7	47.9	1052.4	0.2	>10000
253					1448.2		32.4	
254				>10000	138.3	968.2	1.7	>10000
255					51.3		1.9	
256				>10000	0.1	37.9	<0.1	>10000

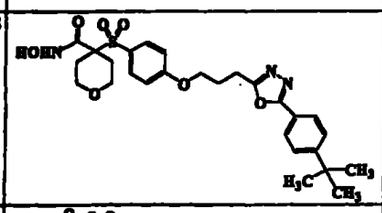
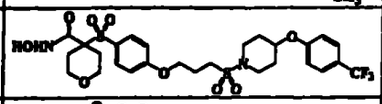
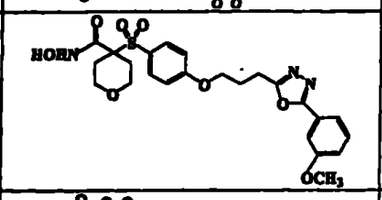
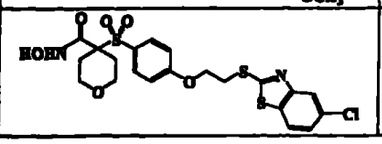
WO 01/09138 PCT/US00/15157

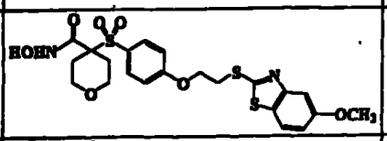
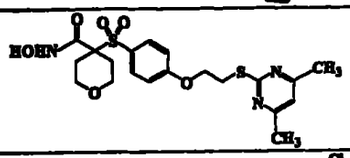
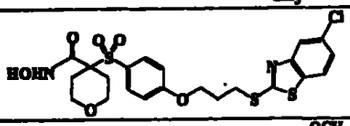
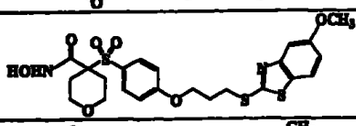
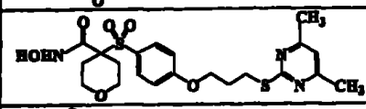
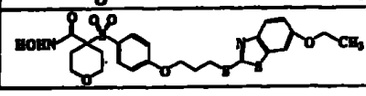
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
257				>10000	173.8	6227	0.5	>10000
258				>10000	173.5	1956	1.7	>10000
259				7256	201.1	1876	0.7	>10000
260				1159	13.2	391.0	1.8	>10000
261				>10000	178.3	1185.0	1.9	>10000
262				>10000	118.3	1702.3	3.0	>10000

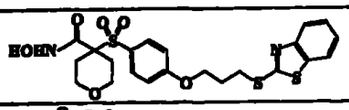
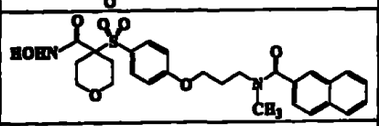
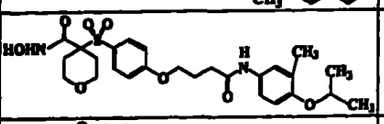
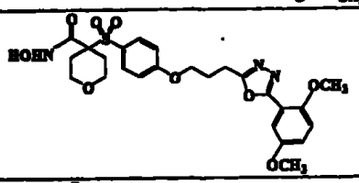
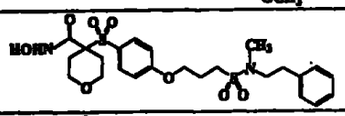
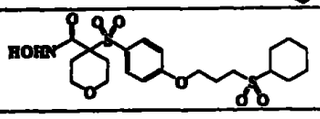
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
263				>10000	87.7	3267.5	3.8	>10000
264				>10000	162.8	287.1	5.3	>10000
265					40.0		0.2	
266				>10000	391.2	202.6	9.1	>10000
267				>10000	18.5	106.7		>10000

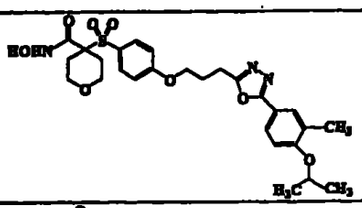
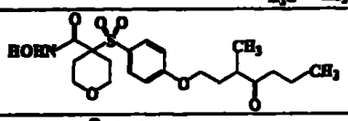
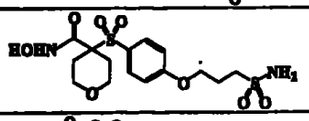
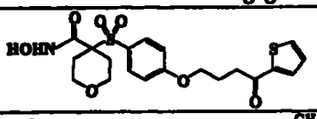
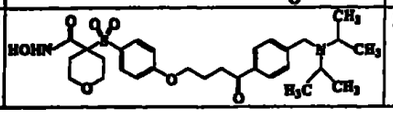
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
268				>10000	125.9	674.0	2.5	>10000
269				>10000	897.9	2755	1.8	>10000
270					521.8		8.1	
271				>10000	8.7	531.8	2.9	>10000
272				399	4.2	152.1	2.8	>10000

Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
273		405.1332	405.1335		1010.7		304.0	
274		402.1223	402.1225	9864	15.4	33.6	4.1	>10000
275					115.2		1.7	
276				6670.4	17.4	196.3	2.8	7019.9
277				>10000	3.5	41.5	0.2	>10000

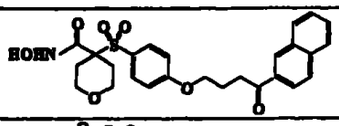
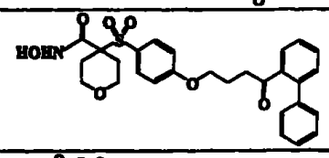
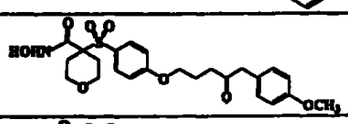
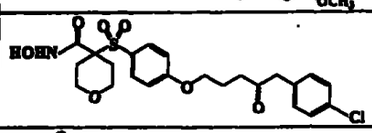
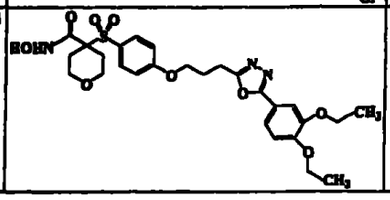
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
278		544.2117	544.2104	>10000	207.9	494	3.7	>10000
279					15.9		9.4	
280		518.1597	518.1578	>10000	170.1	2034	1.5	>10000
281		529.0329	529.0353	>10000	70.4	276.1	1.3	>10000

Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
282		525.0824	525.0827	>10000	43.3	704.3	2.6	>10000
283		468.1263	468.1257		186.2		29.3	
284		543.0485	543.0500	>10000	10.1	18.5	1.1	>10000
285		539.0980	539.0978	>10000	16.7	23.6	1.8	>10000
286		482.1420	482.1421	>10000	74.9	1134.5	4.0	>10000
287		553.1137	553.1137	>10000	3.6	16.4	0.8	>10000

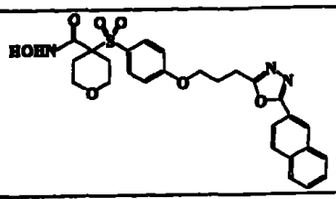
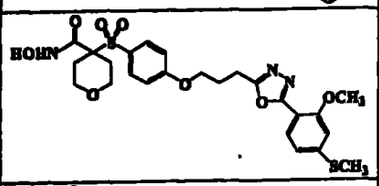
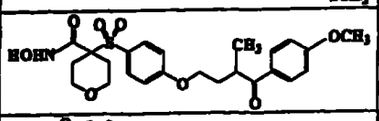
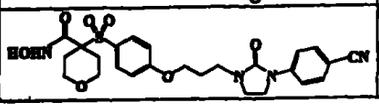
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
288		509.0875	509.0880	>10000	2.3	10.6	0.8	>10000
289		527.1852	527.1838	>10000	2720.2	>10000	10.1	>10000
290				>10000 (>10000)	590.2 (1009.04)	>10000 (>10000)	1.1 (0.547)	>10000 (>10000)
291					100		8.0	
292				970	14.4	163.5	2.4	>10000
293				6147	2.3	447.9	2.6	>10000

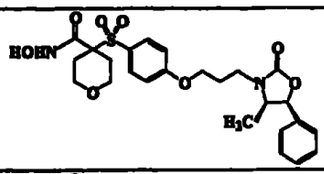
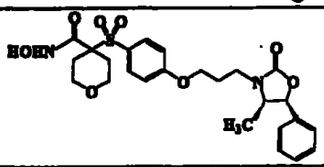
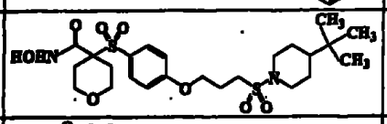
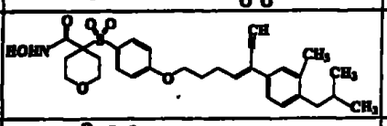
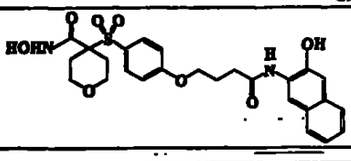
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
294				4623	100.0	447.9	4.3	>10000
295				>10000	15.6	172.1	2.6	>10000
296					1335.9		564.8	
297		454.0944	454.0986	6812	8.1	64.6	0.5	6562
298		561.2634	561.2641		11.9		18.1	

390

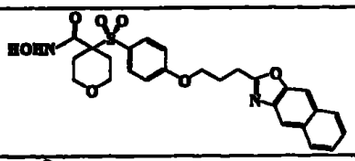
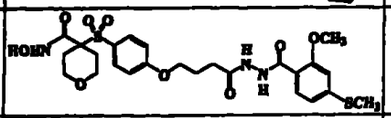
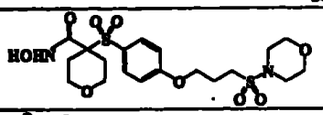
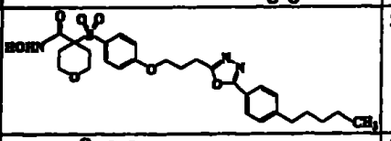
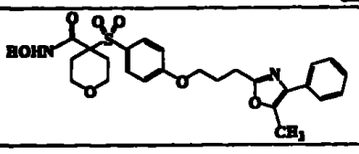
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
299		498.1586	498.1588		3.2		0.1	
300		524.1743	524.1729		12.5		6.7	
301		492.1692	492.1687	3655.3	0.2	9.1	<0.1	319.9
302		496.1197	496.1192	2728.9	0.2	2.9	0.1	94.9
303		576.2016	576.2198		50.0		9.9	

WO 02/057288 PCT/US02/01257

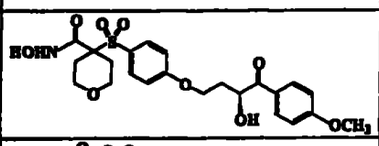
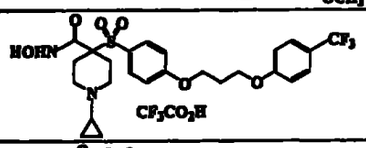
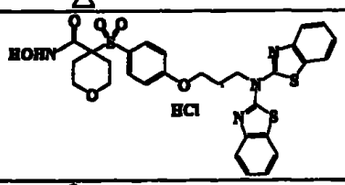
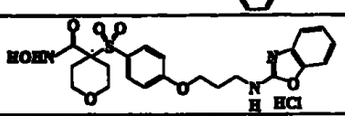
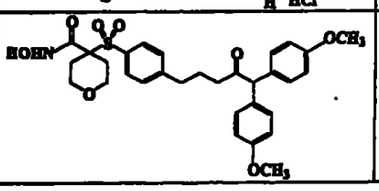
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
304		538.1648	538.1629		138.6		0.2	
305		569.1474	569.1444		175.9		3.9	
306				>10000	92.9	185.2	1.7	>10000
307				8135	135	139.5	4.5	>10000

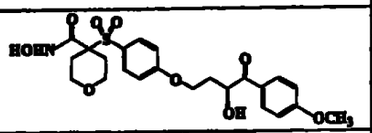
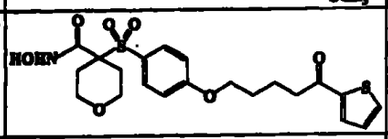
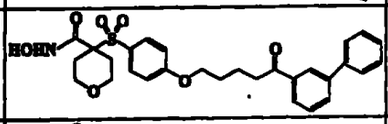
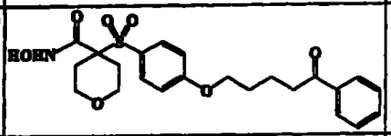
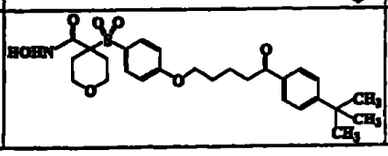
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
308		519.1801	519.1780	>10000	175.8	1601.1	3.7	>10000
309		519.1801	519.1772	>10000	135.3	1557.8	1.8	>10000
310				>10000	32.0	1980.5	3.0	>10000
311		543.2165	543.2165		25.6		2.6	
312		529.1645	529.1635		9.1		0.2	

WO 02/092588 PCT/US02/15357

Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
313		511.1539	511.1535		18.1		<0.1	
314					7.8		2.5	
315					12.8		12.7	
316		558.2274	558.2274	2678	2842	692.0	13.6	>10000
317		501.1695	501.1693	>10000	120.4	244.3	3.1	>10000

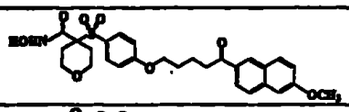
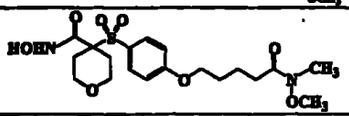
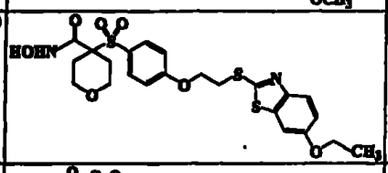
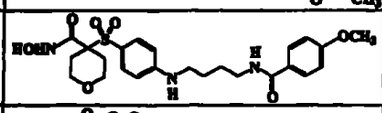
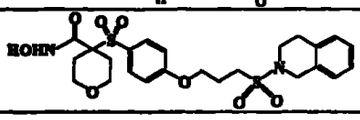
WO 02/092598 PCT/US02/15257

Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
318					615		97.3	
319				>10000	5.8	258	1.0	4225
320					5864		6110	
321				>10000	1701	625.6	3.7	>10000
322		601.2220	601.2226		354		233	

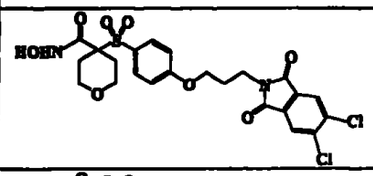
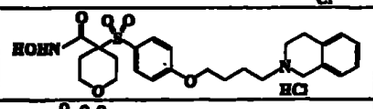
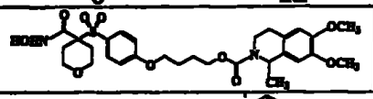
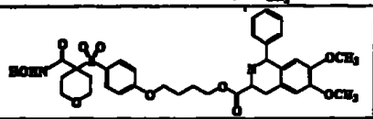
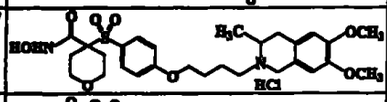
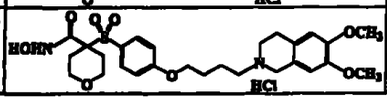
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
323					358.8		108	
324		468.1151	468.1148	2990	4.2	500	0.5	8002
325		538.1899	538.1918	>10000	11.0	4042	0.5	>10000
326		462.1586	462.1582	>10000	7.4	263	0.3	8316
327		518.2212	518.2203	>10000	50.7	5284	0.9	>10000

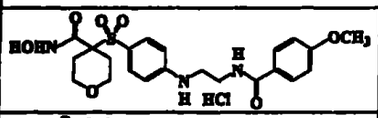
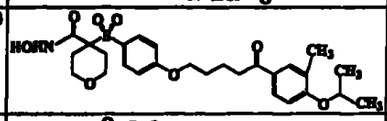
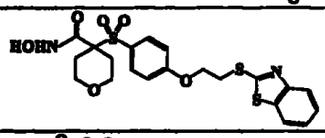
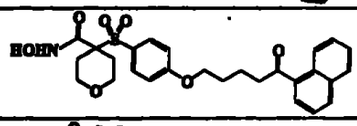
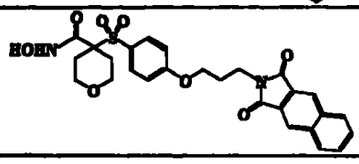
WO 02/072588 PCT/US02/15257

396

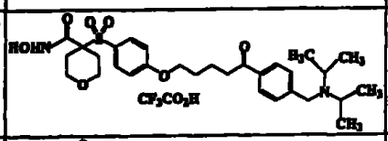
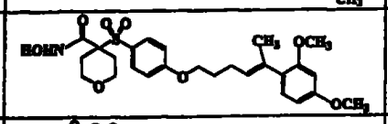
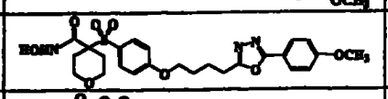
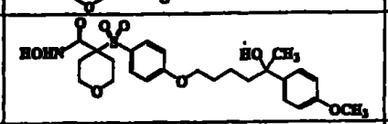
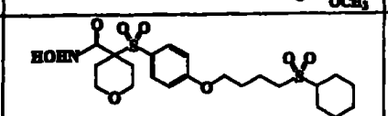
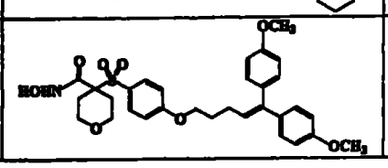
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
328		542.1849	542.1866		61.3		<0.1	
329					103.1		8.6	
330		539.0980	539.0985	>10000	261.7	216	16.0	592
331		506.1961	506.1954		386		261.4	
332				2459	3.6	132.4	2.6	>10000

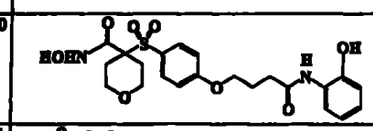
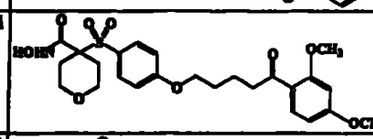
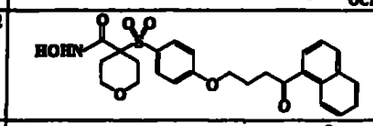
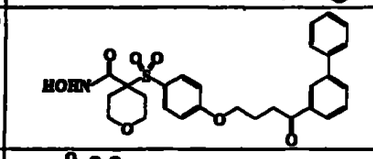
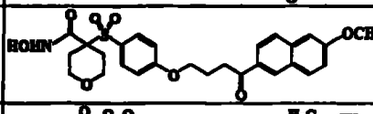
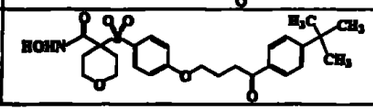
WO 02/092588
PCT/US02/15257

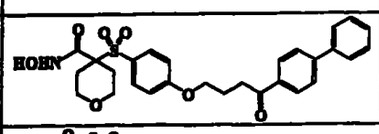
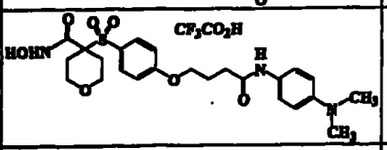
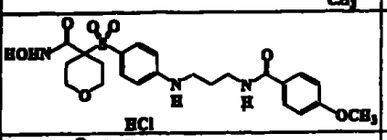
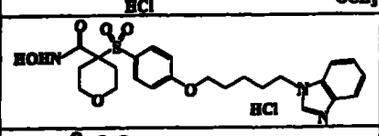
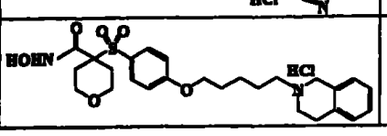
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
333		557.0552	557.0562	>10000	656.3	3240	1.8	>10000
334		489.2059	489.2073	>10000	16.4	866	5.1	2876
335		607.2325	607.233	>10000	2.3	172.3	6.5	>10000
336		669.2482	669.2463		300.6		19.8	
337		563.2427	563.2414		41.9		12.2	
338		549.2271	549.2242		20.6		137.7	

Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
339		478.1648	478.1631		1205.8		932.9	
340		534.2162	534.2161	>10000	253.0	5590	1.9	>10000
341		495.0718	495.0689	>10000	16.8	1122	0.5	6400
342		512.1743	512.1769	>10000	41.2	2165	2.0	>10000
343					7702.4		2.4	

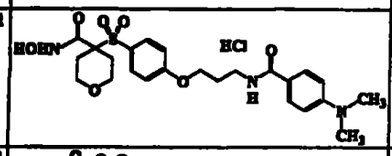
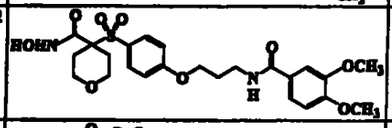
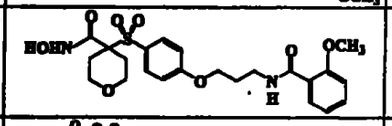
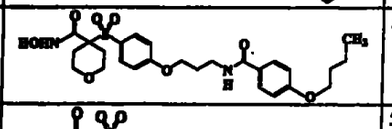
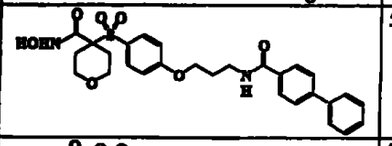
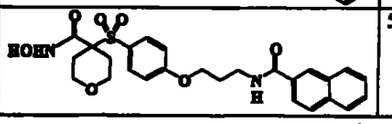
WO 01/68595 PCT/US01/15574

Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
344		575.2791	575.2819		12.7		4.6	
345		520.2005	520.1988		271.1		14.3	
346		532.1754	532.171	>10000	2.6	2010	0.9	>10000
347					10.3		1.8	
348				>10000	61.8	>10000	4.4	>10000
349					505.3		39.0	

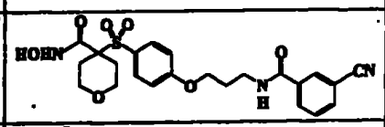
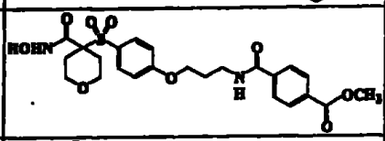
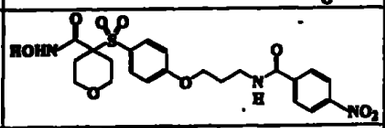
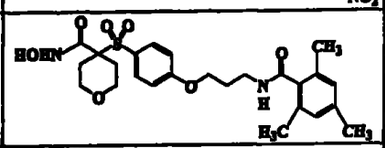
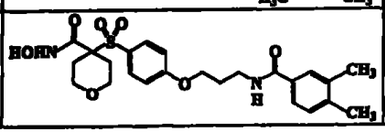
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
350		479.1488	479.1484	3283	2.6	271	0.5	2670
351		522.1798	522.1791	>10000	34.1	2225	1.0	>10000
352		498.1586	498.1576	>10000	33.6	3601	2.0	6238
353		524.1743	524.1703	>10000	25.1	1152	1.8	>10000
354		528.1692	528.1658					
355		504.2056	504.2017	>10000	17.4	1072	1.1	3622

Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
356		524.1743	524.1731	>10000	33.1	1650	0.8	>10000
357		506.1961	506.1964	>10000	10.2	952	1.7	>10000
358		492.1804	492.1813		768.4		14.6	
359		488.1855	488.1862	>10000	2.3	1183	1.0	7956
360		503.2216	503.2226	>10000	9.7	547	6.4	962

WO 02/074788 PCT/US02/07557

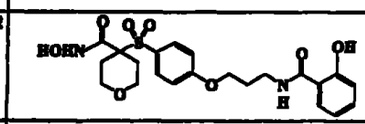
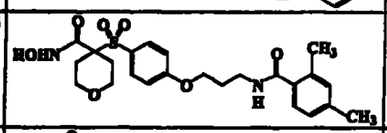
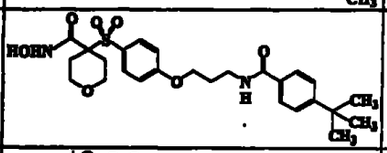
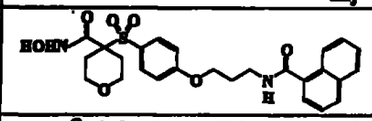
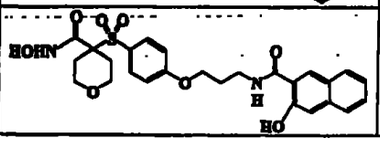
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
361		506.1961	516.1965	6000	500	>10000	0.5	>10000
362		523.1750	523.1763		347		3.7	
363		493.1645	493.1660		430		7	
364		535.2114	535.2105	>10000	250	>10000	1.8	>10000
365		539.1852	539.1846		21		0.6	
366		513.1695	513.1699		347		0.3	

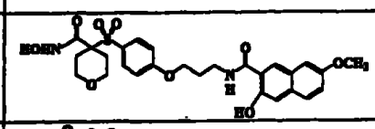
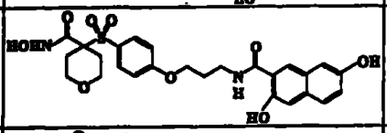
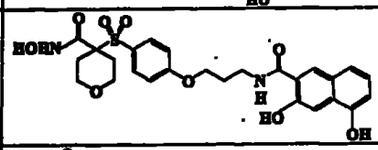
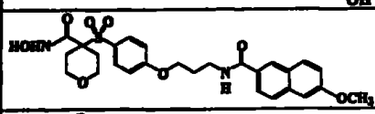
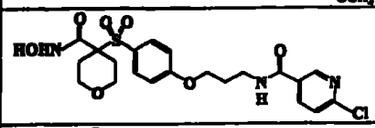
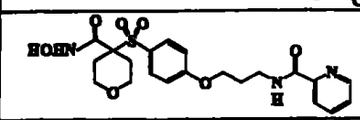
WO 02/074288 PCT/US02/15157

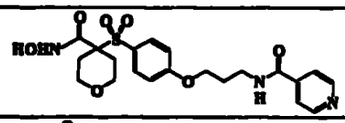
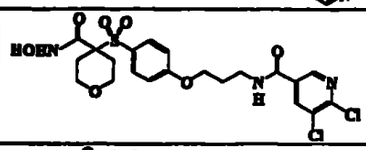
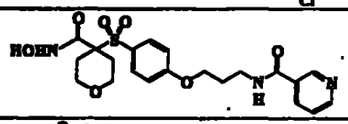
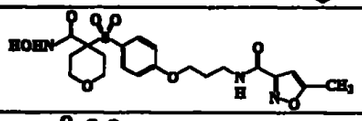
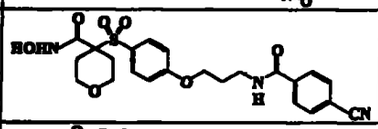
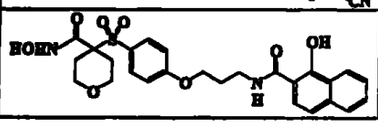
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
367		488.1491	488.1496		235		4.5	
368		521.1594	521.1594	>10000	150	9000	0.8	>10000
369		508.1390	508.1390		155		1.5	
370		505.2008	505.1990		900		37	
371		491.1852	491.1894	>10000	1100	9600	2.4	>10000

WO 02/074788
PCT/US02/15257

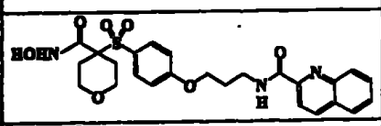
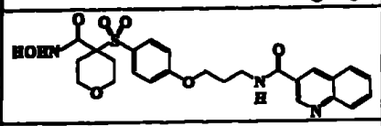
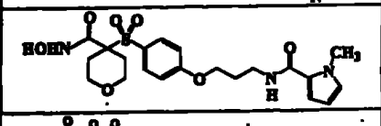
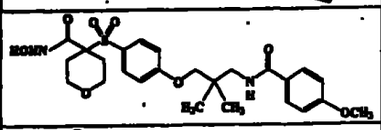
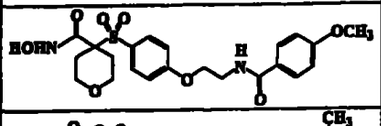
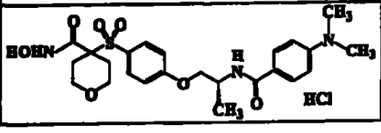
404

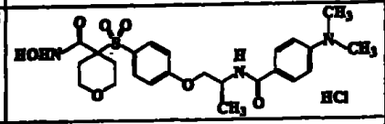
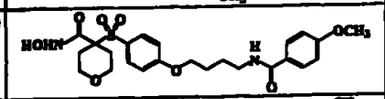
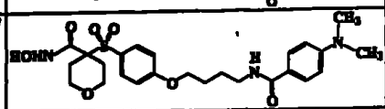
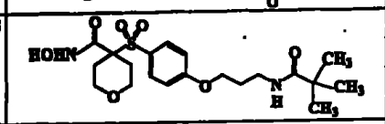
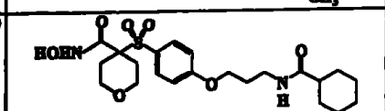
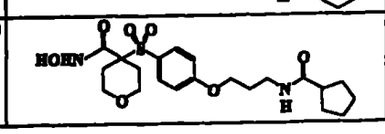
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
372		479.1488	479.1491		210		6	
373		491.1852	491.1843	>10000	940	3945	7	>10000
374		519.2165	519.2148		800		8	
375		513.1695	513.1695		425		17	
376		529.1645	529.1625	>10000	360	>10000	0.8	>10000

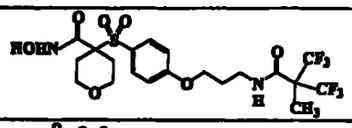
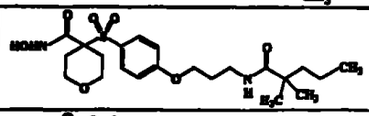
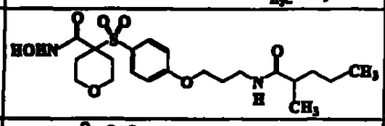
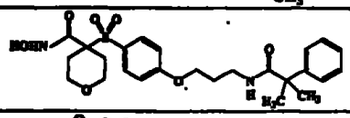
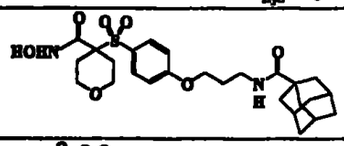
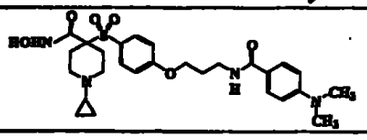
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
377		559.1750	559.1761		1271		5.9	
378		545.1594	545.1596		655		2.7	
379		545.1594	545.1585		258		10	
380		543.1801	543.1835		450		0.2	
381		498.1102	498.1090		193		1.4	
382		464.1491	464.1475		59		1.7	

Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
383		464.1491	464.1487		351		7.5	
384		532.0712	532.0709	>10000	176	2628	0.8	>10000
385		464.1491	464.1490	4341	253	>10000	3.3	>10000
386		468.1441	468.1459	>10000	131	35.3	1.2	9725
387		488.1491	488.1508		83		2.2	
388		529.1645	529.1640		185		2	

WO 97/27188 PCT/US97/01257

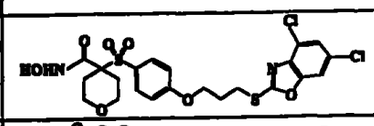
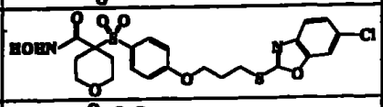
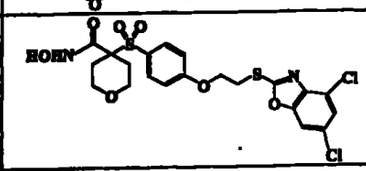
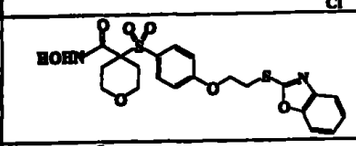
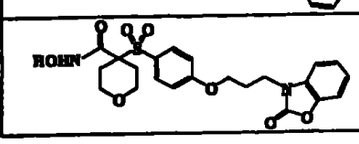
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
389		514.1648	514.1623		47		0.5	
390		514.1648	514.1641	>10000	907	>10000	2.7	>10000
391		466.1648	466.1647		900		7	
392		521.1958	521.1947	>10000	>10000	>10000	40	>10000
393		479.1488	479.1497		50		45	
394		506.1961	506.1961		3200		1900	

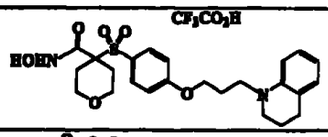
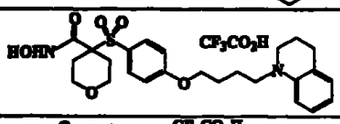
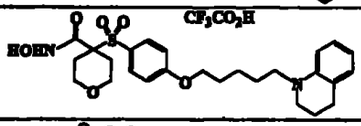
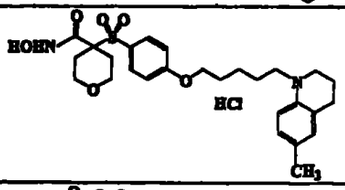
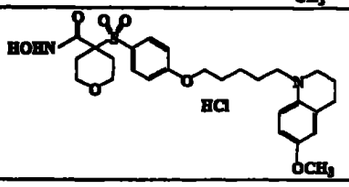
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
395		506.1961	506.1947		6000		305	
396		507.1801	507.1807		4		4	
397		520.2117	520.2093		3		14	
398		433	433		730		22	
399		469.2008	469.1988		650		8	
400		455.1852	455.1843		326		9	

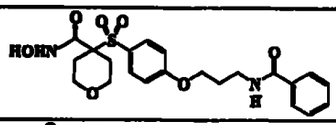
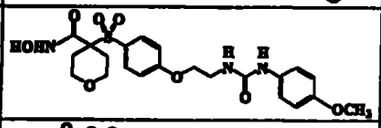
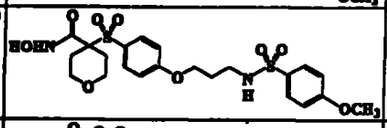
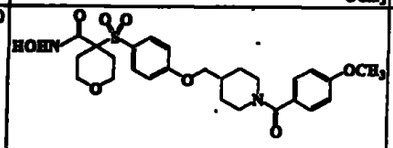
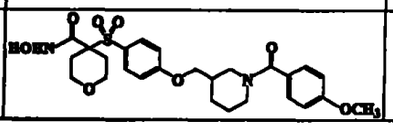
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
401		551.1287	551.1264		700		25	
402		471.2165	471.2144		454		30	
403		457.2008	457.1997	>10000	454	>10000	5.2	>10000
404		505.2008	505.1992		254		15	
405		521.5321	521.2323	>10000	2352	>10000	1.9	>10000
406		545.2434	545.2441	>10000	2200	>10000	4	>10000

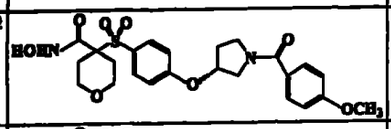
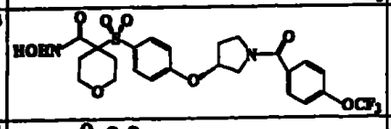
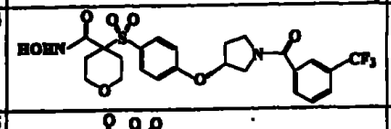
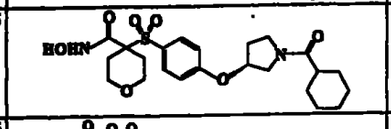
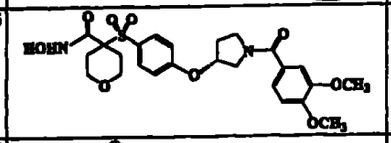
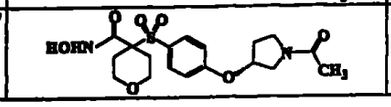
WO 02/092588
PCT/US02/15257

410

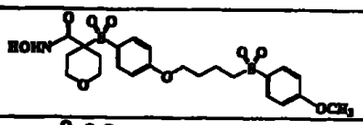
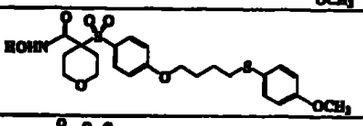
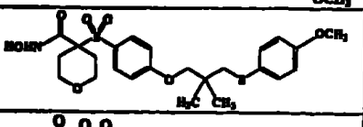
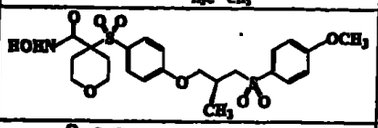
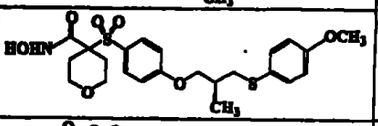
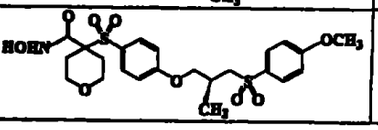
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
407		561.0324	561.0366		285		25	
408		527.0713	527.0694	>10000	90	49	2.5	6813
409		547.0167	547.0196	>10000	23	160	1	5644
410		479.0947	479.0978	4700	12	202	1.1	515
411		463.1175	463.1204	>10000	1517	>10000	587	>10000

Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
412		475.1903	475.0916		313		41	
413		489.2059	489.2068		61		8	
414		503.2216	503.2215		37		14	
415		517.2372	517.2377	>10000	51	1784	15	>10000
416		533.2321	533.2314		17		8.6	

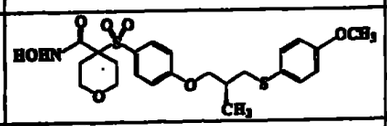
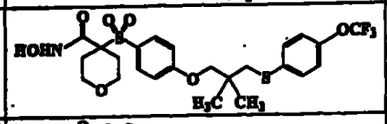
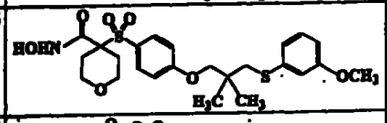
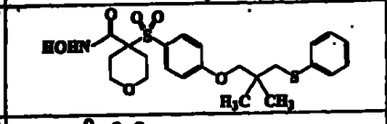
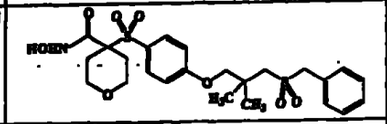
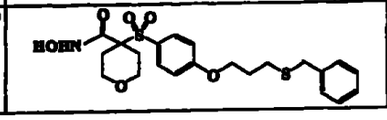
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
417		463.1539	463.1546		315		2.6	
418				>10000	1500	>10000	64	>10000
419					120		4	
420				>10000	67	>10000	4	>10000
421					649		256	

Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
422					7200		1484	
423					9000		1585	
424					485		192	
425					>10000		3308	
426					>10000		5151	
427					251		114	

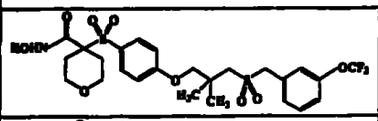
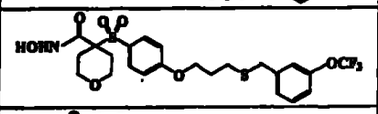
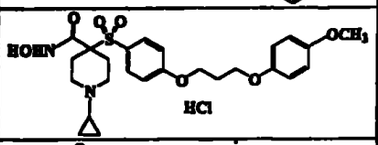
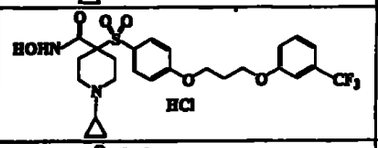
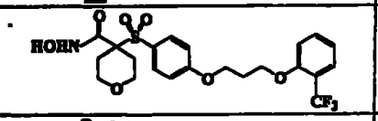
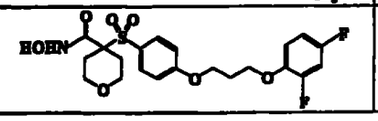
WO 02/092588 PCT/US02/15257

Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
428					20		1.4	
429					6.5	>10000	0.5	>10000
430					2700		195	
431					115		4	
432					7		1.5	
433					220		7	

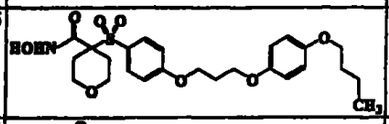
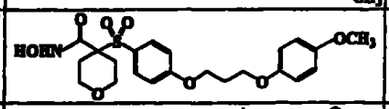
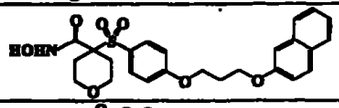
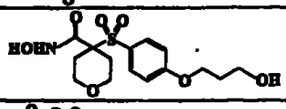
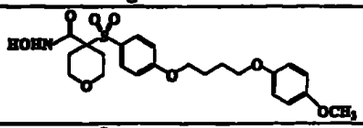
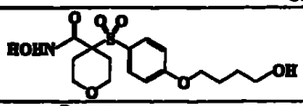
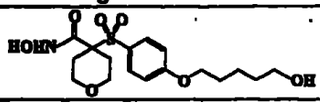
WO 97/27188 PCT/US97/15257

Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
434					1.1		0.6	
435				>10000	>10000		500	
436				>10000	1500		100	
437				>10000	>10000	>10000	90	>10000
438				>10000	505	3800	11	>10000
439				>10000	2000	6000	25	>10000

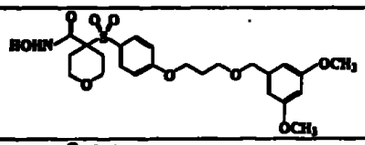
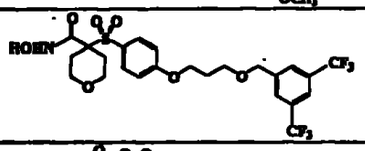
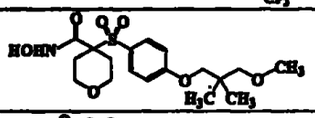
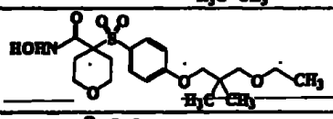
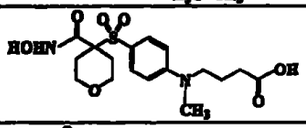
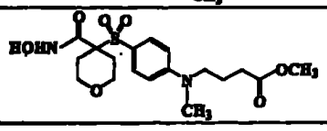
446

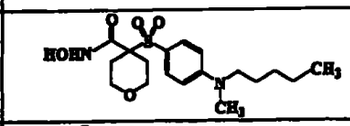
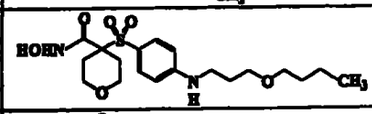
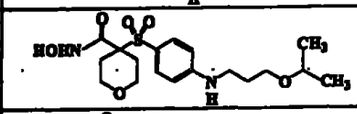
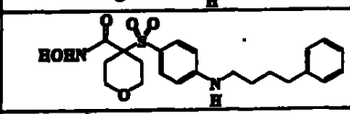
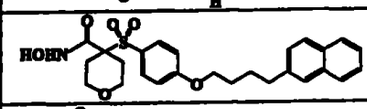
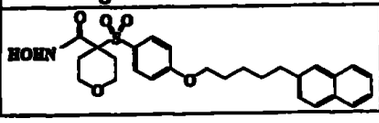
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
440				>10000	4	140	1	2500
441				9000	13	110	2	2290
442				>10000	6.2	5.4	1.8	997
443				>10000	25	375	3.5	2429
444					8.9		7.6	
445				3325	2.2	44	0.5	546

WO 02/092588 PCT/US01/15857

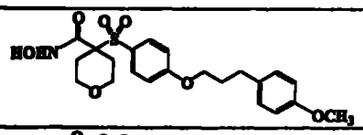
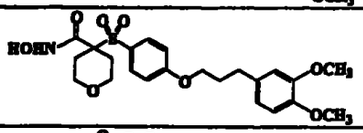
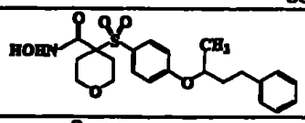
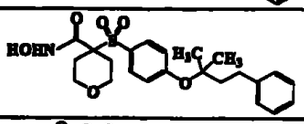
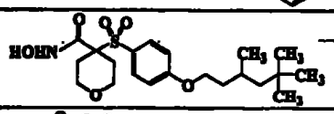
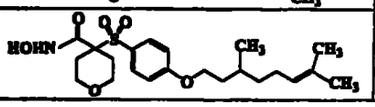
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
446					76		6.6	
447				>10000	8.9	12.2	2	1360
448				3080	9	116	2.7	832
449				1929	3.7	41	7	58
450				>10000	6.6	44	0.9	4937
451					4.7		9	
452					2.2		14.8	

418

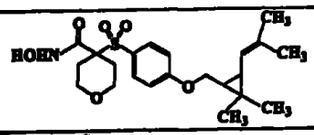
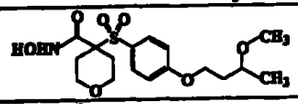
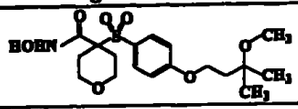
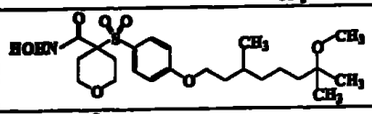
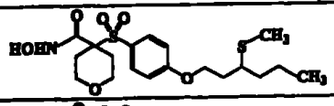
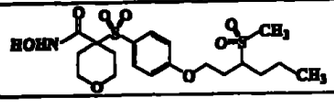
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
453				>10000	13	800	3	5000
454				>10000	165		27	
455					900		690	
456					425		350	
457				>10000	>10000		>10000	
458				>10000	3500		1400	

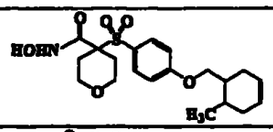
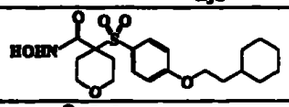
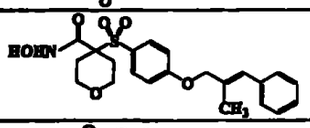
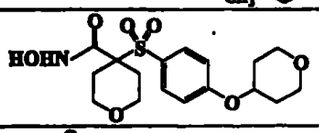
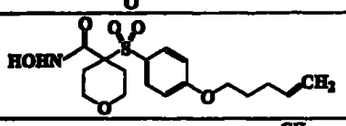
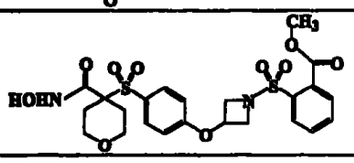
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
459				>10000	700		670	
460				>10000	145	700	25	>10000
461				>10000	2200		590	
462				>10000	11	18	7	6500
463		484.1794	484.1776		17		7	
464		498.195	498.1925		46		1.4	

420

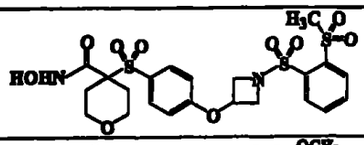
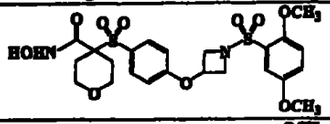
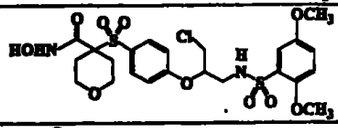
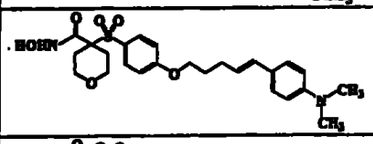
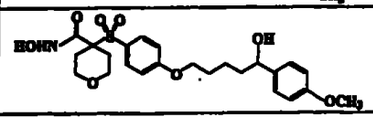
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
465		450.1586	450.1577	>10000	4	180	0.3	1800
466		480.1692	480.1732	>10000	110	45	15	>10000
467				>10000	940	450	120	>10000
468				>10000	2500		1500	
469				>10000	145		60	
470				>10000	7		3	

WO 02/092588 PCT/US02/15257

Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
471				>10000	270		120	
472				>10000	3	40	6	400
473				>10000	5	45	5	600
474				>10000	12		3	
475				>10000	30	120	2	3600
476				>10000	2500	>10000	230	>10000

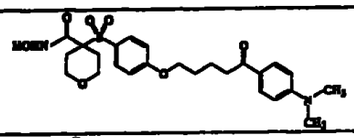
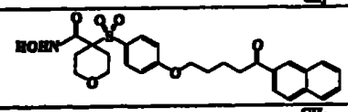
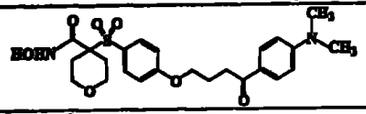
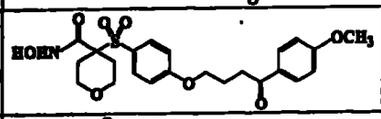
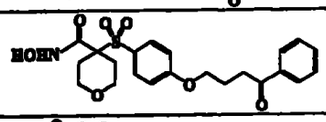
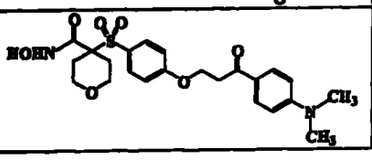
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
477				1300	1.5		2	
478				>10000	1	34	5	1450
479				2700	4	14	3	2000
480				4200	18	60	11	1400
481					1.3		2	
482					3300		40	

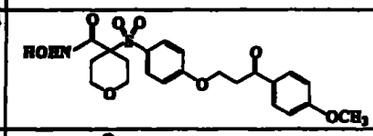
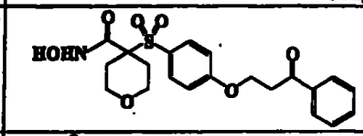
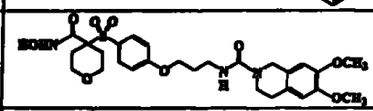
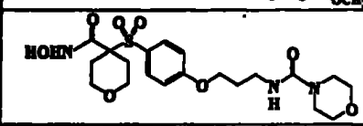
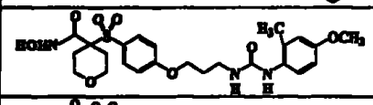
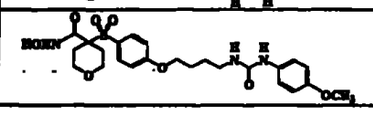
WO 02/092588 PCT/US02/15257

Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
483					2000		29	
484					640		12	
485					4000		64	
486				>10000	106	255	4.6	>10000
487				>10000	3.1	169	0.5	1570

WO 02/092588

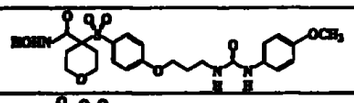
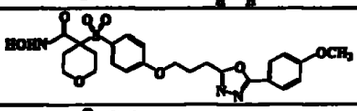
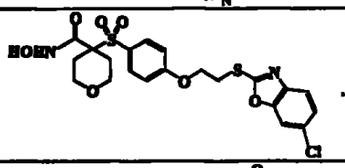
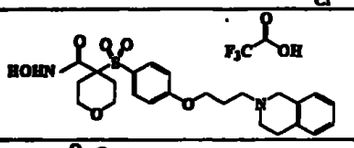
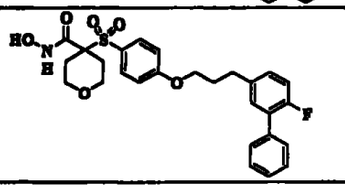
PCT/US02/15257

Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
488		505.2008	505.1991					
489		512.1743	512.1766	>10000	58.2	>10000	0.4	>10000
490		491.1852	491.1856	>10000	18.2	928	0.2	5630
491		478.1536	478.1540	7310	6.8	94.2	0.8	981
492		448.1430	448.1428	3550	3.5	67.3	0.7	574
493		471.1695	471.1695	4770	15.9	752	0.9	3230

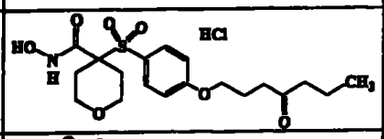
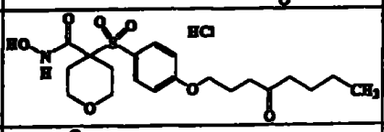
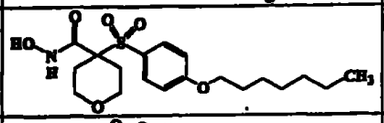
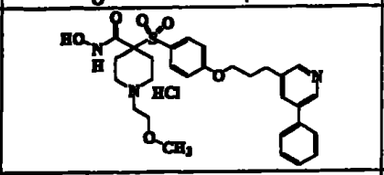
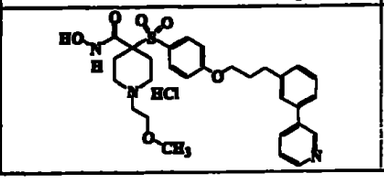
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
494		464.1392	464.1379	1520	<0.1	13.6	<0.1	197
495		434.1273	434.1277	815	1.9	25.8	1.7	505
496		578.2172	578.2164		242		8.4	
497		472.1754	472.1769		1450		23.5	
498		522.191	522.1915		160		14.8	
499		508.1754	508.1753		56.2		7.0	

WO 02/092588
PCT/US02/15257

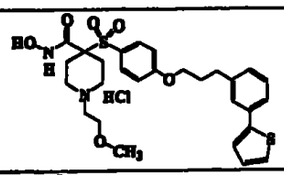
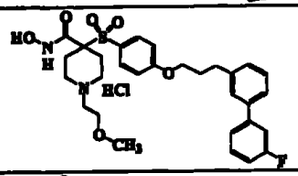
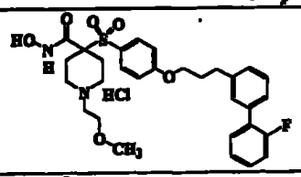
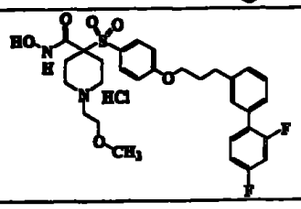
425

Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
500		494.1597	494.1596	2390	1,9	63.2	8.5	2960
501		518.1597	518.158	>10000	184	7710	1.4	>10000
502		513.0557	513.0574	>10000	22.7	160	1.0	5640
503		475.1903	475.1907					
504		514.1700	514.1735	(>10000)	(434)	(2310)	(4.65)	(>10000)

WO 02/092588 PCT/US02/15257

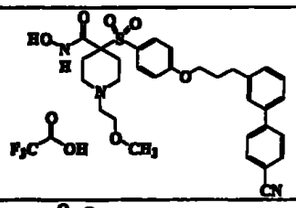
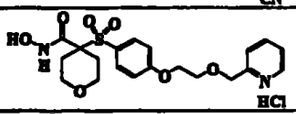
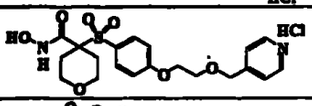
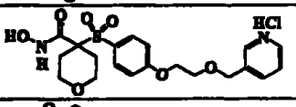
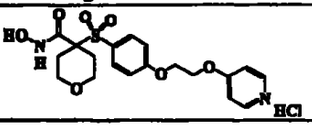
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
505		414.1581	414.1586	(850)	(2.56)	(10.2)	(0.81)	(962)
506		428.1738	428.1751	(1465)	(1.92)	(11.4)	(0.23)	(681)
507		400.1767	400.1788	(3590)	(0.84)	(0.44)	(0.19)	(444)
508		554.2319	554.2347	(4850)	(22.8)	(160)	(0.141)	(2790)
509		554.2319	554.2308	(>10000)	(89.26)	(50.85)	(0.297)	(4158.92)

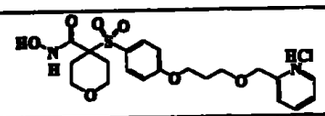
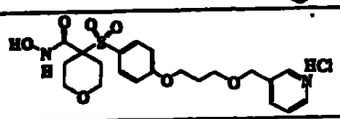
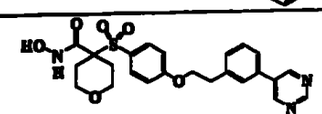
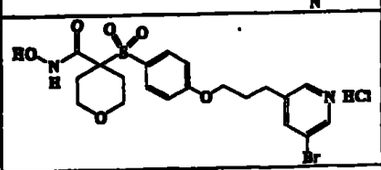
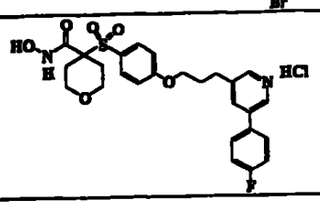
WO 02/072588 PCT/US02/15257

Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
510				(>10000)	(7.85)	(39.82)	(0.25)	(2183.66)
511		571.2273	571.2255	(>10000)	(525.78)	(38.53)	(1.36)	(>10000)
512		571.2273	571.2281	(>10000)	(757.99)	(25.71)	(1.07)	(>10000)
513		589.2178	589.2193	(>10000)	(879.71)	(254.58)	(0.98)	(9274.4)

WO 02/062388 PCT/US02/03257

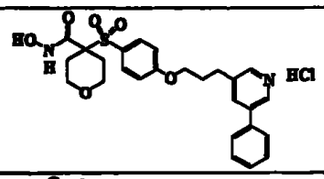
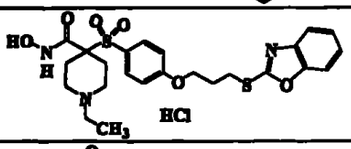
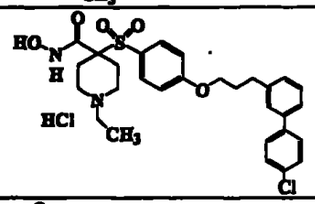
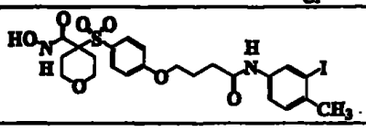
428

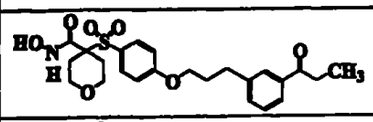
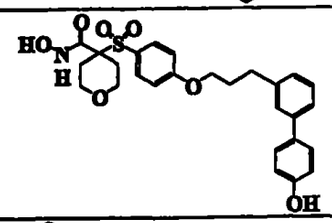
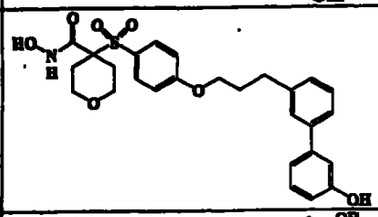
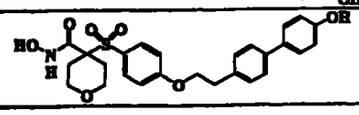
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
514		578.2319	578.2305	(>10000)	(292.63)	(223.53)	(0.28)	(4082.05)
515				>10000	89.76	154.32	24.23	>10000
516				>10000	41.94	119.72	9.55	9434.24
517				>10000	34.66	137.63	6.19	>10000
518				>10000	26.35	115.39	169.48	967.13

Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
519				>10000	170.25	421.64	2.18	>10000
520				>10000	54.24	36.38	0.62	4296.13
521					62.0		5.8	
522				(>10000)	12.9 (32.1)	(135)	0.3	(6290)
523		515.1647	515.1690	8069 (3213)	161.6 (196.7)	1647.2 (1253)	0.3 (0.234)	>10000 (>10000)

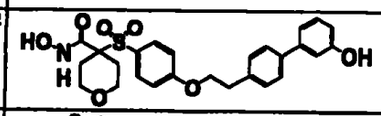
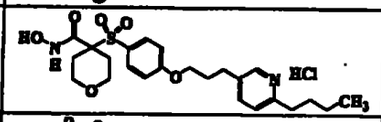
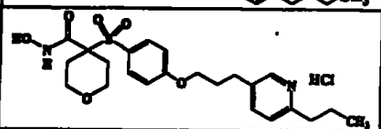
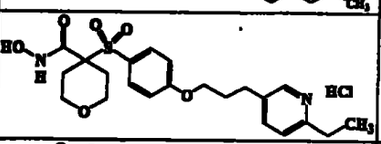
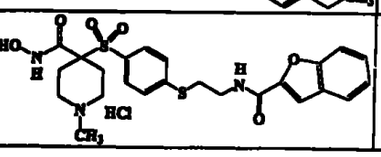
WO 02/092588 PCT/US02/15257

430

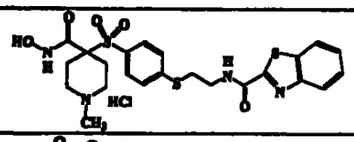
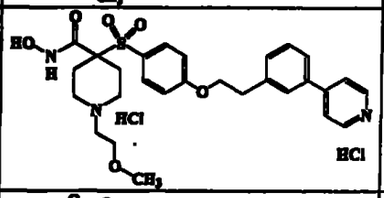
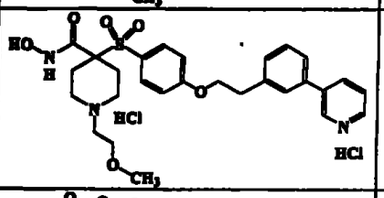
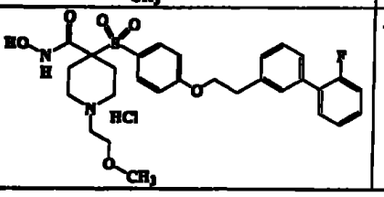
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
524		497.1741	497.1763	>10000	38.3 (51.8)	1841.5 (739.5)	0.2 (0.244)	>10000 (>10000)
525		520.1576	520.1581		7.5		1.5	
526		557.1871	557.1863 557.1843	(>10000)	(1680)	(2070)	(3.96)	(>10000)
527				(5100)	(21.3)	(30.4)	(.044)	(1360)

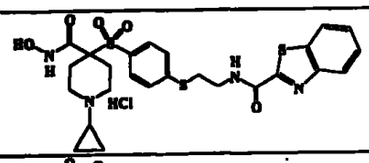
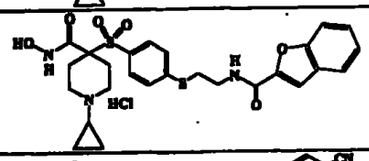
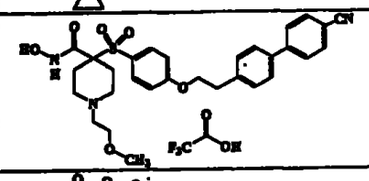
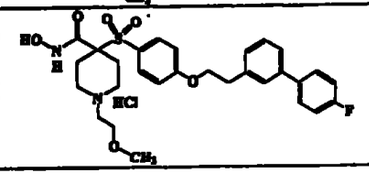
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
528				(>10000)	(83.5)	(238)	(2.57)	(5700)
529		529.2003	529.1982	(>10000)	(3550)	(1870)	(20.2)	(>10000)
530		512.1738	512.1774	(>10000)	(699)	(220)	(7.33)	(>10000)
531		498.1581	498.1614	(>10000)	(337)	(774)	(2.72)	(>10000)

WO 02/02588 PCT/US01/21257

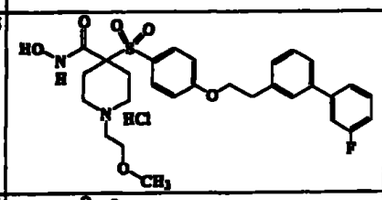
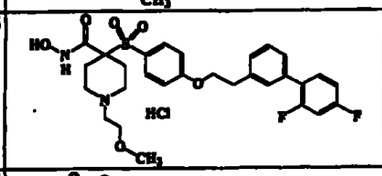
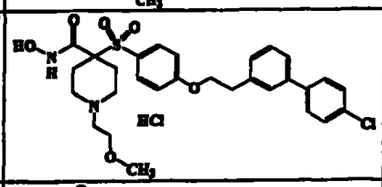
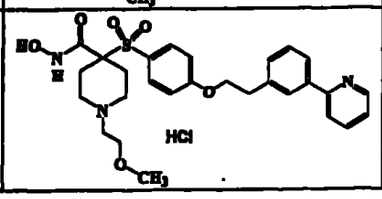
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
532		498.1581	498.1610	(>10000)	(739)	(1320)	(1.02)	(>10000)
533				(>10000)	(29.3)	(141)	(0.226)	(6680)
534				(>10000)	(25.4)	(324)	(0.493)	(6810)
535				(>10000)	(23.2)	(128)	(0.261)	(3870)
536				(>10000)	(744)	(3400)	(3.4)	(>10000)

WO 02/057288 PCT/US02/01257

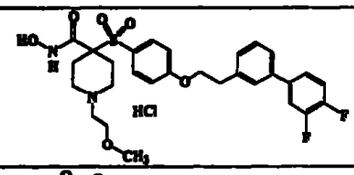
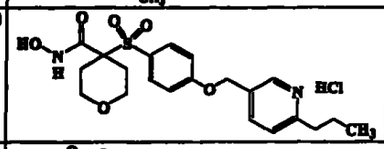
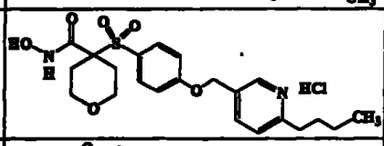
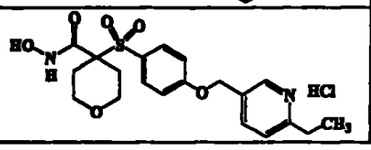
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
537		535.1138	535.1160	(>10000)	(985)	(900)	(0.657)	(>10000)
538		540.2163	540.2142	(>10000)	(24.6)	(117)	(0.184)	(1700)
539		540.2163	540.2160	(9130)	(38.6)	(85.5)	(0.21)	(1180)
540		557.2116	557.2132	(>10000)	(270)	(689)	(0.58)	(>10000)

Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
541		561.1295	561.1266	(>10000)	(302.15)	(269.03)	(0.24)	(>10000)
542		544.1571	544.1566	(>10000)	(234.13)	(921.73)	(0.86)	(>10000)
543		564.2163	564.2192	(>10000)	(124.15)	(207.41)	(0.23)	(3094.73)
544		557.2116	557.2087	(>10000)	(302.23)	(787.01)	(0.898)	(>10000)

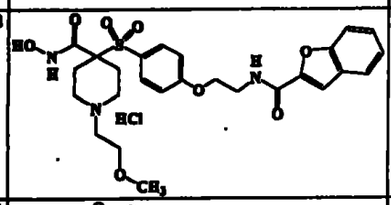
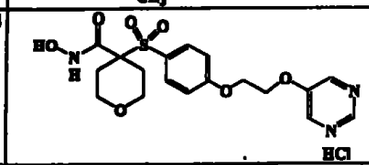
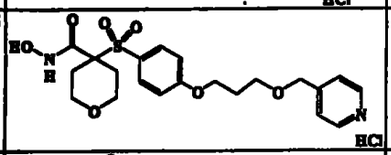
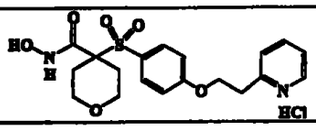
435

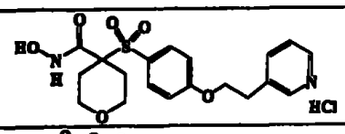
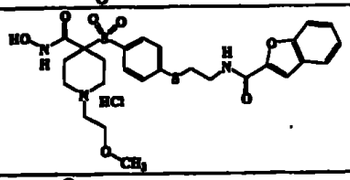
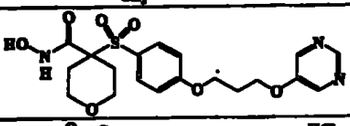
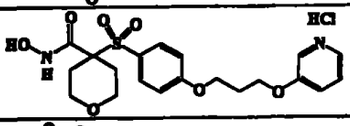
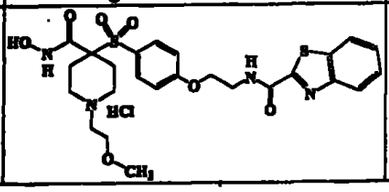
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
545		557.2116	557.2101	(>10000)	(309.81)	(922.55)	(1.11)	(>10000)
546		575.2022	557.5023	(>10000)	(426.17)	(1269.5)	(1.06)	(>10000)
547		573.1821	573.1848	(>10000)	(727.08)	(1863.44)	(2.28)	(>10000)
548		540.2163	540.2193	(>10000)	(1.58)	(278.57)	(0.38)	(7415.08)

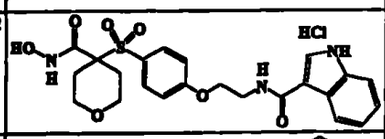
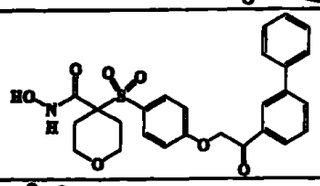
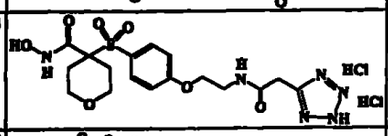
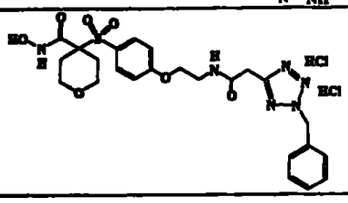
WO 02/096288 PCT/US02/15257

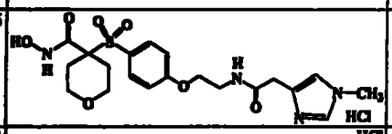
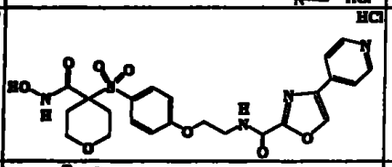
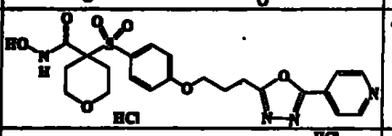
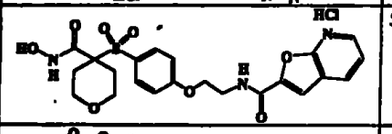
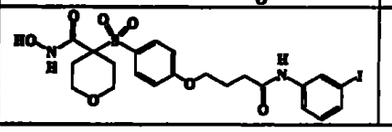
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
549		575.2022	575.2042	(>10000)	(503.95)	(1770.79)	(1.87)	(>10000)
550				(>10000)	(5.49)	(7.51)	(0.52)	(2180)
551				(>10000)	(5.07)	(48.2)	(0.62)	(2055)
552				(>10000)	(4.94)	(2.22)	(1.78)	(2440)

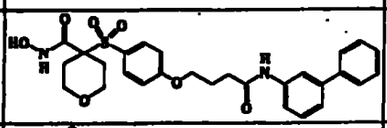
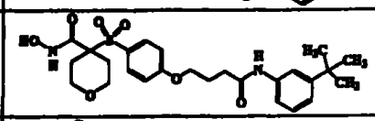
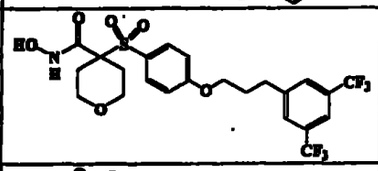
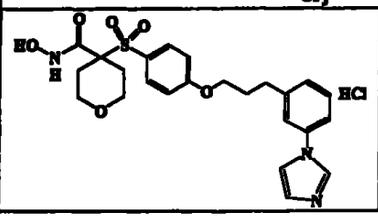
WO 02/092588 PCT/US02/15257

Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
553		546.1905	546.1896	(>10000)	(7.797)	(71.205)	(0.259)	(2257.112)
554				(>10000)	(61.27)	(442.07)	(14.50)	(>10000)
555				(>10000)	(3.383)	(50.012)	(0.261)	(688.63)
556				(8972.84)	(68.058)	(211.92)	(53.22)	(3496.68)

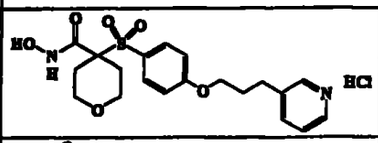
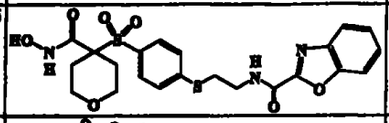
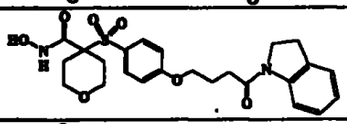
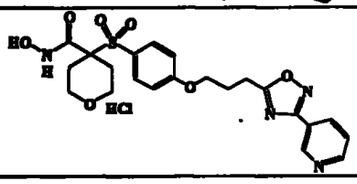
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
557				(>10000)	(6.46)	(33.57)	(3.68)	(52.23)
558		562.1676	562.1714	(>10000)	(352.06)	(1357.7)	(2.163)	(>10000)
559				(>10000)	(11.65)	(57.56)	(1.51)	(845.5)
560				(>10000)	(10.26)	(7.17)	(0.616)	(549.16)
561		579.1400	579.1389	(>10000)	(336.04)	(467.44)	(0.31)	(>10000)

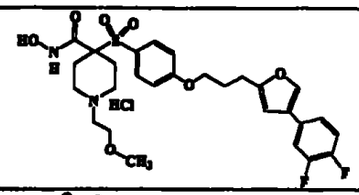
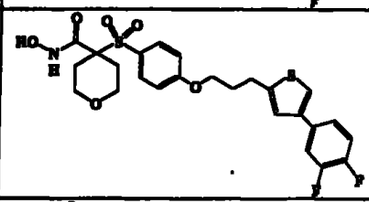
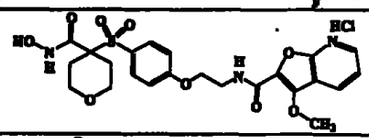
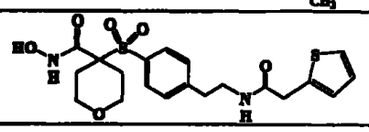
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
562		488.1486	488.1476	(2738.33)	(241.03)	(785.83)	(2.97)	(9265.67)
563		496.1425	496.1453	(>10000)	73.5 (70.11)	(132.06)	1.1 (0.70)	(4400.5)
564		455.1343	455.1345		144.9		19.4	
565		545.1813	545.1825		14.0		1.6	

Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
566		467.1595	467.1643		65.7		18.8	
567		549.0931	549.0955		660.5		21.9	
568		489.1438	489.1435		21.0		1.5	
569		506.1050	506.1028		1405		171.8	
570				(3061.49)	4.8 (10.09)	(6.15)	0.2 (0.142)	(1357.46)

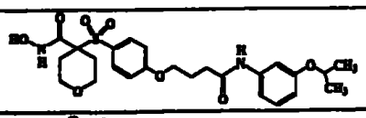
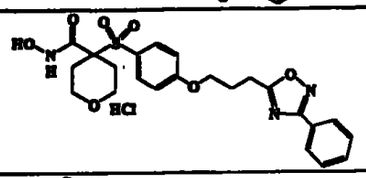
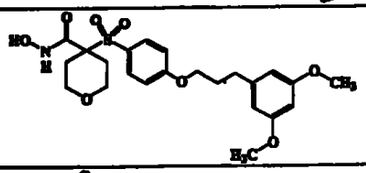
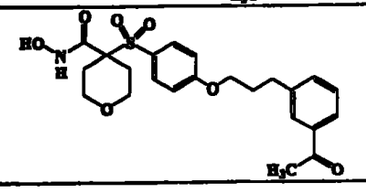
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
571					11.9		1.6	
572					37.3		4.7	
573		556.1223	556.1214		1707.7		75.1	
574				(>10000)	29.4 (112.25)	(83.02)	0.7 (1.32)	(5386.06)

WO 02/092588 PCT/US02/15257

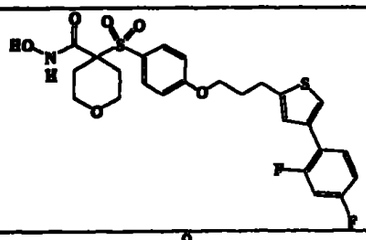
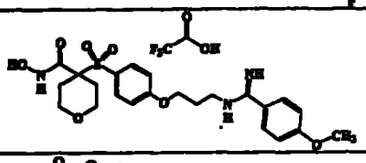
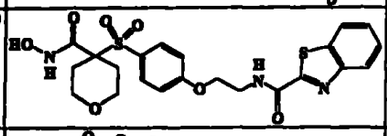
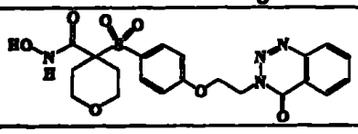
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
575					8.4		2.0	
576		506.1050	506.1069	>10000	232.7	397.0	0.3	>10000
577					48.2		1.2	
578		489.1438	489.1428	(>10000)	20.5 (72.1)	(578)	2.9 (1.72)	(>10000)

Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
579		595.1743	595.1767	>10000	37.8	136.0	0.4	>10000
580		555.1430	555.1454	>10000	136.0	417.2	0.6	>10000
581		536.1156	536.1173		2534.3		29.8	
582		460.1571	460.1573		55.7		25.3	

WO 02/092588 PCT/US02/15257

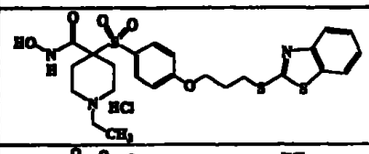
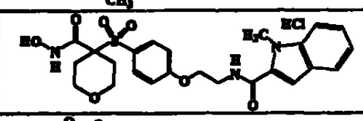
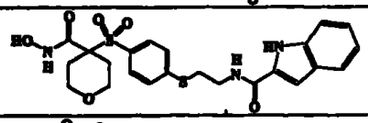
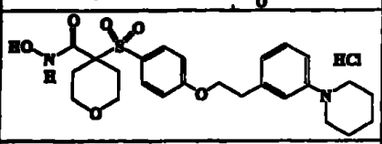
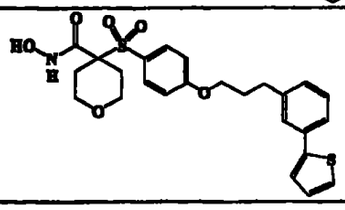
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
583					15.7		1.6	
584				(2760)	72.9 (20.8)	(12.6)	3.6 (0.944)	(6630)
585					85.4		4.0	
586					10.1		0.6	

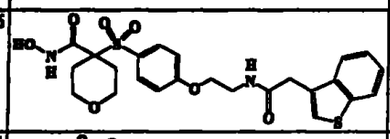
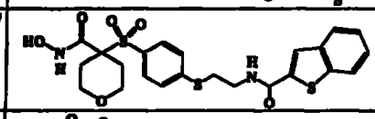
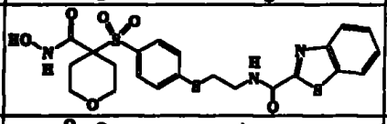
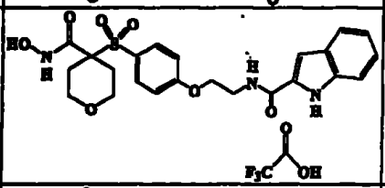
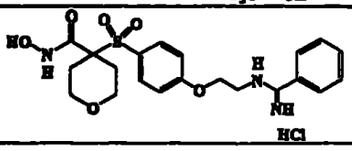
WO 02/092588 PCT/US02/15257

Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
587		538.1164	538.1191	>10000 (>10000)	81.7 (124.9)	1372.9 (8180)	0.1 (1.424)	>10000 (4154)
588		492.1804	492.1773		94.9		15.0	
589		506.1050	506.1054		9.9		0.4	
590					857.7		48.0	

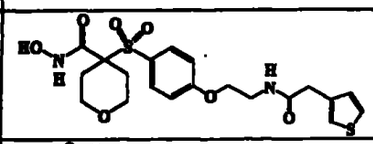
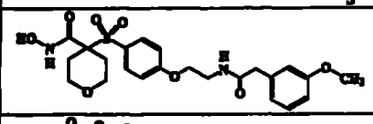
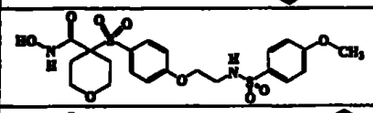
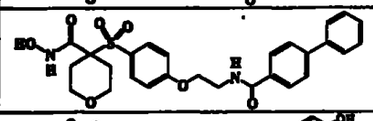
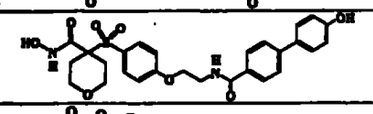
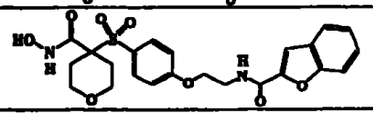
WO 02/092588 PCT/US02/15257

476

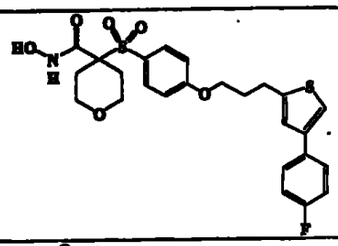
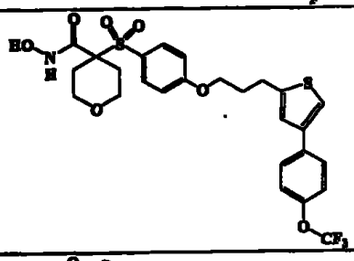
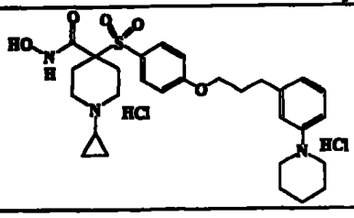
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
591		536.1348	536.1372	>10000 (>10000)	3.5 (4.4)	12.0 (4.22)	0.3 (0.19)	>10000 (8742.7)
592		502.1648	502.1639		336.4		38.7	
593		504.1263	504.1254		6.5		15.6	
594					140.1		3.8	
595		502.1353	502.1359	>10000 (>10000)	482.5 (586.2)	1733 (2056.6)	1.0 (7.245)	>10000 (>10000)

Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
596		519.1260	519.1265	>10000 (>10000)	10.3 (11.2)	194.5 (307.7)	2.7 (0.398)	2491 (1160)
597		521.0875	521.0910		471.1		12.1	
598		522.0827	522.0932	(>10000)	(599.35)	(705.33)	(0.27)	(>10000)
599		488.1491	488.1491	>10000 (>10000)	<0.1 (0.38)	11.6 (11.34)	0.1 (0.24)	57.01
600		448.1542	448.1542		205.7		214.4	

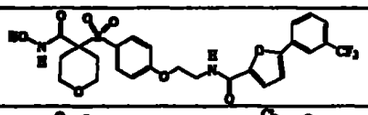
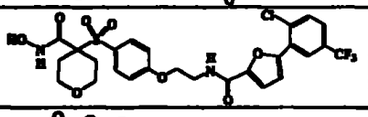
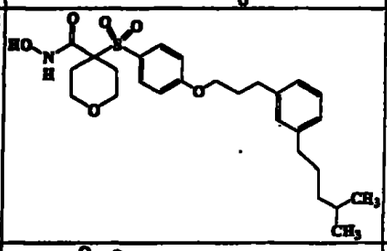
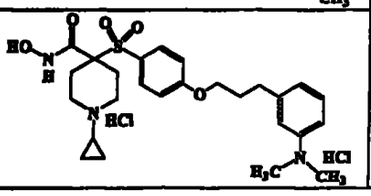
WO 02/092588
PCT/US02/15257

Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
601		469.1103	469.1093	4916	1.9	42.6	1.3	2062
602		493.1639	493.1608		13.7		3.6	
603		515.1158	515.1145		34.0		2.4	
604					36.6		3.3	
605					44.0		3.8	
606		489.1332	489.1326	>10000 (>10000)	5.0 (11.574)	234.0 (105.89)	0.4 (0.432)	2566 (2053.20)

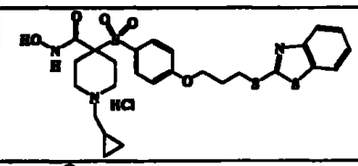
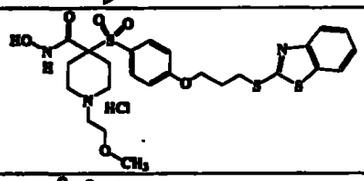
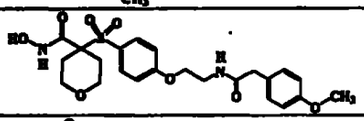
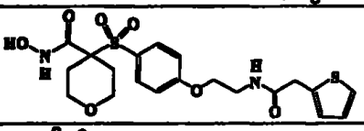
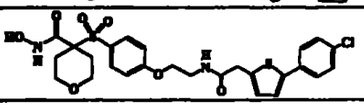
WO 02/092588 PCT/US02/15257

Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
607		520.1264	520.1297	>10000	45.2	2298	0.1	>10000
608		586.1181	586.1160	>10000 (>10000)	342.1 (723.95)	1794 (1368.3)	6.6 (9.34)	>10000 (>10000)
609				>10000	579.9	6887	7.7	>10000

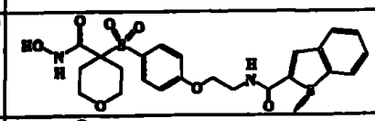
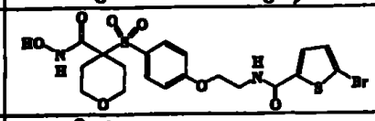
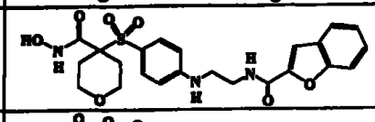
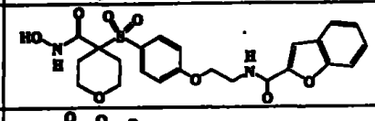
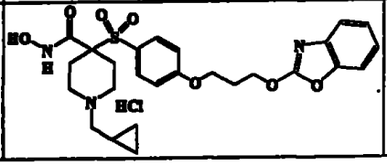
WO 02/092588
PCT/US02/15257

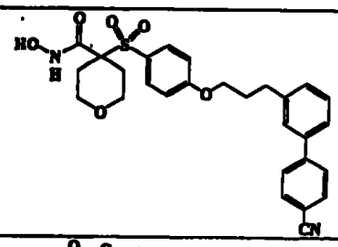
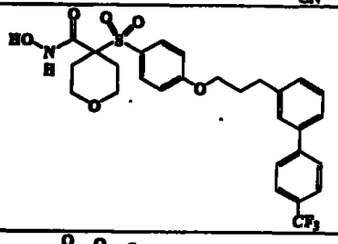
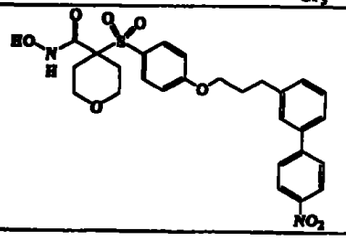
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
610					488.3		4.1	
611					733.2		13.6	
612		504.2414	504.2413		1232.2		16.1	
613					34.3		6.6	

WO 02/092588 PCT/US02/15257

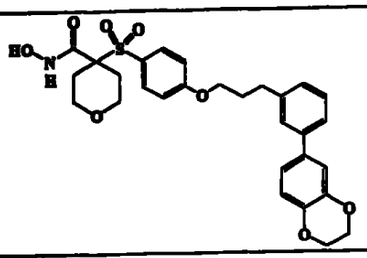
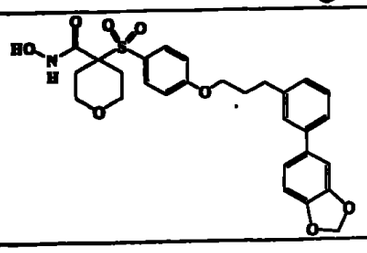
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
614		562.1504	562.1516	>10000	1.8	8.5	0.7	9440
615		566.1443	566.1453	>10000	1.1	3.6	0.4	6696
616		493.1645	493.1617	1584	5.3	54.8	2.0	1969
617		469.1103	469.1086	2074 1112	0.8	413	0.6	4133
618					822.1		27.5	

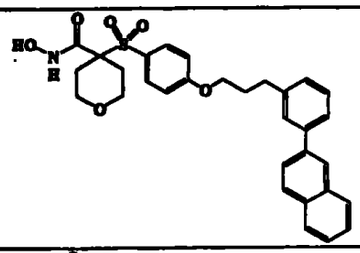
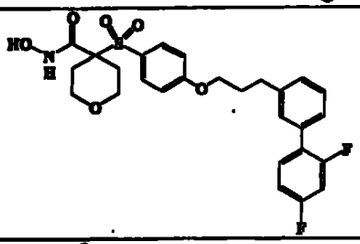
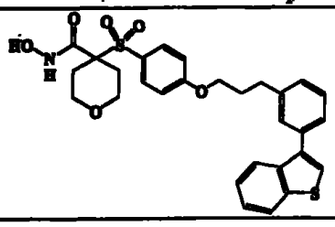
WO 02/092588 PCT/US02/15257

Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
619					66.2		1.5	
620					16.2		4.1	
621		488.1491	488.1489		367.6		17.8	
622		505.1103	505.1120	>10000 (>10000)	273.1 (450.85)	1756 (2077.1)	1.5 (2.68)	>10000 (>10000)
623		546.1733	546.1728	>10000	5.2	3.1	1.2	5520

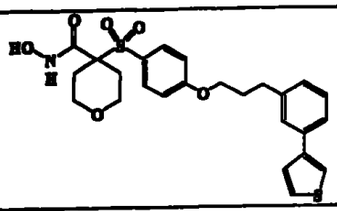
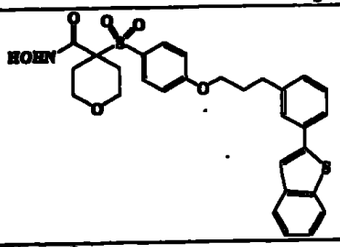
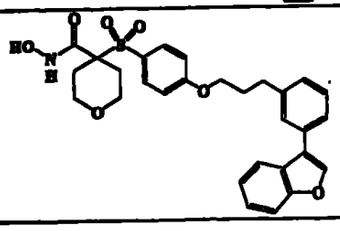
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-3 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
624		521.1746	521.1753	>10000 (>10000)	214.4 (623)	1029 (443)	0.3 (0.9)	>10000 (7580)
625		564.1668	564.1643	(>10000)	3499.5 (6860)	(4600)	33.6 (43.6)	(>10000)
626		558.191	558.1925	>10000 (>10000)	142.8 (645)	885 (1100)	0.4 (7.5)	>10000 (>10000)

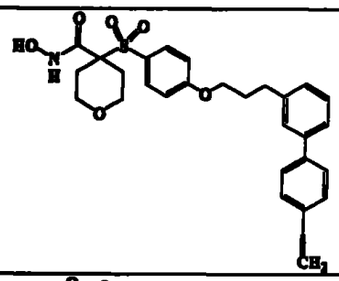
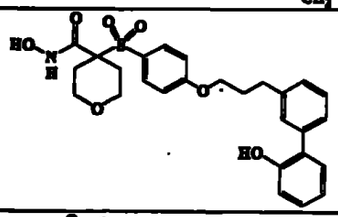
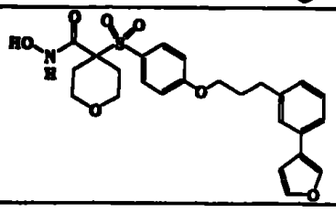
WO 02/074388
PCT/US02/15257

Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
627		554.1849	554.1884	(>10000)	2072.7 (3950)	(3150)	14.9 (40.9)	(>10000)
628		540.1692	540.1712	>10000 (>10000)	1701.3 (2750)	1754 (1930)	3.3 (19.8)	>10000 (>10000)

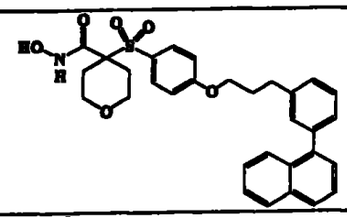
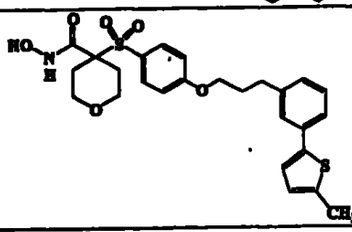
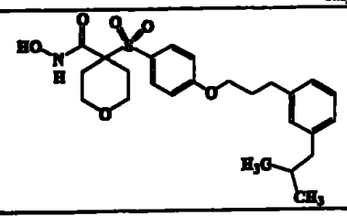
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
629		546.1950	546.1965	(>10000)	536.8 (1020)	(1300)	78.6 (89.1)	(>10000)
630		532.1605	532.1598	>10000 (>10000)	1166.6 (2070)	5990 (2280)	0.4 (6.02)	>10000 (>10000)
631		552.1515	552.1520	(>10000)	2143.2 (4960)	(5810)	117.7 (57.6)	(>10000)

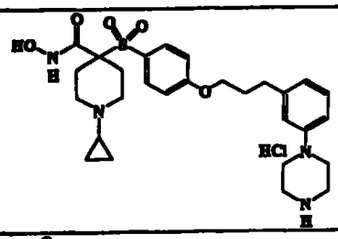
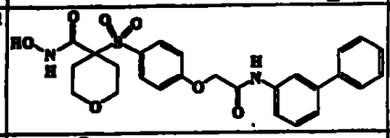
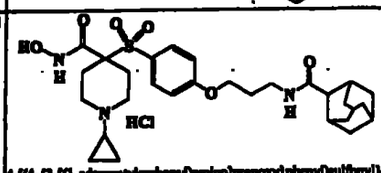
WO 02/092588 PCT/US02/15257

Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
632		502.1358	502.1387	>10000 (>10000)	91.0 (279)	411 (716)	1.6 (6.54)	>10000 (>10000)
633		552.1515	552.1510	(>10000)	2828.1 (4580)	(6780)	117.0 (92.4)	(>10000)
634		536.1743	536.1730	(>10000)	486.4 (983)	(1300)	16.3 (19.4)	(>10000)

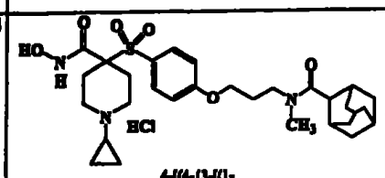
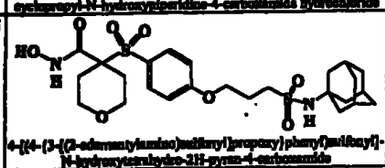
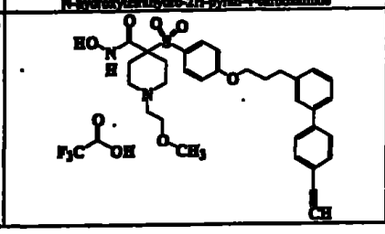
Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
635		522.1950	522.1973	(>10000)	2309.5 (4680)	(4830)	. 20.0 (26.2)	(>10000)
636		512.1743	512.1755	(>10000)	195.0 (527)	(763)	3.2 (3.21)	(>10000)
637		486.1586	486.1576	>10000 (>10000)	137.6 (498)	830 (881)	1.8 (4.63)	>10000 (>10000)

WO 02/092588 PCT/US02/15357

Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
638		546.1950	546.1950	(>10000)	4400.9 (8120)	(8770)	400.4 (68.1)	(>10000)
639		516.1515	516.1501	(>10000)	247.1 (505)	(688)	4.3 (12.5)	(>10000)
640		476.2101	476.2114		324.5		10.4	

Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
641					134.7		5.0	
642		528.1799	528.1771		2889.0		36.9	
643	 4-[[4-(3-[(1-adamantylcarbonyl)amino]propoxy)phenyl]sulfonyl]-1-cyclopropyl-N-hydroxypiperidine-4-carboxamide hydrochloride	560.2794	560.2793		1134.1		11.4	

WO 02/092588 PCT/US02/15257

Ex #	Structure	Calc. Mass	Observed Mass	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
644	 4-[(4-{3-[(1-adamantylcarbonyl)(methyl)amino]propoxy}phenyl)sulfonyl]-1-cyclopropyl-N-hydroxypiperidine-4-carboxamide hydrochloride	574.2951	574.2943		2633.4		20.9	
645	 4-[(4-{3-[(3-adamantylamino)sulfonyl]propoxy}phenyl)sulfonyl]-N-hydroxytetrahydro-2H-pyran-4-carboxamide	557	557	9283	22.9	1726	4.3	>10000
646				(>10000)	(288.84)	(76.21)	(0.16)	(4296.95)

WO 02/02588 PCT/US01/21571

464

* * * * * * * * *

[1115] The above detailed description of preferred embodiments is intended only to acquaint others skilled in the art with the invention, its principles, and its practical application so that others skilled in the art may adapt and apply the invention in its numerous forms, as they may be best suited to the requirements of a particular use. This invention, therefore, is not limited to the above embodiments, and may be variously modified.

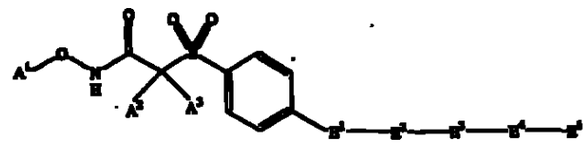
465

CLAIMS

We claim:

1. A compound or salt thereof, wherein:

the compound corresponds in structure to Formula 1-1:



(1-1); and

A^1 is selected from the group consisting of -H, alkylcarbonyl, alkoxycarbonyl, carbocyclylcarbonyl, carbocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclylalkylcarbonyl, carbocyclyloxycarbonyl, carbocyclylalkoxycarbonyl, aminoalkylcarbonyl, alkyl(thiocarbonyl), alkoxy(thiocarbonyl), carbocyclyl(thiocarbonyl), carbocyclylalkyl(thiocarbonyl), heterocyclyl(thiocarbonyl), heterocyclylalkyl(thiocarbonyl), carbocyclyloxy(thiocarbonyl), carbocyclylalkoxy(thiocarbonyl), and aminoalkyl(thiocarbonyl), wherein any member (except -H) of such group optionally is substituted; and

A^2 and A^3, together with the carbon atom to which they are both attached, form an optionally-substituted heterocyclyl containing from 5 to 8 ring members; and

E^1 is selected from the group consisting of -O-, $-S(O)_2-$, -S(O)-, -S-, $-N(R^1)-$, $-C(O)-N(R^1)-$, $-N(R^1)-C(O)-$, and $-C(R^1)(R^2)-$; and

E^2 is selected from the group consisting of alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, and alkylcycloalkylalkyl, wherein any member of such group optionally is substituted; and

E^2 forms a link of at least 2 carbon atoms between E^1 and E^3; and

E^3 is selected from the group consisting of -C(O)-, -O-(CO)-, -C(O)-O-, $-C(NR^3)-$, $-N(R^4)-$, $-N(R^4)-C(NR^3)-$, $-C(NR^3)-N(R^4)-$, $-C(O)-N(R^4)-$, $-N(R^4)-C(O)-$, $-N(R^4)-C(O)-N(R^5)-$, -S-, -S(O)-, $-N(R^4)-S(O)_2-$, $-S(O)_2-N(R^4)-$, $-C(O)-N(R^4)-N(R^5)-C(O)-$, $-C(R^6)(R^6)-C(O)-$, $-C(R^7)(R^8)-$; and

E^4 is selected from the group consisting of a bond, alkyl, and alkenyl, wherein the alkyl or alkenyl optionally is substituted; and

E^5 is selected from the group consisting of -H, -OH, alkyl, alkenyl, alkynyl, alkoxy, alkoxyalkyl, carbocyclyl, and heterocyclyl, wherein any member (except -H or, -OH) of such group optionally is substituted; and

R^1 and R^2 are independently selected from the group consisting of -H and alkyl, wherein the alkyl optionally is substituted; and

R^3 is selected from the group consisting of -H and -OH; and

R^4 and R^5 are independently selected from the group consisting of -H, alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, and heterocyclylalkyl, wherein any member (except -H) of such group optionally is substituted; and

R^6 is selected from the group consisting of -CN and -OH; and

R^7 is selected from the group consisting of -H, halogen, -OH, alkyl, alkoxy, and alkoxyalkyl, wherein the alkyl, alkoxy, or alkoxyalkyl optionally is substituted; and

R^8 is selected from the group consisting of -OH and alkoxy, wherein the alkoxy optionally is substituted; and

neither R^1 nor R^2 forms a ring structure with E^2, E^3, E^4, or E^5; and

neither R^4 nor R^5 forms a ring structure with E^2, E^4, or E^5; and

E^5 is not -H when both E^3 is $-C(R^7)(R^8)-$ and E^4 is a bond.

2. A compound or salt thereof according to claim 1, wherein:

A^1 is selected from the group consisting of -H, C_1-C_8-alkylcarbonyl, C_1-C_8-alkoxycarbonyl, carbocyclylcarbonyl, carbocyclyl-C_1-C_8-alkylcarbonyl, heterocyclylcarbonyl, heterocyclyl-C_1-C_8-alkylcarbonyl, carbocyclyloxycarbonyl, carbocyclyl-C_1-C_8-alkoxycarbonyl, $N(R^9)(R^{10})$-C_1-C_8-alkylcarbonyl, C_1-C_8-alkyl(thiocarbonyl), C_1-C_8-alkoxy(thiocarbonyl), carbocyclyl(thiocarbonyl), carbocyclyl-C_1-C_8-alkyl(thiocarbonyl), heterocyclyl(thiocarbonyl), heterocyclyl-C_1-C_8-alkyl(thiocarbonyl), carbocyclyloxy(thiocarbonyl), carbocyclyl-C_1-C_8-alkoxy(thiocarbonyl), and $N(R^9)(R^{10})$-C_1-C_8-alkyl(thiocarbonyl); and

E^2 is selected from the group consisting of C_2-C_{20}-alkyl, cycloalkyl, C_1-C_{10}-alkylcycloalkyl, cycloalkyl-C_1-C_{10}-alkyl, and C_1-C_{10}-alkylcycloalkyl-C_1-C_{10}-alkyl, wherein any member of such group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, C_1-C_8-alkyl, and halo-C_1-C_8-alkyl; and

E^4 is selected from the group consisting of a bond, C_1-C_{20}-alkyl, and C_2-C_{20}-alkenyl, wherein the C_1-C_{20}-alkyl or C_2-C_{20}-alkenyl optionally is substituted with one or more substituents independently selected from the group consisting of:

halogen, and

carbocyclyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_8-alkyl, C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, halo-C_1-C_8-alkyl, halo-C_1-C_8-alkoxy, halogen-substituted C_1-C_8-alkoxy-C_1-C_8-alkyl, halocarbocyclyl, and halogen-substituted carbocyclyl-C_1-C_8-alkyl; and

E^5 is selected from the group consisting of -H, -OH, C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, C_1-C_{20}-alkoxy, C_1-C_{20}-alkoxy-C_1-C_{20}-alkyl, carbocyclyl, and heterocyclyl, wherein:

the C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, C_1-C_{20}-alkoxy, or C_1-C_{20}-alkoxy-C_1-C_{20}-alkyl optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, and -CN, and

the carbocyclyl or heterocyclyl optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_8-alkyl, C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, $-N(R^{11})(R^{12})$, $-C(O)(R^{13})$, $-S-R^{11}$, $-S(O)_2-R^{11}$, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, halo-C_1-C_8-alkyl, halo-C_1-C_8-alkoxy, halogen-substituted C_1-C_8-alkoxy-C_1-C_8-alkyl, halocarbocyclyl, halogen-substituted carbocyclyl-C_1-C_8-alkyl, C_1-C_8-alkylcarbocyclyl, halogen-substituted C_1-C_8-alkylcarbocyclyl, hydroxycarbocyclyl, and heterocyclyl ; and

R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_8-alkyl, and halo-C_1-C_8-alkyl; and

R^4 and R^5 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl, wherein any member (except -H) of such group optionally is substituted with one or more halogen; and

R^7 is selected from the group consisting of -H, halogen, -OH, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, and halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl; and

R^8 is selected from the group consisting of -OH, C_1-C_6-alkoxy, and halo-C_1-C_6-alkoxy; and

R^9 and R^{10} are independently selected from the group consisting of -H, C_1-C_6-alkyl, C_1-C_6-alkoxycarbonyl, C_1-C_6-alkylcarbonyl, carbocyclyl-C_1-C_6-alkyl, and carbocyclyl-C_1-C_6-alkoxycarbonyl; and

R^{11} and R^{12} are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl, wherein any member (except -H) of such group optionally is substituted with one or more halogen; and

R^{13} is selected from the group consisting of -H, C_1-C_6-alkyl, -O-R^{14}, -N(R^{14})(R^{15}), carbocyclyl-C_1-C_6-alkyl, heterocyclyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halogen-substituted carbocyclyl-C_1-C_6-alkyl, and halogen-substituted heterocyclyl-C_1-C_6-alkyl; and

R^{14} and R^{15} are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl, wherein any member (except -H) of such group optionally is substituted with one or more halogen; and

E^5 is not -H when both E^3 is -C(R^7)(R^8)- and E^4 is a bond.

3. A compound or salt thereof according to claim 2, wherein A^1 is -H.

4. A compound or salt thereof according to claim 3, wherein:

E^2 is C_2-C_6-alkyl optionally substituted with one or more halogen; and

E^4 is selected from the group consisting of a bond, C_1-C_3-alkyl, and C_2-C_3-alkenyl, wherein any member (except the bond) of such group optionally is substituted with one or more substituents independently selected from the group consisting of:

halogen, and

carbocyclyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, carbocyclyl,

carbocyclyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, halocarbocyclyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl; and

E^3 is selected from the group consisting of -H, -OH, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, carbocyclyl, and heterocyclyl, wherein:

the C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkoxy, or C_1-C_6-alkoxy-C_1-C_6-alkyl optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, and -CN, and

the carbocyclyl or heterocyclyl optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^{11})(R^{12})$, -$C(O)(R^{13})$, -S-R^{11}, -$S(O)_2$-R^{11}, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, halocarbocyclyl, halogen-substituted carbocyclyl-C_1-C_6-alkyl, C_1-C_6-alkylcarbocyclyl, halogen-substituted C_1-C_6-alkylcarbocyclyl, hydroxycarbocyclyl, and heteroaryl ; and

R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_6-alkyl, and halo-C_1-C_6-alkyl; and

R^4 and R^5 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl, wherein any member (except -H) of such group optionally is substituted with one or more halogen; and

R^7 is selected from the group consisting of -H, halogen, -OH, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, and halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl; and

R^8 is selected from the group consisting of -OH, C_1-C_6-alkoxy, and halo-C_1-C_6-alkoxy; and

R^{11} and R^{12} are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and

heterocyclyl-C_1-C_6-alkyl, wherein any member (except -H) of such group optionally is substituted with one or more halogen; and

R^{13} is selected from the group consisting of -H, C_1-C_6-alkyl, -O-R^{14}, -N(R^{14})(R^{15}), carbocyclyl-C_1-C_6-alkyl, and heterocyclyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halogen-substituted carbocyclyl-C_1-C_6-alkyl, and halogen-substituted heterocyclyl-C_1-C_6-alkyl; and

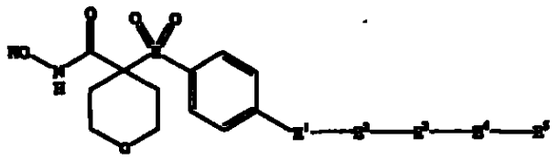
R^{14} and R^{15} are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl, wherein any member (except -H) of such group optionally is substituted with one or more halogen; and

E^5 is not -H when both E^3 is -C(R^7)(R^8)- and E^4 is a bond.

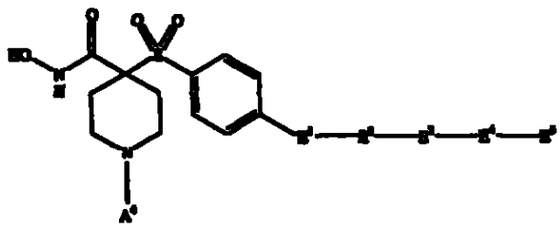
5. A compound or salt thereof according to claim 4, wherein A^2 and A^3, together with the carbon atom to which they both are attached, form an optionally-substituted heterocyclyl containing either 5 or 6 ring members.

6. A compound or salt thereof according to claim 5, wherein:

the compound corresponds in structure to a formula selected from the group consisting of:



(6-1) and



(6-2); and

A^4 is selected from the group consisting of -H, alkyl, alkylcarbonyl, alkylcarbonylalkyl, alkylcarbonylalkylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl,

alkoxycarbonylalkylcarbonyl, alkylsulfonyl, alkyliminocarbonyl, alkenyl, alkynyl, alkoxyalkyl, alkylthioalkyl, alkylsulfonylalkyl, alkylsufoxidoalkyl, alkylthioalkenyl, alkylsulfoxidoalkenyl, alkylsulfonylalkenyl, carbocyclyl, carbocyclylalkyl, carbocyclylalkoxyalkyl, carbocyclylcarbonyl, carbocyclylsulfonyl, carbocyclyliminocarbonyl, carbocyclyloxycarbonyl, carbocylylthioalkyl, carbocylylsulfoxidoalkyl, carbocylylsulfonylalkyl, carbocyclylthioalkenyl, carbocyclylsulfoxidoalkenyl, carbocyclylsulfonylalkenyl, heterocyclyl, heterocyclylalkyl, heterocyclylalkoxyalkyl, heterocyclylcarbonyl, heterocyclylthioalkyl, heterocyclylsulfoxidoalkyl, heterocyclylsulfonylalkyl, heterocyclylthioalkenyl, heterocyclylsulfoxidoalkenyl, heterocyclylsulfonylalkenyl, heterocyclylsulfonyl, heterocyclyliminocarbonyl, heterocyclylalkylcarbonyl, heterocyclylcarbonylalkylcarbonyl, heterocyclylsulfonyl, heterocyclylcarbonylalkyl, aminoalkylcarbonyl, aminocarbonyl, aminocarbonylalkylcarbonyl, aminosulfonyl, aminosulfonylalkyl, aminoalkyl, aminocarbonylalkyl, and aminoalkylsulfonyl, wherein:

any member (except -H) of such group optionally is substituted.

7. A compound or salt thereof according to claim 6, wherein:

A^4 is selected from the group consisting of -H, C_1-C_8-alkyl, C_1-C_8-alkylcarbonyl, C_1-C_8-alkylcarbonyl-C_1-C_8-alkyl, C_1-C_8-alkylcarbonyl-C_1-C_8-alkylcarbonyl, C_1-C_8-alkoxycarbonyl, C_1-C_8-alkoxycarbonyl-C_1-C_8-alkyl, C_1-C_8-alkoxycarbonyl-C_1-C_8-alkylcarbonyl, C_1-C_8-alkylsulfonyl, C_1-C_8-alkyliminocarbonyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, C_1-C_8-alkoxy-C_1-C_8-alkyl, C_1-C_8-alkylthio-C_1-C_8-alkyl, C_1-C_8-alkylthio-C_2-C_8-alkenyl, C_1-C_8-alkylsulfoxido-C_1-C_8-alkyl, C_1-C_8-alkylsulfoxido-C_2-C_8-alkenyl, C_1-C_8-alkylsulfonyl-C_1-C_8-alkyl, C_1-C_8-alkylsulfonyl-C_2-C_8-alkenyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, carbocyclyl-C_1-C_8-alkoxy-C_1-C_8-alkyl, carbocyclylcarbonyl, carbocyclylsulfonyl, carbocyclyliminocarbonyl, carbocyclyloxycarbonyl, carbocyclylthio-C_1-C_8-alkyl, carbocyclylthio-C_2-C_8-alkenyl, carbocyclylsulfoxido-C_1-C_8-alkyl, carbocyclylsulfoxido-C_2-C_8-alkenyl, carbocyclylsulfonyl-C_1-C_8-alkyl, carbocyclylsulfonyl-C_2-C_8-alkenyl, heterocyclyl, heterocyclyl-C_1-C_8-alkyl, heterocyclyl-C_1-C_8-alkoxy-C_1-C_8-alkyl, heterocyclylcarbonyl, heterocyclylthio-C_1-C_8-alkyl, heterocyclylsulfoxido-C_1-C_8-alkyl,

heterocyclylsulfonyl-C_1-C_8-alkyl, heterocyclylthio-C_2-C_8-alkenyl, heterocyclylsulfoxido-C_2-C_8-alkenyl, heterocyclylsulfonyl-C_2-C_8-alkenyl, heterocyclylsulfonyl, heterocyclyliminocarbonyl, heterocyclyl-C_1-C_8-alkylcarbonyl, heterocyclylcarbonyl-C_1-C_8-alkylcarbonyl, heterocyclylsulfonyl, heterocyclylcarbonyl-C_1-C_8-alkyl, N(R^{16})(R^{17})-C_1-C_8-alkylcarbonyl, N(R^{16})(R^{17})-carbonyl, N(R^{16})(R^{17})-carbonyl-C_1-C_8-alkylcarbonyl, N(R^{16})(R^{17})-sulfonyl, N(R^{16})(R^{17})-sulfonyl-C_1-C_8-alkyl, N(R^{16})(R^{17})-C_1-C_8-alkyl, N(R^{16})(R^{17})-carbonyl-C_1-C_8-alkyl, and N(R^{16})(R^{17})-C_1-C_8-alkylsulfonyl, wherein:

any member (except -H) of such group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -CN, -C(O)-OH, -SH, $-SO_3H$, and NO_2; and

R^{16} and R^{17} are independently selected from the group consisting of -H, -OH, C_1-C_8-alkyl, C_1-C_8-alkyl-carbonyl, C_1-C_8-alkoxy-C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, C_1-C_8-alkyl-thio-C_1-C_8-alkyl, C_1-C_8-alkyl-sulfoxido-C_1-C_8-alkyl, C_1-C_8-alkyl-sulfonyl-C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, carbocyclylcarbonyl, carbocyclyl-C_1-C_8-alkoxy-C_1-C_8-alkyl, carbocyclylthio-C_1-C_8-alkyl, carbocyclylsulfoxido-C_1-C_8-alkyl, carbocyclylsulfonyl-C_1-C_8-alkyl, heterocyclyl, heterocyclyl-C_1-C_8-alkyl, heterocyclyl-C_1-C_8-alkoxy-C_1-C_8-alkyl, heterocyclylcarbonyl, heterocyclylthio-C_1-C_8-alkyl, heterocyclylsulfoxido-C_1-C_8-alkyl, heterocyclylsulfonyl-C_1-C_8-alkyl, aminocarbonyl-C_1-C_8-alkyl, C_1-C_8-alkyloxycarbonylamino-C_1-C_8-alkyl, and amino-C_1-C_8-alkyl, wherein:

any member (except -H or OH) of such group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -CN, -C(O)-OH, -SH, $-SO_3H$, and NO_2, and

the nitrogen of the amino-C_1-C_8-alkyl optionally is substituted with 1 or 2 substituents independently selected from the group consisting of C_1-C_8-alkyl, C_1-C_8-alkylcarbonyl, carbocyclyl, and carbocyclyl-C_1-C_8-alkyl, and

no greater than one of R^{16} or R^{17} is -OH.

8. A compound or salt thereof according to claim 7, wherein A^4 is selected from the group consisting of -H, C_1-C_8-alkyl, C_1-C_8-alkoxy-C_1-C_8-alkyl, carbocyclyl,

carbocyclyl-C_1-C_6-alkyl, C_1-C_6-alkylsulfonyl, C_3-C_6-alkenyl, C_3-C_6-alkynyl, wherein any member (except -H) of such group optionally is substituted with halogen.

9. A compound or salt thereof according to claim 8, wherein A^4 is selected from the group consisting of -H, C_1-C_4-alkyl, C_1-C_2-alkoxy-C_1-C_3-alkyl, C_3-C_6-cycloalkyl, C_3-C_6-cycloalkyl-C_1-C_3-alkyl, phenyl, phenyl-C_1-C_3-alkyl, C_1-C_2-alkylsulfonyl, C_3-C_4-alkenyl, C_3-C_4-alkynyl, wherein any member (except -H) of such group optionally is substituted with halogen.

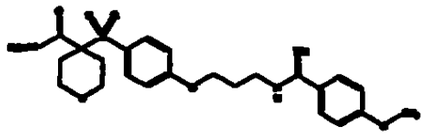
10. A compound or salt thereof according to claim 9, wherein A^4 is selected from the group consisting of -H, ethyl, methoxyethyl, cyclopropyl, cyclopropylmethyl, benzyl, methylsulfonyl, C_3-alkenyl, and C_3-alkynyl, wherein any member (except -H) of such group optionally is substituted with halogen.

11. A compound or salt thereof according to claim 10, wherein A^4 is selected from the group consisting of -H, ethyl, methoxyethyl, cyclopropyl, cyclopropylmethyl, and benzyl, wherein any member (except -H) of such group optionally is substituted with halogen.

12. A compound or salt thereof according to claim 7, wherein the salt comprises an acid selected from the group consisting of HCl and CF_3COOH.

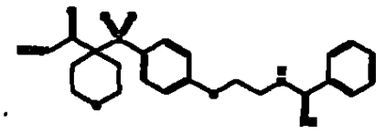
13. A compound or salt thereof according to claim 7, wherein E^3 is $-N(R^4)-C(NR^3)-$.

14. A compound or salt thereof according to claim 13, wherein the compound corresponds in structure to a formula selected from the group consisting of:



(14-1)

and



(14-2).

15. A compound or salt thereof according to claim 7, wherein E^3 is -C(O)-.

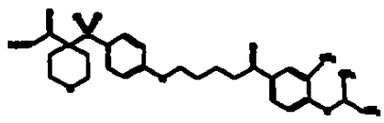
16. A compound or salt thereof according to claim 15, wherein E^5 is carbocyclyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^{11})(R^{12})$, $-C(O)(R^{13})$, $-S-R^{11}$, $-S(O)_2-R^{11}$, aryl, aryl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, haloaryl, halogen-substituted aryl-C_1-C_6-alkyl, C_1-C_6-alkylaryl, halogen-substituted C_1-C_6-alkylaryl, hydroxyaryl, and heteroaryl.

17. A compound or salt thereof according to claim 16, wherein E^5 is aryl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^{11})(R^{12})$, $-C(O)(R^{13})$, $-S-R^{11}$, $-S(O)_2-R^{11}$, aryl, aryl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, haloaryl, halogen-substituted aryl-C_1-C_6-alkyl, C_1-C_6-alkylaryl, halogen-substituted C_1-C_6-alkylaryl, hydroxyaryl, and heteroaryl.

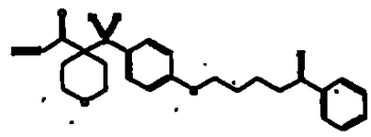
18. A compound or salt thereof according to claim 17, wherein E^5 is phenyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^{11})(R^{12})$, $-C(O)(R^{13})$, $-S-R^{11}$, $-S(O)_2-R^{11}$, aryl, aryl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, haloaryl, halogen-substituted aryl-C_1-C_6-alkyl, C_1-C_6-alkylaryl, halogen-substituted C_1-C_6-alkylaryl, hydroxyaryl, and heteroaryl.

475

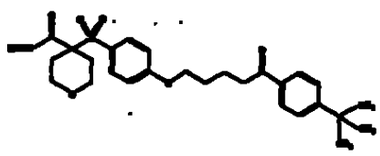
19. A compound or salt thereof according to claim 18, wherein the compound corresponds in structure to a formula selected from the group consisting of:



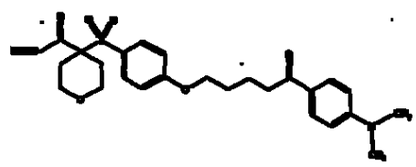
(19-1),



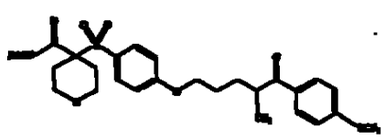
(19-2),



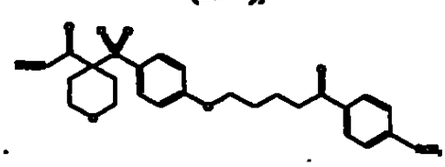
(19-3),



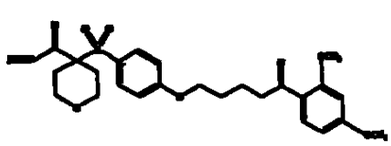
(19-4),



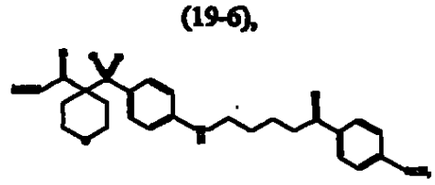
(19-5),



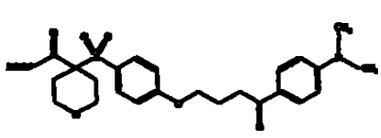
(19-6),



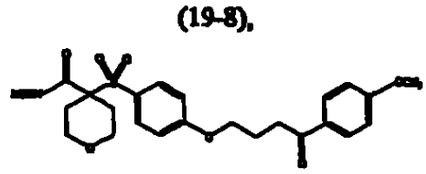
(19-7),



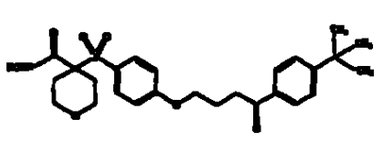
(19-8),



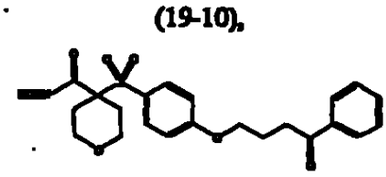
(19-9),



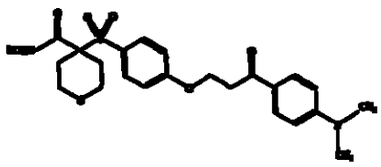
(19-10),



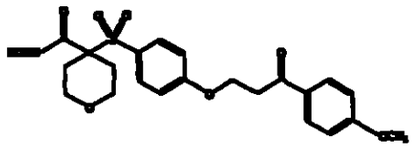
(19-11),



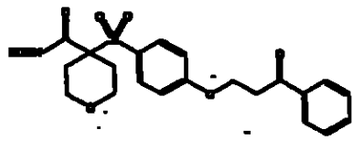
(19-12),



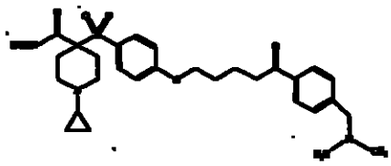
(19-13),



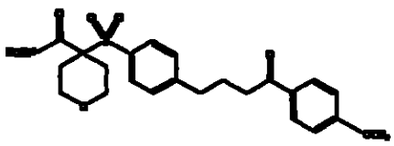
(19-14),



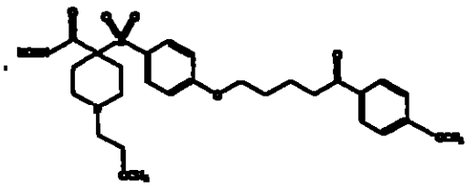
(19-15),



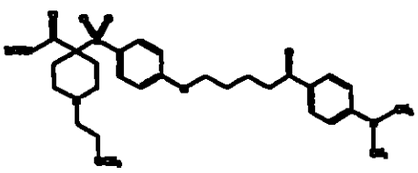
(19-16),



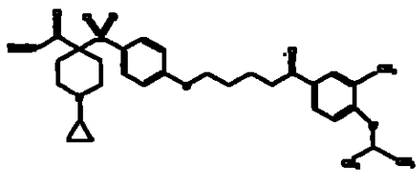
(19-17),



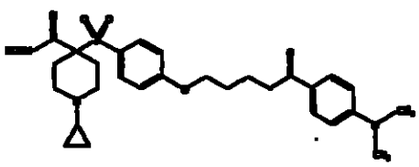
(19-18),



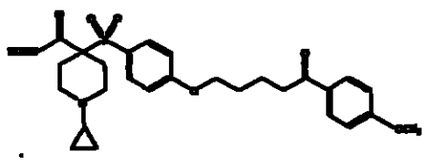
(19-19),



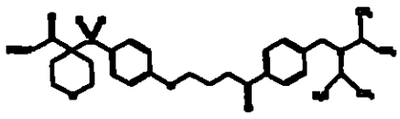
(19-20),



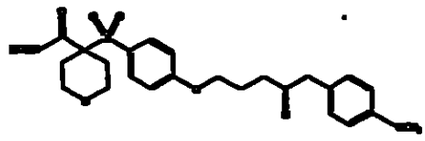
(19-21),



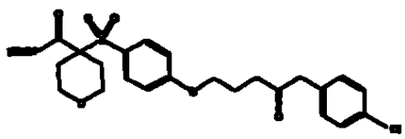
(19-22),



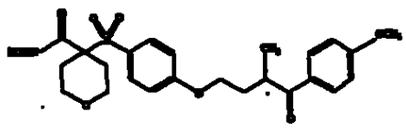
(19-23),



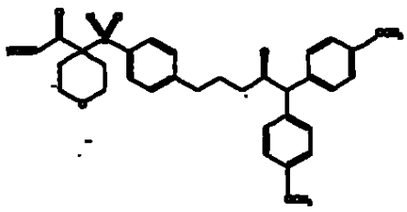
(19-24),



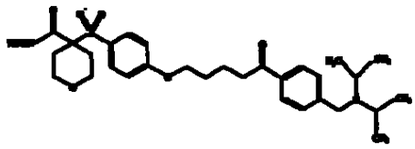
(19-25),



(19-26),



(19-27), and



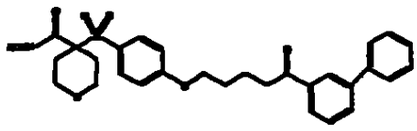
(19-28).

20. A compound or salt thereof according to claim 17, wherein R^5 is phenyl which is:

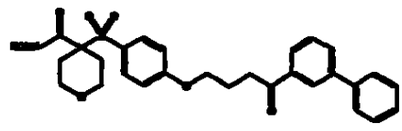
substituted with one or more substituents independently selected from the group consisting of aryl, haloaryl, aryl-C_1-C_6-alkyl, and halogen-substituted aryl-C_1-C_6-alkyl; and

optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^{11})(R^{12})$, -$C(O)(R^{13})$, -S-R^{11}, -$S(O)_2$-R^{11}, aryl, aryl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, haloaryl, halogen-substituted aryl-C_1-C_6-alkyl, C_1-C_6-alkylaryl, halogen-substituted C_1-C_6-alkylaryl, hydroxyaryl, and heteroaryl.

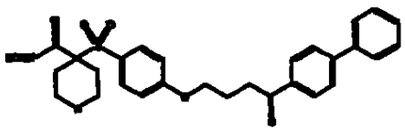
21. A compound or salt thereof according to claim 20, wherein the compound corresponds in structure to a formula selected from the group consisting of:



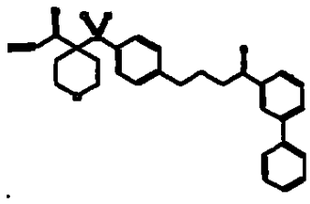
(21-1),



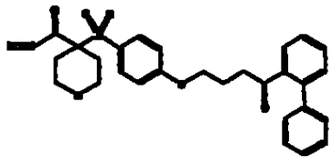
(21-2),



(21-3),



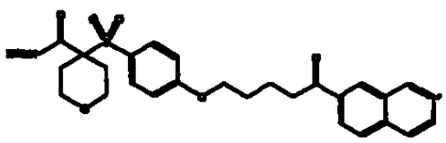
(21-4), and



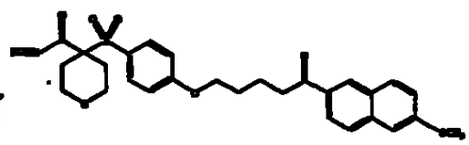
(21-5).

22. A compound or salt thereof according to claim 17, wherein E^5 is naphthalenyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^{11})(R^{12})$, $-C(O)(R^{13})$, $-S-R^{11}$, $-S(O)_2-R^{11}$, aryl, aryl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, haloaryl, halogen-substituted aryl-C_1-C_6-alkyl, C_1-C_6-alkylaryl, halogen-substituted C_1-C_6-alkylaryl, hydroxyaryl, and heteroaryl.

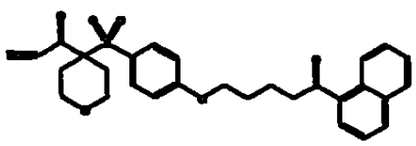
23. A compound or salt thereof according to claim 22, wherein the compound corresponds in structure to a formula selected from the group consisting of:



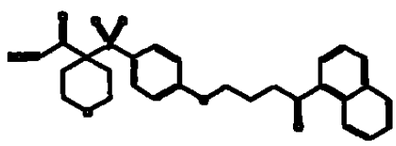
(23-1),



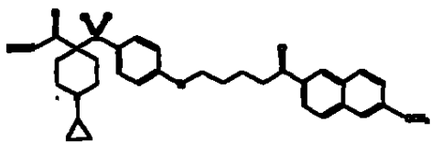
(23-2),



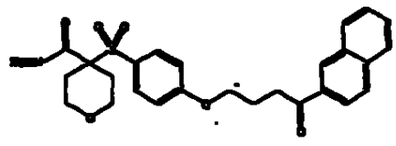
(23-3),



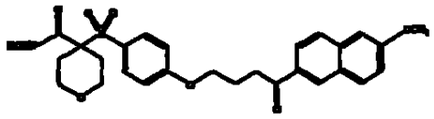
(23-4),



(23-5),



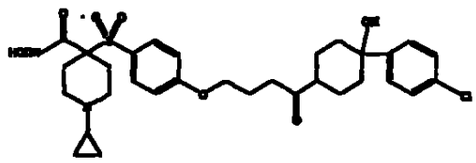
(23-6), and



(23-7).

24. A compound or salt thereof according to claim 16, wherein E^5 is C_5-C_6-cycloalkyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^{11})(R^{12})$, -$C(O)(R^{13})$, -S-R^{11}, -$S(O)_2$-R^{11}, aryl, aryl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, haloaryl, halogen-substituted aryl-C_1-C_6-alkyl, C_1-C_6-alkylaryl, halogen-substituted C_1-C_6-alkylaryl, hydroxyaryl, and heteroaryl.

25. A compound or salt thereof according to claim 24, wherein the compound corresponds in structure to the following formula:

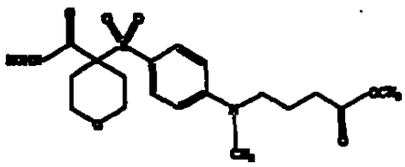


(25-1).

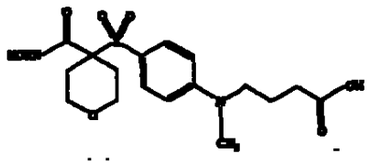
26. A compound or salt thereof according to claim 15, wherein E^5 is selected from the group consisting of -H, -OH, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkoxy, and C_1-C_6-alkoxy-C_1-C_6-alkyl, wherein:

the C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkoxy, or C_1-C_6-alkoxy-C_1-C_6-alkyl optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, and, -CN.

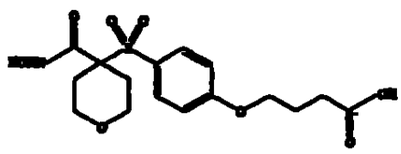
27. A compound or salt thereof according to claim 26, wherein the compound corresponds in structure to a formula selected from the group consisting of:



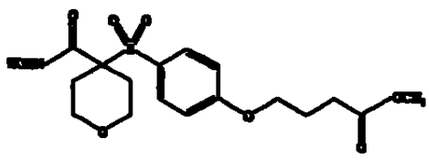
(27-1),



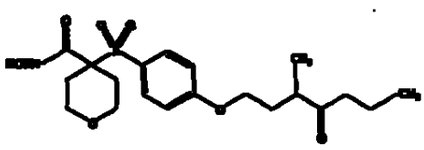
(27-2),



(27-3),

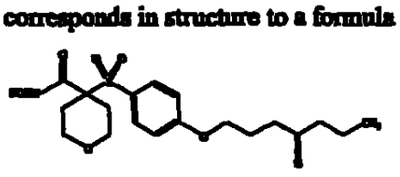


(27-4), and

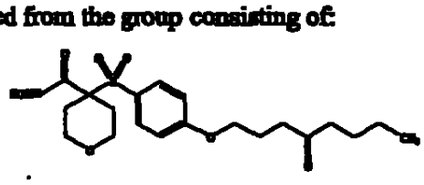


(27-5).

28. A compound or salt thereof according to claim 26, wherein the compound corresponds in structure to a formula selected from the group consisting of:



and

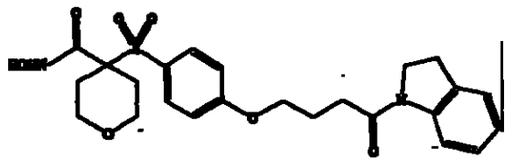


(28-1) (28-2).

29. A compound or salt thereof according to claim 15, wherein E^5 is heterocyclyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^{11})(R^{12})$, $-C(O)(R^{13})$, $-S-R^{11}$, $-S(O)_2-R^{11}$, aryl, aryl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, haloaryl, halogen-substituted aryl-C_1-C_6-alkyl, C_1-C_6-alkylaryl, halogen-substituted C_1-C_6-alkylaryl, hydroxyaryl, and heteroaryl.

481

30. A compound or salt thereof according to claim 29, wherein the compound corresponds in structure to the following formula:



(30-1).

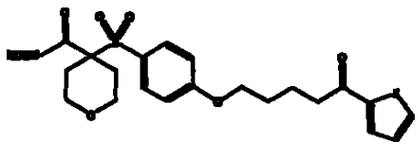
31. A compound or salt thereof according to claim 29, wherein E^5 is selected from the group consisting of furanyl, tetrahydropyranyl, dihydrofuranyl, tetrahydrofuranyl, thiophenyl, dihydrothiophenyl, tetrahydrothiophenyl, pyrrolyl, isopyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, isoimidazolyl, imidazolinyl, imidazolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, triazolyl, tetrazolyl, dithiolyl, oxathiolyl, oxazolyl, isoxazolyl, oxazolidinyl, isoxazolidinyl, thiazolyl, isothiazolyl, thiazolinyl, isothiazolinyl, thiazolidinyl, isothiazolidinyl, thiodiazolyl, oxathiazolyl, oxadiazolyl, oxatriazolyl, dioxazolyl, oxathiazolyl, oxathiolyl, oxathiolanyl, pyranyl, dihydropyranyl, pyridinyl, piperidinyl, diazinyl, piperazinyl, triazinyl, oxazinyl, isoxazinyl, oxathiazinyl, oxadiazinyl, morpholinyl, azepinyl, oxepinyl, thiepinyl, diazepinyl, indolizinyl, pyrindinyl, pyranopyrrolyl, 4H-quinolizinyl, purinyl, naphthyridinyl, pyridopyridinyl, pteridinyl, indolyl, isoindolyl, indoleninyl, isoindazolyl, benzazinyl, phthalazinyl, quinoxalinyl, quinazolinyl, benzodiazinyl, benzopyranyl, benzothiopyranyl, benzoxazolyl, indoxazinyl, anthranilyl, benzodioxolyl, benzodioxanyl, benzoxadiazolyl, benzofuranyl, isobenzofuranyl, benzothienyl, isobenzothienyl, benzothiazolyl, benzothiadiazolyl, benzimidazolyl, benzotriazolyl, benzoxazinyl, benzisoxazinyl, tetrahydroisoquinolinyl, carbazolyl, xanthenyl, and acridinyl, wherein:

any member of such group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^{11})(R^{12})$, $-C(O)(R^{13})$, $-S-R^{11}$, $-S(O)_2-R^{11}$, aryl, aryl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, haloaryl,

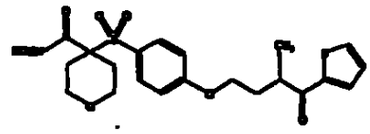
halogen-substituted aryl-C_1-C_6-alkyl, C_1-C_6-alkylaryl, halogen-substituted C_1-C_6-alkylaryl, hydroxyaryl, and heteroaryl.

32. A compound or salt thereof according to claim 31, wherein E^5 is thiophenyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^{11})(R^{12})$, $-C(O)(R^{13})$, $-S-R^{11}$, $-S(O)_2-R^{11}$, aryl, aryl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, haloaryl, halogen-substituted aryl-C_1-C_6-alkyl, C_1-C_6-alkylaryl, halogen-substituted C_1-C_6-alkylaryl, hydroxyaryl, and heteroaryl.

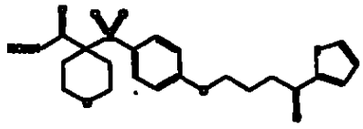
33. A compound or salt thereof according to claim 32, wherein the compound corresponds in structure to a formula selected from the group consisting of:



(33-1),



(33-2), and



(33-3).

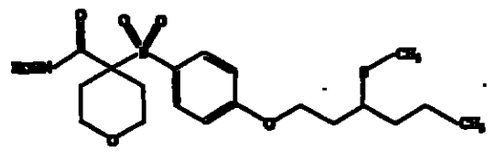
34. A compound or salt thereof according to claim 7, wherein E^3 is -S-.

35. A compound or salt thereof according to claim 34, wherein E^5 is selected from the group consisting of -H, -OH, C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, C_1-C_8-alkoxy, and C_1-C_8-alkoxy-C_1-C_8-alkyl, wherein:

the C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, C_1-C_8-alkoxy, or C_1-C_8-alkoxy-C_1-C_8-alkyl optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, and -CN.

483

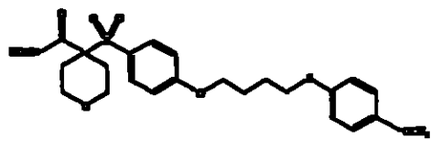
36. A compound or salt thereof according to claim 35, wherein the compound corresponds in structure to the following formula:



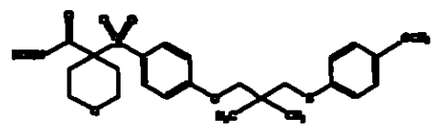
(36-1).

37. A compound or salt thereof according to claim 34, wherein E^5 is phenyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^{11})(R^{12})$, $-C(O)(R^{13})$, $-S-R^{11}$, $-S(O)_2-R^{11}$, aryl, aryl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, haloaryl, halogen-substituted aryl-C_1-C_6-alkyl, C_1-C_6-alkylaryl, halogen-substituted C_1-C_6-alkylaryl, hydroxyaryl, and heteroaryl.

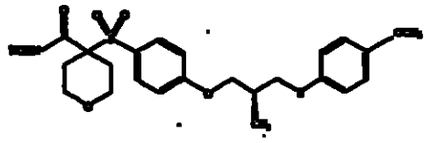
38. A compound or salt thereof according to claim 37, wherein the compound corresponds in structure to a formula selected from the group consisting of:



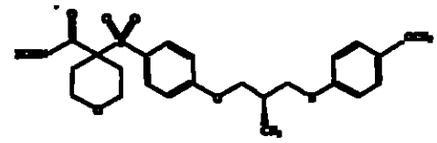
(38-1),



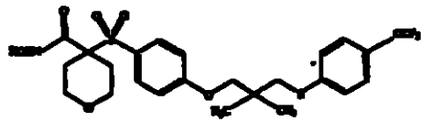
(38-2),



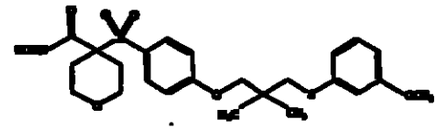
(38-3),



(38-4),

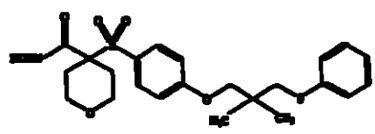


(38-5),

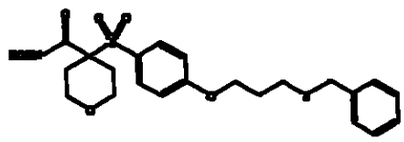


(38-6),

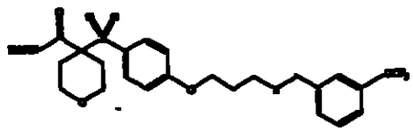
484



(38-7),



(38-8), and



(38-9).

39. A compound or salt thereof according to claim 34, wherein E^5 is heterocyclyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^{11})(R^{12})$, -$C(O)(R^{13})$, -S-R^{11}, -$S(O)_2$-R^{11}, aryl, aryl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, haloaryl, halogen-substituted aryl-C_1-C_6-alkyl, C_1-C_6-alkylaryl, halogen-substituted C_1-C_6-alkylaryl, hydroxyaryl, and heteroaryl.

40. A compound or salt thereof according to claim 39, wherein E^5 is selected from the group consisting of furanyl, tetrahydropyranyl, dihydrofuranyl, tetrahydrofuranyl, thiophenyl, dihydrothiophenyl, tetrahydrothiophenyl, pyrrolyl, isopyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, isoimidazolyl, imidazolinyl, imidazolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, triazolyl, tetrazolyl, dithiolyl, oxathiolyl, oxazolyl, isoxazolyl, oxazolidinyl, isoxazolidinyl, thiazolyl, isothiazolyl, thiazolinyl, isothiazolinyl, thiazolidinyl, isothiazolidinyl, thiodiazolyl, oxathiazolyl, oxadiazolyl, oxatriazolyl, dioxazolyl, oxathiazolyl, oxathiolyl, oxathiolanyl, pyranyl, dihydropyranyl, pyridinyl, piperidinyl, diazinyl, piperazinyl, triazinyl, oxazinyl, isoxazinyl, oxathiazinyl, oxadiazinyl, morpholinyl, azepinyl, oxepinyl, thiepinyl, diazepinyl, indolizinyl, pyrindinyl, pyranopyrrolyl, 4H-quinolizinyl, purinyl, naphthyridinyl, pyridopyridinyl, pteridinyl, indolyl, isoindolyl, indoleninyl, isoindazolyl, benzazinyl, phthalazinyl, quinoxalinyl, quinazolinyl, benzodiazinyl, benzopyranyl, benzothiopyranyl, benzoxazolyl, indoxazinyl, anthranilyl, benzodioxolyl, benzodioxanyl, benzoxadiazolyl, benzofuranyl,

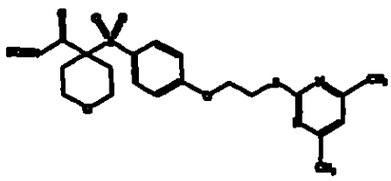
485

isobenzofuranyl, benzothienyl, isobenzothienyl, benzothiazolyl, benzothiadiazolyl, benzimidazolyl, benzotriazolyl, benzoxazinyl, benzisoxazinyl, tetrahydroisoquinolinyl, carbazolyl, xanthenyl, and acridinyl, wherein:

any member of such group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^{11})(R^{12})$, $-C(O)(R^{13})$, $-S-R^{11}$, $-S(O)_2-R^{11}$, aryl, aryl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, haloaryl, halogen-substituted aryl-C_1-C_6-alkyl, C_1-C_6-alkylaryl, halogen-substituted C_1-C_6-alkylaryl, hydroxyaryl, and heteroaryl.

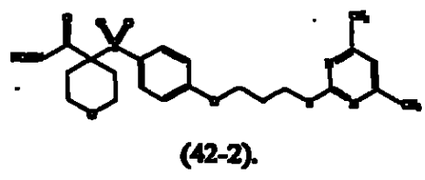
41. A compound or salt thereof according to claim 40, wherein E^5 is pyrimidinyl optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^{11})(R^{12})$, $-C(O)(R^{13})$, $-S-R^{11}$, $-S(O)_2-R^{11}$, aryl, aryl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, haloaryl, halogen-substituted aryl-C_1-C_6-alkyl, C_1-C_6-alkylaryl, halogen-substituted C_1-C_6-alkylaryl, hydroxyaryl, and heteroaryl.

42. A compound or salt thereof according to claim 41, wherein the compound corresponds in structure to a formula selected from the group consisting of:



(42-1)

and



(42-2).

43. A compound or salt thereof according to claim 39, wherein E^5 is 2-fused-ring heterocyclyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^{11})(R^{12})$, $-C(O)(R^{13})$, $-S-R^{11}$, $-S(O)_2-R^{11}$, aryl, aryl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted

C_1-C_6-alkoxy-C_1-C_6-alkyl, haloaryl, halogen-substituted aryl-C_1-C_6-alkyl, C_1-C_6-alkylaryl, halogen-substituted C_1-C_6-alkylaryl, hydroxyaryl, and heteroaryl.

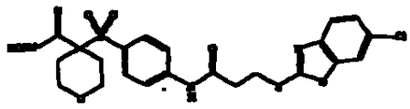
44. A compound or salt thereof according to claim 43, wherein E^5 is selected from the group consisting of indolizinyl, pyrindinyl, pyranopyrrolyl, 4H-quinolizinyl, purinyl, naphthyridinyl, pyridopyridinyl, pteridinyl, indolyl, isoindolyl, indoleninyl, isoindazolyl, benzazinyl, phthalazinyl, quinoxalinyl, quinazolinyl, benzodiazinyl, benzopyranyl, benzothiopyranyl, benzoxazolyl, indoxazinyl, anthranilyl, benzodioxolyl, benzodioxanyl, benzoxadiazolyl, benzofuranyl, isobenzofuranyl, benzothienyl, isobenzothienyl, benzothiazolyl, benzothiadiazolyl, benzimidazolyl, benzotriazolyl, benzoxazinyl, benziscoxazinyl, and tetrahydroisoquinolinyl, wherein:

any member of such group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^{11})(R^{12})$, $-C(O)(R^{13})$, $-S-R^{11}$, $-S(O)_2-R^{11}$, aryl, aryl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, haloaryl, halogen-substituted aryl-C_1-C_6-alkyl, C_1-C_6-alkylaryl, halogen-substituted C_1-C_6-alkylaryl, hydroxyaryl, and heteroaryl.

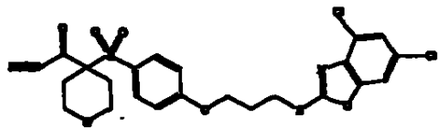
45. A compound or salt thereof according to claim 44, wherein E^5 is selected from the group consisting of benzoxazolyl and benzothiazolyl, wherein any member of such group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^{11})(R^{12})$, $-C(O)(R^{13})$, $-S-R^{11}$, $-S(O)_2-R^{11}$, aryl, aryl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, haloaryl, halogen-substituted aryl-C_1-C_6-alkyl, C_1-C_6-alkylaryl, halogen-substituted C_1-C_6-alkylaryl, hydroxyaryl, and heteroaryl.

487

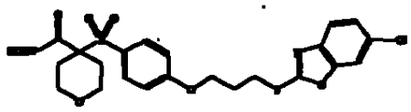
46. A compound or salt thereof according to claim 45, wherein the compound corresponds in structure to a formula selected from the group consisting of:



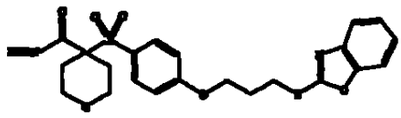
(46-1),



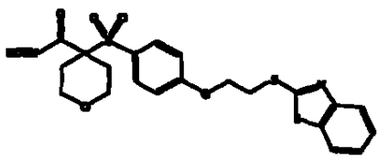
(46-2),



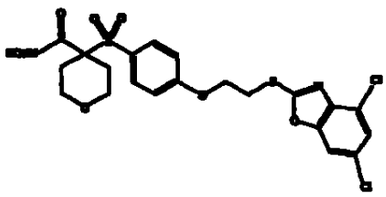
(46-3),



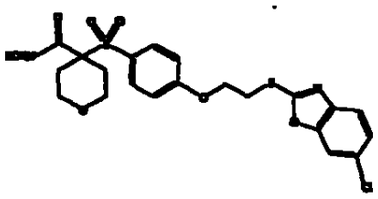
(46-4),



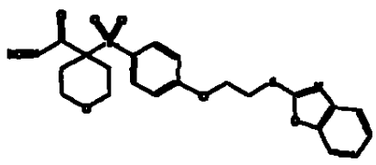
(46-5),



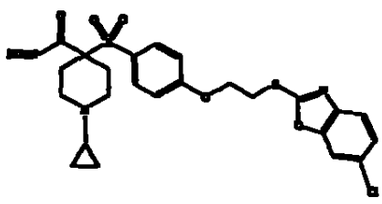
(46-6),



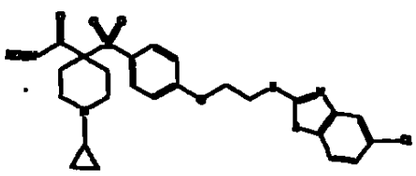
(46-7),



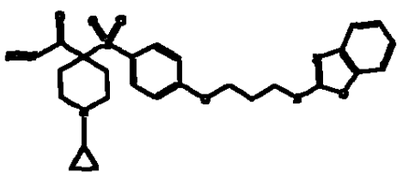
(46-8),



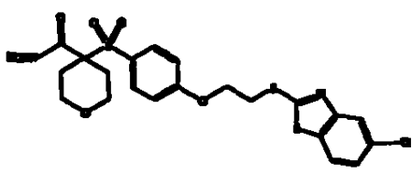
(46-9),



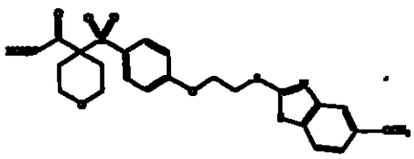
(46-10),



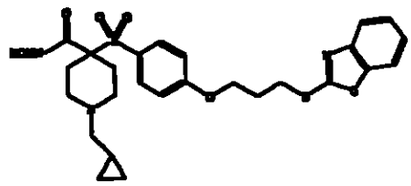
(46-11),



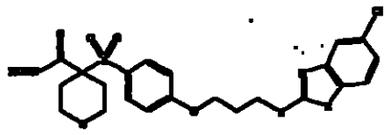
(46-12),



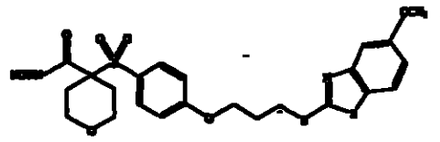
(46-13),



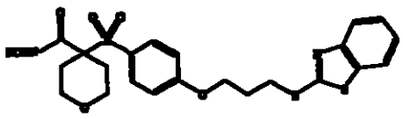
(46-14),



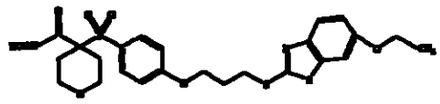
(46-15),



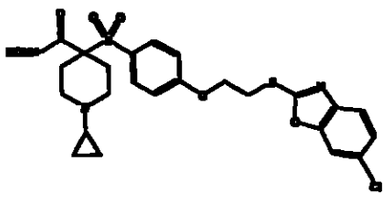
(46-16),



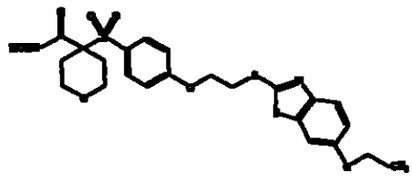
(46-17),



(46-18),

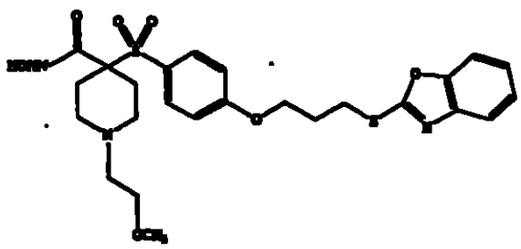


(46-19), and



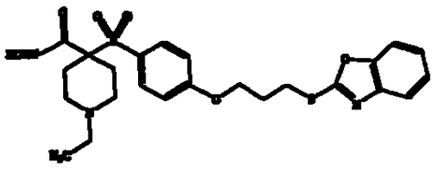
(46-20).

47. A compound or salt thereof according to claim 45, wherein the compound corresponds in structure to the following formula:

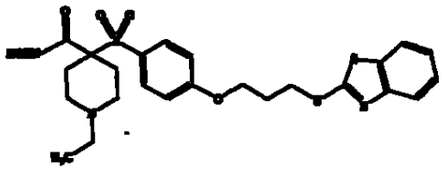


(47-1).

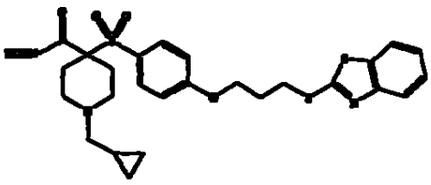
48. A compound or salt thereof according to claim 45, wherein the compound corresponds in structure to the following formula:



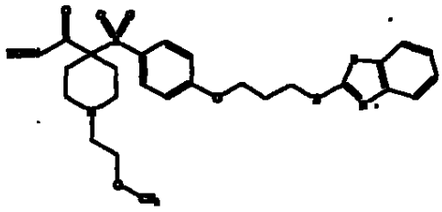
(48-1),



(48-2),



(48-3), and



(48-4).

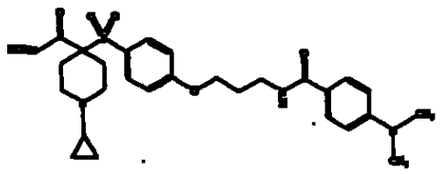
49. A compound or salt thereof according to claim 7, wherein E^3 is $-N(R^4)-C(O)-$.

50. A compound or salt thereof according to claim 49, wherein E^5 is carbocyclyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^{11})(R^{12})$, $-C(O)(R^{13})$, $-S-R^{11}$, $-S(O)_2-R^{11}$, aryl, aryl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, haloaryl, halogen-substituted aryl-C_1-C_6-alkyl, C_1-C_6-alkylaryl, halogen-substituted C_1-C_6-alkylaryl, hydroxyaryl, and heteroaryl.

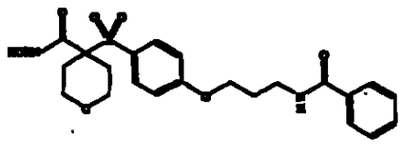
51. A compound or salt thereof according to claim 50, wherein E^5 is phenyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^{11})(R^{12})$, $-C(O)(R^{13})$, $-S-R^{11}$, $-S(O)_2-R^{11}$, aryl, aryl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, haloaryl, halogen-substituted aryl-C_1-C_6-alkyl, C_1-C_6-alkylaryl, halogen-substituted C_1-C_6-alkylaryl, hydroxyaryl, and heteroaryl.

490

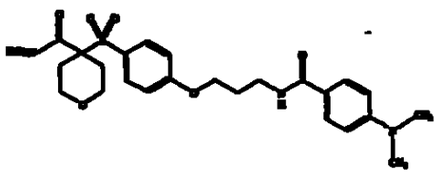
52. A compound or salt thereof according to claim 51, wherein the compound corresponds in structure to a formula selected from the group consisting of:



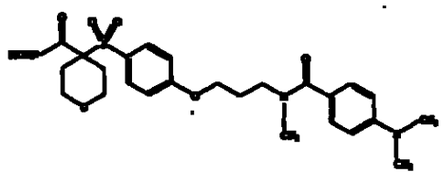
(52-1),



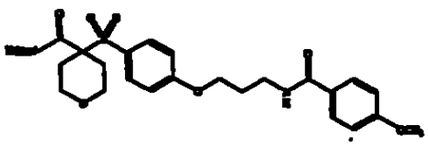
(52-2),



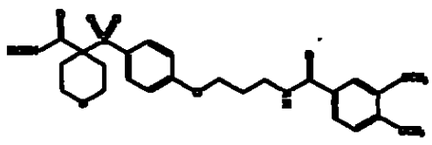
(52-3),



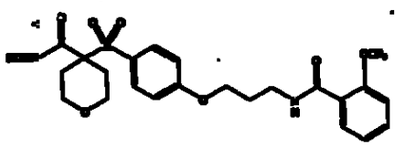
(52-4),



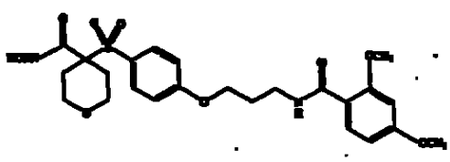
(52-5),



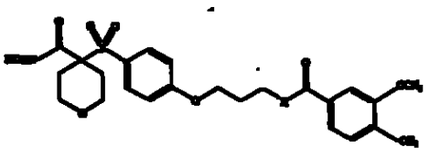
(52-6),



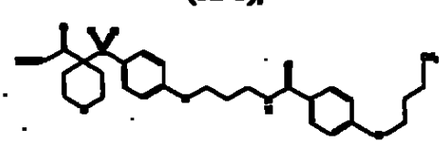
(52-7),



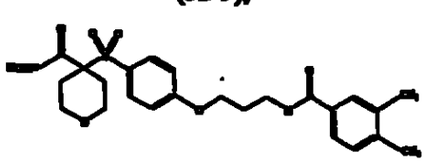
(52-8),



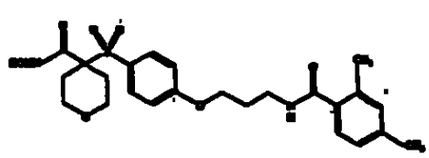
(52-9),



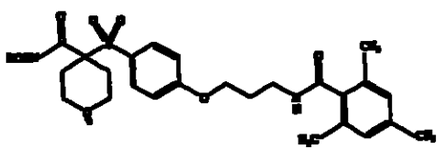
(52-10),



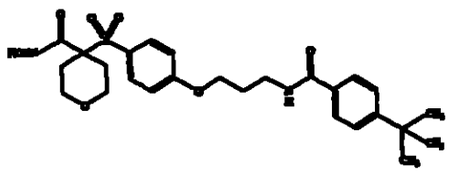
(52-11),



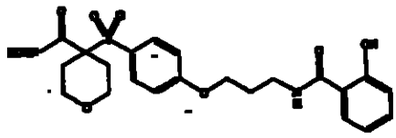
(52-12),



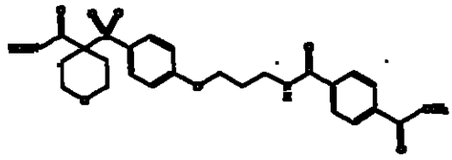
(52-13),



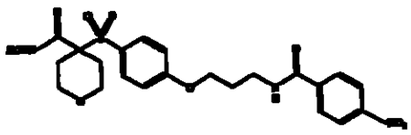
(52-14),



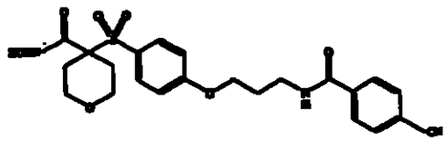
(52-15),



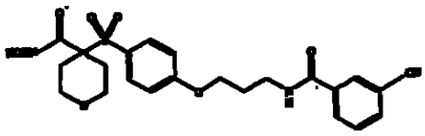
(52-16),



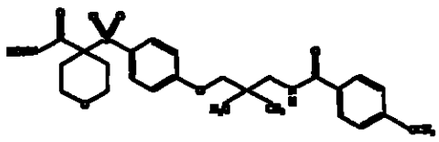
(52-17),



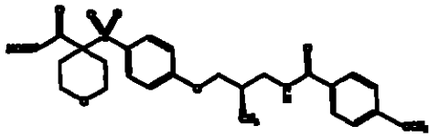
(52-18),



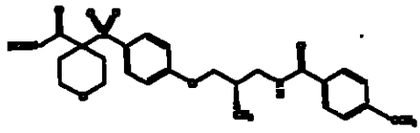
(52-19),



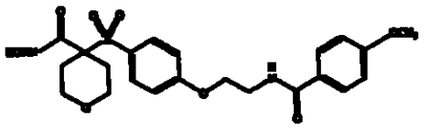
(52-20),



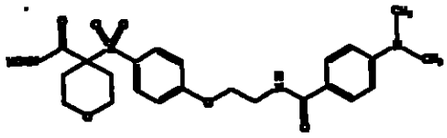
(52-21),



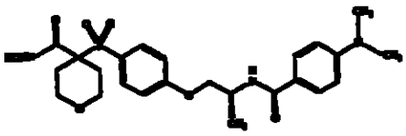
(52-22),



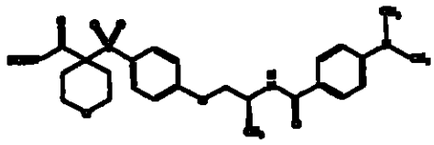
(52-23),



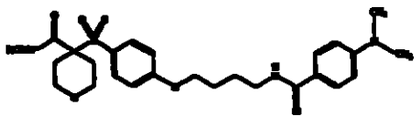
(52-24),



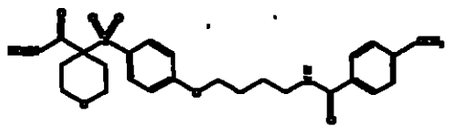
(52-25),



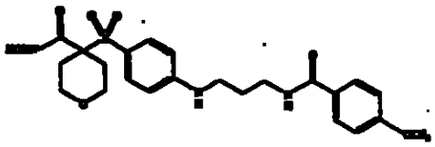
(52-26),



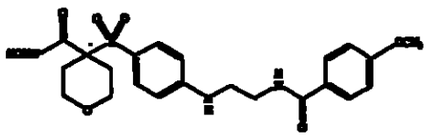
(52-27),



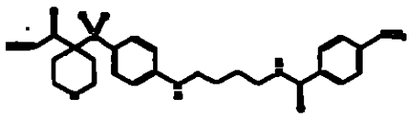
(52-28),



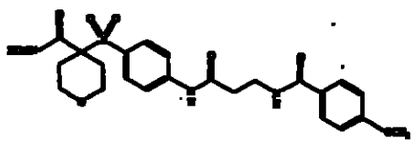
(52-29),



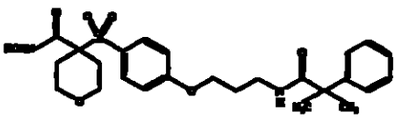
(52-30),



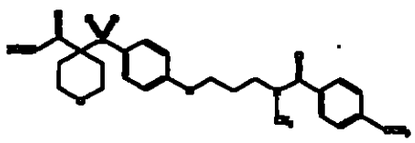
(52-31),



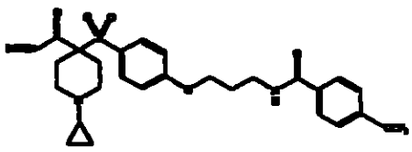
(52-32),



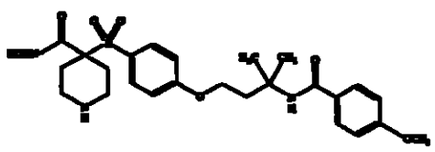
(52-33),



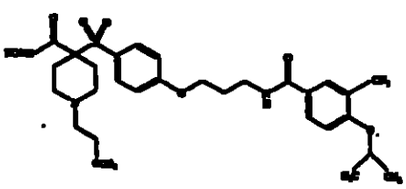
(52-34),



(52-35),

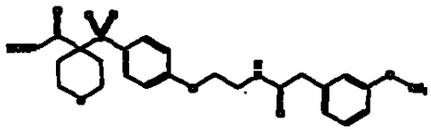


(52-36), and

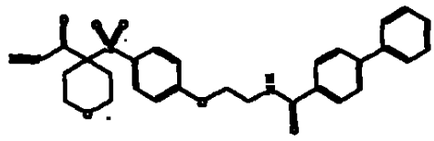


(52-37).

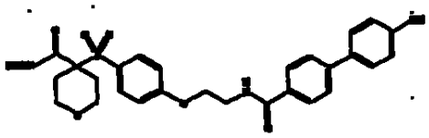
53. A compound or salt thereof according to claim 51, wherein the compound corresponds in structure to a formula selected from the group consisting of:



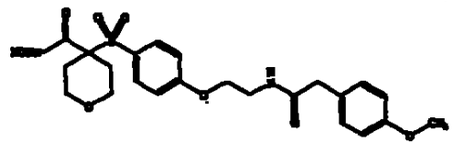
(53-1),



(53-2),

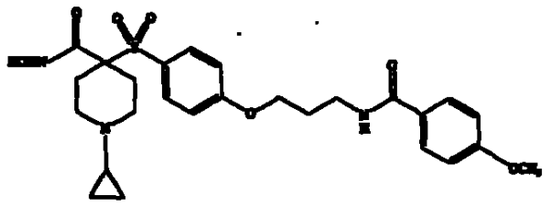


(53-3), and



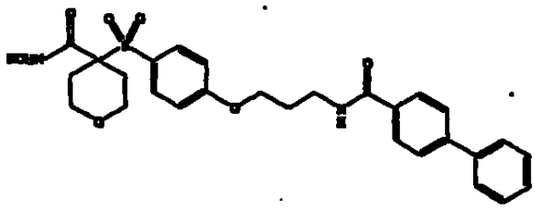
(53-4).

54. A compound or salt thereof according to claim 51, wherein the compound corresponds in structure to the following formula:



(54-1).

55. A compound or salt thereof according to claim 51, wherein the compound corresponds in structure to the following formula:

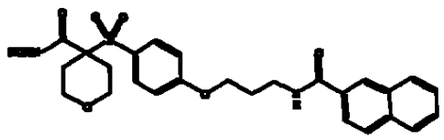


(55-1).

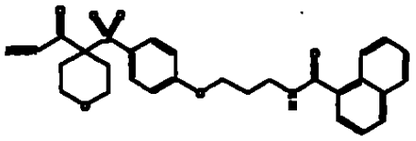
56. A compound or salt thereof according to claim 50, wherein E^5 is naphthalenyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy,

C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^{11})(R^{12})$, -$C(O)(R^{13})$, -S-R^{11}, -$S(O)_2$-R^{11}, aryl, aryl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, haloaryl, halogen-substituted aryl-C_1-C_6-alkyl, C_1-C_6-alkylaryl, halogen-substituted C_1-C_6-alkylaryl, hydroxyaryl, and heteroaryl.

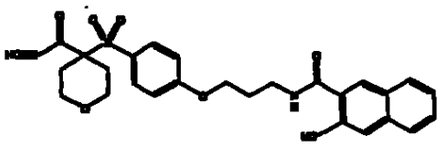
57. A compound or salt thereof according to claim 56, wherein the compound corresponds in structure to a formula selected from the group consisting of:



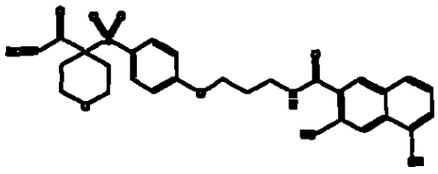
(57-1),



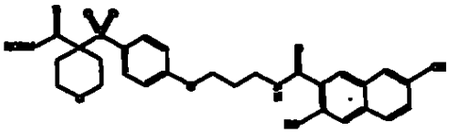
(57-2),



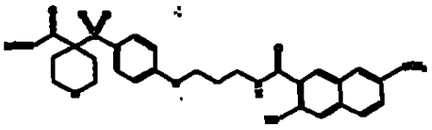
(57-3),



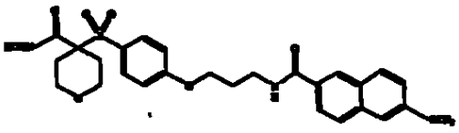
(57-4),



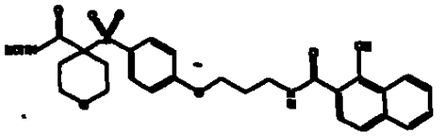
(57-5),



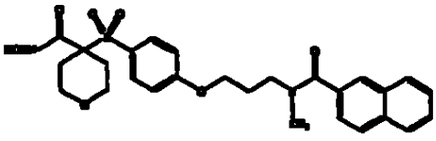
(57-6),



(57-7),



(57-8), and

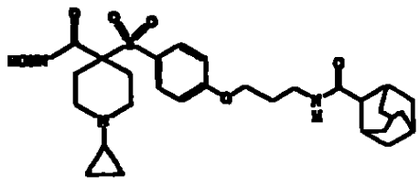


(57-9).

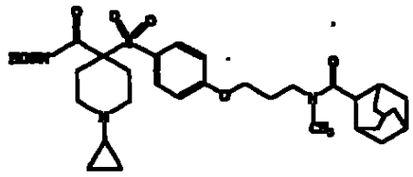
58. A compound or salt thereof according to claim 50, wherein E^5 is cycloalkyl optionally substituted with one or more substituents independently selected from the group

consisting of halogen, -OH, -NO_2, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^{11})(R^{12})$, -$C(O)(R^{13})$, -S-R^{11}, -$S(O)_2$-R^{11}, aryl, aryl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, haloaryl, halogen-substituted aryl-C_1-C_6-alkyl, C_1-C_6-alkylaryl, halogen-substituted C_1-C_6-alkylaryl, hydroxyaryl, and heteroaryl.

59. A compound or salt thereof according to claim 58, wherein the compound corresponds in structure to a formula selected from the group consisting of:

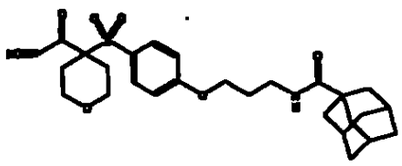


and



(59-1) (59-2).

60. A compound or salt thereof according to claim 58, wherein the compound corresponds in structure to the following formula:

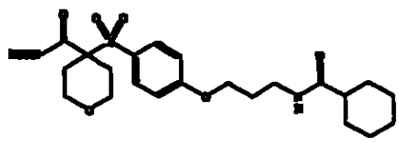


(60-1).

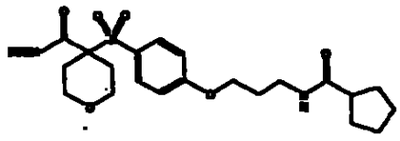
61. A compound or salt thereof according to claim 58, wherein E^5 is C_5-C_6-cycloalkyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^{11})(R^{12})$, -$C(O)(R^{13})$, -S-R^{11}, -$S(O)_2$-R^{11}, aryl, aryl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, haloaryl, halogen-substituted aryl-C_1-C_6-alkyl, C_1-C_6-alkylaryl, halogen-substituted C_1-C_6-alkylaryl, hydroxyaryl, and heteroaryl.

496

62. A compound or salt thereof according to claim 61, wherein the compound corresponds in structure to a formula selected from the group consisting of:



and



(62-1) (62-2).

63. A compound or salt thereof according to claim 49, wherein E^5 is heterocyclyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^{11})(R^{12})$, -$C(O)(R^{13})$, -S-R^{11}, -$S(O)_2$-R^{11}, aryl, aryl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, haloaryl, halogen-substituted aryl-C_1-C_6-alkyl, C_1-C_6-alkylaryl, halogen-substituted C_1-C_6-alkylaryl, hydroxyaryl, and heteroaryl.

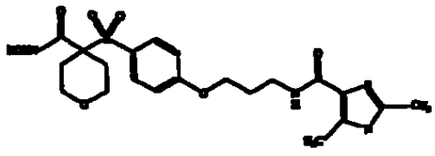
64. A compound or salt thereof according to claim 63, wherein E^5 is selected from the group consisting of furanyl, tetrahydropyranyl, dihydrofuranyl, tetrahydrofuranyl, thiophenyl, dihydrothiophenyl, tetrahydrothiophenyl, pyrrolyl, isopyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, isoimidazolyl, imidazolinyl, imidazolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, triazolyl, tetrazolyl, dithiolyl, oxathiolyl, oxazolyl, isoxazolyl, oxazolidinyl, isoxazolidinyl, thiazolyl, isothiazolyl, thiazolinyl, isothiazolinyl, thiazolidinyl, isothiazolidinyl,, thiodiazolyl, oxathiazolyl, oxadiazolyl, oxatriazolyl, dioxazolyl, oxathiazolyl, oxathiolyl, oxathiolanyl, pyranyl, dihydropyranyl, pyridinyl, piperidinyl, diazinyl, piperazinyl, triazinyl, oxazinyl, isoxazinyl, oxathiazinyl, oxadiazinyl, morpholinyl, azepinyl, oxepinyl, thiepinyl, diazepinyl, indolizinyl, pyrindinyl, pyranopyrrolyl, 4H-quinolizinyl, purinyl, naphthyridinyl, pyridopyridinyl, pteridinyl, indolyl, isoindolyl, indoleninyl, isoindazolyl, benzazinyl, phthalazinyl, quinoxalinyl, quinazolinyl, benzodiazinyl, benzopyranyl, benzothiopyranyl, benzoxazolyl, indoxazinyl, anthranilyl, benzodioxolyl, benzodioxanyl, benzoxadiazolyl, benzofuranyl, isobenzofuranyl, benzothienyl, isobenzothienyl, benzothiazolyl, benzothiadiazolyl,

benzimidazolyl, benzotriazolyl, benzoxazinyl, benzisoxazinyl, tetrahydroisoquinolinyl, carbazolyl, xanthenyl, and acridinyl, wherein:

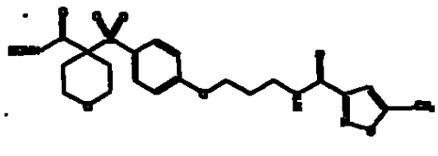
any member of such group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^{11})(R^{12})$, $-C(O)(R^{13})$, $-S-R^{11}$, $-S(O)_2-R^{11}$, aryl, aryl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, haloaryl, halogen-substituted aryl-C_1-C_6-alkyl, C_1-C_6-alkylaryl, halogen-substituted C_1-C_6-alkylaryl, hydroxyaryl, and heteroaryl.

65. A compound or salt thereof according to claim 64, wherein E^5 is selected from the group consisting of pyridinyl, pyrrolyl, isopyrrolyl, oxazolyl, isoxazole, thiazolyl, furanyl, morpholinyl, tetrazolyl, imidazolyl, thienyl, wherein any member of such group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^{11})(R^{12})$, $-C(O)(R^{13})$, $-S-R^{11}$, $-S(O)_2-R^{11}$, aryl, aryl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, haloaryl, halogen-substituted aryl-C_1-C_6-alkyl, C_1-C_6-alkylaryl, halogen-substituted C_1-C_6-alkylaryl, hydroxyaryl, and heteroaryl.

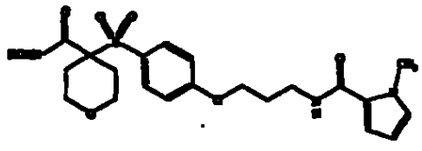
66. A compound or salt thereof according to claim 65, wherein the compound corresponds in structure to a formula selected from the group consisting of:



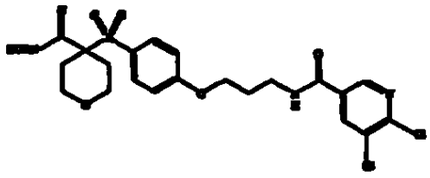
(66-1),



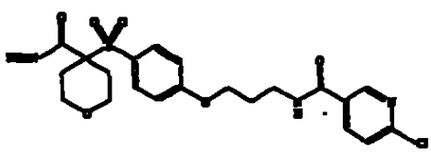
(66-2),



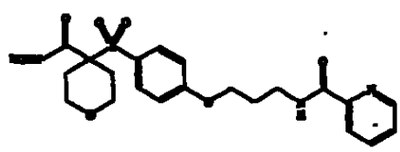
(66-3),



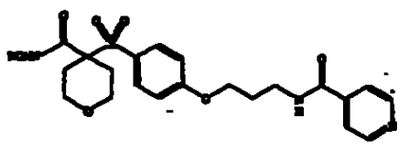
(66-4),



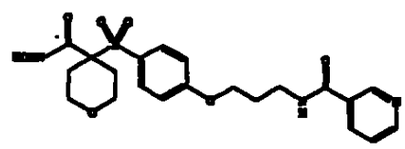
(66-5),



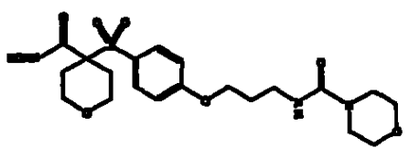
(66-6),



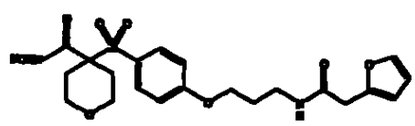
(66-7),



(66-8),

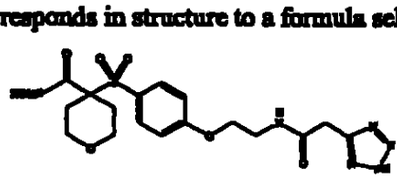


(66-9), and

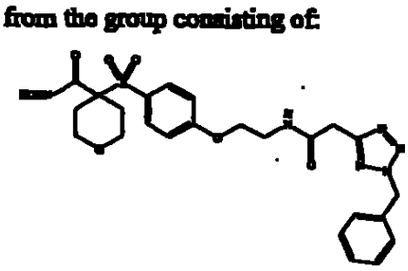


(66-10).

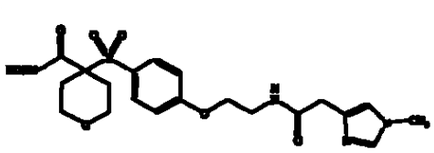
67. A compound or salt thereof according to claim 65, wherein the compound corresponds in structure to a formula selected from the group consisting of:



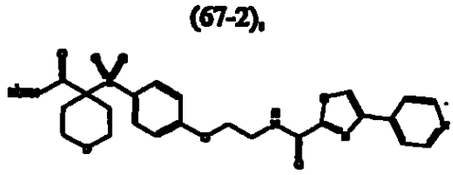
(67-1),



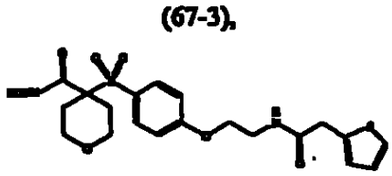
(67-2),



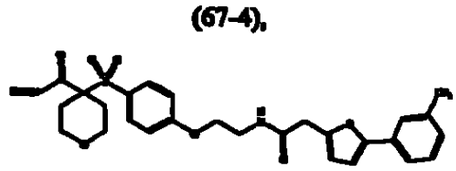
(67-3),



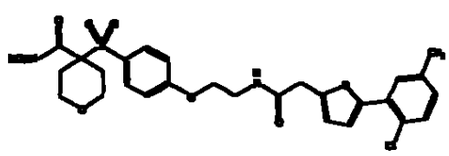
(67-4),



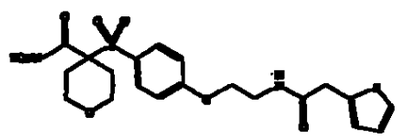
(67-5),



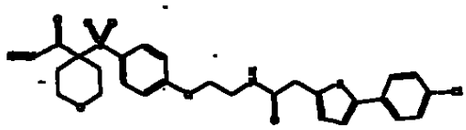
(67-6),



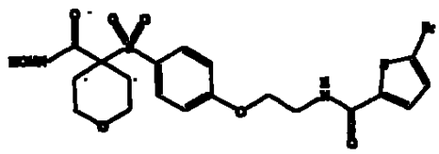
(67-7),



(67-8),



(67-9), and



(67-10).

68. A compound or salt thereof according to claim 63, wherein E^5 is 2-fused-ring heterocyclyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^{11})(R^{12})$, -$C(O)(R^{13})$, -S-R^{11}, -$S(O)_2$-R^{11}, aryl, aryl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, haloaryl, halogen-substituted aryl-C_1-C_6-alkyl, C_1-C_6-alkylaryl, halogen-substituted C_1-C_6-alkylaryl, hydroxyaryl, and heteroaryl.

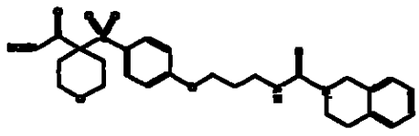
69. A compound or salt thereof according to claim 68, wherein E^5 is selected from the group consisting of indolizinyl, pyrindinyl, pyranopyrrolyl, 4H-quinolizinyl, purinyl, naphthyridinyl, pyridopyridinyl, pteridinyl, indolyl, isoindolyl, indolenninyl, isoindazolyl, benzazinyl, phthalazinyl, quinoxalinyl, quinazolinyl, benzodiazinyl, benzopyranyl, benzothiopyranyl, benzoxazolyl, indoxazinyl, anthranilyl, benzodioxolyl, benzodioxanyl, benzoxadiazolyl, benzofuranyl, isobenzofuranyl, benzothienyl, isobenzothienyl, benzothiazolyl, benzothiadiazolyl, benzimidazolyl, benzotriazolyl, benzoxazinyl, benziscxazinyl, and tetrahydroisoquinolinyl, wherein:

any member of such group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^{11})(R^{12})$, -$C(O)(R^{13})$, -S-R^{11}, -$S(O)_2$-R^{11}, aryl, aryl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, haloaryl, halogen-substituted aryl-C_1-C_6-alkyl, hydroxyaryl, and heteroaryl.

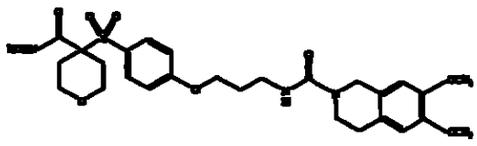
500

70. A compound or salt thereof according to claim 69, wherein E^5 is selected from the group consisting of benzazinyl, benzofuranyl, tetrahydroisoquinolinyl, indolyl, benzoxazolyl, benzothienyl, and benzothiazolyl, wherein any member of such group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^{11})(R^{12})$, $-C(O)(R^{13})$, $-S-R^{11}$, $-S(O)_z-R^{11}$, aryl, aryl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, haloaryl, halogen-substituted aryl-C_1-C_6-alkyl, C_1-C_6-alkylaryl, halogen-substituted C_1-C_6-alkylaryl, hydroxyaryl, and heteroaryl.

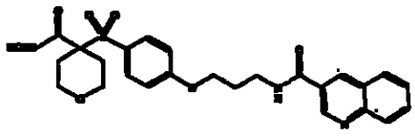
71. A compound or salt thereof according to claim 70, wherein the compound corresponds in structure to a formula selected from the group consisting of:



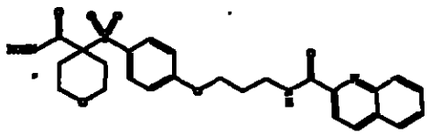
(71-1),



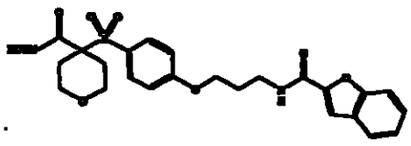
(71-2),



(71-3),

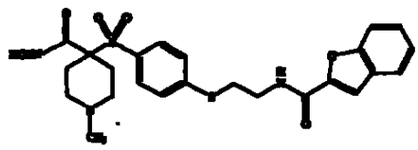


(71-4), and

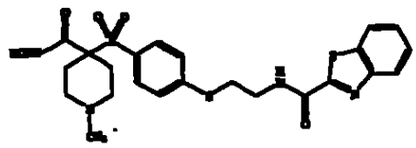


(71-5).

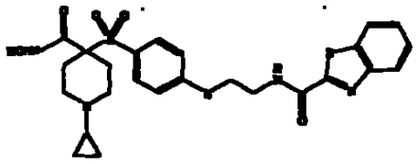
72. A compound or salt thereof according to claim 70, wherein the compound corresponds in structure to a formula selected from the group consisting of:



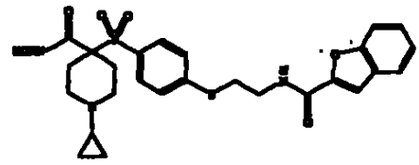
(72-1),



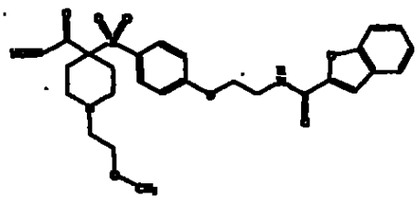
(72-2),



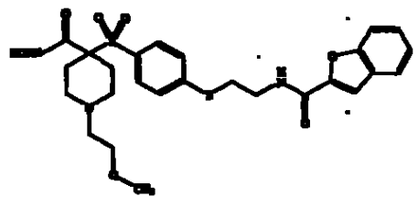
(72-3),



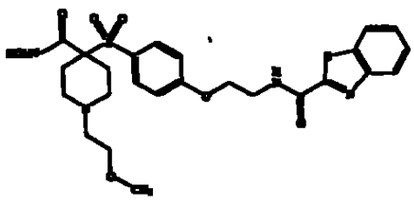
(72-4),



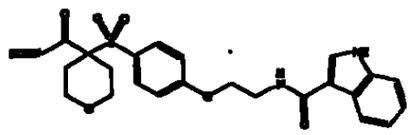
(72-5),



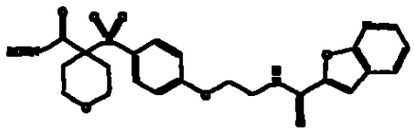
(72-6),



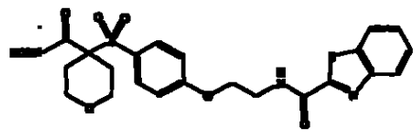
(72-7),



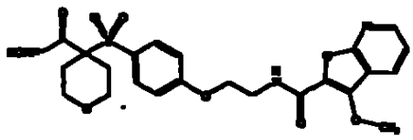
(72-8),



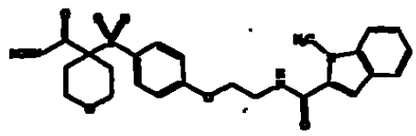
(72-9),



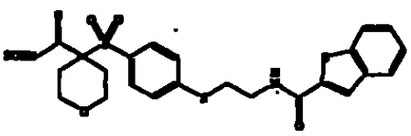
(72-10),



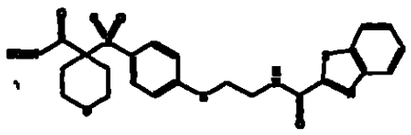
(72-11),



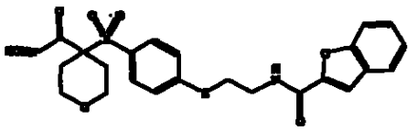
(72-12),



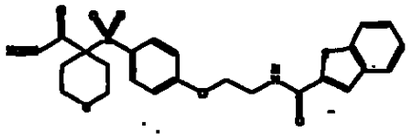
(72-13),



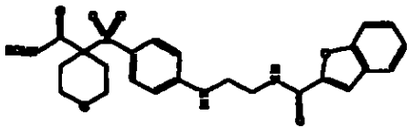
(72-14),



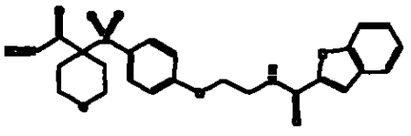
(72-15),



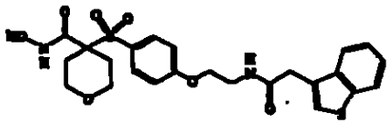
(72-16),



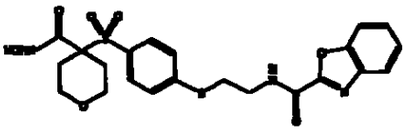
(72-17),



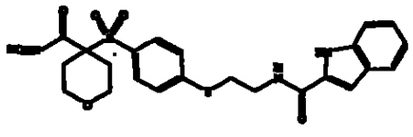
(72-18),



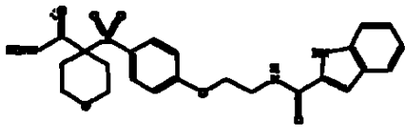
(72-19),



(72-20),



(72-21), and

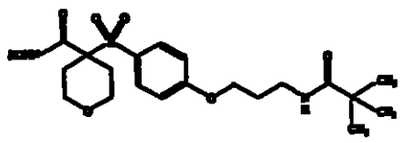


(72-22).

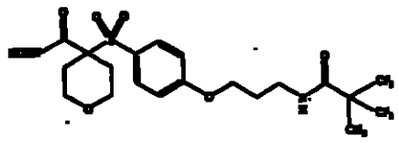
73. A compound or salt thereof according to claim 49, wherein E^5 is selected from the group consisting of -OH, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkoxy, or C_1-C_6-alkoxy-C_1-C_6-alkyl, wherein any member (except -OH) of such group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, and -CN.

503

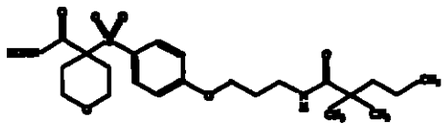
74. A compound or salt thereof according to claim 73, wherein the compound corresponds in structure to a formula selected from the group consisting of:



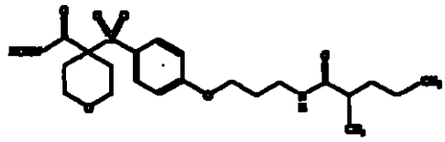
(74-1),



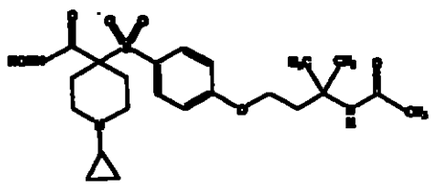
(74-2),



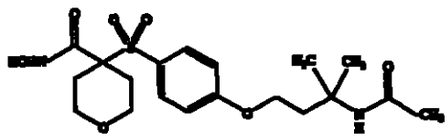
(74-3),



(74-4),



(74-5), and



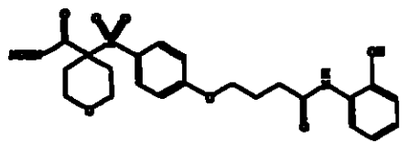
(74-6).

75. A compound or salt thereof according to claim 7, wherein E^3 is -C(O)-N(R^4)-.

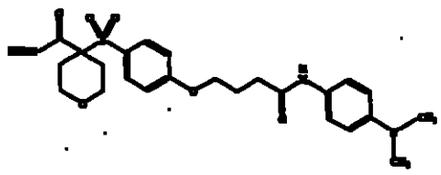
76. A compound or salt thereof according to claim 75, wherein E^5 is phenyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, -N(R^{11})(R^{12}), -C(O)(R^{13}), -S-R^{11}, -S(O)$_2$-R^{11}, aryl, aryl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, haloaryl, halogen-substituted aryl-C_1-C_6-alkyl, C_1-C_6-alkylaryl, halogen-substituted C_1-C_6-alkylaryl, hydroxyaryl, and heteroaryl.

504

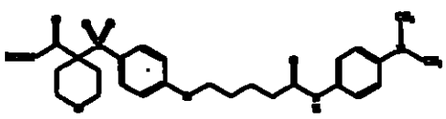
77. A compound or salt thereof according to claim 76, wherein the compound corresponds in structure to a formula selected from the group consisting of:



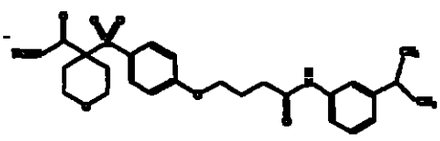
(77-1),



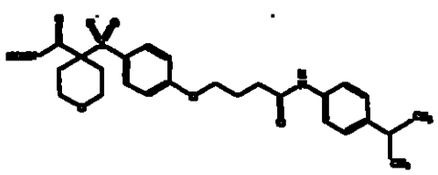
(77-2),



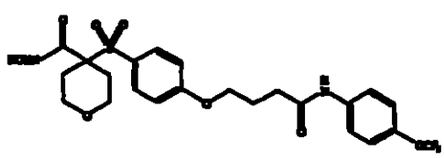
(77-3),



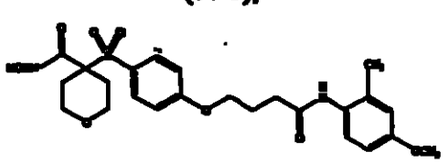
(77-4),



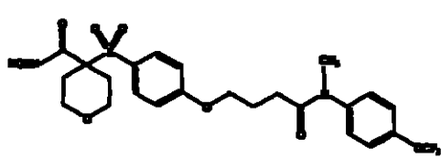
(77-5),



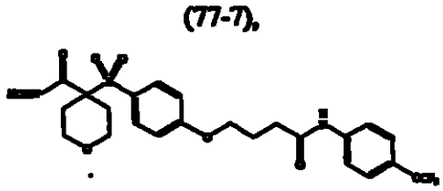
(77-6),



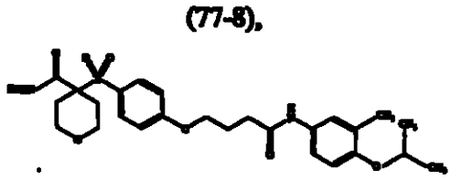
(77-7),



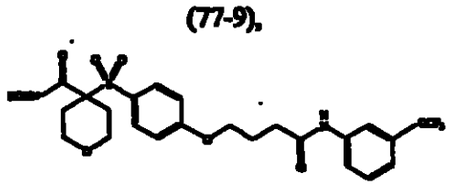
(77-8),



(77-9),

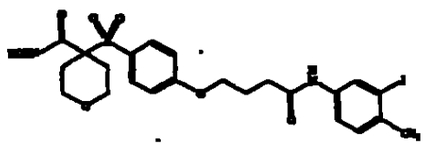


(77-10), and

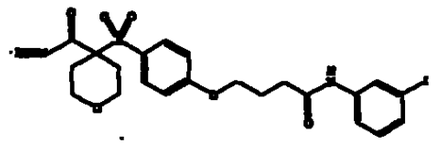


(77-11).

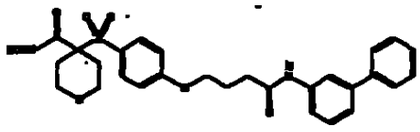
78. A compound or salt thereof according to claim 76, wherein the compound corresponds in structure to a formula selected from the group consisting of:



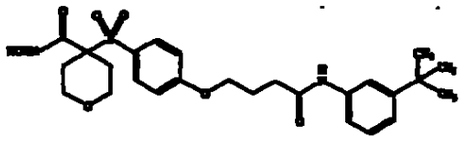
(78-1),



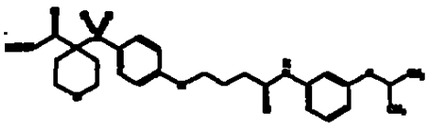
(78-2),



(78-3),



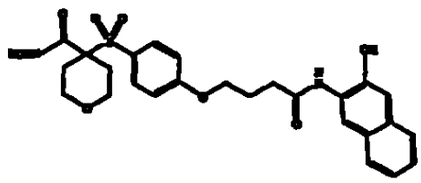
(78-4), and



(78-5).

79. A compound or salt thereof according to claim 75, wherein E^5 is naphthalenyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^{11})(R^{12})$, -$C(O)(R^{13})$, -S-R^{11}, -$S(O)_2$-R^{11}, aryl, aryl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, haloaryl, halogen-substituted aryl-C_1-C_6-alkyl, C_1-C_6-alkylaryl, halogen-substituted C_1-C_6-alkylaryl, hydroxyaryl, and heteroaryl.

80. A compound or salt thereof according to claim 79, wherein the compound corresponds in structure to the following formula:

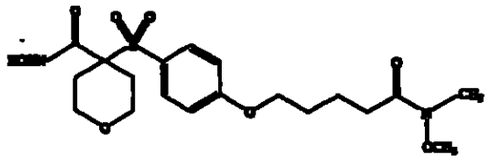


(80-1).

506

81. A compound or salt thereof according to claim 75, wherein E^5 is selected from the group consisting of -OH, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkoxy, or C_1-C_6-alkoxy-C_1-C_6-alkyl, wherein any member (except -OH) of such group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, and -CN.

82. A compound or salt thereof according to claim 81, wherein the compound corresponds in structure to the following formula:

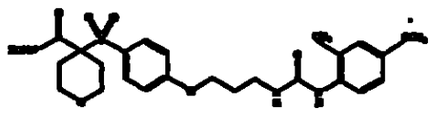


(82-1).

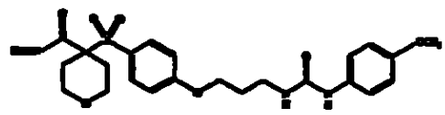
83. A compound or salt thereof according to claim 7, wherein E^3 is $-N(R^4)-C(O)-N(R^5)-$.

84. A compound or salt thereof according to claim 83, wherein E^5 is phenyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^{11})(R^{12})$, $-C(O)(R^{13})$, $-S-R^{11}$, $-S(O)_2-R^{11}$, aryl, aryl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, haloaryl, halogen-substituted aryl-C_1-C_6-alkyl, C_1-C_6-alkylaryl, halogen-substituted C_1-C_6-alkylaryl, hydroxyaryl, and heteroaryl.

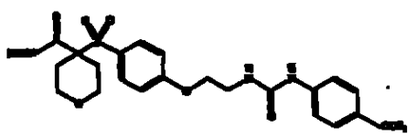
85. A compound or salt thereof according to claim 84, wherein the compound corresponds in structure to a formula selected from the group consisting of:



(85-1),



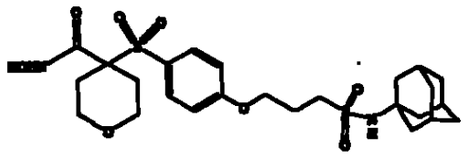
(85-2), and



(85-3).

86. A compound or salt thereof according to claim 7, wherein E^3 is $-S(O)_2-N(R^4)-$.

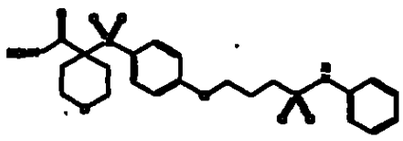
87. A compound or salt thereof according to claim 86, wherein the compound corresponds in structure to the following formula:



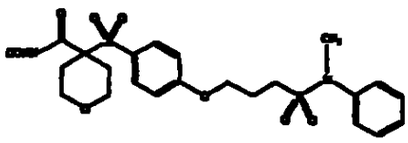
(87-3).

88. A compound or salt thereof according to claim 86, wherein E^5 is phenyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^{11})(R^{12})$, $-C(O)(R^{13})$, $-S-R^{11}$, $-S(O)_2-R^{11}$, aryl, aryl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, haloaryl, halogen-substituted aryl-C_1-C_6-alkyl, C_1-C_6-alkylaryl, halogen-substituted C_1-C_6-alkylaryl, hydroxyaryl, and heteroaryl.

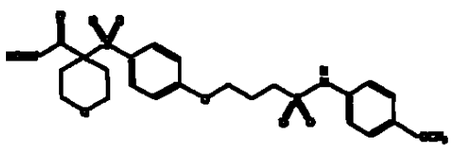
89. A compound or salt thereof according to claim 88, wherein the compound corresponds in structure to a formula selected from the group consisting of:



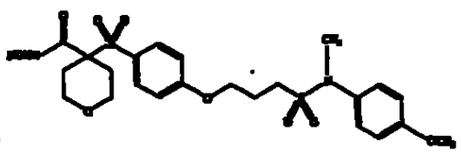
(89-1),



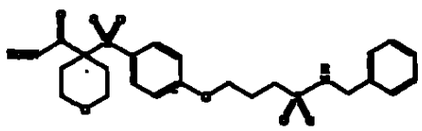
(89-2),



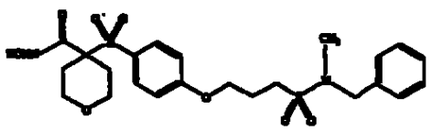
(89-3),



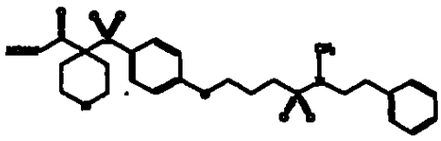
(89-4),



(89-5),



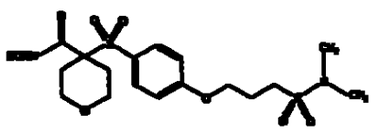
(89-6), and



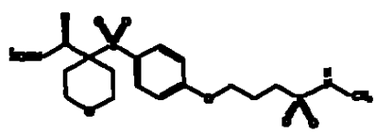
(89-7).

90. A compound or salt thereof according to claim 86, wherein E^5 is selected from the group consisting of -H, -OH, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkoxy, or C_1-C_6-alkoxy-C_1-C_6-alkyl, wherein any member (except -H or -OH) of such group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, and -CN.

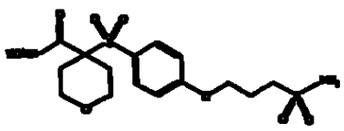
91. A compound or salt thereof according to claim 90, wherein the compound corresponds in structure to a formula selected from the group consisting of:



(91-1),



(91-2), and

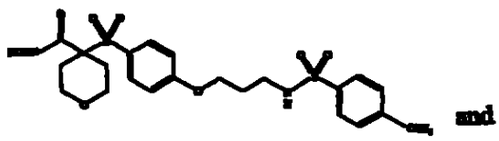


(91-3).

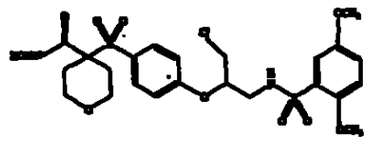
92. A compound or salt thereof according to claim 7, wherein E^3 is $-N(R^4)-S(O)_2-$.

93. A compound or salt thereof according to claim 92, wherein E^5 is phenyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^{11})(R^{12})$, $-C(O)(R^{13})$, $-S-R^{11}$, $-S(O)_2-R^{11}$, aryl, aryl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, haloaryl, halogen-substituted aryl-C_1-C_6-alkyl, C_1-C_6-alkylaryl, halogen-substituted C_1-C_6-alkylaryl, hydroxyaryl, and heteroaryl.

94. A compound or salt thereof according to claim 93, wherein the compound corresponds in structure to a formula selected from the group consisting of:

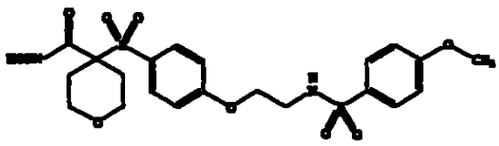


and



(94-1) (94-2).

95. A compound or salt thereof according to claim 93, wherein the compound corresponds in structure to the following formula:



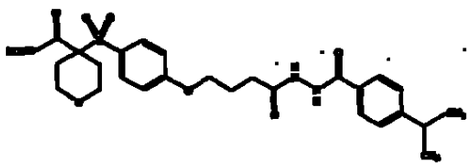
(95-1).

96. A compound or salt thereof according to claim 7, wherein E^3 is $-C(O)-N(R^4)-N(R^5)-C(O)-$.

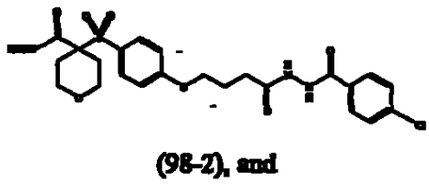
97. A compound or salt thereof according to claim 96, wherein E^5 is phenyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^{11})(R^{12})$, $-C(O)(R^{13})$, $-S-R^{11}$, $-S(O)_2-R^{11}$, aryl, aryl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted

C_1-C_6-alkoxy-C_1-C_6-alkyl, haloaryl, halogen-substituted aryl-C_1-C_6-alkyl, C_1-C_6-alkylaryl, halogen-substituted C_1-C_6-alkylaryl, hydroxyaryl, and heteroaryl.

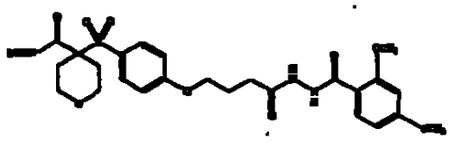
98. A compound or salt thereof according to claim 97, wherein the compound corresponds in structure to a formula selected from the group consisting of:



(98-1),



(98-2), and

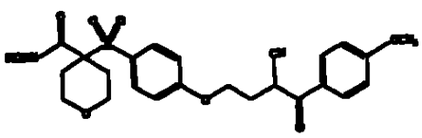


(98-3).

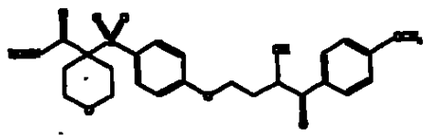
99. A compound or salt thereof according to claim 7, wherein E^3 is $-C(R^4)(R^6)-C(O)-$.

100. A compound or salt thereof according to claim 99, wherein E^5 is phenyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^{11})(R^{12})$, $-C(O)(R^{13})$, $-S-R^{11}$, $-S(O)_2-R^{11}$, aryl, aryl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, haloaryl, halogen-substituted aryl-C_1-C_6-alkyl, C_1-C_6-alkylaryl, halogen-substituted C_1-C_6-alkylaryl, hydroxyaryl, and heteroaryl.

101. A compound or salt thereof according to claim 100, wherein the compound corresponds in structure to a formula selected from the group consisting of:

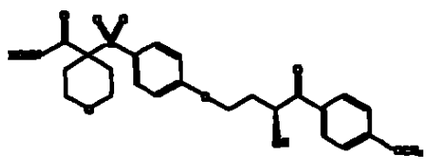


and



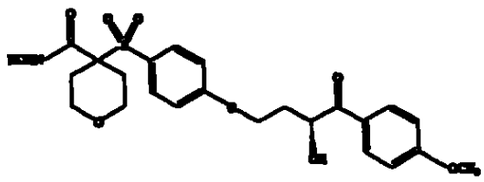
(101-1) (101-2).

102. A compound or salt thereof according to claim 100, wherein the compound corresponds in structure to the following formula:



(102-1).

103. A compound or salt thereof according to claim 100, wherein the compound corresponds in structure to the following formula:



(103-1).

104. A compound or salt thereof according to claim 7, wherein E^3 is -O-C(O)-.

105. A compound or salt thereof according to claim 104, wherein E^5 is heterocyclyl optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^{11})(R^{12})$, $-C(O)(R^{13})$, $-S-R^{11}$, $-S(O)_2-R^{11}$, aryl, aryl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, haloaryl, halogen-substituted aryl-C_1-C_6-alkyl, C_1-C_6-alkylaryl, halogen-substituted C_1-C_6-alkylaryl, hydroxyaryl, and heteroaryl.

512

106. A compound or salt thereof according to claim 105, wherein E^5 is 2-fused-ring heterocyclyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^{11})(R^{12})$, $-C(O)(R^{13})$, $-S-R^{11}$, $-S(O)_2-R^{11}$, aryl, aryl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, haloaryl, halogen-substituted aryl-C_1-C_6-alkyl, C_1-C_6-alkylaryl, halogen-substituted C_1-C_6-alkylaryl, hydroxyaryl, and heteroaryl.

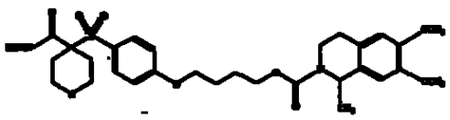
107. A compound or salt thereof according to claim 106, wherein E^5 is selected from the group consisting of indolizinyl, pyrindinyl, pyranopyrrolyl, 4H-quinolizinyl, purinyl, naphthyridinyl, pyridopyridinyl, pteridinyl, indolyl, isoindolyl, indoleninyl, isoindazolyl, benzazinyl, phthalazinyl, quinoxalinyl, quinazolinyl, benzodiazinyl, benzopyranyl, benzothiopyranyl, benzoxazolyl, indoxazinyl, anthranilyl, benzodioxolyl, benzodioxanyl, benzoxadiazolyl, benzofuranyl, isobenzofuranyl, benzothienyl, isobenzothienyl, benzothiazolyl, benzothiadiazolyl, benzimidazolyl, benzotriazolyl, benzoxazinyl, benzisoxazinyl, and tetrahydroisoquinolinyl, wherein:

any member of such group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^{11})(R^{12})$, $-C(O)(R^{13})$, $-S-R^{11}$, $-S(O)_2-R^{11}$, aryl, aryl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, haloaryl, halogen-substituted aryl-C_1-C_6-alkyl, C_1-C_6-alkylaryl, halogen-substituted C_1-C_6-alkylaryl, hydroxyaryl, and heteroaryl.

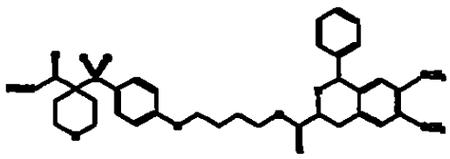
108. A compound or salt thereof according to claim 107, wherein E^5 is tetrahydroisoquinolinyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^{11})(R^{12})$, $-C(O)(R^{13})$, $-S-R^{11}$, $-S(O)_2-R^{11}$, aryl, aryl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, haloaryl, halogen-substituted

aryl-C_1-C_6-alkyl, C_1-C_6-alkylaryl, halogen-substituted C_1-C_6-alkylaryl, hydroxyaryl, and heteroaryl.

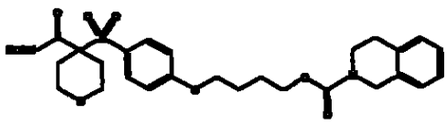
109. A compound or salt thereof according to claim 108, wherein the compound corresponds in structure to a formula selected from the group consisting of:



(109-1),



(109-2), and



(109-3).

110. A compound or salt thereof according to claim 7, wherein E^3 is -N(R^4)-.

111. A compound or salt thereof according to claim 110, wherein E^5 is heterocyclyl optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, -N(R^{11})(R^{12}), -C(O)(R^{13}), -S-R^{11}, -S(O)$_2$-R^{11}, aryl, aryl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, haloaryl, halogen-substituted aryl-C_1-C_6-alkyl, C_1-C_6-alkylaryl, halogen-substituted C_1-C_6-alkylaryl, hydroxyaryl, and heteroaryl.

112. A compound or salt thereof according to claim 111, wherein E^5 is 2-fused-ring heterocyclyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, -N(R^{11})(R^{12}), -C(O)(R^{13}), -S-R^{11}, -S(O)$_2$-R^{11}, aryl, aryl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, haloaryl, halogen-substituted

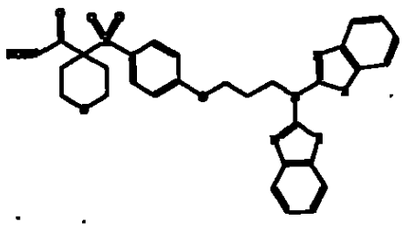
aryl-C_1-C_6-alkyl, C_1-C_6-alkylaryl, halogen-substituted C_1-C_6-alkylaryl, hydroxyaryl, and heteroaryl.

113. A compound or salt thereof according to claim 112, wherein E^5 is selected from the group consisting of indolizinyl, pyrindinyl, pyranopyrrolyl, 4H-quinolizinyl, purinyl, naphthyridinyl, pyridopyridinyl, pteridinyl, indolyl, isoindolyl, indoleninyl, isoindazolyl, benzazinyl, phthalazinyl, quinoxalinyl, quinazolinyl, benzodiazinyl, benzopyranyl, benzothiopyranyl, benzoxazolyl, indoxazinyl, anthranilyl, benzodioxolyl, benzodioxanyl, benzoxadiazolyl, benzofuranyl, isobenzofuranyl, benzothienyl, isobenzothienyl, benzothiazolyl, benzothiadiazolyl, benzimidazolyl, benzotriazolyl, benzoxazinyl, benzisoxazinyl, and tetrahydroisoquinolinyl, wherein:

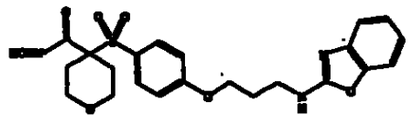
any member of such group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^{11})(R^{12})$, $-C(O)(R^{13})$, $-S-R^{11}$, $-S(O)_2-R^{11}$, aryl, aryl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, haloaryl, halogen-substituted aryl-C_1-C_6-alkyl, C_1-C_6-alkylaryl, halogen-substituted C_1-C_6-alkylaryl, hydroxyaryl, and heteroaryl.

114. A compound or salt thereof according to claim 113, wherein E^5 is selected from the group consisting of benzoxazolyl, benzothiazolyl, and benzimidazolyl, wherein any member of such group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^{11})(R^{12})$, $-C(O)(R^{13})$, $-S-R^{11}$, $-S(O)_2-R^{11}$, aryl, aryl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, haloaryl, halogen-substituted aryl-C_1-C_6-alkyl, C_1-C_6-alkylaryl, halogen-substituted C_1-C_6-alkylaryl, hydroxyaryl, and heteroaryl.

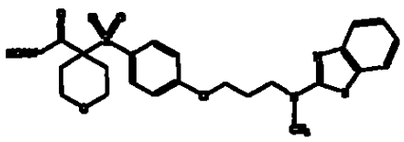
115. A compound or salt thereof according to claim 114, wherein the compound corresponds in structure to a formula selected from the group consisting of:



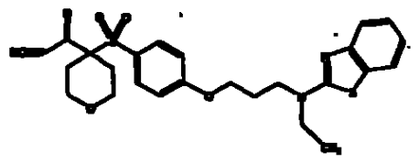
(115-1),



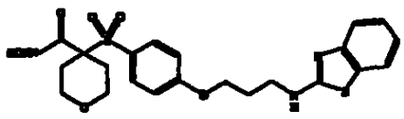
(115-2),



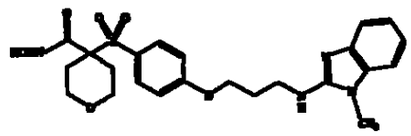
(115-3),



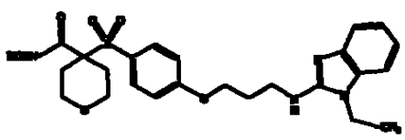
(115-4),



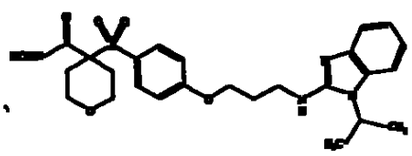
(115-5),



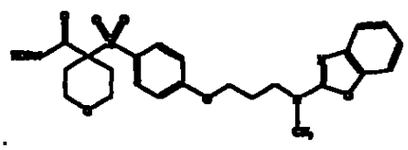
(115-6),



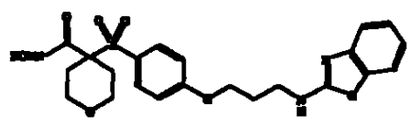
(115-7),



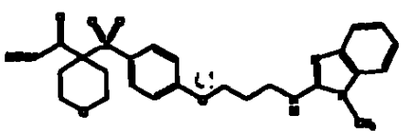
(115-8),



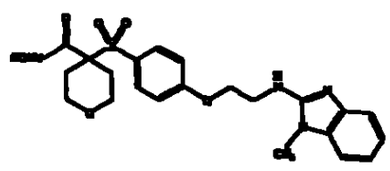
(115-9),



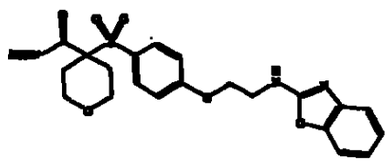
(115-10),



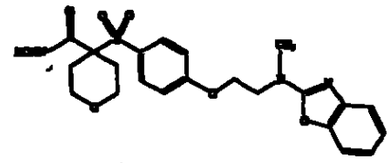
(115-11),



(115-12),



(115-13), and

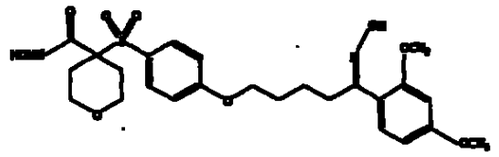


(115-14).

116. A compound or salt thereof according to claim 7, wherein E^3 is $-C(NR^3)-$.

117. A compound or salt thereof according to claim 116, wherein E^5 is phenyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^{11})(R^{12})$, $-C(O)(R^{13})$, $-S-R^{11}$, $-S(O)_2-R^{11}$, aryl, aryl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, haloaryl, halogen-substituted aryl-C_1-C_6-alkyl, C_1-C_6-alkylaryl, halogen-substituted C_1-C_6-alkylaryl, hydroxyaryl, and heteroaryl.

118. A compound or salt thereof according to claim 117, wherein the compound corresponds in structure to the following formula:



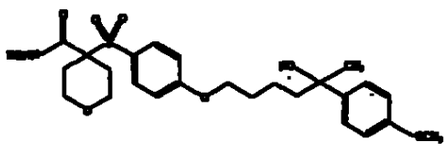
(118-1).

119. A compound or salt thereof according to claim 7, wherein E^3 is $-C(R^7)(R^8)-$.

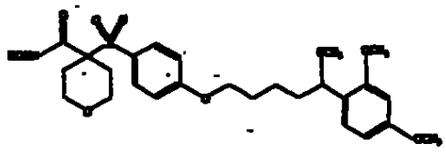
120. A compound or salt thereof according to claim 119, wherein E^5 is phenyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^{11})(R^{12})$, $-C(O)(R^{13})$, $-S-R^{11}$, $-S(O)_2-R^{11}$, aryl, aryl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted

C_1-C_6-alkoxy-C_1-C_6-alkyl, haloaryl, halogen-substituted aryl-C_1-C_6-alkyl, C_1-C_6-alkylaryl, halogen-substituted C_1-C_6-alkylaryl, hydroxyaryl, and heteroaryl.

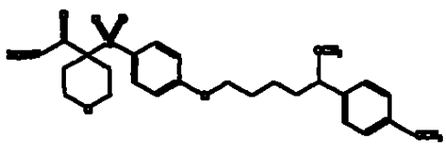
121. A compound or salt thereof according to claim 120, wherein the compound corresponds in structure to a formula selected from the group consisting of:



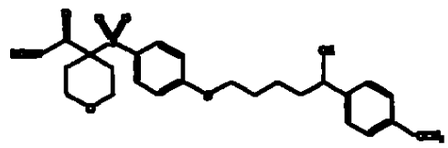
(121-1),



(121-2)



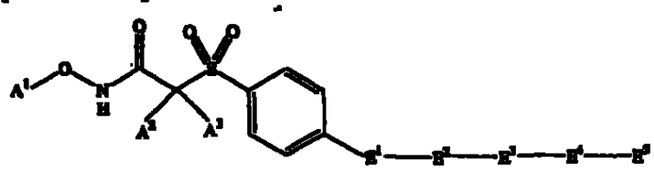
(121-3), and



(121-4).

122. A compound or salt thereof, wherein:

the compound corresponds in structure to Formula 122-1:



(122-1); and

A^1 is selected from the group consisting of -H, alkylcarbonyl, alkoxycarbonyl, carbocyclylcarbonyl, carbocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclylalkylcarbonyl, carbocyclyloxycarbonyl, carbocyclylalkoxycarbonyl, aminoalkylcarbonyl, alkyl(thiocarbonyl), alkoxy(thiocarbonyl), carbocyclyl(thiocarbonyl), carbocyclylalkyl(thiocarbonyl), heterocyclyl(thiocarbonyl), heterocyclylalkyl(thiocarbonyl), carbocyclyloxy(thiocarbonyl), carbocyclylalkoxy(thiocarbonyl), and aminoalkyl(thiocarbonyl), wherein any member (except -H) of such group optionally is substituted; and

A^2 and A^3, together with the carbon atom to which they are both attached, form an optionally-substituted heterocyclyl containing from 5 to 8 ring members; and

E^1 is selected from the group consisting of -O-, -S(O)$_2$-, -S(O)-, -N(R^1)-, -C(O)-N(R^1)-, -N(R^1)-C(O)-, and -C(R^1)(R^2)-; and

E^2 is selected from the group consisting of alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, and alkylcycloalkylalkyl, wherein any member of such group optionally is substituted; and

E^2 forms a link of at least 2 carbon atoms between E^1 and E^3; and

E^3 is selected from the group consisting of carbocyclyl and heterocyclyl, wherein the carbocyclyl or heterocyclyl has 5 or 6 ring members and optionally is substituted; and

E^4 is selected from the group consisting of a bond, alkyl, alkenyl, -O-, and, -N(R^3)-, wherein the alkyl or alkenyl optionally is substituted; and

E^5 is selected from the group consisting of carbocyclyl and heterocyclyl, wherein the carbocyclyl or heterocyclyl optionally is substituted; and

R^1 and R^2 are independently selected from the group consisting of -H and alkyl, wherein the alkyl optionally is substituted; and

R^3 is selected from the group consisting of -H and alkyl, wherein the alkyl optionally is substituted; and

neither R^1 nor R^2 forms a ring structure with E^2, E^3, E^4, or E^5.

123. A compound or salt thereof according to claim 122, wherein:

A^1 is selected from the group consisting of -H, C_1-C_8-alkylcarbonyl, C_1-C_8-alkoxycarbonyl, carbocyclylcarbonyl, carbocyclyl-C_1-C_8-alkylcarbonyl, heterocyclylcarbonyl, heterocyclyl-C_1-C_8-alkylcarbonyl, carbocyclyloxycarbonyl, carbocyclyl-C_1-C_8-alkoxycarbonyl, N(R^4)(R^5)-C_1-C_8-alkylcarbonyl, C_1-C_8-alkyl(thiocarbonyl), C_1-C_8-alkoxy(thiocarbonyl), carbocyclyl(thiocarbonyl), carbocyclyl-C_1-C_8-alkyl(thiocarbonyl), heterocyclyl(thiocarbonyl), heterocyclyl-C_1-C_8-alkyl(thiocarbonyl), carbocyclyloxy(thiocarbonyl), carbocyclyl-C_1-C_8-alkoxy(thiocarbonyl), and N(R^4)(R^5)-C_1-C_8-alkyl(thiocarbonyl); and

E^2 is selected from the group consisting of C_2-C_{20}-alkyl, cycloalkyl, C_1-C_{10}-alkylcycloalkyl, cycloalkyl-C_1-C_{10}-alkyl, C_1-C_{10}-alkylcycloalkyl-C_1-C_{10}-alkyl, wherein any member of such group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, C_1-C_6-alkyl, and halo-C_1-C_6-alkyl; and

E^3 is selected from the group consisting of carbocyclyl and heterocyclyl, wherein the carbocyclyl or heterocyclyl:

has 5 or 6 ring members, and

optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, keto, C_1-C_8-alkyl, C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl, wherein:

any such substituent (except halogen, -OH, or keto) optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, C_1-C_8-alkyl, C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, C_1-C_8-alkylthio, halo-C_1-C_8-alkyl, halo-C_1-C_8-alkoxy, halo-C_1-C_8-alkylthio, and halogen-substituted C_1-C_8-alkoxy-C_1-C_8-alkyl; and

E^4 is selected from the group consisting of a bond, -O-, -N(R^3)-, C_1-C_{20}-alkyl, and C_2-C_{20}-alkenyl, wherein the C_1-C_{20}-alkyl or C_2-C_{20}-alkenyl optionally is substituted with one or more substituents independently selected from the group consisting of:

halogen, and

carbocyclyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_8-alkyl, C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, halo-C_1-C_8-alkyl, halo-C_1-C_8-alkoxy, halocarbocyclyl, halogen-substituted carbocyclyl-C_1-C_8-alkyl, and halogen-substituted C_1-C_8-alkoxy-C_1-C_8-alkyl; and

E^5 is selected from the group consisting of carbocyclyl and heterocyclyl, wherein the carbocyclyl or heterocyclyl optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, keto, C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, -N(R^6)(R^7), -C(O)(R^8), -S-R^6, -S(O)$_2$-R^6, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, halo-C_1-C_8-alkyl, halo-C_1-C_8-alkoxy, halogen-substituted C_1-C_8-alkoxy-C_1-C_8-alkyl, halocarbocyclyl, and halogen-substituted carbocyclyl-C_1-C_8-alkyl; and

R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_8-alkyl, and halo-C_1-C_8-alkyl; and

R^3 is selected from the group consisting of -H, C_1-C_6-alkyl, and halo-C_1-C_6-alkyl; and

R^4 and R^5 are independently selected from the group consisting of -H, C_1-C_6-alkyl, C_1-C_6-alkoxycarbonyl, C_1-C_6-alkylcarbonyl, carbocyclyl-C_1-C_6-alkyl, and carbocyclyl-C_1-C_6-alkoxycarbonyl; and

R^6 and R^7 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, heterocyclyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halocarbocyclyl, halogen-substituted carbocyclyl-C_1-C_6-alkyl, haloheterocyclyl, and halogen-substituted heterocyclyl-C_1-C_6-alkyl; and

R^8 is selected from the group consisting of -H, C_1-C_6-alkyl, -O-R^9, -N(R^9)(R^{10}), carbocyclyl-C_1-C_6-alkyl, heterocyclyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halogen-substituted carbocyclyl-C_1-C_6-alkyl, and halogen-substituted heterocyclyl-C_1-C_6-alkyl; and

R^9 and R^{10} are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, heterocyclyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halocarbocyclyl, halogen-substituted carbocyclyl-C_1-C_6-alkyl, haloheterocyclyl, and halogen-substituted heterocyclyl-C_1-C_6-alkyl.

124. A compound or salt thereof according to claim 123, wherein A^1 is -H.

125. A compound or salt thereof according to claim 124, wherein:

E^2 is C_2-C_6-alkyl optionally substituted with one or more halogen; and

E^3 is selected from the group consisting of carbocyclyl and heterocyclyl, wherein the carbocyclyl or heterocyclyl:

has 5 or 6 ring members, and

optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, keto, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl, wherein:

any such substituent (except halogen, -OH, or keto) optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, C_1-C_6-alkylthio, halo-C_1-C_6-alkyl,

halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, and halo-C_1-C_6-alkylthio; and

E^4 is selected from the group consisting of a bond, -O-, -N(R^3)-, C_1-C_3-alkyl, and C_2-C_3-alkenyl, wherein the C_1-C_3-alkyl or C_2-C_3-alkenyl optionally is substituted with one or more substituents independently selected from the group consisting of:

halogen, and

carbocyclyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, halocarbocyclyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl; and

E^5 is selected from the group consisting of carbocyclyl and heterocyclyl, wherein the carbocyclyl or heterocyclyl optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, keto, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, -N(R^6)(R^7), -C(O)(R^6), -S-R^6, -S(O)$_2$-R^6, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, halocarbocyclyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl; and

R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_6-alkyl, and halo-C_1-C_6-alkyl; and

R^3 is selected from the group consisting of -H, C_1-C_6-alkyl, and halo-C_1-C_6-alkyl; and

R^6 and R^7 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl, wherein any member (except -H) of such group optionally is substituted with one or more halogen; and

R^8 is selected from the group consisting of -H, C_1-C_6-alkyl, -O-R^9, -N(R^9)(R^{10}), carbocyclyl-C_1-C_6-alkyl, heterocyclyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halogen-substituted carbocyclyl-C_1-C_6-alkyl, and halogen-substituted heterocyclyl-C_1-C_6-alkyl; and

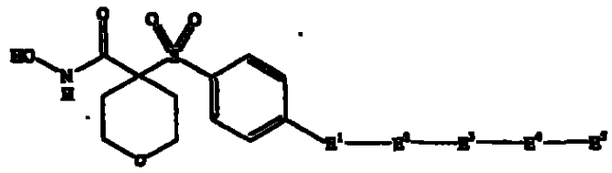
R^9 and R^{10} are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, heterocyclyl-C_1-C_6-alkyl,

halo-C_1-C_6-alkyl, halocarbocyclyl, halogen-substituted carbocyclyl-C_1-C_6-alkyl, haloheterocyclyl, and halogen-substituted heterocyclyl-C_1-C_6-alkyl.

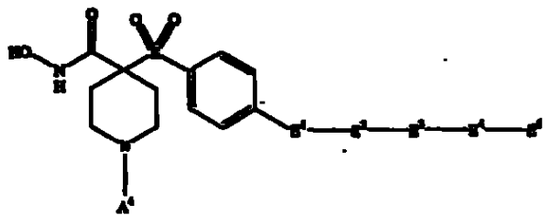
126. A compound or salt thereof according to claim 125, wherein A^2 and A^3, together with the carbon atom to which they both are attached, form an optionally-substituted heterocyclyl containing either 5 or 6 ring members.

127. A compound or salt thereof according to claim 126, wherein:

the compound corresponds in structure to a formula selected from the group consisting of:



(127-1) and



(127-2); and

A^4 is selected from the group consisting of -H, alkyl, alkylcarbonyl, alkylcarbonylalkyl, alkylcarbonylalkylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkoxycarbonylalkylcarbonyl, alkylsulfonyl, alkyliminocarbonyl, alkenyl, alkynyl, alkoxyalkyl, alkylthioalkyl, alkylsulfonylalkyl, alkylsulfoxidoalkyl, alkylthioalkenyl, alkylsulfoxidoalkenyl, alkylsulfonylalkenyl, carbocyclyl, carbocyclylalkyl, carbocyclylalkoxyalkyl, carbocyclylcarbonyl, carbocyclylsulfonyl, carbocyclyliminocarbonyl, carbocyclyloxycarbonyl, carbocylylthioalkyl, carbocylylsulfoxidoalkyl, carbocylylsulfonylalkyl, carbocyclylthioalkenyl, carbocyclylsulfoxidoalkenyl, carbocyclylsulfonylalkenyl, heterocyclyl, heterocyclylalkyl, heterocyclylalkoxyalkyl, heterocyclylcarbonyl, heterocyclylthioalkyl,

heterocyclylsulfoxidoalkyl, heterocyclylsulfonylalkyl, heterocyclylthioalkenyl, heterocyclylsulfoxidoalkenyl, heterocyclylsulfonylalkenyl, heterocyclylsulfonyl, heterocyclyliminocarbonyl, heterocyclylalkylcarbonyl, heterocyclylcarbonylalkylcarbonyl, heterocyclylsulfonyl, heterocyclylcarbonylalkyl, aminoalkylcarbonyl, aminocarbonyl, aminocarbonylalkylcarbonyl, aminosulfonyl, aminosulfonylalkyl, aminoalkyl, aminocarbonylalkyl, and aminoalkylsulfonyl, wherein:

any member (except -H) of such group optionally is substituted.

128. A compound or salt thereof according to claim 127, wherein:

A^4 is selected from the group consisting of -H, C_1-C_8-alkyl, C_1-C_8-alkylcarbonyl, C_1-C_8-alkylcarbonyl-C_1-C_8-alkyl, C_1-C_8-alkylcarbonyl-C_1-C_8-alkylcarbonyl, C_1-C_8-alkoxycarbonyl, C_1-C_8-alkoxycarbonyl-C_1-C_8-alkyl, C_1-C_8-alkoxycarbonyl-C_1-C_8-alkylcarbonyl, C_1-C_8-alkylsulfonyl, C_1-C_8-alkyliminocarbonyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, C_1-C_8-alkoxy-C_1-C_8-alkyl, C_1-C_8-alkylthio-C_1-C_8-alkyl, C_1-C_8-alkylthio-C_2-C_8-alkenyl, C_1-C_8-alkylsulfoxido-C_1-C_8-alkyl, C_1-C_8-alkylsulfoxido-C_2-C_8-alkenyl, C_1-C_8-alkylsulfonyl-C_1-C_8-alkyl, C_1-C_8-alkylsulfonyl-C_2-C_8-alkenyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, carbocyclyl-C_1-C_8-alkoxy-C_1-C_8-alkyl, carbocyclylcarbonyl, carbocyclylsulfonyl, carbocyclyliminocarbonyl, carbocyclyloxycarbonyl, carbocyclylthio-C_1-C_8-alkyl, carbocyclylthio-C_2-C_8-alkenyl, carbocyclylsulfoxido-C_1-C_8-alkyl, carbocyclylsulfoxido-C_2-C_8-alkenyl, carbocyclylsulfonyl-C_1-C_8-alkyl, carbocyclylsulfonyl-C_2-C_8-alkenyl, heterocyclyl, heterocyclyl-C_1-C_8-alkyl, heterocyclyl-C_1-C_8-alkoxy-C_1-C_8-alkyl, heterocyclylcarbonyl, heterocyclylthio-C_1-C_8-alkyl, heterocyclylsulfoxido-C_1-C_8-alkyl, heterocyclylsulfonyl-C_1-C_8-alkyl, heterocyclylthio-C_2-C_8-alkenyl, heterocyclylsulfoxido-C_2-C_8-alkenyl, heterocyclylsulfonyl-C_2-C_8-alkenyl, heterocyclylsulfonyl, heterocyclyliminocarbonyl, heterocyclyl-C_1-C_8-alkylcarbonyl, heterocyclylcarbonyl-C_1-C_8-alkylcarbonyl, heterocyclylsulfonyl, heterocyclylcarbonyl-C_1-C_8-alkyl; $N(R^{11})(R^{12})$-C_1-C_8-alkylcarbonyl, $N(R^{11})(R^{12})$-carbonyl, $N(R^{11})(R^{12})$-carbonyl-C_1-C_8-alkylcarbonyl,

$N(R^{11})(R^{12})$-sulfonyl, $N(R^{11})(R^{12})$-sulfonyl-C_1-C_8-alkyl, $N(R^{11})(R^{12})$-C_1-C_8-alkyl, $N(R^{11})(R^{12})$-carbonyl-C_1-C_8-alkyl, and $N(R^{11})(R^{12})$-C_1-C_8-alkylsulfonyl, wherein:

any member (except -H) of such group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -CN, -C(O)-OH, -SH, $-SO_3H$, and NO_2; and

R^{11} and R^{12} are independently selected from the group consisting of -H, -OH, C_1-C_8-alkyl, C_1-C_8-alkyl-carbonyl, C_1-C_8-alkoxy-C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, C_1-C_8-alkyl-thio-C_1-C_8-alkyl, C_1-C_8-alkyl-sulfoxido-C_1-C_8-alkyl, C_1-C_8-alkyl-sulfonyl-C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, carbocyclylcarbonyl, carbocyclyl-C_1-C_8-alkoxy-C_1-C_8-alkyl, carbocyclylthio-C_1-C_8-alkyl, carbocyclylsulfoxido-C_1-C_8-alkyl, carbocyclylsulfonyl-C_1-C_8-alkyl, heterocyclyl, heterocyclyl-C_1-C_8-alkyl, heterocyclyl-C_1-C_8-alkoxy-C_1-C_8-alkyl, heterocyclylcarbonyl, heterocyclylthio-C_1-C_8-alkyl, heterocyclylsulfoxido-C_1-C_8-alkyl, heterocyclylsulfonyl-C_1-C_8-alkyl, aminocarbonyl-C_1-C_8-alkyl, C_1-C_8-alkyloxycarbonylamino-C_1-C_8-alkyl, and amino-C_1-C_8-alkyl, wherein:

any member (except -H or -OH) of such group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -CN, -C(O)-OH, -SH, $-SO_3H$, and NO_2, and

the nitrogen of the amino-C_1-C_8-alkyl optionally is substituted with 1 or 2 substituents independently selected from the group consisting of C_1-C_8-alkyl, C_1-C_8-alkylcarbonyl, carbocyclyl, and carbocyclyl-C_1-C_8-alkyl, and

no greater than one of R^{11} or R^{12} is -OH.

129. A compound or salt thereof according to claim 128, wherein A^4 is selected from the group consisting of -H, C_1-C_8-alkyl, C_1-C_8-alkoxy-C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, C_1-C_8-alkylsulfonyl, C_3-C_8-alkenyl, C_3-C_8-alkynyl, wherein any member (except -H) of such group optionally is substituted with halogen.

130. A compound or salt thereof according to claim 129, wherein A^4 is selected from the group consisting of -H, C_1-C_4-alkyl, C_1-C_2-alkoxy-C_1-C_3-alkyl, C_3-C_6-cycloalkyl, C_3-C_6-cycloalkyl-C_1-C_3-alkyl, phenyl, phenyl-C_1-C_2-alkyl, C_1-C_2-alkylsulfonyl,

C_3-C_4-alkenyl, C_3-C_4-alkynyl, wherein any member (except -H) of such group optionally is substituted with halogen.

131. A compound or salt thereof according to claim 130, wherein A^4 is selected from the group consisting of -H, ethyl, methoxyethyl, cyclopropyl, cyclopropylmethyl, benzyl, methylsulfonyl, C_3-alkenyl, and C_3-alkynyl, wherein any member (except -H) of such group optionally is substituted with halogen.

132. A compound or salt thereof according to claim 131, wherein A^4 is selected from the group consisting of -H, ethyl, methoxyethyl, cyclopropyl, cyclopropylmethyl, and benzyl, wherein any member (except -H) of such group optionally is substituted with halogen.

133. A compound or salt thereof according to claim 128, wherein the salt comprises an acid selected from the group consisting of HCl and CF_3COOH.

134. A compound or salt thereof according to claim 128, wherein E^2 is C_2-C_5-alkyl optionally substituted with one or more halogen.

135. A compound or salt thereof according to claim 134, wherein E^2 is $-(CH_2)_m-$, and m is from 2 to 5.

136. A compound or salt thereof according to claim 135, wherein E^4 is a bond.

137. A compound or salt thereof according to claim 128, wherein E^3 is heterocyclyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, keto, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, heterocyclyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, and halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, wherein:

any such substituent (except halogen, -OH, or keto) optionally is substituted with one or more substituents independently selected from the group

consisting of halogen, -OH, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, C_1-C_6-alkylthio, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, and halo-C_1-C_6-alkylthio.

138. A compound or salt thereof according to claim 137, wherein E^3 is selected from the group consisting of furanyl, tetrahydropyranyl, dihydrofuranyl, tetrahydrofuranyl, thiophenyl, dihydrothiophenyl, tetrahydrothiophenyl, pyrrolyl, isopyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, isoimidazolyl, imidazolinyl, imidazolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, triazolyl, tetrazolyl, dithiolyl, oxathiolyl, oxazolyl, isoxazolyl, oxazolidinyl, isoxazolidinyl, thiazolyl, isothiazolyl, thiazolinyl, isothiazolinyl, thiazolidinyl, isothiazolidinyl, thiodiazolyl, oxathiazolyl, oxadiazolyl, oxatriazolyl, dioxazolyl, oxathiazolyl, oxathiolyl, oxathiolanyl, pyranyl, dihydropyranyl, pyridinyl, piperidinyl, diazinyl, piperazinyl, triazinyl, oxazinyl, isoxazinyl, oxathiazinyl, oxadiazinyl, morpholinyl, azepinyl, oxepinyl, thiepinyl, diazepinyl, indolizinyl, pyrindinyl, pyranopyrrolyl, 4H-quinolizinyl, purinyl, naphthyridinyl, pyridopyridinyl, pteridinyl, indolyl, isoindolyl, indolenlnyl, isoindazolyl, benzazinyl, phthalazinyl, quinoxalinyl, quinazolinyl, benzodiazinyl, benzopyranyl, benzothiopyranyl, benzoxazolyl, indoxazinyl, anthranilyl, benzodioxolyl, benzodioxanyl, benzoxadiazolyl, benzofuranyl, isobenzofuranyl, benzothienyl, isobenzothienyl, benzothiazolyl, benzothiadiazolyl, benzimidazolyl, benzotriazolyl, benzoxazinyl, benzisoxazinyl, tetrahydroisoquinolinyl, carbazolyl, xanthenyl, and acridinyl, wherein

any member of such group optionally is substituted (to the extent such member contains a substitutable hydrogen(s)) with one or more substituents independently selected from the group consisting of halogen, -OH, keto, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, heterocyclyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, and halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, wherein:

any such substituent (except halogen, -OH, or keto) optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, C_1-C_6-alkylthio, halo-C_1-C_6-alkyl,

halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, and halo-C_1-C_6-alkylthio.

139. A compound or salt thereof according to claim 137, wherein E^3 contains no greater than one heteroatom ring member.

140. A compound or salt thereof according to claim 139, wherein E^3 is selected from the group consisting of furanyl, tetrahydropyranyl, dihydrofuranyl, tetrahydrofuranyl, thiophenyl, dihydrothiophenyl, tetrahydrothiophenyl, pyrrolinyl, pyrrolyl, isopyrrolyl, pyrrolidinyl, pyridinyl, piperidinyl, pyranyl, dihydropyranyl, and tetrahydropyranyl, wherein:

any member of such group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, keto, C_1-C_6-alkyl, C_1-C_6-alkoxy, and C_1-C_6-alkoxy-C_1-C_6-alkyl, wherein:

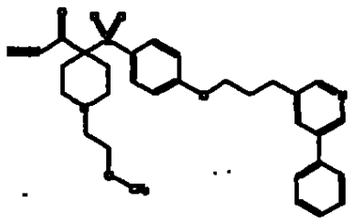
any such substituent (except halogen, -OH, or keto) optionally is substituted with one or more substituents independently selected from the group consisting of halogen and -OH.

141. A compound or salt thereof according to claim 139, wherein E^3 is pyridinyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, C_1-C_6-alkyl, C_1-C_6-alkoxy, and C_1-C_6-alkoxy-C_1-C_6-alkyl, wherein:

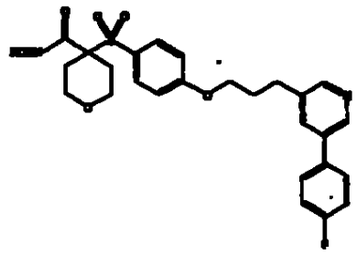
any such substituent (except halogen or -OH) optionally is substituted with one or more substituents independently selected from the group consisting of halogen and -OH.

142. A compound or salt thereof according to claim 141, wherein E^5 is phenyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^6)(R^7)$, $-C(O)(R^5)$, $-S-R^6$, $-S(O)_2-R^6$, phenyl, phenyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, halophenyl, and halogen-substituted phenyl-C_1-C_6-alkyl.

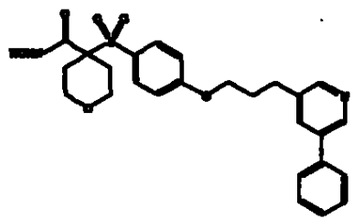
143. A compound or salt thereof according to claim 142, wherein the compound corresponds in structure to a formula selected from the group consisting of:



(143-1),

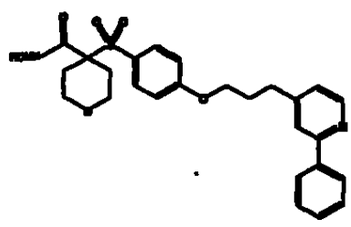


(143-2), and



(143-3).

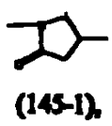
144. A compound or salt thereof according to claim 142, wherein the compound corresponds in structure to the following formula:



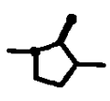
(144-1).

145. A compound or salt thereof according to claim 139, wherein:

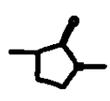
E^3 is selected from the group consisting of:



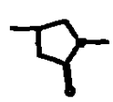
(145-1),



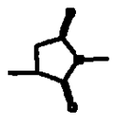
(145-2),

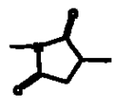


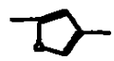
(145-3),

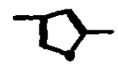


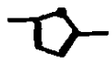
(145-4),

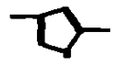

(145-5),

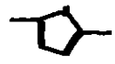

(145-6),

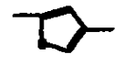

(145-7),

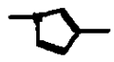

(145-8),


(145-9),

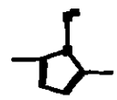

(145-10),

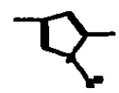

(145-11),

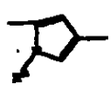

(145-12),


(145-13),


(145-14),


(145-15),


(145-16), and


(145-17); and

any member of such group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl, wherein:

any such substituent (except halogen or -OH) optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, C_1-C_6-alkylthio, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, and halo-C_1-C_6-alkylthio; and

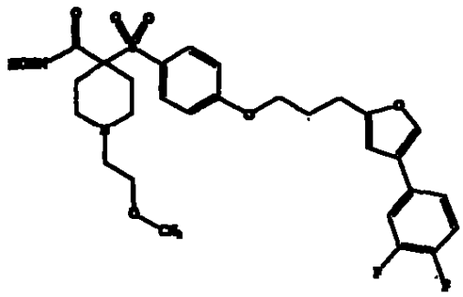
R^{14} is selected from the group consisting of halogen, -OH, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl, wherein

any member (except halogen or -OH) of such group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, C_1-C_6-alkylthio, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, and halo-C_1-C_6-alkylthio.

146. A compound or salt thereof according to claim 145, wherein B^3 is furanyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, keto, C_1-C_6-alkyl, C_1-C_6-alkoxy, and C_1-C_6-alkoxy-C_1-C_6-alkyl, wherein:

any such substituent (except halogen, -OH, or keto) optionally is substituted with one or more substituents independently selected from the group consisting of halogen and -OH.

147. A compound or salt thereof according to claim 146, wherein the compound corresponds in structure to the following formula:



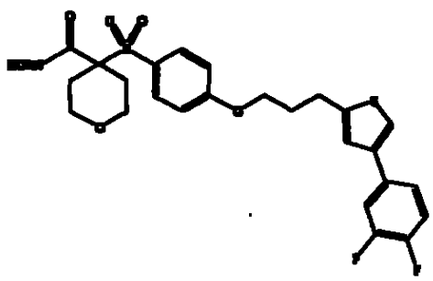
(147-1).

148. A compound or salt thereof according to claim 145, wherein B^3 is thienyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, keto, C_1-C_6-alkyl, C_1-C_6-alkoxy, and C_1-C_6-alkoxy-C_1-C_6-alkyl, wherein:

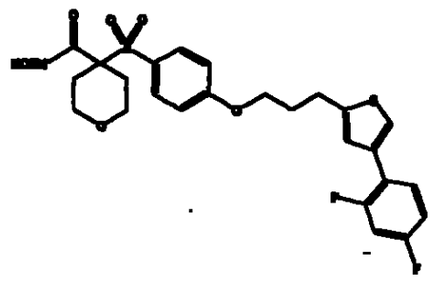
any such substituent (except halogen, -OH, or keto) optionally is substituted with one or more substituents independently selected from the group consisting of halogen and -OH.

531

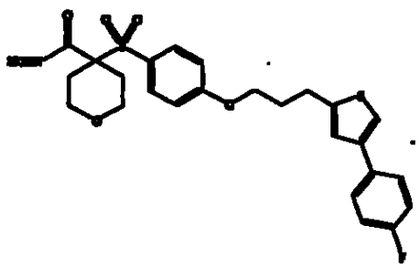
149. A compound or salt thereof according to claim 148, wherein the compound corresponds in structure to a formula selected from the group consisting of:



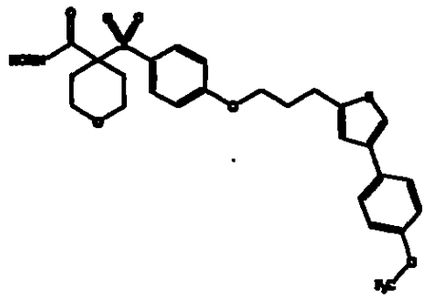
(149-1),



(149-2),

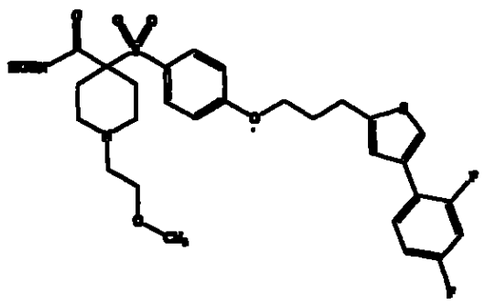


(149-3), and



(149-4).

150. A compound or salt thereof according to claim 148, wherein the compound corresponds in structure to the following formula:



(150-1).

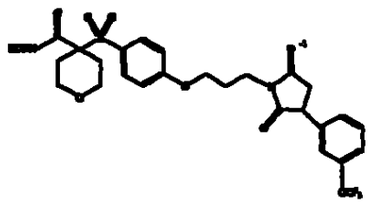
151. A compound or salt thereof according to claim 145, wherein E^3 is pyrrolidinyl optionally substituted with one or more substituents independently selected

from the group consisting of halogen, -OH, keto, C_1-C_6-alkyl, C_1-C_6-alkoxy, and C_1-C_6-alkoxy-C_1-C_6-alkyl, wherein:

any such substituent (except halogen, -OH, or keto) optionally is substituted with one or more substituents independently selected from the group consisting of halogen and -OH.

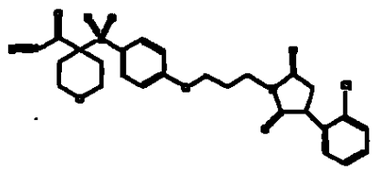
152. A compound or salt thereof according to claim 151, wherein E^5 is phenyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^6)(R^7)$, $-C(O)(R^8)$, $-S-R^6$, $-S(O)_2-R^6$, phenyl, phenyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, halophenyl, and halogen-substituted phenyl-C_1-C_6-alkyl.

153. A compound or salt thereof according to claim 152, wherein the compound corresponds in structure to a formula selected from the group consisting of:



(153-1)

and



(153-2).

154. A compound or salt thereof according to claim 137, wherein E^3 contains no greater and no less than two heteroatom ring members.

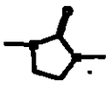
155. A compound or salt thereof according to claim 154, wherein E^3 is selected from the group consisting of pyrazolyl, pyrazolinyl, pyrazolidinyl, imidazolyl, isoimidazolyl, imidazolinyl, imidazolidinyl, dithiolyl, thiazolyl, isothiazolyl, thiazolinyl, isothiazolinyl, thiazolidinyl, isothiazolidinyl, oxathiolyl, oxathiolanyl, oxazolyl, isoxazolyl, oxazolidinyl, isoxazolidinyl, pyridinyl, piperazinyl, pyrimidinyl, pyridazinyl, oxazinyl, and morpholinyl, wherein:

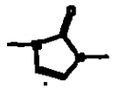
any member of such group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, keto, C_1-C_6-alkyl, C_1-C_6-alkoxy, and C_1-C_6-alkoxy-C_1-C_6-alkyl, wherein:

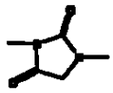
any such substituent (except halogen, -OH, or keto) optionally is substituted with one or more substituents independently selected from the group consisting of halogen and -OH.

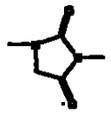
156. A compound or salt thereof according to claim 154, wherein:

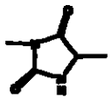
E^3 is selected from the group consisting of:

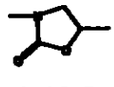

(156-1),

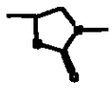

(156-2),

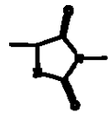

(156-3),

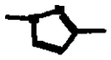

(156-4),

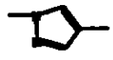

(156-5),

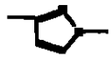

(156-6),


(156-7),


(156-8),


(156-9),

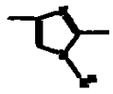

(156-10),

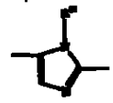

(156-11),

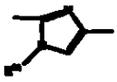

(156-12),

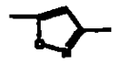

(156-13),


(156-14),

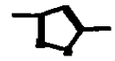

(156-15),

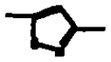

(156-16),

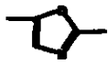

(156-17),

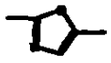

(156-18),

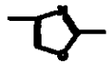

(156-19),

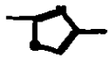

(156-20),

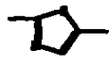

(156-21),

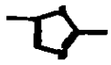

(156-22),

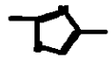

(156-23),

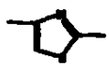

(156-24),


(156-25),


(156-26),


(156-27),


(156-28), and



(156-29); and

any member of such group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl, wherein:

any such substituent (except halogen or -OH) optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, C_1-C_6-alkylthio, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, and halo-C_1-C_6-alkylthio; and

R^{14} is selected from the group consisting of halogen, -OH, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl, wherein:

any member (except halogen or -OH) of such group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, C_1-C_6-alkylthio, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, and halo-C_1-C_6-alkylthio.

157. A compound or salt thereof according to claim 156, wherein E^3 is selected from the group consisting of oxazolyl and isoxazolyl, wherein:

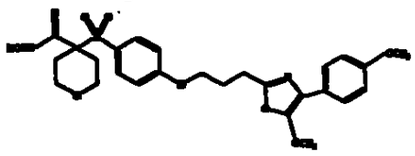
the oxazolyl or isoxazolyl is optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, C_1-C_6-alkyl, C_1-C_6-alkoxy, and C_1-C_6-alkoxy-C_1-C_6-alkyl, wherein:

any such substituent (except halogen or -OH) optionally is substituted with one or more substituents independently selected from the group consisting of halogen and -OH.

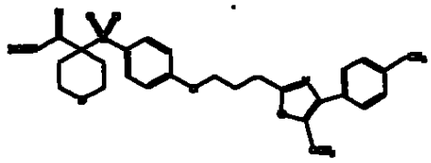
158. A compound or salt thereof according to claim 157, wherein E^3 is phenyl optionally substituted with one or more substituents independently selected from the group

consisting of halogen, -OH, -NO_2, -CN, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^5)(R^7)$, -$C(O)(R^5)$, -S-R^6, -$S(O)_2$-R^6, phenyl, phenyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, halophenyl, and halogen-substituted phenyl-C_1-C_6-alkyl.

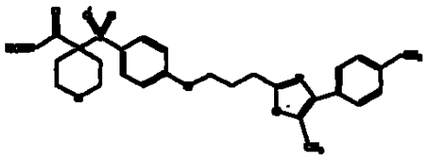
159. A compound or salt thereof according to claim 158, wherein the compound corresponds in structure to a formula selected from the group consisting of:



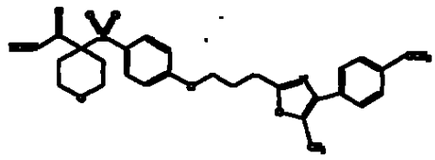
(159-1),



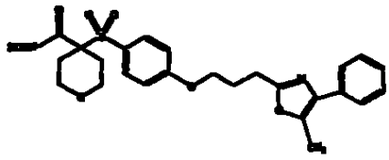
(159-2),



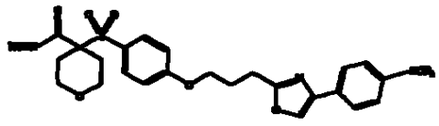
(159-3),



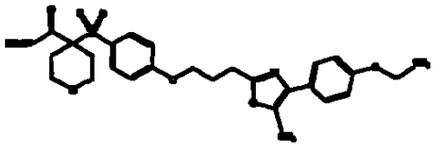
(159-4),



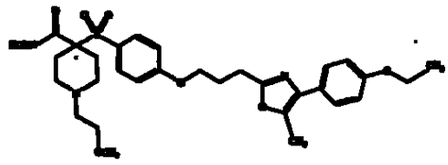
(159-5),



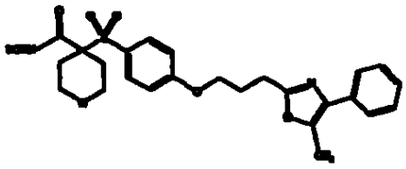
(159-6),



(159-7),



(159-8), and



(159-9).

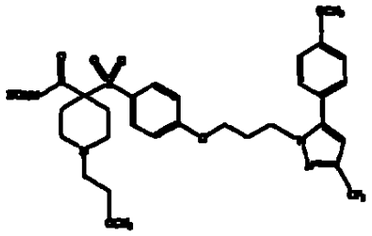
160. A compound or salt thereof according to claim 156, wherein E^3 is selected from the group consisting of pyrazolyl and isoimidazolyl, wherein:

the pyrazolyl and isoimidazolyl optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, C_1-C_6-alkyl, C_1-C_6-alkoxy, and C_1-C_6-alkoxy-C_1-C_6-alkyl, wherein:

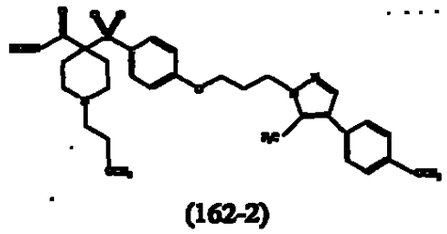
any such substituent (except halogen or -OH) optionally is substituted with one or more substituents independently selected from the group consisting of halogen and -OH.

161. A compound or salt thereof according to claim 160, wherein E^5 is phenyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^5)(R^7)$, $-C(O)(R^8)$, $-S-R^6$, $-S(O)_2-R^6$, phenyl, phenyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, halophenyl, and halogen-substituted phenyl-C_1-C_6-alkyl.

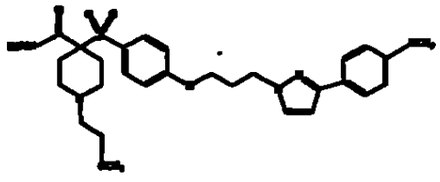
162. A compound or salt thereof according to claim 161, wherein the compound corresponds in structure to a formula selected from the group consisting of:



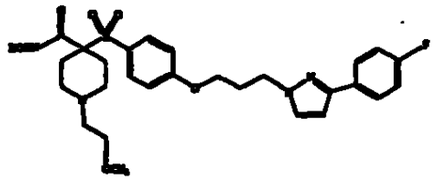
(162-1),



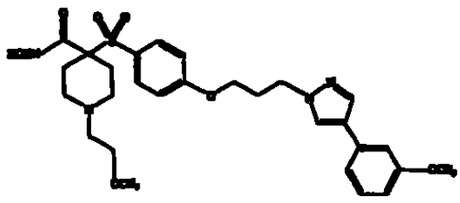
(162-2)



(162-3),



(162-4), and



(162-5).

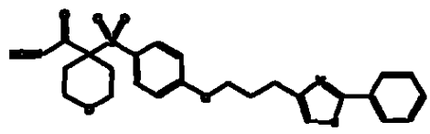
163. A compound or salt thereof according to claim 156, wherein E^5 is selected from the group consisting of thiazolyl and isothiazolyl, wherein:

the thiazolyl and isothiazolyl optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, C_1-C_6-alkyl, C_1-C_6-alkoxy, and C_1-C_6-alkoxy-C_1-C_6-alkyl, wherein:

any such substituent (except halogen or -OH) optionally is substituted with one or more substituents independently selected from the group consisting of halogen and -OH.

164. A compound or salt thereof according to claim 163, wherein E^5 is phenyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^6)(R^7)$, $-C(O)(R^8)$, $-S-R^6$, $-S(O)_2-R^6$, phenyl, phenyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, halophenyl, and halogen-substituted phenyl-C_1-C_6-alkyl.

165. A compound or salt thereof according to claim 164, wherein the compound corresponds in structure to the following formula:



(165-1).

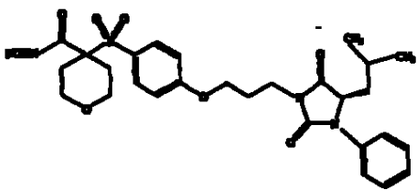
166. A compound or salt thereof according to claim 156, wherein E^3 is selected from the group consisting of pyrazolidinyl and iimidazolidinyl, wherein:

the pyrazolidinyl and imidazolidinyl optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, keto, C_1-C_6-alkyl, C_1-C_6-alkoxy, and C_1-C_6-alkoxy-C_1-C_6-alkyl, wherein:

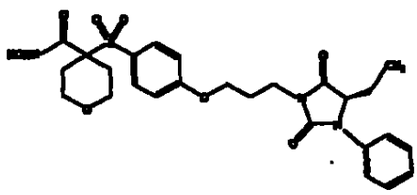
any such substituent (except halogen, -OH, or keto) optionally is substituted with one or more substituents independently selected from the group consisting of halogen and -OH.

167. A compound or salt thereof according to claim 166, wherein E^5 is phenyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^6)(R^7)$, $-C(O)(R^8)$, $-S-R^6$, $-S(O)_2-R^6$, phenyl, phenyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, halophenyl, and halogen-substituted phenyl-C_1-C_6-alkyl.

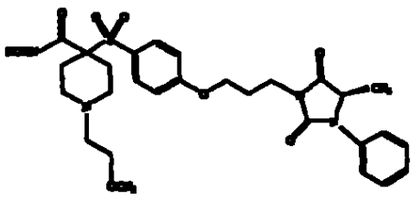
168. A compound or salt thereof according to claim 167, wherein the compound corresponds in structure to a formula selected from the group consisting of:



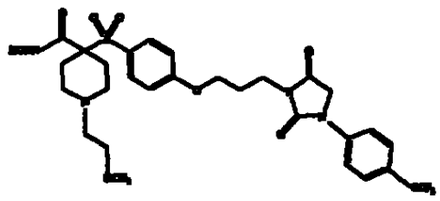
(168-1),



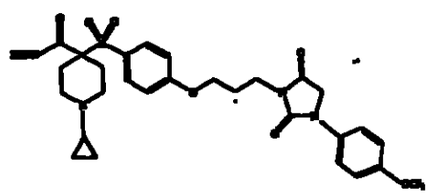
(168-2),



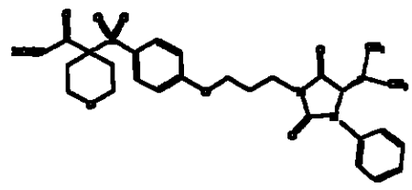
(168-3),



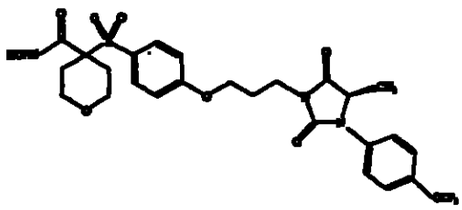
(168-4),



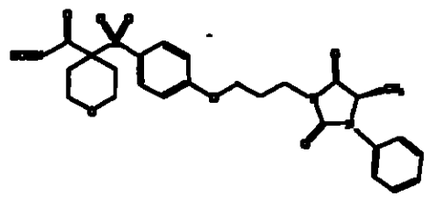
(168-5),



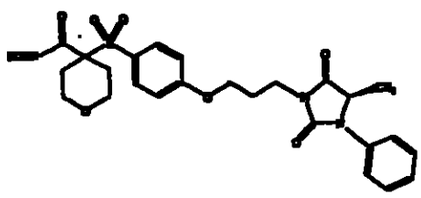
(168-6),



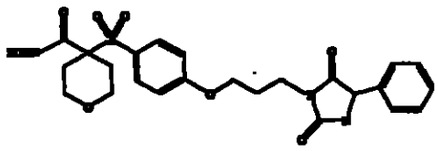
(168-7),



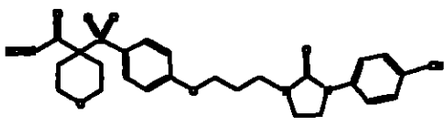
(168-8),



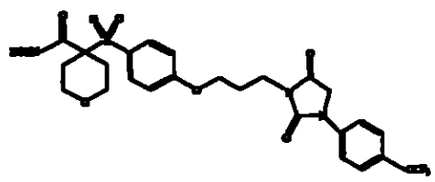
(168-9),



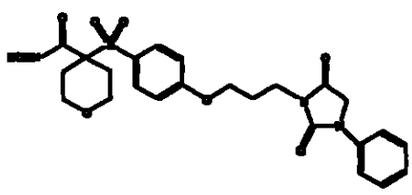
(168-10),



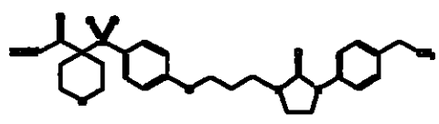
(168-11),



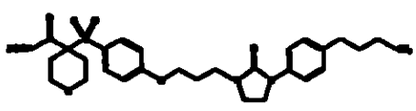
(168-12),



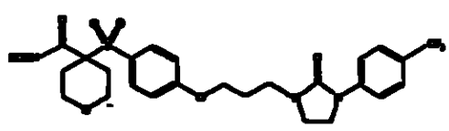
(168-13),



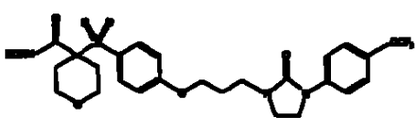
(168-14),



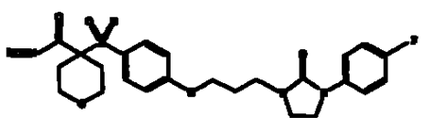
(168-15),



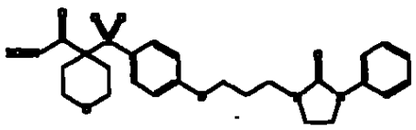
(168-16),



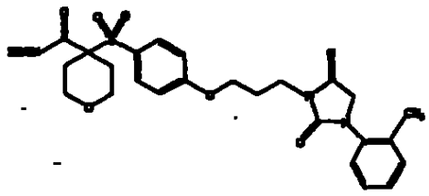
(168-17),



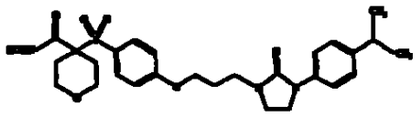
(168-18),



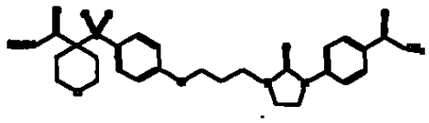
(168-19),



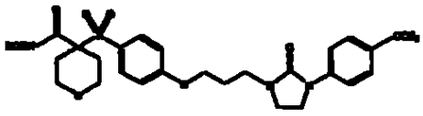
(168-20),



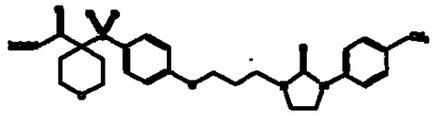
(168-21),



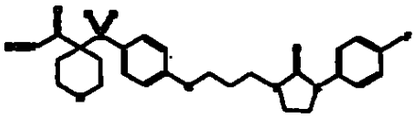
(168-22),



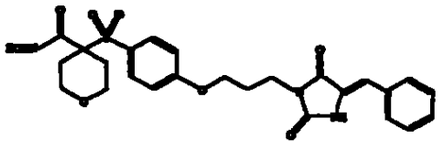
(168-23),



(168-24),



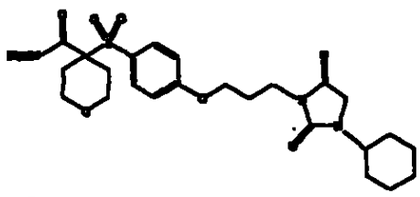
(168-25), and



(168-26).

169. A compound or salt thereof according to claim 166, wherein E^5 is C_3-C_6-cycloalkyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^6)(R^7)$, -$C(O)(R^8)$, -S-R^6, -$S(O)_2$-R^6, phenyl, phenyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, halophenyl, and halogen-substituted phenyl-C_1-C_6-alkyl.

170. A compound or salt thereof according to claim 169, wherein the compound corresponds in structure to the following formula:



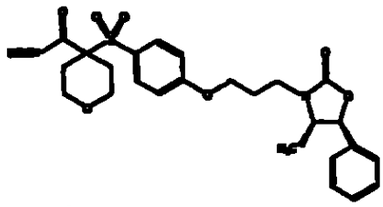
(170-1).

171. A compound or salt thereof according to claim 156, wherein E^3 is oxazolidinyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, keto, C_1-C_6-alkyl, C_1-C_6-alkoxy, and C_1-C_6-alkoxy-C_1-C_6-alkyl, wherein:

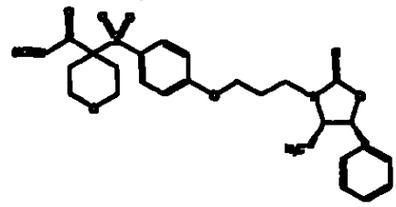
any such substituent (except halogen, -OH, or keto) optionally is substituted with one or more substituents independently selected from the group consisting of halogen and -OH.

172. A compound or salt thereof according to claim 171, wherein E^5 is phenyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^6)(R^7)$, $-C(O)(R^8)$, $-S-R^6$, $-S(O)_2-R^6$, phenyl, phenyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, halophenyl, and halogen-substituted phenyl-C_1-C_6-alkyl.

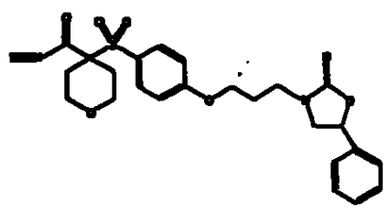
173. A compound or salt thereof according to claim 172, wherein the compound corresponds in structure to a formula selected from the group consisting of:



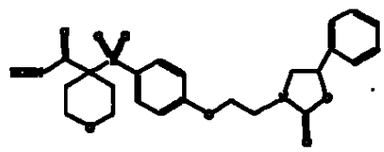
(173-1),



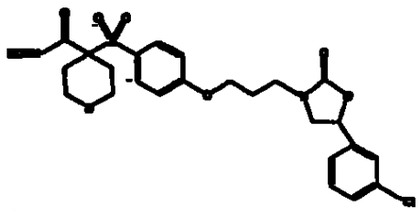
(173-2),



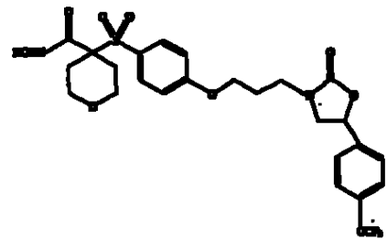
(173-3),



(173-4),



(173-5), and



(173-6).

174. A compound or salt thereof according to claim 137, wherein E^3 contains no greater and no less than 3 heteroatoms.

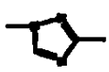
175. A compound or salt thereof according to claim 174, wherein E^3 is selected from the group consisting of oxadiazolyl, thiadiazolyl, and triazolyl, wherein:

the triazolyl optionally is substituted with a substituent selected from the group consisting of halogen, -OH, C_1-C_6-alkyl, C_1-C_6-alkoxy, and C_1-C_6-alkoxy-C_1-C_6-alkyl,

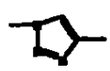
any such substituent (except halogen or -OH) optionally is substituted with one or more substituents independently selected from the group consisting of halogen and -OH.

176. A compound or salt thereof according to claim 174, wherein:

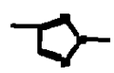
E^3 is selected from the group consisting of:



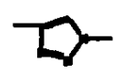
(176-1),



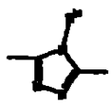
(176-2),

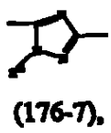


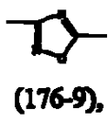
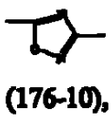
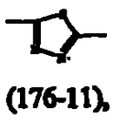
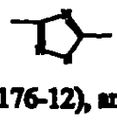
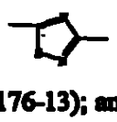
(176-3),



(176-4),


(176-5),

(176-6),

(176-7),

(176-8),

(176-9),

(176-10),

(176-11),

(176-12), and

(176-13); and

any member of such group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl, wherein:

any such substituent (except halogen or -OH) optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, C_1-C_6-alkylthio, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, and halo-C_1-C_6-alkylthio; and

R^{14} is selected from the group consisting of halogen, -OH, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl, wherein:

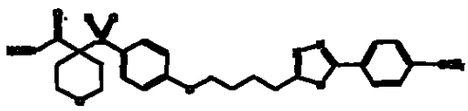
any member (except halogen or -OH) of such group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, C_1-C_6-alkylthio, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, and halo-C_1-C_6-alkylthio.

177. A compound or salt thereof according to claim 176, wherein E^3 is oxadiazolyl.

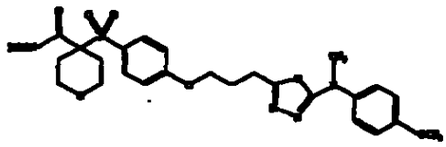
178. A compound or salt thereof according to claim 177, wherein E^3 is phenyl optionally substituted with one or more substituents independently selected from the group

consisting of halogen, -OH, -NO_2, -CN, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^6)(R^7)$, -$C(O)(R^8)$, -S-R^6, -$S(O)_2$-R^6, phenyl, phenyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, halophenyl, and halogen-substituted phenyl-C_1-C_6-alkyl.

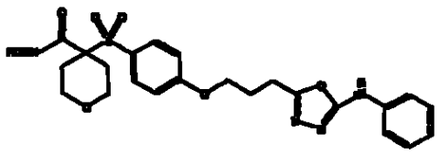
179. A compound or salt thereof according to claim 178, wherein the compound corresponds in structure to a formula selected from the group consisting of:



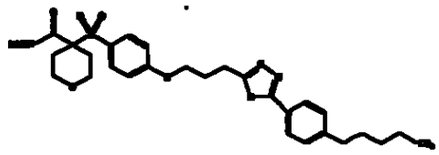
(179-1),



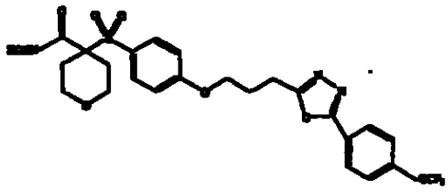
(179-2),



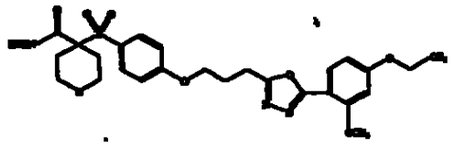
(179-3),



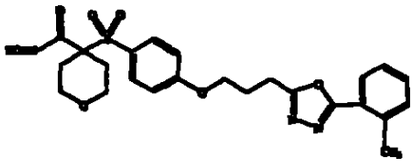
(179-4),



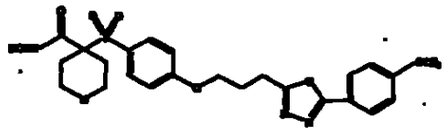
(179-5),



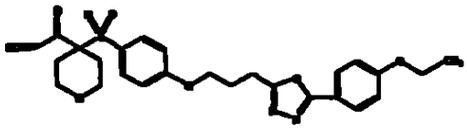
(179-6),



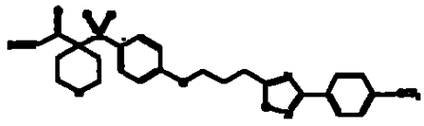
(179-7),



(179-8),

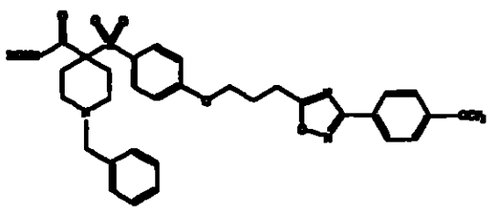


(179-9),

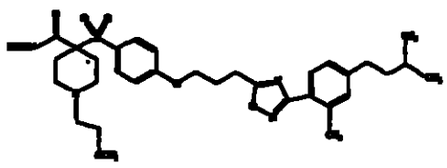


(179-10),

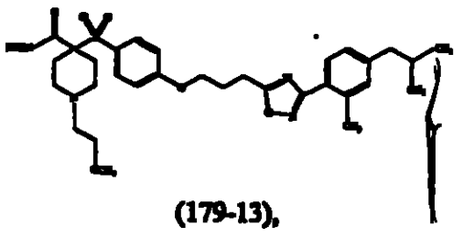
545



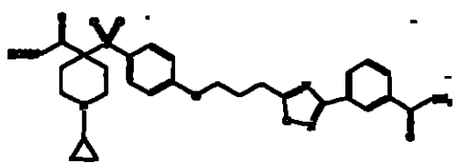
(179-11),



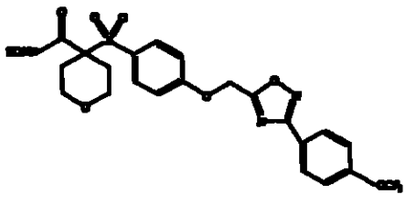
(179-12),



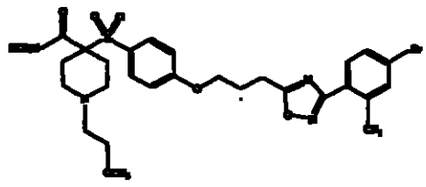
(179-13),



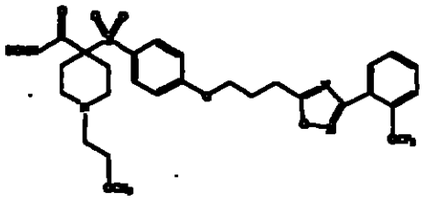
(179-14),



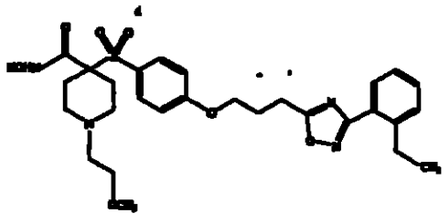
(179-15),



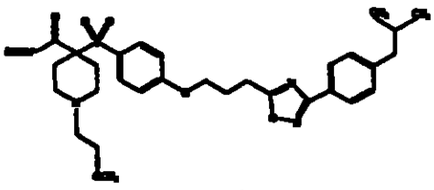
(179-16),



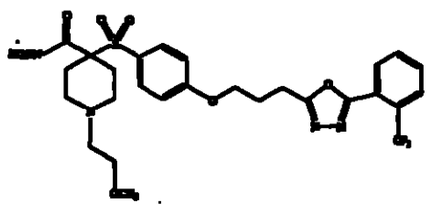
(179-18),



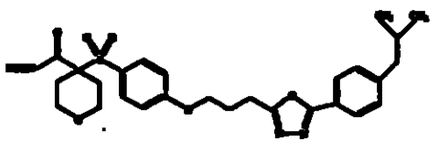
(179-19),



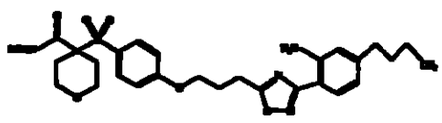
(179-20),



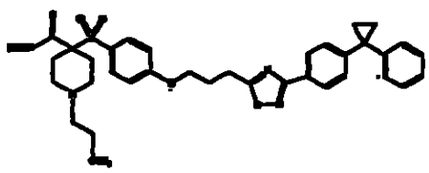
(179-21),



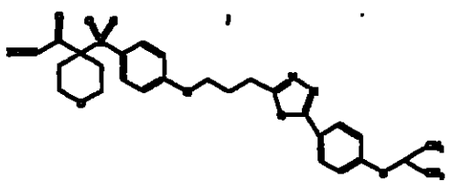
(179-22),



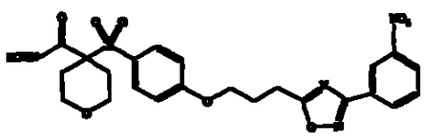
(179-23),



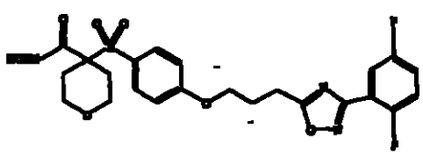
(179-24),



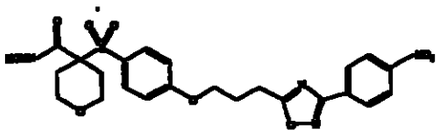
(179-25),



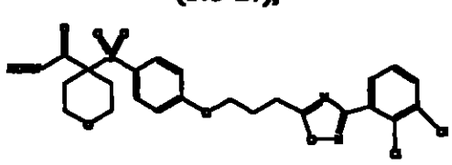
(179-26),



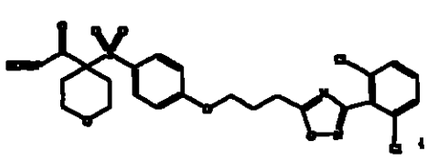
(179-27),



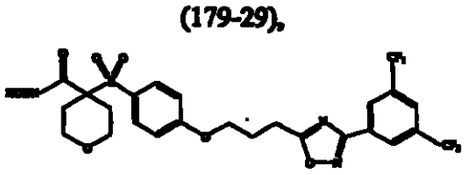
(179-28),



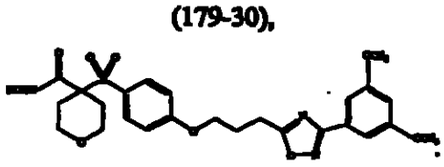
(179-29),



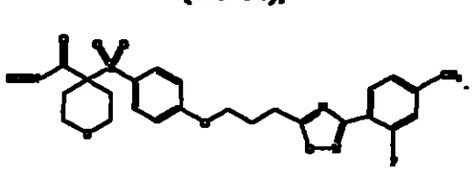
(179-30),



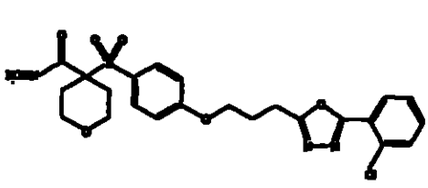
(179-31),



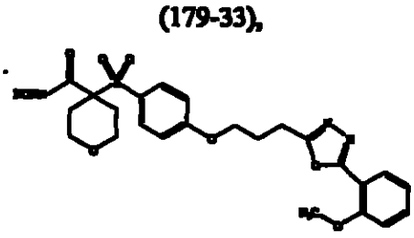
(179-32),



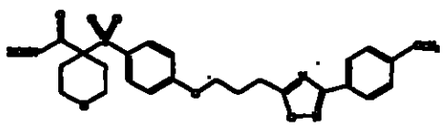
(179-33),



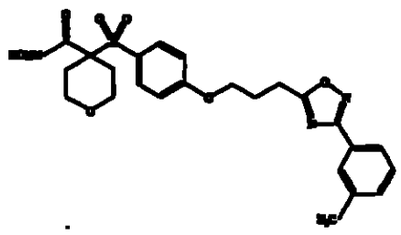
(179-34),



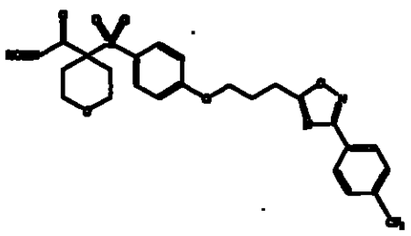
(179-35),



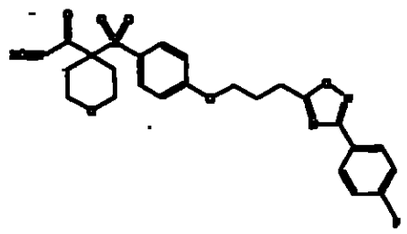
(179-36),



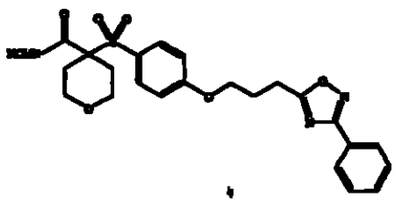
(179-37),



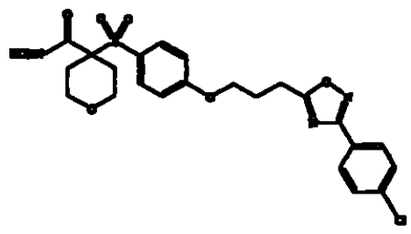
(179-38),



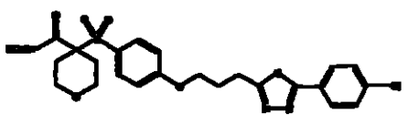
(179-39),



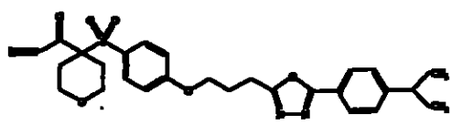
(179-40),



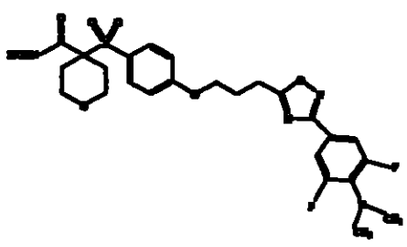
(179-41),



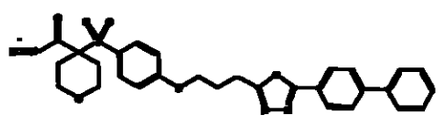
(179-42),



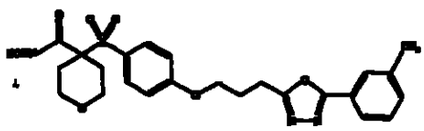
(179-43),



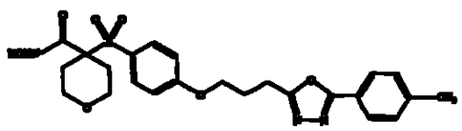
(179-44),



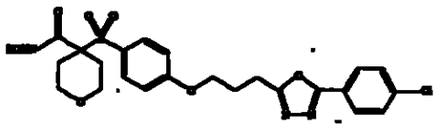
(179-45),



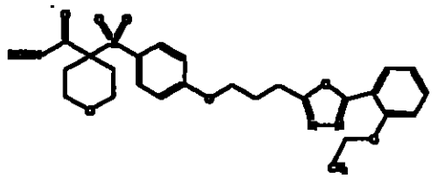
(179-46),



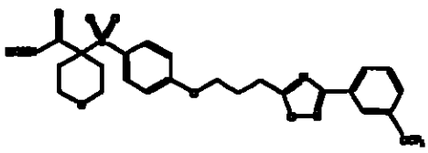
(179-47),



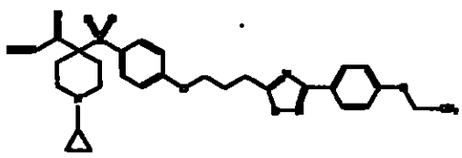
(179-48),



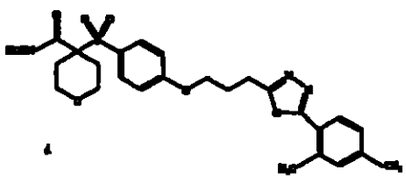
(179-49),



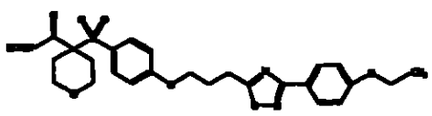
(179-50),



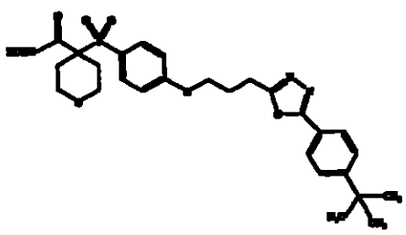
(179-51),



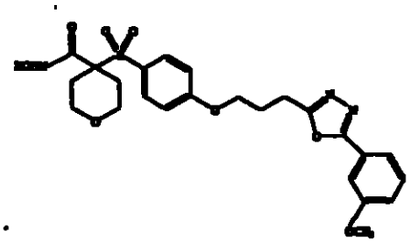
(179-52),



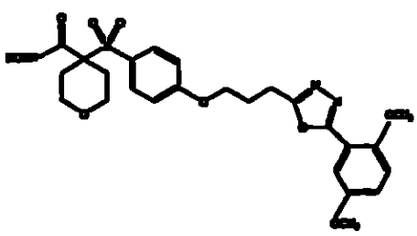
(179-53),



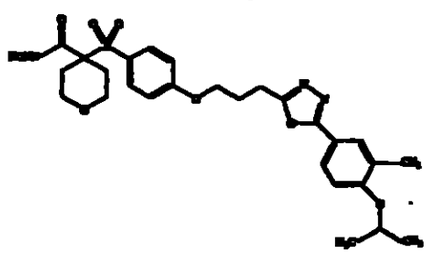
(179-54),



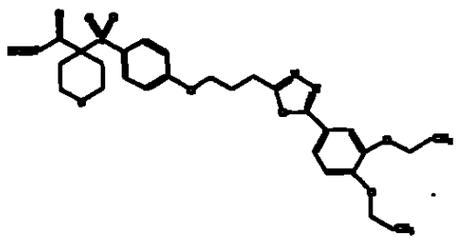
(179-55),



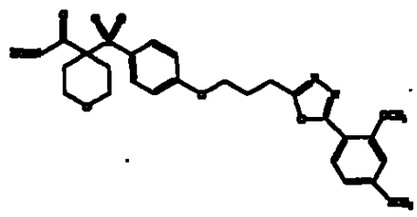
(179-56),



(179-57),

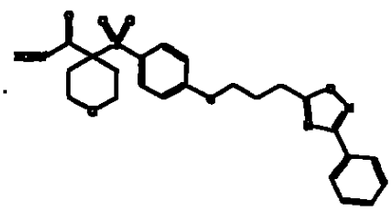


(179-58), and

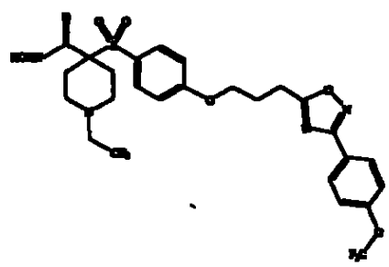


(179-59).

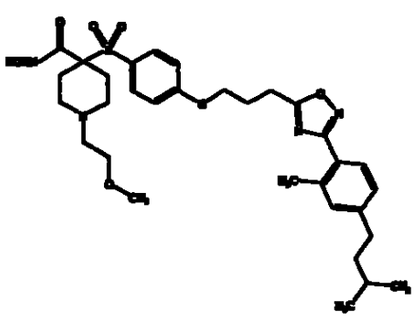
180. A compound or salt thereof according to claim 178, wherein the compound corresponds in structure to a formula selected from the group consisting of:



(180-1),

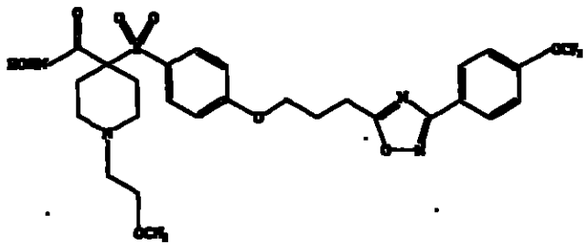


(180-2), and



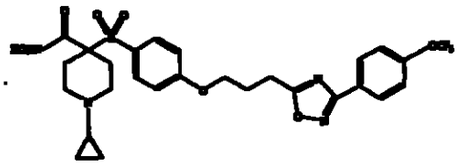
(180-3).

181. A compound or salt thereof according to claim 178, wherein the compound corresponds in structure to the following formula:



181-1

182. A compound or salt thereof according to claim 178, wherein the compound corresponds in structure to the following formula:

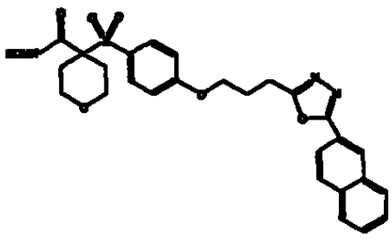


(182-1).

183. A compound or salt thereof according to claim 177, wherein E^5 is naphthalenyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^6)(R^7)$, -$C(O)(R^8)$, -S-R^6, -$S(O)_2$-R^6, phenyl, phenyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, halophenyl, and halogen-substituted phenyl-C_1-C_6-alkyl.

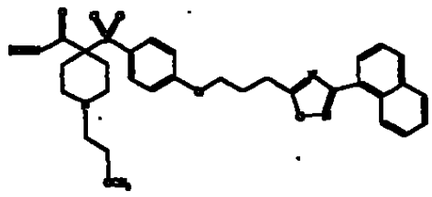
551

184. A compound or salt thereof according to claim 183, wherein the compound corresponds in structure to a formula selected from the group consisting of:



(184-1)

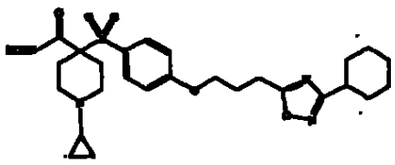
and



(184-2).

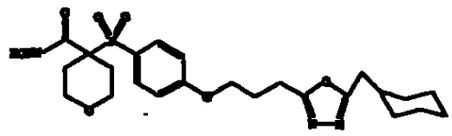
185. A compound or salt thereof according to claim 177, wherein E^5 is C_3-C_6-cycloalkyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^6)(R^7)$, -$C(O)(R^8)$, -S-R^6, -$S(O)_2$-R^6, phenyl, phenyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, halophenyl, and halogen-substituted phenyl-C_1-C_6-alkyl.

186. A compound or salt thereof according to claim 185, wherein the compound corresponds in structure to a formula selected from the group consisting of:



(186-1)

and

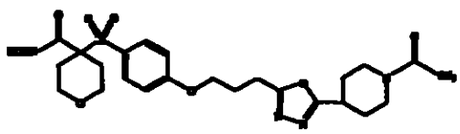


(186-2).

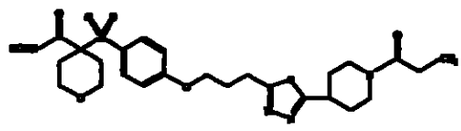
187. A compound or salt thereof according to claim 177, wherein E^5 is heterocyclyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, keto, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^6)(R^7)$, -$C(O)(R^8)$, -S-R^6, -$S(O)_2$-R^6, phenyl, phenyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, halophenyl, and halogen-substituted phenyl-C_1-C_6-alkyl.

552

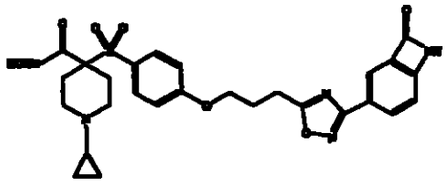
188. A compound or salt thereof according to claim 187, wherein the compound corresponds in structure to a formula selected from the group consisting of:



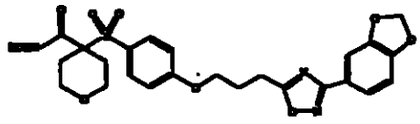
(188-1)



(188-2),

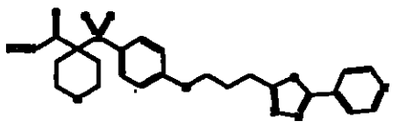


(188-3), and



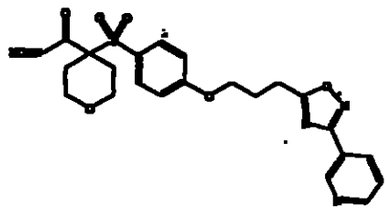
(188-4).

189. A compound or salt thereof according to claim 187, wherein the compound corresponds in structure to a formula selected from the group consisting of:



(189-1)

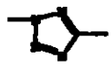
and



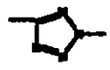
(189-2).

190. A compound or salt thereof according to claim 137, wherein E^3 contains at least 4 heteroatom ring members.

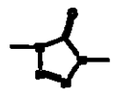
191. A compound or salt thereof according to claim 190, wherein E^3 is selected from the group consisting of:



(191-1),



(191-2), and

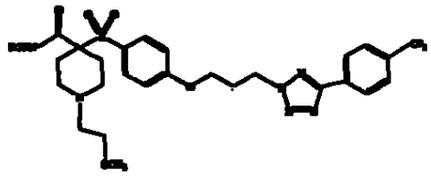


(191-3).

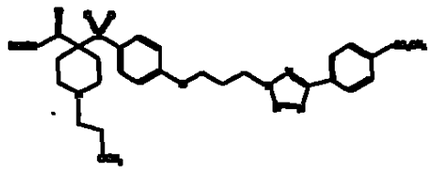
553

192. A compound or salt thereof according to claim 191, wherein E^5 is phenyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^6)(R^7)$, -$C(O)(R^8)$, -S-R^6, -$S(O)_2$-R^6, phenyl, phenyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, halophenyl, and halogen-substituted phenyl-C_1-C_6-alkyl.

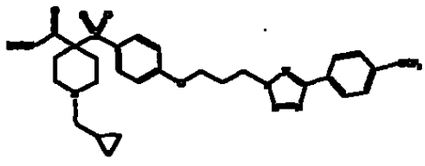
193. A compound or salt thereof according to claim 192, wherein the compound corresponds in structure to a formula selected from the group consisting of:



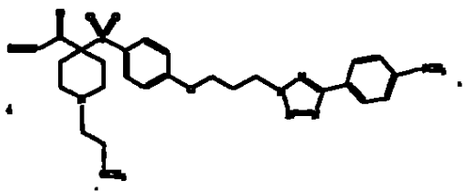
(193-1),



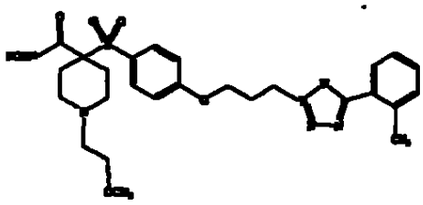
(193-2),



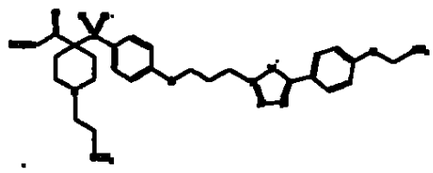
(193-3),



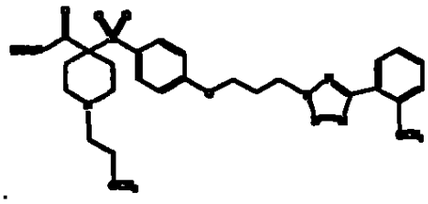
(193-4),



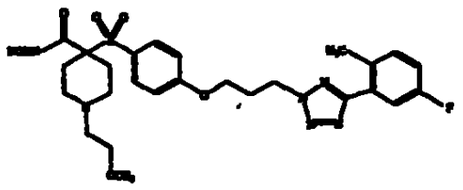
(193-5),



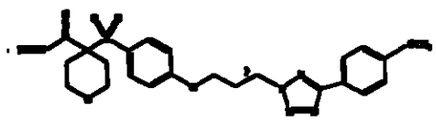
(193-6),



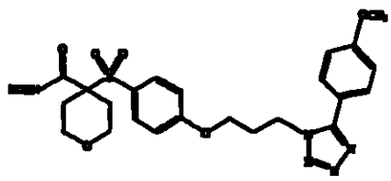
(193-7),



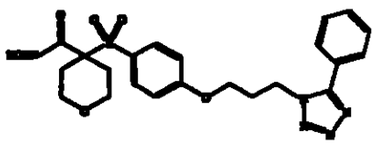
(193-8),



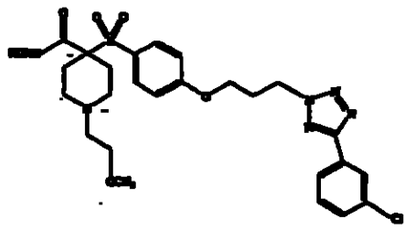
(193-9),



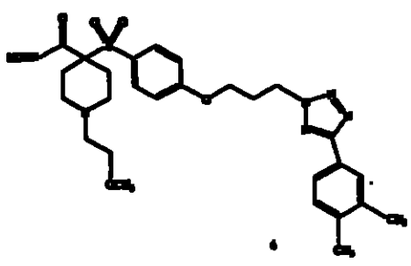
(193-10),



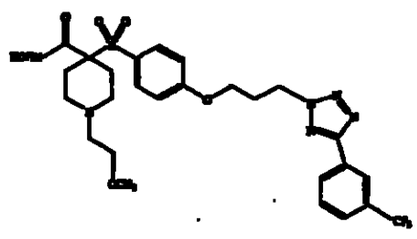
(193-11),



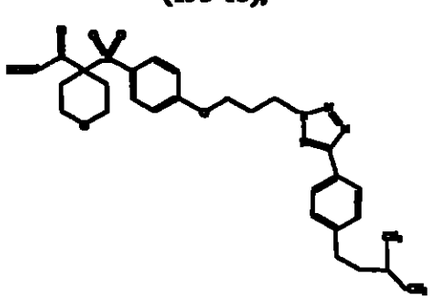
(193-12),



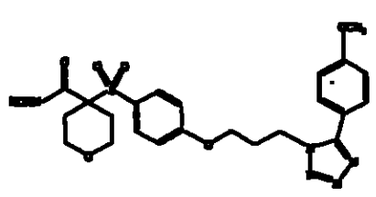
(193-13),



(193-14),

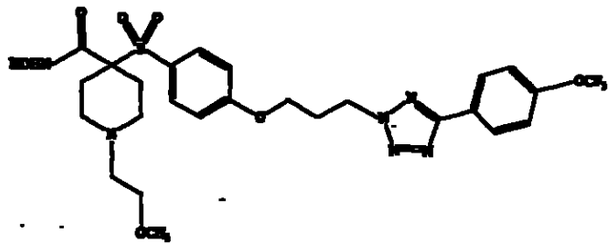


(193-15), and



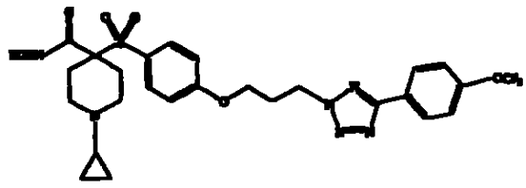
(193-16).

194. A compound or salt thereof according to claim 192, wherein the compound corresponds in structure to the following formula:



(194-1).

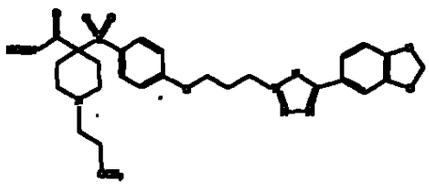
195. A compound or salt thereof according to claim 192, wherein the compound corresponds in structure to the following formula:



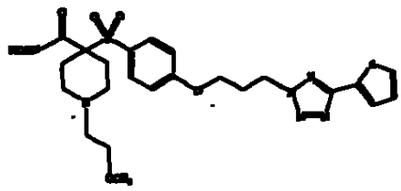
(195-1).

196. A compound or salt thereof according to claim 191, wherein R^5 is heterocyclyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, keto, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^6)(R^7)$, -$C(O)(R^8)$, -S-R^6, -$S(O)_2$-R^6, phenyl, phenyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, halophenyl, and halogen-substituted phenyl-C_1-C_6-alkyl.

197. A compound or salt thereof according to claim 196, wherein the compound corresponds in structure to a formula selected from the group consisting of:



and



(197-1) (197-2).

198. A compound or salt thereof according to claim 128, wherein E^3 is cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclopentadienyl, cyclohexyl, cyclohexenyl, cyclohexadienyl, phenyl, naphthalenyl, tetrahydronaphthalenyl, indenyl, isoindenyl, indanyl, bicyclodecanyl, anthracenyl, phenanthrenyl, benzonaphthenyl, fluorenecyl, decalinyl, and norpinanyl, wherein:

any member of such group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, keto, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl, wherein:

any such substituent (except halogen, -OH, or keto) optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, C_1-C_6-alkylthio, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, and halo-C_1-C_6-alkylthio.

199. A compound or salt thereof according to claim 198, wherein E^3 is phenyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl, wherein:

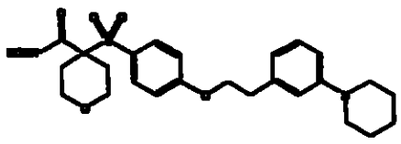
any such substituent (except halogen or -OH) optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl,

C_1-C_6-alkylthio, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, and halo-C_1-C_6-alkylthio.

200. A compound or salt thereof according to claim 199, wherein E^5 is selected from the group consisting of piperidinyl, piperazinyl, imidazolyl, furanyl, thienyl, pyridinyl, pyrimidyl, benzodioxolyl, benzodioxanyl, benzofuryl, and benzothienyl, wherein

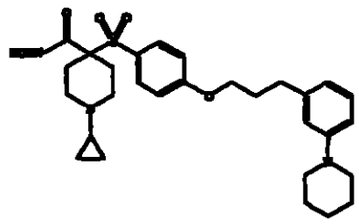
any member of such group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^6)(R^7)$, $-C(O)(R^8)$, $-S-R^6$, $-S(O)_2-R^6$, phenyl, phenyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, halophenyl, and halogen-substituted phenyl-C_1-C_6-alkyl.

201. A compound or salt thereof according to claim 200, wherein the compound corresponds in structure to a formula selected from the group consisting of:



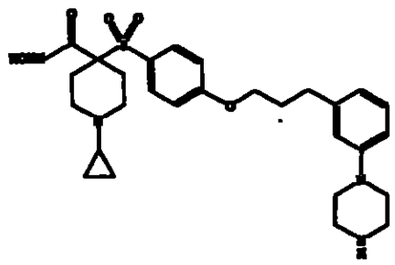
(201-1)

and



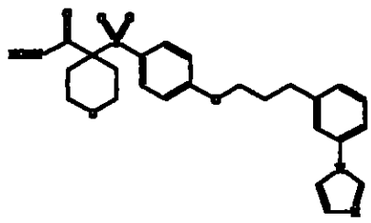
(201-2).

202. A compound or salt thereof according to claim 200, wherein the compound corresponds in structure to the following formula:



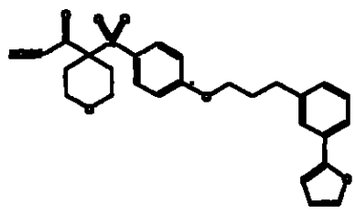
(202-1).

203. A compound or salt thereof according to claim 200, wherein the compound corresponds in structure to the following formula:



(203-1).

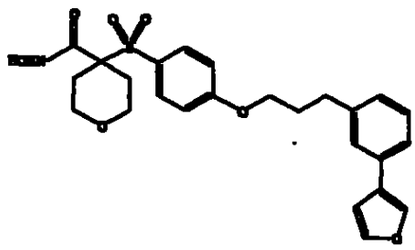
204. A compound or salt thereof according to claim 200, wherein the compound corresponds in structure to the following formula:



(204-1).

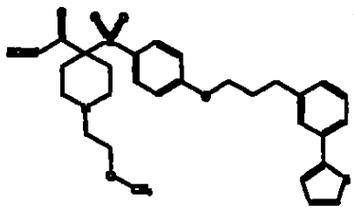
559

205. A compound or salt thereof according to claim 200, wherein the compound corresponds in structure to the following formula:

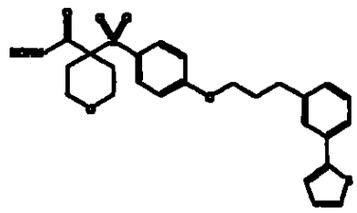


(205-1).

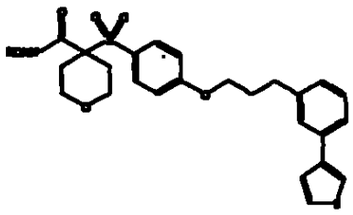
206. A compound or salt thereof according to claim 200, wherein the compound corresponds in structure to a formula selected from the group consisting of:



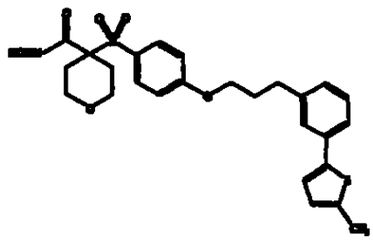
(206-1),



(206-2),

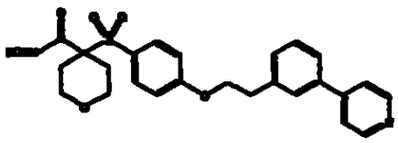


(206-3), and

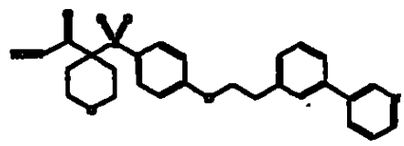


(206-4).

207. A compound or salt thereof according to claim 200, wherein the compound corresponds in structure to a formula selected from the group consisting of:

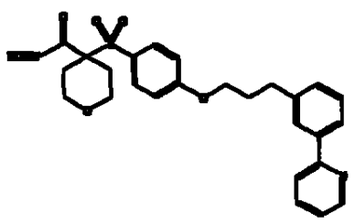


(207-1),

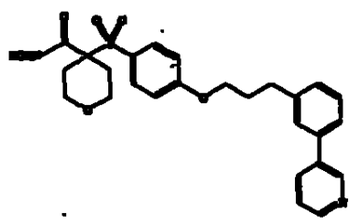


(207-2),

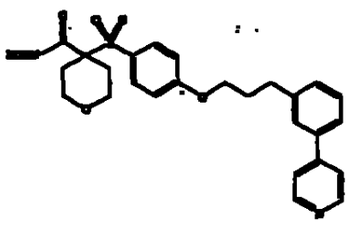
560



(207-3),

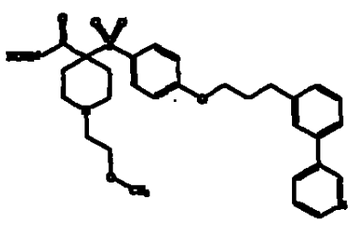


(207-4), and

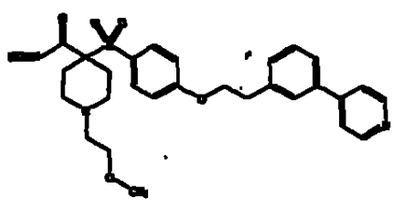


(207-5).

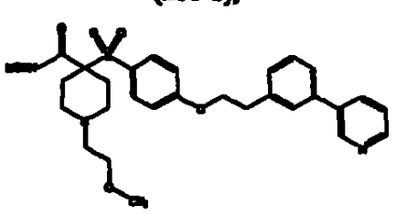
208. A compound or salt thereof according to claim 200, wherein the compound corresponds in structure to a formula selected from the group consisting of:



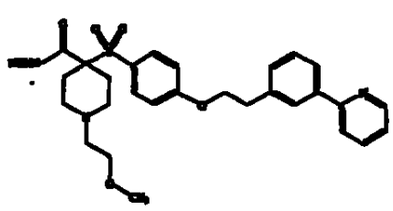
(208-1),



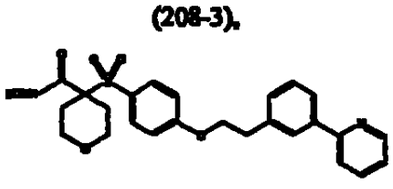
(208-2),



(208-3),



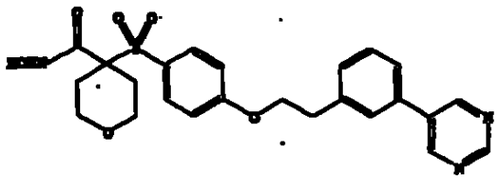
(208-4), and



(208-5).

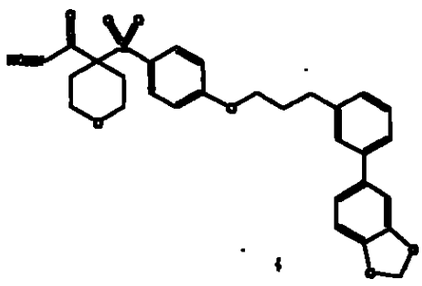
561

209. A compound or salt thereof according to claim 200, wherein the compound corresponds in structure to the following formula:



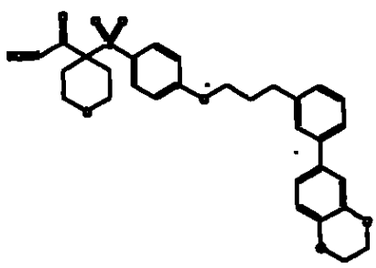
(209-1).

210. A compound or salt thereof according to claim 200, wherein the compound corresponds in structure to the following formula:



(210-1).

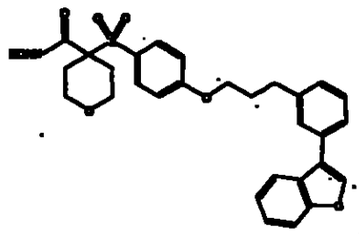
211. A compound or salt thereof according to claim 200, wherein the compound corresponds in structure to the following formula:



(211-1).

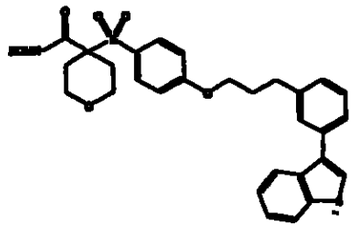
562

212. A compound or salt thereof according to claim 200, wherein the compound corresponds in structure to the following formula:



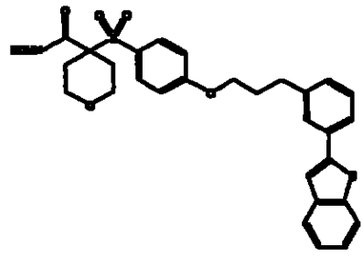
(212-1).

213. A compound or salt thereof according to claim 200, wherein the compound corresponds in structure to a formula selected from the group consisting of:



(213-1)

and



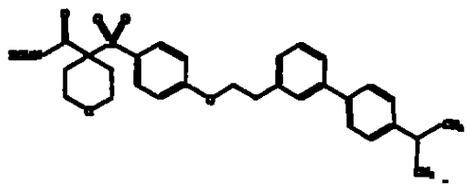
(213-1).

214. A compound or salt thereof according to claim 199, wherein E^5 is selected from the group consisting of phenyl and naphthalenyl, wherein:

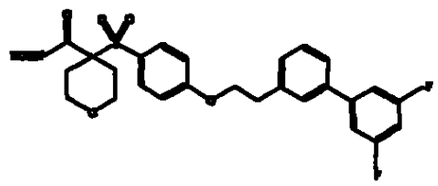
the phenyl and naphthalenyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^6)(R^7)$, $-C(O)(R^5)$, $-S-R^6$, $-S(O)_2-R^6$, phenyl, phenyl-C_1-C_6-alkyl, halo-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, halophenyl, and halogen-substituted phenyl-C_1-C_6-alkyl.

563

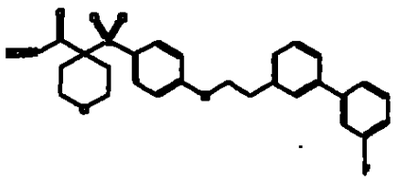
215. A compound or salt thereof according to claim 214, wherein the compound corresponds in structure to a formula selected from the group consisting of:



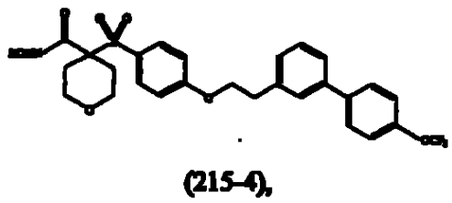
(215-1),



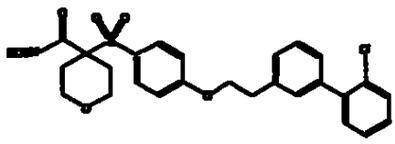
(215-2),



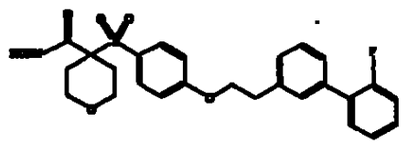
(215-3),



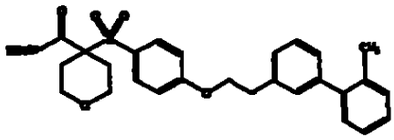
(215-4),



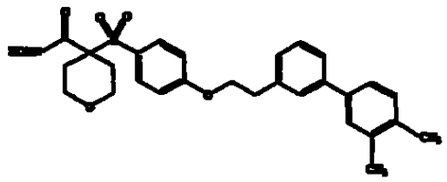
(215-5),



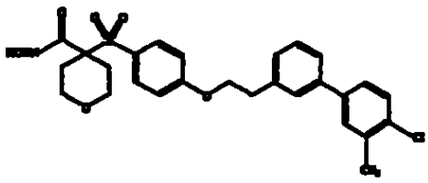
(215-6),



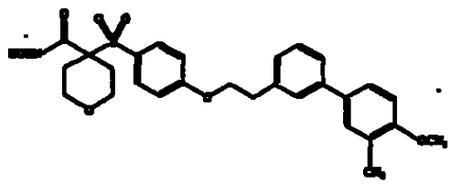
(215-7),



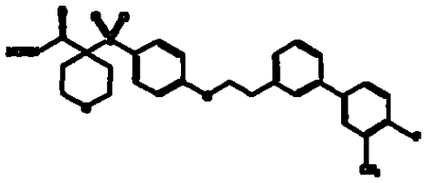
(215-8),



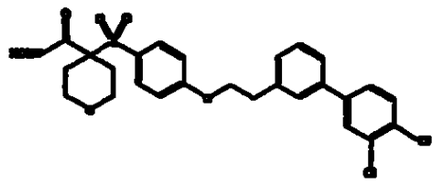
(215-9),



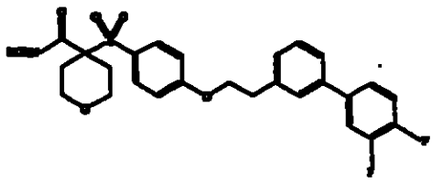
(215-10),



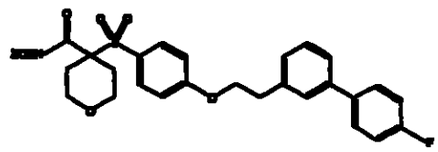
(215-11),



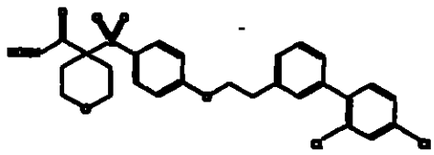
(215-12),



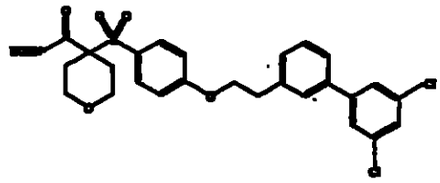
(215-13),



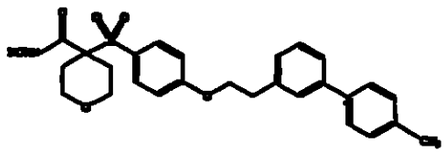
(215-14),



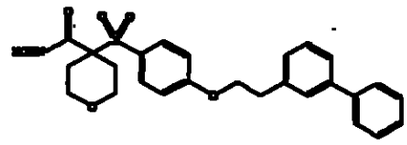
(215-15),



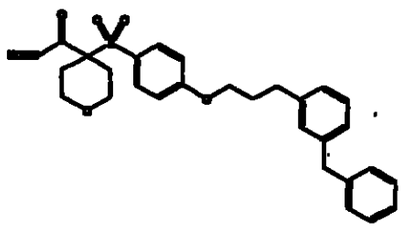
(215-16),



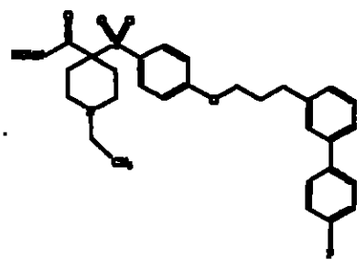
(215-17),



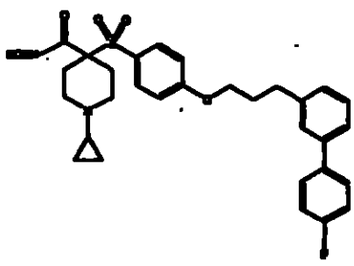
(215-18),



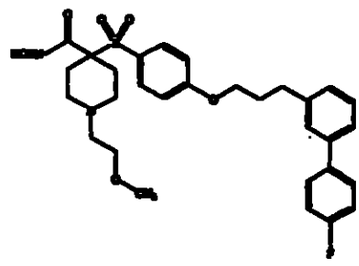
(215-19),



(215-20),

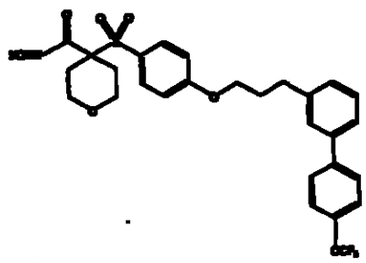


(215-21),

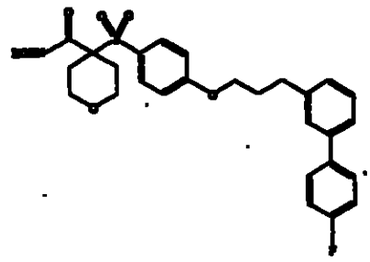


(215-22),

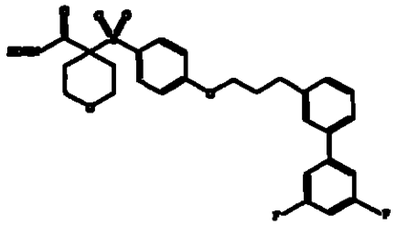
565



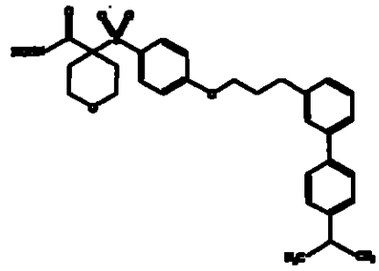
(215-23),



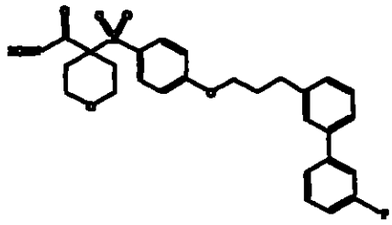
(215-24),



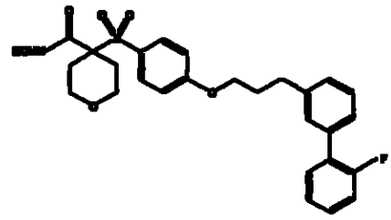
(215-25),



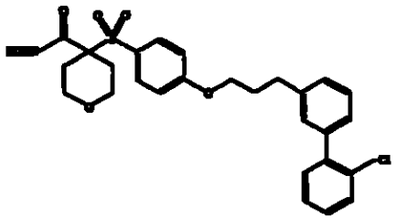
(215-26),



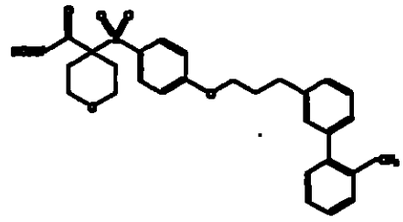
(215-27),



(215-28),

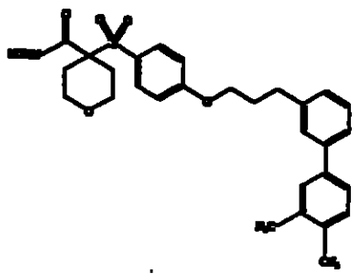


(215-29),

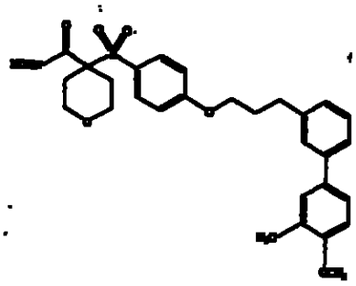


(215-30),

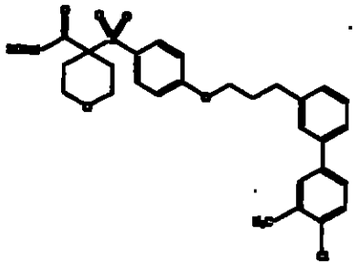
566



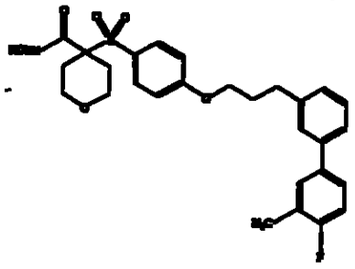
(215-31),



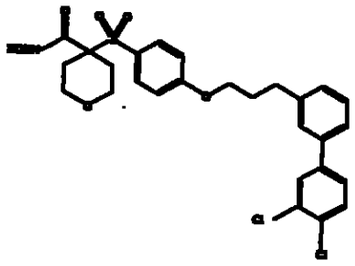
(215-32),



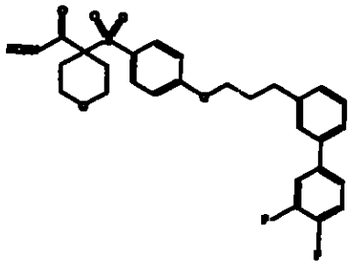
(215-33),



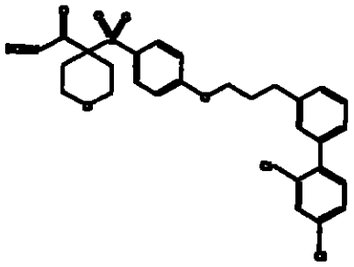
(215-34),



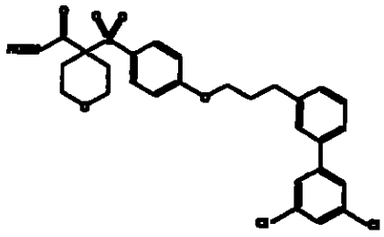
(215-35),



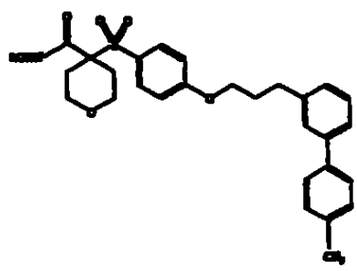
(215-36),



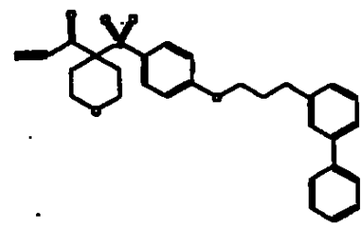
(215-37),



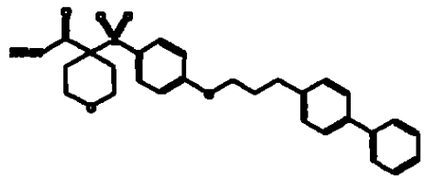
(215-38),



(215-39),

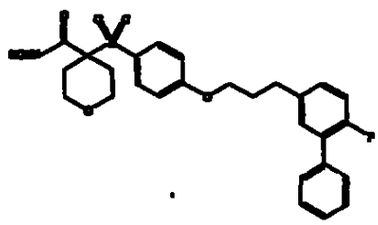


(215-40), and

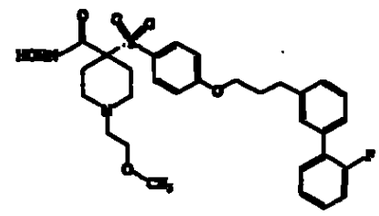


(215-41).

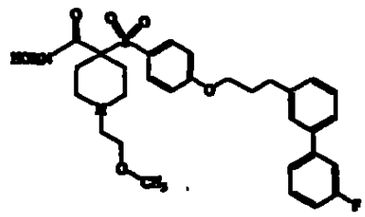
216. A compound or salt thereof according to claim 214, wherein the compound corresponds in structure to a formula selected from the group consisting of:



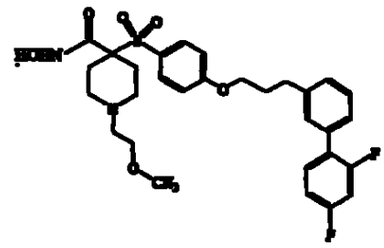
(216-1),



(216-2),

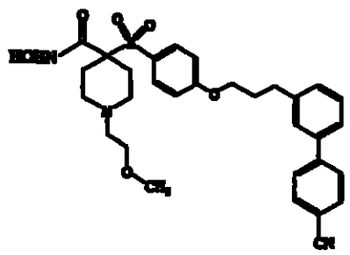


(216-3),

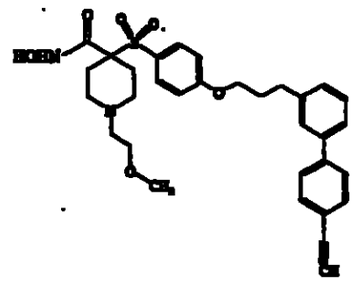


(216-4),

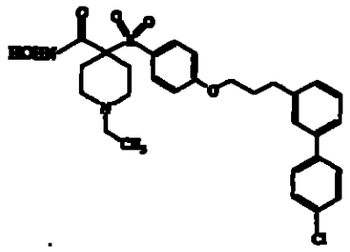
568



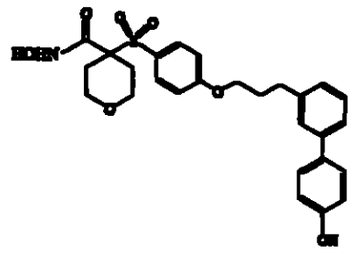
(216-5),



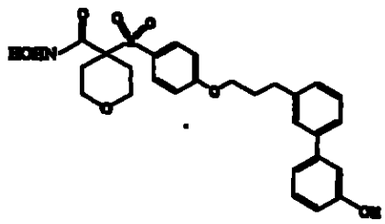
(216-6),



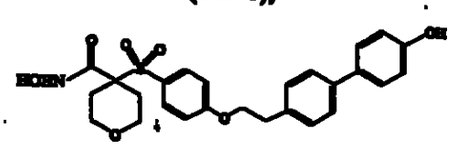
(216-7),



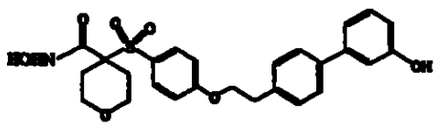
(216-8),



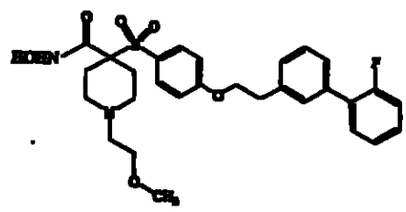
(216-9),



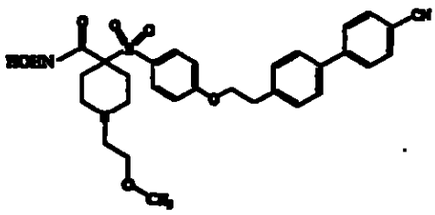
(216-10),



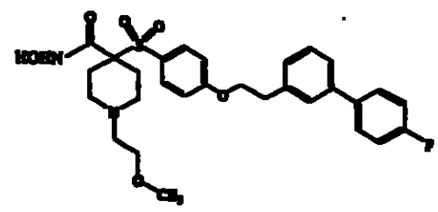
(216-11),



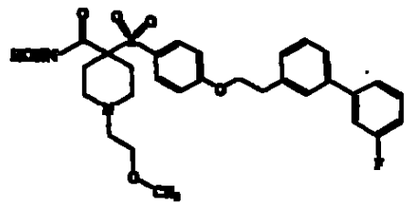
(216-12),



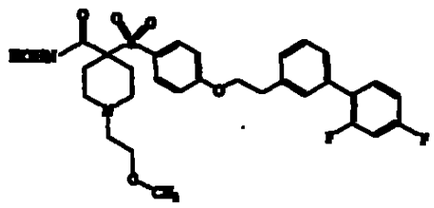
(216-13),



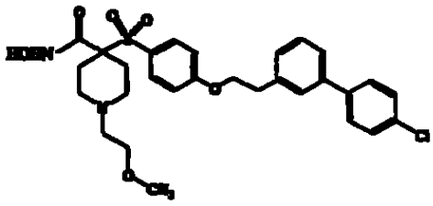
(216-14),



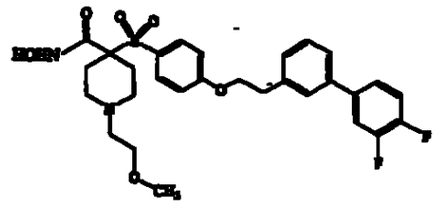
(216-15),



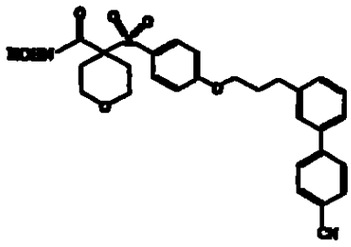
(216-16),



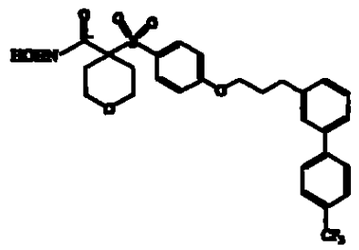
(216-17),



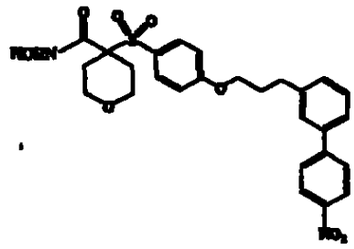
(216-18),



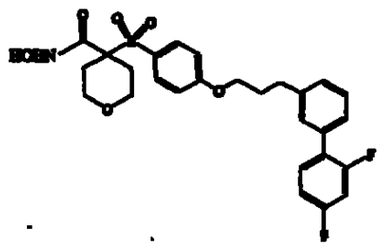
(216-19),



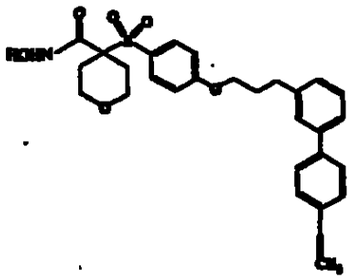
(216-20),



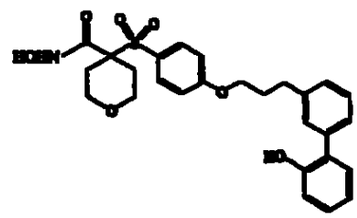
(216-21),



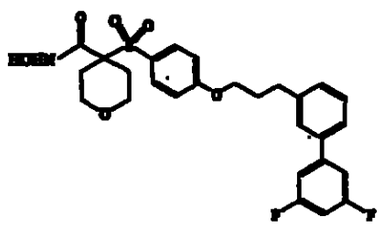
(216-22),



(216-23),

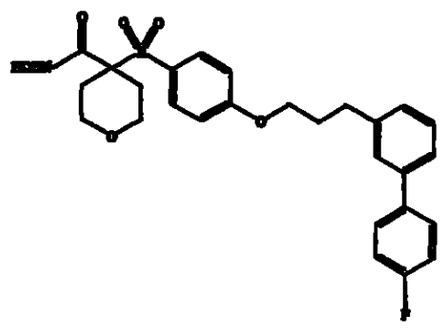


(216-24), and



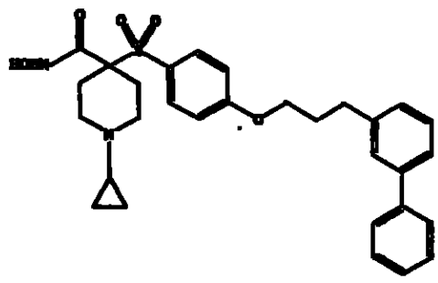
(216-25).

217. A compound or salt thereof according to claim 214, wherein the compound corresponds in structure to the following formula:



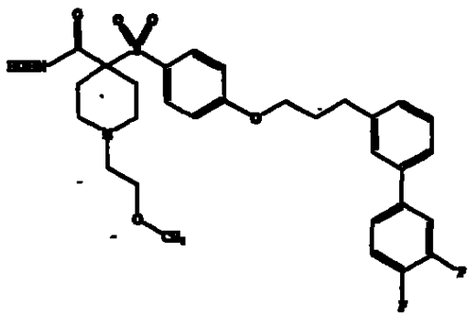
(217-1).

218. A compound or salt thereof according to claim 214, wherein the compound corresponds in structure to the following formula:



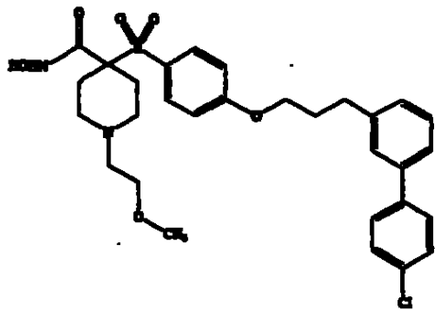
(218-1).

219. A compound or salt thereof according to claim 214, wherein the compound corresponds in structure to the following formula:



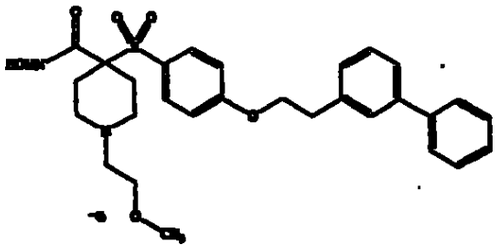
(219-1).

220. A compound or salt thereof according to claim 214, wherein the compound corresponds in structure to the following formula:



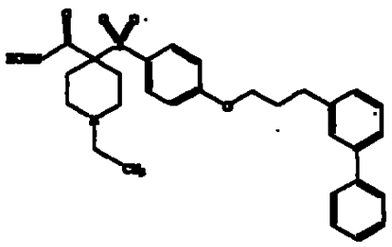
(220-1).

221. A compound or salt thereof according to claim 214, wherein the compound corresponds in structure to the following formula:



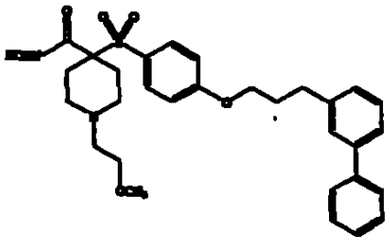
(221-1).

222. A compound or salt thereof according to claim 214, wherein the compound corresponds in structure to the following formula:



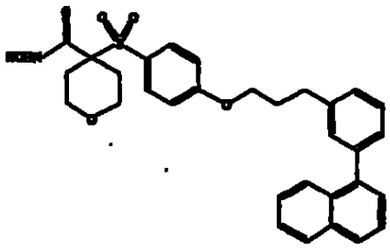
(222-1).

223. A compound or salt thereof according to claim 214, wherein the compound corresponds in structure to the following formula:



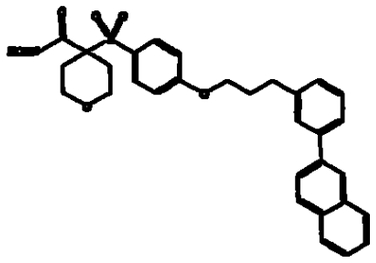
(223-1).

224. A compound or salt thereof according to claim 214, wherein the compound corresponds in structure to the following formula:



(224-1)

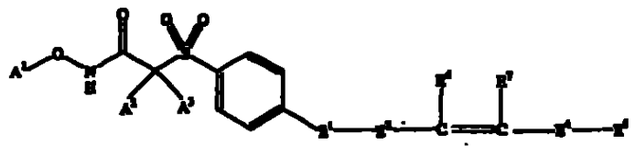
and



(224-2).

225. A compound or salt thereof, wherein:

the compound corresponds in structure to Formula 225-1:



(225-1);

A^1 is selected from the group consisting of -H, alkylcarbonyl, alkoxycarbonyl, carbocyclylcarbonyl, carbocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclylalkylcarbonyl, carbocyclyloxycarbonyl, carbocyclylalkoxycarbonyl, aminoalkylcarbonyl, alkyl(thiocarbonyl), alkoxy(thiocarbonyl), carbocyclyl(thiocarbonyl), carbocyclylalkyl(thiocarbonyl), heterocyclyl(thiocarbonyl), heterocyclylalkyl(thiocarbonyl), carbocyclyloxy(thiocarbonyl), carbocyclylalkoxy(thiocarbonyl), and aminoalkyl(thiocarbonyl), wherein any member (except -H) of such group optionally is substituted; and

A^2 and A^3, together with the carbon atom to which they are both attached, form an optionally-substituted heterocyclyl containing from 5 to 8 ring members; and

E^1 is selected from the group consisting of -O-, $-S(O)_z-$, -S(O)-, $-N(R^1)-$, $-C(O)-N(R^1)-$, $-N(R^1)-C(O)-$, and $-C(R^1)(R^2)-$; and

E^2 is selected from the group consisting of alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, and alkylcycloalkylalkyl, wherein any member of such group optionally is substituted; and

E^4 is selected from the group consisting of a bond and alkyl, wherein the alkyl optionally is substituted; and

E^5 is selected from the group consisting of alkyl, alkenyl, alkynyl, alkoxy, alkoxyalkyl, carbocyclyl, and heterocyclyl, wherein any member of such group optionally is substituted; and

E^6 is selected from the group consisting of -H, halogen, and alkyl, wherein the alkyl optionally is substituted;

E^7 is selected from the group consisting of -H, alkyl, alkenyl, alkynyl, $-S(O)_z-R^3$, $-NO_2$, $-C(O)-N(R^3)(R^4)$, $-(C)(OR^3)$, carbocyclyl, carbocyclylalkyl, alkoxycarbocyclyl,

-CN, -C=N-OH, and -C=NH, wherein the alkyl, alkenyl, alkynyl, carbocyclyl, carbocyclylalkyl, or alkoxycarbocyclyl optionally is substituted; and

R^1 and R^2 are independently selected from the group consisting of -H and alkyl, wherein the alkyl optionally is substituted; and

R^3 and R^4 are independently selected from the group consisting of -H, alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, heterocyclylalkyl, wherein any member (except -H) of such group optionally is substituted; and

neither R^1 nor R^2 forms a ring structure with E^2, E^4, E^5, E^6, or E^7.

226. A compound or salt thereof according to claim 225, wherein:

A^1 is selected from the group consisting of -H, C_1-C_8-alkylcarbonyl, C_1-C_8-alkoxycarbonyl, carbocyclylcarbonyl, carbocyclyl-C_1-C_8-alkylcarbonyl, heterocyclylcarbonyl, heterocyclyl-C_1-C_8-alkylcarbonyl, carbocyclyloxycarbonyl, carbocyclyl-C_1-C_8-alkoxycarbonyl, $N(R^5)(R^6)$-C_1-C_8-alkylcarbonyl, C_1-C_8-alkyl(thiocarbonyl), C_1-C_8-alkoxy(thiocarbonyl), carbocyclyl(thiocarbonyl), carbocyclyl-C_1-C_8-alkyl(thiocarbonyl), heterocyclyl(thiocarbonyl), heterocyclyl-C_1-C_8-alkyl(thiocarbonyl), carbocyclyloxy(thiocarbonyl), carbocyclyl-C_1-C_8-alkoxy(thiocarbonyl), and $N(R^5)(R^6)$-C_1-C_8-alkyl(thiocarbonyl); and

E^2 is selected from the group consisting of C_1-C_{20}-alkyl, cycloalkyl, C_1-C_{10}-alkylcycloalkyl, cycloalkyl-C_1-C_{10}-alkyl, and C_1-C_{10}-alkylcycloalkyl-C_1-C_{10}-alkyl, wherein any member of such group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, C_1-C_6-alkyl, and halo-C_1-C_6-alkyl; and

E^4 is selected from the group consisting of a bond, C_1-C_{20}-alkyl, and halo-C_1-C_{20}-alkyl; and

E^5 is selected from the group consisting of C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, C_1-C_{20}-alkoxy, C_1-C_{20}-alkoxy-C_1-C_{20}-alkyl, carbocyclyl, and heterocyclyl, wherein:

the C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, C_1-C_{20}-alkoxy, or C_1-C_{20}-alkoxy-C_1-C_{20}-alkyl optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, and -CN, and

the carbocyclyl or heterocyclyl optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, keto, C_1-C_8-alkyl, halo-C_1-C_8-alkyl, C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, halo-C_1-C_8-alkoxy, $-N(R^7)(R^8)$, $-C(O)(R^9)$, $-S-R^7$, $-S(O)_2-R^7$, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_8-alkyl, and halogen-substituted C_1-C_8-alkoxy-C_1-C_8-alkyl; and

E^6 is selected from the group consisting of -H, halogen, and C_1-C_8-alkyl, wherein the C_1-C_8-alkyl optionally is substituted with one or more halogen;

E^7 is selected from the group consisting of -H, C_1-C_8-alkyl, C_1-C_8-alkenyl, C_1-C_8-alkynyl, $-S(O)_2-R^3$, $-NO_2$, $-C(O)-N(R^3)(R^4)$, $-(C)(OR^3)$, carbocyclyl, carbocycyl-C_1-C_8-alkyl, C_1-C_8-alkoxycarbocyclyl, -CN, -C=N-OH, and -C=NH, wherein the C_1-C_8-alkyl, C_1-C_8-alkenyl, C_1-C_8-alkynyl, carbocyclyl, carbocycyl-C_1-C_8-alkyl, or C_1-C_8-alkoxycarbocyclyl optionally is substituted with one or more halogen; and

R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_8-alkyl, and halo-C_1-C_8-alkyl; and

R^3 and R^4 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, heterocyclyl-C_1-C_8-alkyl, wherein any member (except -H) of such group optionally is substituted with one or more halogen; and

R^5 and R^6 are independently selected from the group consisting of -H, C_1-C_8-alkyl, C_1-C_8-alkoxycarbonyl, C_1-C_8-alkylcarbonyl, carbocyclyl-C_1-C_8-alkyl, and carbocyclyl-C_1-C_8-alkoxycarbonyl; and

R^7 and R^8 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl, wherein any member (except -H) of such group optionally is substituted with one or more halogen; and

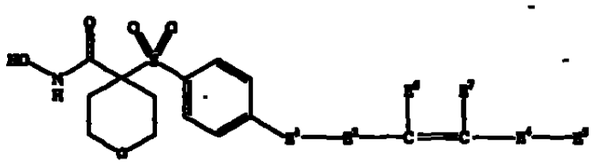
R^9 is selected from the group consisting of -H, C_1-C_8-alkyl, $-O-R^{10}$, $-N(R^{10})(R^{11})$, carbocyclyl-C_1-C_8-alkyl, and heterocyclyl-C_1-C_8-alkyl, wherein the C_1-C_8-alkyl, carbocyclyl-C_1-C_8-alkyl, or heterocyclyl-C_1-C_8-alkyl optionally is substituted with one or more halogen; and

R^{10} and R^{11} are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and

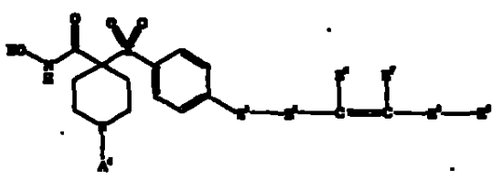
heterocyclyl-C_1-C_8-alkyl, wherein any member (except -H) of such group optionally is substituted with one or more halogen.

227. A compound or salt thereof according to claim 226, wherein:

the compound corresponds in structure to a formula selected from the group consisting of:



(227-1) and



(227-2); and

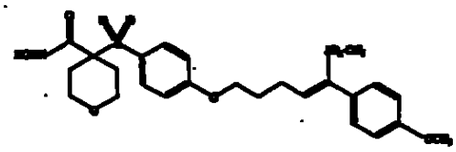
A^4 is selected from the group consisting of -H, alkyl, alkylcarbonyl, alkylcarbonylalkyl, alkylcarbonylalkylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkoxycarbonylalkylcarbonyl, alkylsulfonyl, alkyliminocarbonyl, alkenyl, alkynyl, alkoxyalkyl, alkylthioalkyl, alkylsulfonylalkyl, alkylsufoxidoalkyl, alkylthioalkenyl, alkylsulfoxidoalkenyl, alkylsulfonylalkenyl, carbocyclyl, carbocyclylalkyl, carbocyclylalkoxyalkyl, carbocyclylcarbonyl, carbocyclylsulfonyl, carbocyclyliminocarbonyl, carbocyclyloxycarbonyl, carbocylylthioalkyl, carbocylylsulfoxidoalkyl, carbocylylsulfonylalkyl, carbocyclylthioalkenyl, carbocyclylsulfoxidoalkenyl, carbocyclylsulfonylalkenyl, heterocyclyl, heterocyclylalkyl, heterocyclylalkoxyalkyl, heterocyclylcarbonyl, heterocyclylthioalkyl, heterocyclylsulfoxidoalkyl, heterocyclylsulfonylalkyl, heterocyclylthioalkenyl, heterocyclylsulfoxidoalkenyl, heterocyclylsulfonylalkenyl, heterocyclylsulfonyl, heterocyclyliminocarbonyl, heterocyclylalkylcarbonyl, heterocyclylcarbonylalkylcarbonyl, heterocyclylsulfonyl, heterocyclylcarbonylalkyl, aminoalkylcarbonyl, aminocarbonyl, aminocarbonylalkylcarbonyl, aminosulfonyl, aminosulfonylalkyl, aminoalkyl, aminocarbonylalkyl, and aminoalkylsulfonyl, wherein:

any member (except -H) of such group optionally is substituted.

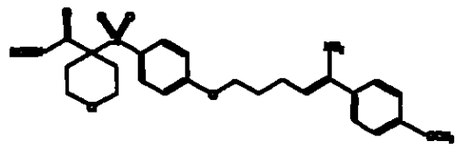
228. A compound or salt thereof according to claim 227, wherein E^5 is phenyl optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halo-C_1-C_6-alkoxy, -$N(R^7)(R^8)$, -$C(O)(R^5)$, -S-R^7, -$S(O)_2$-R^7, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl.

229. A compound or salt thereof according to claim 228, wherein E^4 is a bond.

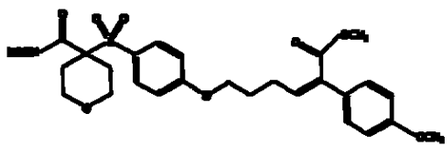
230. A compound or salt thereof according to claim 229, wherein the compound corresponds in structure to a formula selected from the group consisting of:



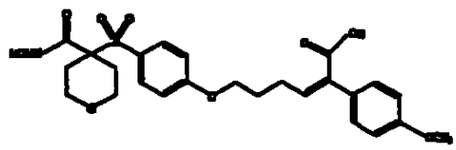
(230-1),



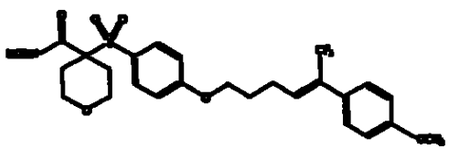
(230-2),



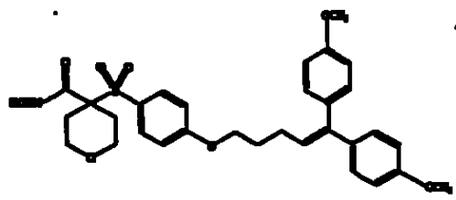
(230-3),



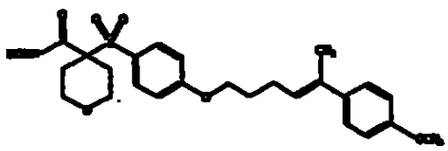
(230-4),



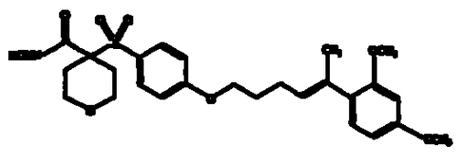
(230-5),



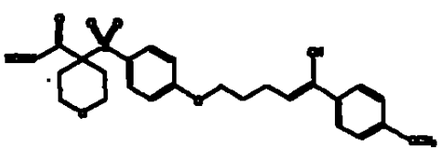
(230-6),



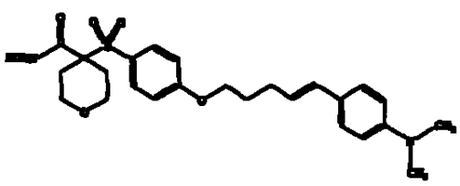
(230-7),



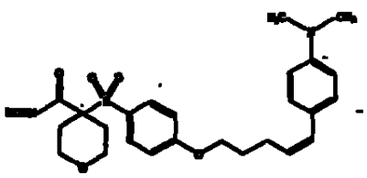
(230-8),



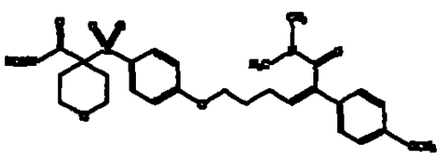
(230-9),



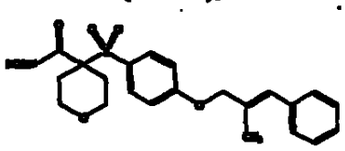
(230-10),



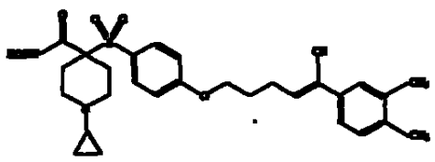
(230-11),



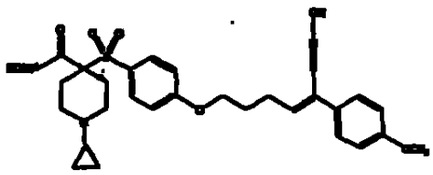
(230-12),



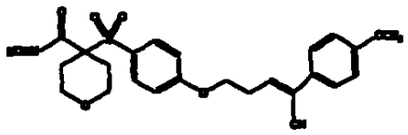
(230-13),



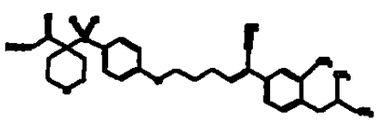
(230-14),



(230-15),

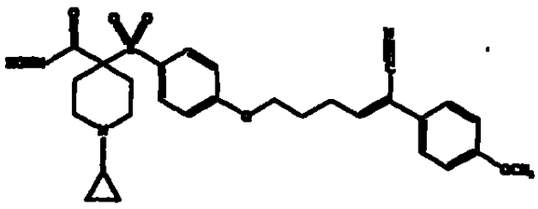


(230-16), and



(230-17).

231. A compound or salt thereof according to claim 229, wherein the compound corresponds in structure to the following formula:



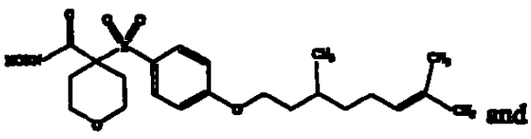
(231-1).

232. A compound or salt thereof according to claim 227, wherein E^5 is selected from the group consisting of C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, C_1-C_6-alkoxy, and C_1-C_6-alkoxy-C_1-C_6-alkyl, wherein:

any member of such group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, and -CN.

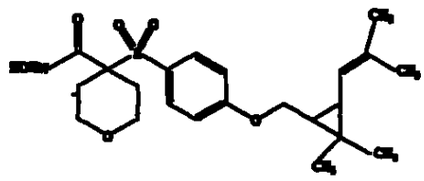
233. A compound or salt thereof according to claim 232, wherein E^5 is C_1-C_6-alkyl.

234. A compound or salt thereof according to claim 233, wherein the compound corresponds in structure to a formula selected from the group consisting of:



and

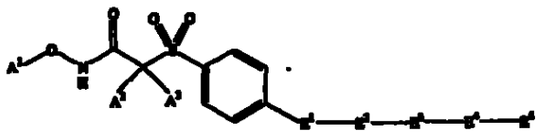
(234-1)



(234-2).

235. A compound or salt thereof, wherein:

the compound corresponds in structure to Formula 235-1:



(235-1);

A^1 is selected from the group consisting of -H, alkylcarbonyl, alkoxycarbonyl, carbocyclylcarbonyl, carbocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclylalkylcarbonyl, carbocyclyloxycarbonyl, carbocyclylalkoxycarbonyl, aminoalkylcarbonyl, alkyl(thiocarbonyl), alkoxy(thiocarbonyl), carbocyclyl(thiocarbonyl), carbocyclylalkyl(thiocarbonyl), heterocyclyl(thiocarbonyl), heterocyclylalkyl(thiocarbonyl), carbocyclyloxy(thiocarbonyl),

580

carbocyclylalkoxy(thiocarbonyl), and aminoalkyl(thiocarbonyl), wherein any member (except -H) of such group optionally is substituted; and

A^2 and A^3, together with the carbon atom to which they are both attached, form an optionally-substituted heterocyclyl containing from 5 to 8 ring members; and

E^1 is selected from the group consisting of -O-, $-S(O)_2-$, -S(O)-, $-N(R^3)-$, $-C(O)-N(R^3)-$, $-N(R^3)-C(O)-$, and $-C(R^1)(R^2)-$; and

E^2 is selected from the group consisting of a bond, alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, and alkylcycloalkylalkyl, wherein any member (except for the bond) of such group optionally is substituted; and

E^3 is carbonylpyrrollidinyl, wherein the carbonylpyrrollidinyl optionally is substituted; and

E^4 is selected from the group consisting of a bond, alkyl, and alkenyl, wherein the alkyl or alkenyl optionally is substituted; and

E^5 is selected from the group consisting of alkyl, alkenyl, alkynyl, alkoxy, alkoxyalkyl, carbocyclyl, and heterocyclyl, wherein any member of such group optionally is substituted; and

R^1 and R^2 are independently selected from the group consisting of -H and alkyl, wherein the alkyl optionally is substituted; and

neither R^1 nor R^2 forms a ring structure with E^2, E^3, E^4, or E^5.

236. A compound or salt thereof according to claim 235, wherein:

A^1 is selected from the group consisting of -H, C_1-C_8-alkylcarbonyl, C_1-C_8-alkoxycarbonyl, carbocyclylcarbonyl, carbocyclyl-C_1-C_8-alkylcarbonyl, heterocyclylcarbonyl, heterocyclyl-C_1-C_8-alkylcarbonyl, carbocyclyloxycarbonyl, carbocyclyl-C_1-C_8-alkoxycarbonyl, $N(R^3)(R^4)$-C_1-C_8-alkylcarbonyl, C_1-C_8-alkyl(thiocarbonyl), C_1-C_8-alkoxy(thiocarbonyl), carbocyclyl(thiocarbonyl), carbocyclyl-C_1-C_8-alkyl(thiocarbonyl), heterocyclyl(thiocarbonyl), heterocyclyl-C_1-C_8-alkyl(thiocarbonyl), carbocyclyloxy(thiocarbonyl), carbocyclyl-C_1-C_8-alkoxy(thiocarbonyl), and $N(R^3)(R^4)$-C_1-C_8-alkyl(thiocarbonyl); and

E^2 is selected from the group consisting of a bond, C_1-C_{20}-alkyl, cycloalkyl, C_1-C_{10}-alkylcycloalkyl, cycloalkyl-C_1-C_{10}-alkyl, and C_1-C_{10}-alkylcycloalkyl-C_1-C_{10}-alkyl, wherein any member of such group (except for the bond) optionally is substituted with one

or more substituents independently selected from the group consisting of halogen, C_1-C_6-alkyl, and halo-C_1-C_6-alkyl; and

E^3 is carbonylpyrrollidinyl, wherein the carbonylpyrrollidinyl optionally is substituted with one or more halogen; and

E^4 is selected from the group consisting of a bond, C_1-C_{20}-alkyl, halo-C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, and halo-C_2-C_{20}-alkenyl; and

E^5 is selected from the group consisting of C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, C_1-C_{20}-alkoxy, C_1-C_{20}-alkoxy-C_1-C_{20}-alkyl, carbocyclyl, and heterocyclyl, wherein:

the C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, C_1-C_{20}-alkoxy, or C_1-C_{20}-alkoxy-C_1-C_{20}-alkyl optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, and -CN, and

the carbocyclyl or heterocyclyl optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, keto, C_1-C_8-alkyl, halo-C_1-C_8-alkyl, C_1-C_8-alkoxy, halo-C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, halogen-substituted C_1-C_8-alkoxy-C_1-C_8-alkyl, $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_8-alkyl, and halogen-substituted carbocyclyl-C_1-C_8-alkyl; and

R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_8-alkyl, and halo-C_1-C_8-alkyl; and

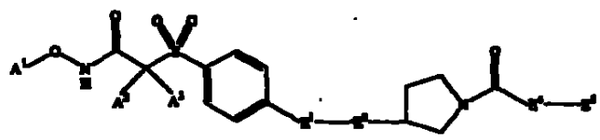
R^3 and R^4 are independently selected from the group consisting of -H, C_1-C_8-alkyl, C_1-C_8-alkoxycarbonyl, C_1-C_8-alkylcarbonyl, carbocyclyl-C_1-C_8-alkyl, and carbocyclyl-C_1-C_8-alkoxycarbonyl; and

R^5 and R^6 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl, wherein any member (except -H) of such group optionally is substituted with one or more halogen; and

R^7 is selected from the group consisting of -H, C_1-C_8-alkyl, $-O-R^8$, $-N(R^8)(R^8)$, carbocyclyl-C_1-C_8-alkyl, and heterocyclyl-C_1-C_8-alkyl, wherein the C_1-C_8-alkyl, carbocyclyl-C_1-C_8-alkyl, or heterocyclyl-C_1-C_8-alkyl optionally is substituted with one or more halogen; and

R^8 and R^9 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl, wherein any member (except -H) of such group optionally is substituted with one or more halogen.

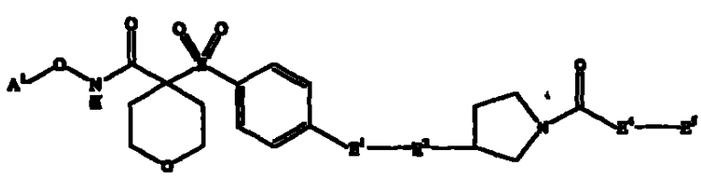
237. A compound or salt thereof according to claim 236, wherein the compound corresponds in structure to Formula 237-1:



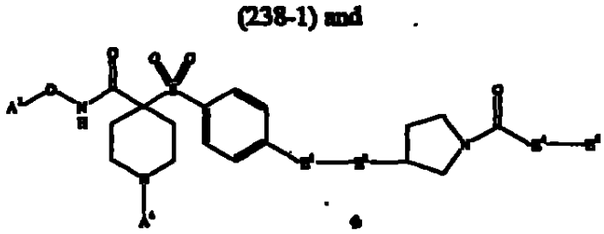
(237-1).

238. A compound or salt thereof according to claim 237, wherein:

the compound corresponds in structure to a formula selected from the group consisting of:



(238-1) and



(238-2); and

A^4 is selected from the group consisting of -H, alkyl, alkylcarbonyl, alkylcarbonylalkyl, alkylcarbonylalkylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkoxycarbonylalkylcarbonyl, alkylsulfonyl, alkyliminocarbonyl, alkenyl, alkynyl, alkoxyalkyl, alkylthioalkyl, alkylsulfonylalkyl, alkylsufoxidoalkyl, alkylthioalkenyl, alkylsulfoxidoalkenyl, alkylsulfonylalkenyl, carbocyclyl, carbocyclylalkyl, carbocyclylalkoxyalkyl, carbocyclylcarbonyl, carbocyclylsulfonyl, carbocyclyliminocarbonyl, carbocyclyloxycarbonyl, carbocylylthioalkyl,

carbocylylsulfoxidoalkyl, carbocylylsulfonylalkyl, carbocyclylthioalkenyl, carbocyclylsulfoxidoalkenyl, carbocyclylsulfonylalkenyl, heterocyclyl, heterocyclylalkyl, heterocyclylalkoxyalkyl, heterocyclylcarbonyl, heterocyclylthioalkyl, heterocyclylsulfoxidoalkyl, heterocyclylsulfonylalkyl, heterocyclylthioalkenyl, heterocyclylsulfoxidoalkenyl, heterocyclylsulfonylalkenyl, heterocyclylsulfonyl, heterocyclyliminocarbonyl, heterocyclylalkylcarbonyl, heterocyclylcarbonylalkylcarbonyl, heterocyclylsulfonyl, heterocyclylcarbonylalkyl, aminoalkylcarbonyl, aminocarbonyl, aminocarbonylalkylcarbonyl, aminosulfonyl, aminosulfonylalkyl, aminoalkyl, aminocarbonylalkyl, and aminoalkylsulfonyl, wherein:

any member (except -H) of such group optionally is substituted.

239. A compound or salt thereof according to claim 238, wherein E^5 is selected from the group consisting of carbocyclyl and heterocyclyl, wherein:

the carbocyclyl or heterocyclyl optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, keto, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl.

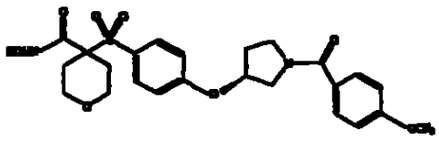
240. A compound or salt thereof according to claim 239, wherein E^5 is carbocyclyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, keto, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl.

241. A compound or salt thereof according to claim 240, wherein E^5 is phenyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted

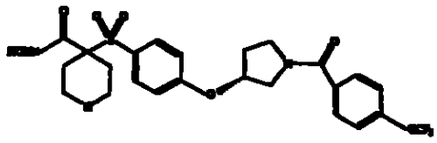
C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl.

242. A compound or salt thereof according to claim 241, wherein E^4 is a bond.

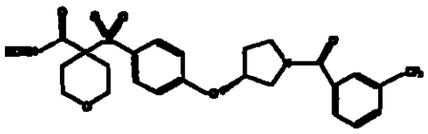
243. A compound or salt thereof according to claim 242, wherein the compound corresponds in structure to a formula selected from the group consisting of:



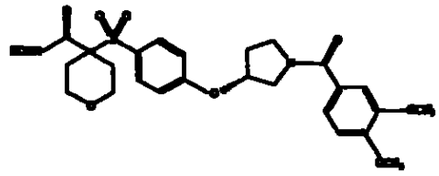
(243-1)



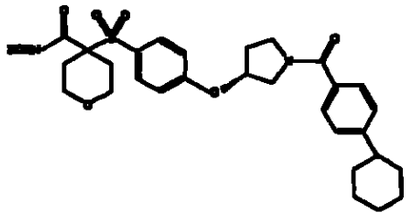
(243-2),



(243-3),



(243-4), and

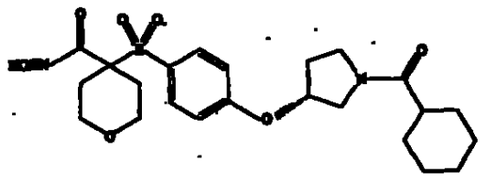


(243-5).

244. A compound or salt thereof according to claim 240, wherein E^5 is C_3-C_6-cycloalkyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, keto, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl.

245. A compound or salt thereof according to claim 244, wherein E^4 is a bond.

246. A compound or salt thereof according to claim 245, wherein the compound corresponds in structure to the following formula:



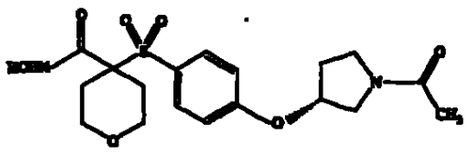
(246-1).

247. A compound or salt thereof according to claim 238, wherein E^5 is selected from the group consisting of C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, wherein:

the C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, C_1-C_8-alkoxy, or C_1-C_8-alkoxy-C_1-C_8-alkyl optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, and -CN.

248. A compound or salt thereof according to claim 247, wherein E^4 is a bond, and E^5 is C_1-C_8-alkyl.

249. A compound or salt thereof according to claim 248, wherein the compound corresponds in structure to the following formula:

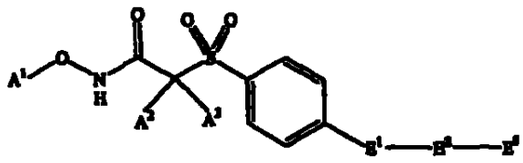


(249-1)

586

250. A compound or salt thereof, wherein:

the compound corresponds in structure to Formula 250-1:



(250-1); and

A^1 is selected from the group consisting of -H, alkylcarbonyl, alkoxycarbonyl, carbocyclylcarbonyl, carbocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclylalkylcarbonyl, carbocyclyloxycarbonyl, carbocyclylalkoxycarbonyl, aminoalkylcarbonyl, alkyl(thiocarbonyl), alkoxy(thiocarbonyl), carbocyclyl(thiocarbonyl), carbocyclylalkyl(thiocarbonyl), heterocyclyl(thiocarbonyl), heterocyclylalkyl(thiocarbonyl), carbocyclyloxy(thiocarbonyl), carbocyclylalkoxy(thiocarbonyl), and aminoalkyl(thiocarbonyl), wherein any member (except -H) of such group optionally is substituted; and

A^2 and A^3, together with the carbon atom to which they are both attached, form an optionally-substituted heterocyclyl containing from 5 to 8 ring members; and

E^1 is selected from the group consisting of -O-, $-S(O)_2-$, -S(O)-, $-N(R^1)-$, $-C(O)-N(R^1)-$, $-N(R^1)-C(O)-$, and $-C(R^1)(R^2)-$; and

E^2 is selected from the group consisting of alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, and alkylcycloalkylalkyl, wherein any member of such group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, alkyl, and haloalkyl; and

E^3 is selected from the group consisting of alkyl, alkenyl, alkynyl, cycloalkyl, cyclopentenyl, cyclopentadienyl, cyclohexenyl, and cyclohexadienyl, wherein

the alkyl, alkenyl, or alkynyl (a) contains at least 4 carbon atoms, and (b) optionally is substituted with one or more substituents selected from the group consisting of -OH, $-NO_2$, -CN, and halogen, and

the cycloalkyl, cyclopentenyl, cyclopentadienyl, cyclohexenyl, or cyclohexadienyl optionally is substituted; and

R^1 and R^2 are independently selected from the group consisting of -H and alkyl, wherein the alkyl optionally is substituted; and

neither R^1 nor R^2 forms a ring structure with E^5.

251. A compound or salt thereof according to claim 250, wherein:

A^1 is selected from the group consisting of -H, C_1-C_8-alkylcarbonyl, C_1-C_8-alkoxycarbonyl, carbocyclylcarbonyl, carbocyclyl-C_1-C_8-alkylcarbonyl, heterocyclylcarbonyl, heterocyclyl-C_1-C_8-alkylcarbonyl, carbocyclyloxycarbonyl, carbocyclyl-C_1-C_8-alkoxycarbonyl, $N(R^3)(R^4)$-C_1-C_8-alkylcarbonyl, C_1-C_8-alkyl(thiocarbonyl), C_1-C_8-alkoxy(thiocarbonyl), carbocyclyl(thiocarbonyl), carbocyclyl-C_1-C_8-alkyl(thiocarbonyl), heterocyclyl(thiocarbonyl), heterocyclyl-C_1-C_8-alkyl(thiocarbonyl), carbocyclyloxy(thiocarbonyl), carbocyclyl-C_1-C_8-alkoxy(thiocarbonyl), and $N(R^3)(R^4)$-C_1-C_8-alkyl(thiocarbonyl); and

E^2 is selected from the group consisting of C_1-C_{20}-alkyl, cycloalkyl, C_1-C_{10}-alkylcycloalkyl, cycloalkyl-C_1-C_{10}-alkyl, and C_1-C_{10}-alkylcycloalkyl-C_1-C_{10}-alkyl, wherein any member of such group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, C_1-C_8-alkyl, and halo-C_1-C_8-alkyl; and

E^5 is selected from the group consisting of C_4-C_{20}-alkyl, C_4-C_{20}-alkenyl, and C_4-C_{20}-alkynyl, cycloalkyl, cyclopentenyl, cyclopentadienyl, cyclohexenyl, and cyclohexadienyl, wherein:

the C_4-C_{20}-alkyl, C_4-C_{20}-alkenyl, or C_4-C_{20}-alkynyl optionally is substituted with one or more substituents independently selected from the group consisting of -OH, $-NO_2$, -CN, and halogen, and

the cycloalkyl, cyclopentenyl, cyclopentadienyl, cyclohexenyl, or cyclohexadienyl optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, keto, C_1-C_8-alkyl, halo-C_1-C_8-alkyl, C_1-C_8-alkoxy, halo-C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, halogen-substituted C_1-C_8-alkoxy-C_1-C_8-alkyl, $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_8-alkyl, and halogen-substituted carbocyclyl-C_1-C_8-alkyl; and

R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_8-alkyl, and halo-C_1-C_8-alkyl; and

R^3 and R^4 are independently selected from the group consisting of -H, C_1-C_8-alkyl, C_1-C_8-alkoxycarbonyl, C_1-C_8-alkylcarbonyl, carbocyclyl-C_1-C_8-alkyl, and carbocyclyl-C_1-C_8-alkoxycarbonyl; and

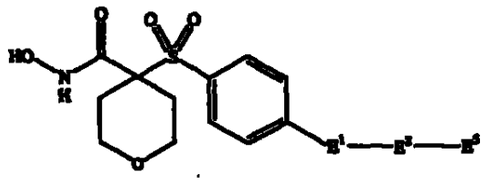
R^5 and R^6 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl, wherein any member (except -H) of such group optionally is substituted with one or more halogen; and

R^7 is selected from the group consisting of -H, C_1-C_8-alkyl, -O-R^8, -N(R^8)(R^9), carbocyclyl-C_1-C_8-alkyl, and heterocyclyl-C_1-C_8-alkyl, wherein the C_1-C_8-alkyl, carbocyclyl-C_1-C_8-alkyl, or heterocyclyl-C_1-C_8-alkyl optionally is substituted with one or more halogen; and

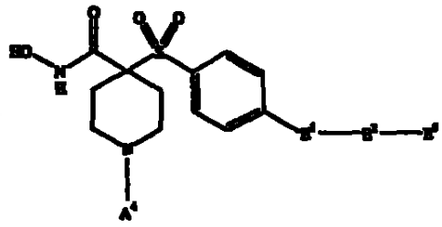
R^8 and R^9 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl, wherein any member (except -H) of such group optionally is substituted with one or more halogen.

252. A compound or salt thereof according to claim 251, wherein:

the compound corresponds in structure to a formula selected from the group consisting of:



(252-1) and



(252-2); and

A^4 is selected from the group consisting of -H, alkyl, alkylcarbonyl, alkylcarbonylalkyl, alkylcarbonylalkylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl,

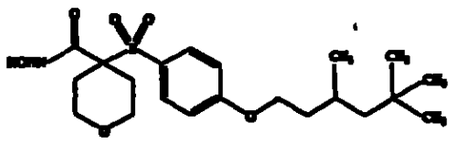
alkoxycarbonylalkylcarbonyl, alkylsulfonyl, alkyliminocarbonyl, alkenyl, alkynyl, alkoxyalkyl, alkylthioalkyl, alkylsulfonylalkyl, alkylsulfoxidoalkyl, alkylthioalkenyl, alkylsulfoxidoalkenyl, alkylsulfonylalkenyl, carbocyclyl, carbocyclylalkyl, carbocyclylalkoxyalkyl, carbocyclylcarbonyl, carbocyclylsulfonyl, carbocyclyliminocarbonyl, carbocyclyloxycarbonyl, carbocylylthioalkyl, carbocylylsulfoxidoalkyl, carbocylylsulfonylalkyl, carbocyclylthioalkenyl, carbocyclylsulfoxidoalkenyl, carbocyclylsulfonylalkenyl, heterocyclyl, heterocyclylalkyl, heterocyclylalkoxyalkyl, heterocyclylcarbonyl, heterocyclylthioalkyl, heterocyclylsulfoxidoalkyl, heterocyclylsulfonylalkyl, heterocyclylthioalkenyl, heterocyclylsulfoxidoalkenyl, heterocyclylsulfonylalkenyl, heterocyclylsulfonyl, heterocyclyliminocarbonyl, heterocyclylalkylcarbonyl, heterocyclylcarbonylalkylcarbonyl, heterocyclylsulfonyl, heterocyclylcarbonylalkyl, aminoalkylcarbonyl, aminocarbonyl, aminocarbonylalkylcarbonyl, aminosulfonyl, aminosulfonylalkyl, aminoalkyl, aminocarbonylalkyl, and aminoalkylsulfonyl, wherein:

any member (except -H) of such group optionally is substituted.

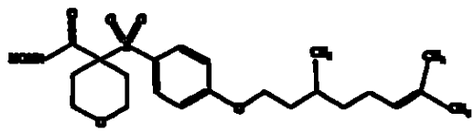
253. A compound or salt thereof according to claim 252, wherein E^5 is selected from the group consisting of C_4-C_8-alkyl, C_4-C_8-alkenyl, and C_4-C_8-alkynyl, wherein:

the C_4-C_8-alkyl, C_4-C_8-alkenyl, or C_4-C_8-alkynyl optionally is substituted with one or more substituents independently selected from the group consisting of -OH, -NO_2, -CN, and halogen.

254. A compound or salt thereof according to claim 253, wherein the compound corresponds in structure to a formula selected from the group consisting of:

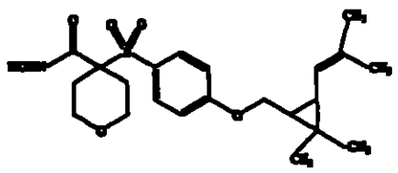


(254-1),

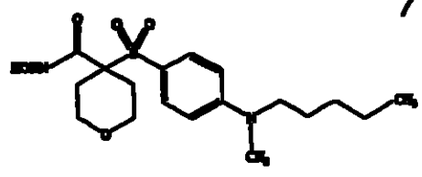


(254-2),

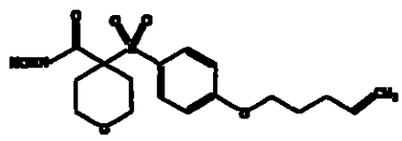
590



(254-3),

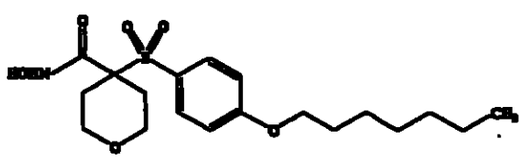


(254-4), and



(254-5).

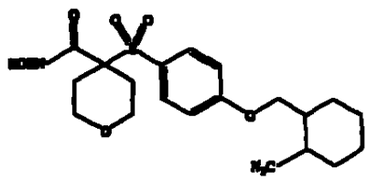
255. A compound or salt thereof according to claim 253, wherein the compound corresponds in structure to the following formula:



(255-1).

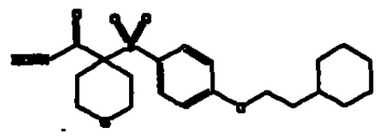
256. A compound or salt thereof according to claim 252, wherein E^5 is C_3-C_6-cycloalkyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, keto, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_z$-R^5, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl.

257. A compound or salt thereof according to claim 256, wherein the compound corresponds in structure to a formula selected from the group consisting of:



(257-1)

and

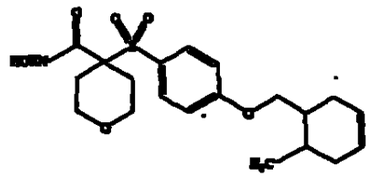


(257-2).

258. A compound or salt thereof according to claim 252, wherein E^5 is selected from the group consisting of cyclopentenyl, cyclopentadienyl, cyclohexenyl, and cyclohexadienyl, wherein:

any member of such group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, keto, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl.

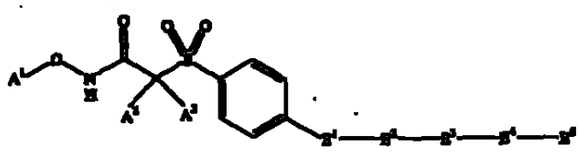
259. A compound or salt thereof according to claim 258, wherein the compound corresponds in structure to the following formula:



(259-1).

260. A compound or salt thereof, wherein:

the compound corresponds in structure to Formula 260-1:



(260-1); and

A^1 is selected from the group consisting of -H, alkylcarbonyl, alkoxycarbonyl, carbocyclylcarbonyl, carbocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclylalkylcarbonyl, carbocyclyloxycarbonyl, carbocyclylalkoxycarbonyl, aminoalkylcarbonyl, alkyl(thiocarbonyl), alkoxy(thiocarbonyl), carbocyclyl(thiocarbonyl), carbocyclylalkyl(thiocarbonyl), heterocyclyl(thiocarbonyl), heterocyclylalkyl(thiocarbonyl), carbocyclyloxy(thiocarbonyl), carbocyclylalkoxy(thiocarbonyl), and aminoalkyl(thiocarbonyl), wherein any member (except -H) of such group optionally is substituted; and

A^2 and A^3, together with the carbon atom to which they are both attached, form an optionally-substituted heterocyclyl containing from 5 to 8 ring members; and

E^1 is selected from the group consisting of -O-, $-S(O)_2-$, -S(O)-, $-N(R^1)-$, $-C(O)-N(R^1)-$, $-N(R^1)-C(O)-$, and $-C(R^1)(R^2)-$; and

E^2 is selected from the group consisting of alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, and alkylcycloalkylalkyl, wherein any member of such group optionally is substituted; and

E^3 is carbonylpiperidinyl, wherein the carbonylpiperidinyl optionally is substituted; and

E^4 is selected from the group consisting of a bond, alkyl, and alkenyl, wherein the alkyl or alkenyl optionally is substituted; and

E^5 is selected from the group consisting of alkyl, alkenyl, alkynyl, alkoxy, alkoxyalkyl, carbocyclyl, and heterocyclyl, wherein any member of such group optionally is substituted; and

R^1 and R^2 are independently selected from the group consisting of -H and alkyl, wherein the alkyl optionally is substituted; and

neither R^1 nor R^2 forms a ring structure with E^2, E^3, E^4, or E^5.

261. A compound or salt thereof according to claim 260, wherein:

A^1 is selected from the group consisting of -H, C_1-C_8-alkylcarbonyl, C_1-C_8-alkoxycarbonyl, carbocyclylcarbonyl, carbocyclyl-C_1-C_8-alkylcarbonyl, heterocyclylcarbonyl, heterocyclyl-C_1-C_8-alkylcarbonyl, carbocyclyloxycarbonyl, carbocyclyl-C_1-C_8-alkoxycarbonyl, $N(R^3)(R^4)$-C_1-C_8-alkylcarbonyl, C_1-C_8-alkyl(thiocarbonyl), C_1-C_8-alkoxy(thiocarbonyl), carbocyclyl(thiocarbonyl), carbocyclyl-C_1-C_8-alkyl(thiocarbonyl), heterocyclyl(thiocarbonyl), heterocyclyl-C_1-C_8-alkyl(thiocarbonyl), carbocyclyloxy(thiocarbonyl), carbocyclyl-C_1-C_8-alkoxy(thiocarbonyl), and $N(R^3)(R^4)$-C_1-C_8-alkyl(thiocarbonyl); and

E^2 is selected from the group consisting of C_1-C_{20}-alkyl, cycloalkyl, C_1-C_{10}-alkylcycloalkyl, cycloalkyl-C_1-C_{10}-alkyl, and C_1-C_{10}-alkylcycloalkyl-C_1-C_{10}-alkyl, wherein any member of such group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, C_1-C_6-alkyl, and halo-C_1-C_6-alkyl; and

E^3 is carbonylpiperidinyl, wherein the carbonylpiperidinyl optionally is substituted with one or more halogen; and

E^4 is selected from the group consisting of a bond, C_1-C_{20}-alkyl, halo-C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, and halo-C_2-C_{20}-alkenyl; and

E^5 is selected from the group consisting of C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, C_1-C_{20}-alkoxy, C_1-C_{20}-alkoxy-C_1-C_{20}-alkyl, carbocyclyl, and heterocyclyl, wherein:

the C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, C_1-C_{20}-alkoxy, or C_1-C_{20}-alkoxy-C_1-C_{20}-alkyl optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, and -CN, and

the carbocyclyl or heterocyclyl optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, keto, C_1-C_8-alkyl, halo-C_1-C_8-alkyl, C_1-C_8-alkoxy, halo-C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, halogen-substituted C_1-C_8-alkoxy-C_1-C_8-alkyl, $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbocyclyl, halocarbocyclyl, and carbocyclyl-C_1-C_8-alkyl; and

R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_8-alkyl, and halo-C_1-C_8-alkyl; and

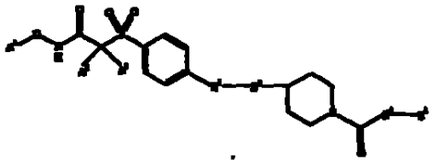
R^3 and R^4 are independently selected from the group consisting of -H, C_1-C_8-alkyl, C_1-C_8-alkoxycarbonyl, C_1-C_8-alkylcarbonyl, carbocyclyl-C_1-C_8-alkyl, and carbocyclyl-C_1-C_8-alkoxycarbonyl; and

R^5 and R^6 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl, wherein any member (except -H) of such group optionally is substituted with one or more halogen; and

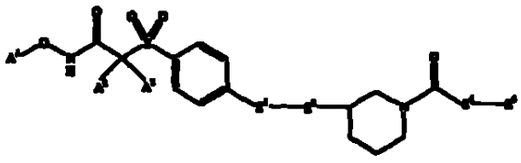
R^7 is selected from the group consisting of -H, C_1-C_8-alkyl, -O-R^8, -N(R^8)(R^9), carbocyclyl-C_1-C_8-alkyl, and heterocyclyl-C_1-C_8-alkyl, wherein the C_1-C_8-alkyl, carbocyclyl-C_1-C_8-alkyl, or heterocyclyl-C_1-C_8-alkyl optionally is substituted with one or more halogen; and

R^8 and R^9 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl, wherein any member (except -H) of such group optionally is substituted with one or more halogen.

262. A compound or salt thereof according to claim 261, wherein the compound corresponds in structure to a formula selected from the group consisting of:



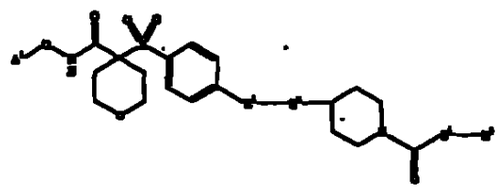
(262-1) and



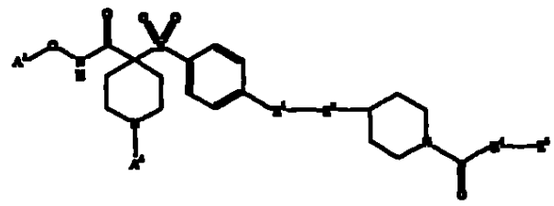
(262-2).

595

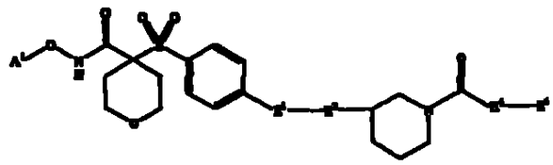
263. A compound or salt thereof according to claim 262, wherein the compound corresponds in structure to a formula selected from the group consisting of:



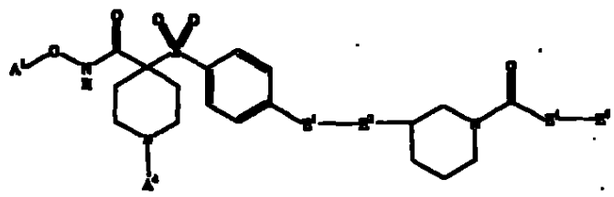
(263-1),



(263-2),



(263-3), and



(263-4); and

A^4 is selected from the group consisting of -H, alkyl, alkylcarbonyl, alkylcarbonylalkyl, alkylcarbonylalkylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkoxycarbonylalkylcarbonyl, alkylsulfonyl, alkyliminocarbonyl, alkenyl, alkynyl, alkoxyalkyl, alkylthioalkyl, alkylsulfonylalkyl, alkylsufoxidoalkyl, alkylthioalkenyl, alkylsulfoxidoalkenyl, alkylsulfonylalkenyl, carbocyclyl, carbocyclylalkyl, carbocyclylalkoxyalkyl, carbocyclylcarbonyl, carbocyclylsulfonyl, carbocyclyliminocarbonyl, carbocyclyloxycarbonyl, carbocylylthioalkyl, carbocylylsulfoxidoalkyl, carbocylylsulfonylalkyl, carbocyclylthioalkenyl, carbocyclylsulfoxidoalkenyl, carbocyclylsulfonylalkenyl, heterocyclyl, heterocyclylalkyl,

596

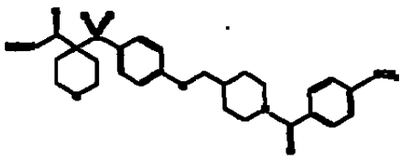
heterocyclylalkoxyalkyl, heterocyclylcarbonyl, heterocyclylthioalkyl, heterocyclylsulfoxidoalkyl, heterocyclylsulfonylalkyl, heterocyclylthioalkenyl, heterocyclylsulfoxidoalkenyl, heterocyclylsulfonylalkenyl, heterocyclylsulfonyl, heterocyclyliminocarbonyl, heterocyclylalkylcarbonyl, heterocyclylcarbonylalkylcarbonyl, heterocyclylsulfonyl, heterocyclylcarbonylalkyl, aminoalkylcarbonyl, aminocarbonyl, aminocarbonylalkylcarbonyl, aminosulfonyl, aminosulfonylalkyl, aminoalkyl, aminocarbonylalkyl, and aminoalkylsulfonyl, wherein:

any member (except -H) of such group optionally is substituted.

264. A compound or salt thereof according to claim 263, wherein E^5 is phenyl optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl.

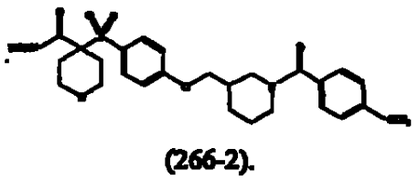
265. A compound or salt thereof according to claim 264, wherein E^4 is a bond.

266. A compound or salt thereof according to claim 265, wherein the compound corresponds in structure to a formula selected from the group consisting of:



(266-1)

and

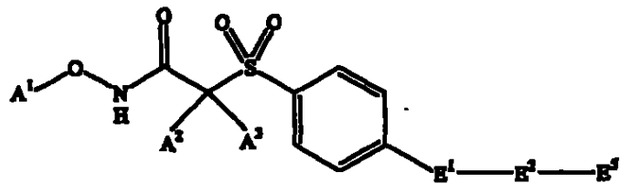


(266-2).

597

267. A compound or salt thereof, wherein:

the compound corresponds in structure to Formula 267-1:



(267-1); and

A^1 is selected from the group consisting of -H, alkylcarbonyl, alkoxycarbonyl, carbocyclylcarbonyl, carbocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclylalkylcarbonyl, carbocyclyloxycarbonyl, carbocyclylalkoxycarbonyl, aminoalkylcarbonyl, alkyl(thiocarbonyl), alkoxy(thiocarbonyl), carbocyclyl(thiocarbonyl), carbocyclylalkyl(thiocarbonyl), heterocyclyl(thiocarbonyl), heterocyclylalkyl(thiocarbonyl), carbocyclyloxy(thiocarbonyl), carbocyclylalkoxy(thiocarbonyl), and aminoalkyl(thiocarbonyl), wherein any member (except -H) of such group optionally is substituted; and

A^2 and A^3, together with the carbon atom to which they are both attached, form an optionally-substituted heterocyclyl containing from 5 to 8 ring members; and

E^1 is selected from the group consisting of -O-, $-S(O)_2-$, -S(O)-, $-N(R^1)-$, $-C(O)-N(R^1)-$, $-N(R^1)-C(O)-$, and $-C(R^1)(R^2)-$; and

E^2 is selected from the group consisting of alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, and alkylcycloalkylalkyl, wherein any member of such group optionally is substituted; and

E^2 forms a link of at least 3 carbon atoms between E^1 and E^5; and

E^5 is selected from the group consisting of optionally-substituted heterocyclyl, optionally-substituted fused-ring carbocyclyl, and substituted single-ring carbocyclyl; and

R^1 and R^2 are independently selected from the group consisting of -H and alkyl, wherein the alkyl optionally is substituted; and

neither R^1 nor R^2 forms a ring structure with E^5.

268. A compound or salt thereof according to claim 267, wherein:

A^1 is selected from the group consisting of -H, C_1-C_8-alkylcarbonyl, C_1-C_8-alkoxycarbonyl, carbocyclylcarbonyl, carbocyclyl-C_1-C_8-alkylcarbonyl, heterocyclylcarbonyl, heterocyclyl-C_1-C_8-alkylcarbonyl, carbocyclyloxycarbonyl, carbocyclyl-C_1-C_8-alkoxycarbonyl, $N(R^3)(R^4)$-C_1-C_8-alkylcarbonyl, C_1-C_8-alkyl(thiocarbonyl), C_1-C_8-alkoxy(thiocarbonyl), carbocyclyl(thiocarbonyl), carbocyclyl-C_1-C_8-alkyl(thiocarbonyl), heterocyclyl(thiocarbonyl), heterocyclyl-C_1-C_8-alkyl(thiocarbonyl), carbocyclyloxy(thiocarbonyl), carbocyclyl-C_1-C_8-alkoxy(thiocarbonyl), and $N(R^3)(R^4)$-C_1-C_8-alkyl(thiocarbonyl); and

E^2 is selected from the group consisting of C_3-C_{20}-alkyl, cycloalkyl, C_1-C_{10}-alkyl-cycloalkyl, cycloalkyl-C_1-C_{10}-alkyl, and C_1-C_{10}-alkyl-cycloalkyl-C_1-C_{10}-alkyl, wherein the any member of such group optionally is substituted with one or more halogen; and

E^3 is selected from the group consisting of single-ring carbocyclyl, fused-ring carbocyclyl, and heterocyclyl, wherein:

the single-ring carbocyclyl:

is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, keto, C_1-C_8-alkyl, halo-C_1-C_8-alkyl, C_1-C_8-alkoxy, halo-C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, halogen-substituted C_1-C_8-alkoxy-C_1-C_8-alkyl, $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_8-alkyl, halogen-substituted carbocyclyl-C_1-C_8-alkyl, optionally is substituted on the same atom with two substituents independently selected from the group consisting of alkyl and haloalkyl, the two substituents together forming C_3-C_6-cycloalkyl or halo-C_3-C_6-cycloalkyl, and

the heterocyclyl or fused-ring carbocyclyl:

optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, keto, C_1-C_8-alkyl, halo-C_1-C_8-alkyl, C_1-C_8-alkoxy, halo-C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, halogen-substituted C_1-C_8-alkoxy-C_1-C_8-alkyl, $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$,

carbocyclyl, halocarbocyclyl, and carbocyclyl-C_1-C_6-alkyl, optionally is substituted on the same atom with two substituents independently selected from the group consisting of alkyl and haloalkyl, the two substituents together forming C_3-C_6-cycloalkyl or halo-C_3-C_6-cycloalkyl; and

R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_6-alkyl, and halo-C_1-C_6-alkyl; and

R^3 and R^4 are independently selected from the group consisting of -H, C_1-C_6-alkyl, C_1-C_6-alkoxycarbonyl, C_1-C_6-alkylcarbonyl, carbocyclyl-C_1-C_6-alkyl, and carbocyclyl-C_1-C_6-alkoxycarbonyl; and

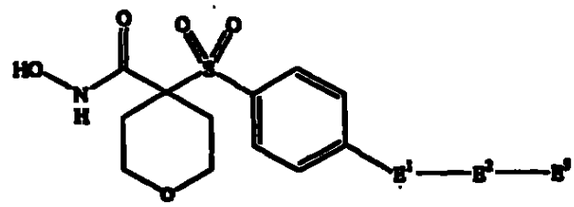
R^5 and R^6 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl, wherein any member (except -H) of such group optionally is substituted with one or more halogen; and

R^7 is selected from the group consisting of -H, C_1-C_6-alkyl, -O-R^8, -N(R^8)(R^9), carbocyclyl-C_1-C_6-alkyl, and heterocyclyl-C_1-C_6-alkyl, wherein the C_1-C_6-alkyl, carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl optionally is substituted with one or more halogen; and

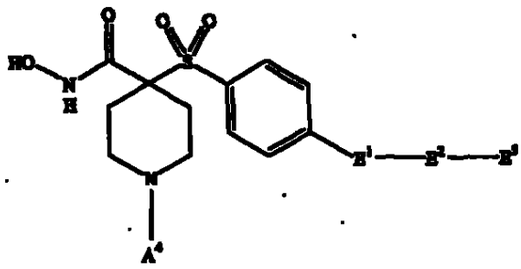
R^8 and R^9 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl, wherein any member (except -H) of such group optionally is substituted with one or more halogen.

269. A compound or salt thereof according to claim 268, wherein:

the compound corresponds in structure to a formula selected from the group consisting of:



(269-1) and



(269-2); and

A^4 is selected from the group consisting of -H, alkyl, alkylcarbonyl, alkylcarbonylalkyl, alkylcarbonylalkylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkoxycarbonylalkylcarbonyl, alkylsulfonyl, alkyliminocarbonyl, alkenyl, alkynyl, alkoxyalkyl, alkylthioalkyl, alkylsulfonylalkyl, alkylsufoxidoalkyl, alkylthioalkenyl, alkylsulfoxidoalkenyl, alkylsulfonylalkenyl, carbocyclyl, carbocyclylalkyl, carbocyclylalkoxyalkyl, carbocyclylcarbonyl, carbocyclylsulfonyl, carbocyclyliminocarbonyl, carbocyclyloxycarbonyl, carbocylylthioalkyl, carbocylylsulfoxidoalkyl, carbocylylsulfonylalkyl, carbocyclylthioalkenyl, carbocyclylsulfoxidoalkenyl, carbocyclylsulfonylalkenyl, heterocyclyl, heterocyclylalkyl, heterocyclylalkoxyalkyl, heterocyclylcarbonyl, heterocyclylthioalkyl, heterocylylsulfoxidoalkyl, heterocylylsulfonylalkyl, heterocylylthioalkenyl, heterocylylsulfoxidoalkenyl, heterocylylsulfonylalkenyl, heterocylylsulfonyl, heterocylyliminocarbonyl, heterocylylalkylcarbonyl, heterocylylcarbonylalkylcarbonyl, heterocylylsulfonyl, heterocylylcarbonylalkyl, aminoalkylcarbonyl, aminocarbonyl, aminocarbonylalkylcarbonyl, aminosulfonyl, aminosulfonylalkyl, aminoalkyl, aminocarbonylalkyl, and aminoalkylsulfonyl, wherein:

any member (except -H) of such group optionally is substituted.

270. A compound or salt thereof according to claim 269, wherein E^5 is single-ring carbocyclyl, which:

is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, keto, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbocyclyl,

601

halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl; and

optionally is substituted on the same atom with two substituents independently selected from the group consisting of alkyl and haloalkyl, the two substituents together forming C_3-C_6-cycloalkyl or halo-C_3-C_6-cycloalkyl.

271. A compound or salt thereof according to claim 270, wherein E^5 is single-ring carbocyclyl substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, keto, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl.

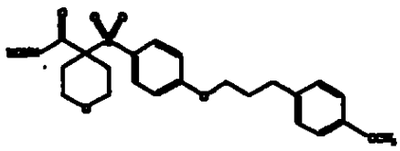
272. A compound or salt thereof according to claim 271, wherein E^5 is selected from the group consisting of cyclopropyl, cyclobutyl, cyclopentyl, cyclopentenyl, cyclopentadienyl, cyclohexyl, cyclohexenyl, cyclohexadienyl, and phenyl, wherein a member of such group:

is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, keto, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl.

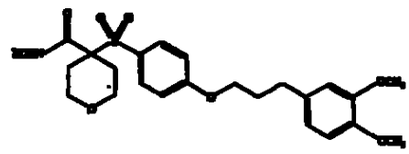
273. A compound or salt thereof according to claim 272, wherein E^5 is phenyl substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl.

602

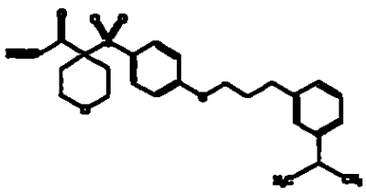
274. A compound or salt thereof according to claim 273, wherein the compound corresponds in structure to a formula selected from the group consisting of:



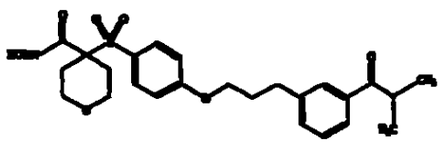
(274-1),



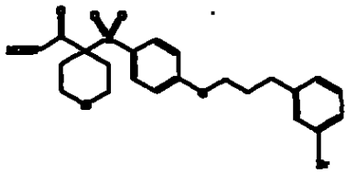
(274-2),



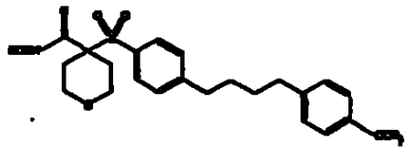
(274-3),



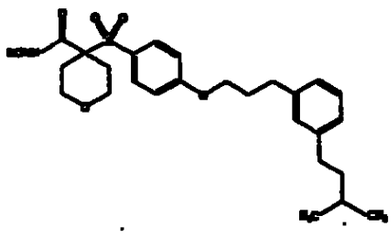
(274-4),



(274-5),



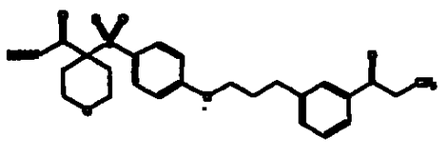
(274-6), and



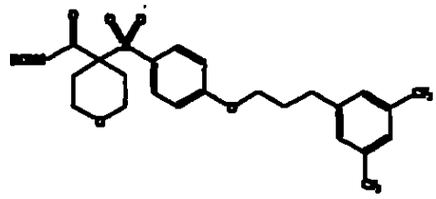
(274-7).

603

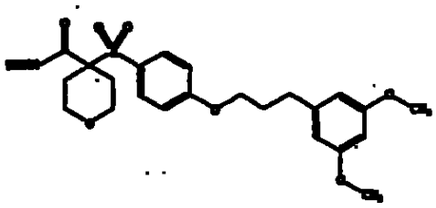
275. A compound or salt thereof according to claim 273, wherein the compound corresponds in structure to a formula selected from the group consisting of:



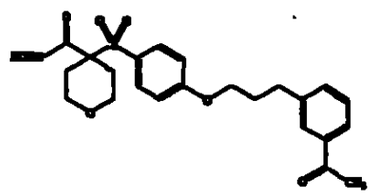
(275-1),



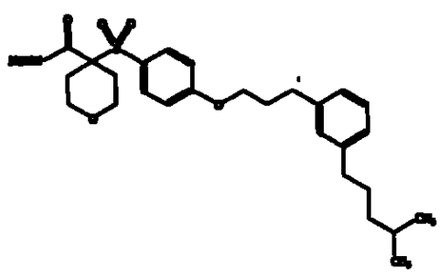
(275-2),



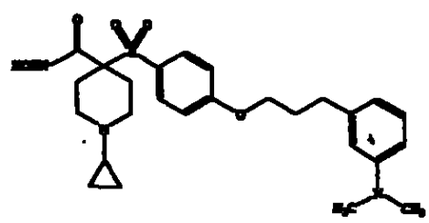
(275-3),



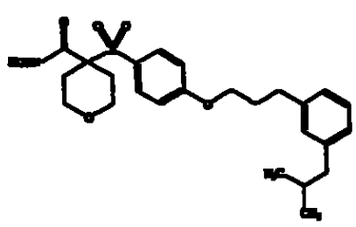
(275-4),



(275-5),



(275-6), and



(275-7).

276. A compound or salt thereof according to claim 269, wherein E^5 is fused-ring carbocyclyl, which:

optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, keto, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl,

604

halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl; and

optionally is substituted on the same atom with two substituents independently selected from the group consisting of alkyl and haloalkyl, the two substituents together forming C_3-C_6-cycloalkyl or halo-C_3-C_6-cycloalkyl.

277. A compound or salt thereof according to claim 276, wherein E^5 is fused-ring carbocyclyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, keto, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl.

278. A compound or salt thereof according to claim 277, wherein E^5 is selected from the group consisting of naphthalenyl, tetrahydronaphthalenyl, indenyl, isoindenyl, indanyl, bicyclodecanyl, anthracenyl, phenanthrene, benzonaphthenyl, fluorenyl, decalinyl, and norpinanyl, wherein a member of such group:

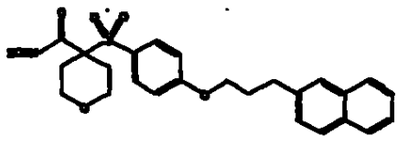
optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, keto, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl.

279. A compound or salt thereof according to claim 278, wherein E^5 is naphthalenyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbocyclyl,

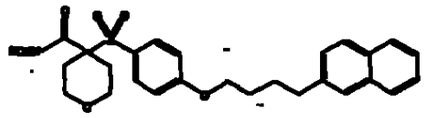
605

halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl.

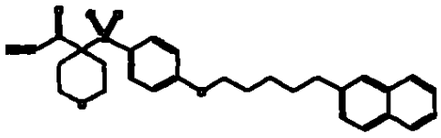
280. A compound or salt thereof according to claim 279, wherein the compound corresponds in structure to a formula selected from the group consisting of:



(280-1),



(280-2), and



(280-3).

281. A compound or salt thereof according to claim 269, wherein E^5 is heterocyclyl, which:

optionally is substituted on the same atom with two substituents independently selected from the group consisting of alkyl and haloalkyl, the two substituents together forming C_3-C_6-cycloalkyl or halo-C_3-C_6-cycloalkyl; and

optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, keto, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl.

606

282. A compound or salt thereof according to claim 281, wherein E^5 is heterocyclyl, which:

is substituted on the same atom with two substituents independently selected from the group consisting of alkyl and haloalkyl, the two substituents together forming C_3-C_6-cycloalkyl or halo-C_3-C_6-cycloalkyl; and

optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, keto, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl.

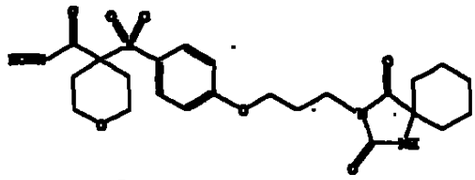
283. A compound or salt thereof according to claim 282, wherein E^5 is selected from the group consisting of dihydrofuranyl, tetrahydrofuranyl, dihydrothiophenyl, tetrahydrothiophenyl, pyrrolinyl, pyrrolidinyl, imidazolinyl, imidazolidinyl, pyrazolinyl, pyrazolidinyl, dithiolyl, oxathiolyl, thiazolinyl, isothiazolinyl, thiazolidinyl, isothiazolidinyl, oxathiolanyl, pyranyl, dihydropyranyl, piperidinyl, piperazinyl, and morpholinyl, wherein a member of such group:

is substituted on the same atom with two substituents independently selected from the group consisting of alkyl and haloalkyl, the two substituents together forming C_3-C_6-cycloalkyl or halo-C_3-C_6-cycloalkyl; and

optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, keto, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl.

607

284. A compound or salt thereof according to claim 283, wherein the compound corresponds in structure to the following formula:



(284-1).

285. A compound or salt thereof according to claim 281, wherein E^5 is heterocyclyl optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, keto, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl.

286. A compound or salt thereof according to claim 285, wherein E^5 is selected from the group consisting of furanyl, tetrahydropyranyl, dihydrofuranyl, tetrahydrofuranyl, thiophenyl, dihydrothiophenyl, tetrahydrothiophenyl, pyrrolyl, isopyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, isoimidazolyl, imidazolinyl, imidazolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, triazolyl, tetrazolyl, dithiolyl, oxathiolyl, oxazolyl, isoxazolyl, oxazolidinyl, isoxazolidinyl, thiazolyl, isothiazolyl, thiazolinyl, isothiazolinyl, thiazolidinyl, isothiazolidinyl, thiodiazolyl, oxathiazolyl, oxadiazolyl, oxatriazolyl, dioxazolyl, oxathiazolyl, oxathiolyl, oxathiolanyl, pyranyl, dihydropyranyl, pyridinyl, piperidinyl, diazinyl, piperazinyl, triazinyl, oxazinyl, isoxazinyl, oxathiazinyl, oxadiazinyl, morpholinyl, azepinyl, oxepinyl, thiepinyl, and diazepinyl, wherein a member of such group:

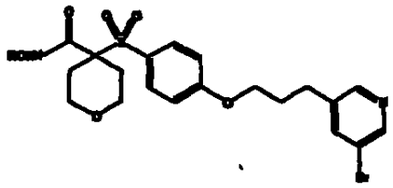
optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, keto, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5,

606

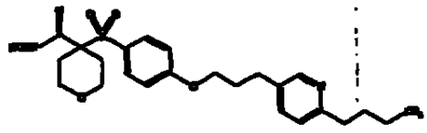
$-S(O)_2-R^5$, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl.

287. A compound or salt thereof according to claim 286, wherein E^5 is pyridinyl optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, keto, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl.

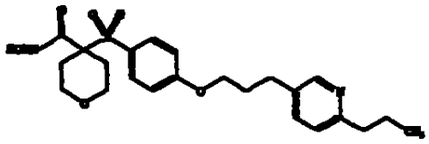
288. A compound or salt thereof according to claim 287, wherein the compound corresponds in structure to a formula selected from the group consisting of:



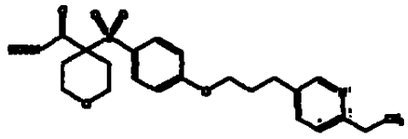
(288-1),



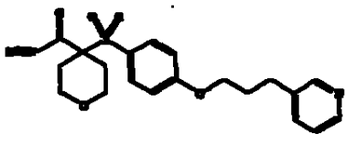
(288-2),



(288-3),



(288-4), and



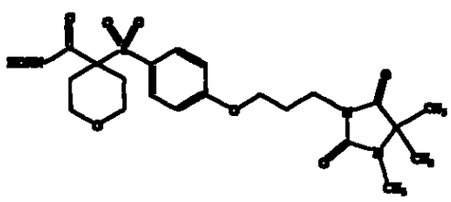
(288-5).

289. A compound or salt thereof according to claim 286, wherein E^5 is selected from the group consisting of imidazolyl, imidazolinyl, imidazolidinyl, pyrazolyl, pyrazolinyl, and pyrazolidinyl, wherein a member of such group:

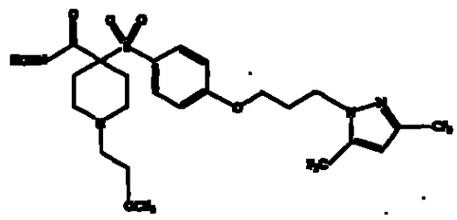
609

optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, keto, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl.

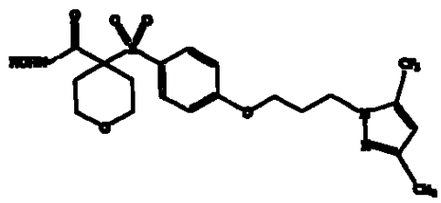
290. A compound or salt thereof according to claim 289, wherein the compound corresponds in structure to a formula selected from the group consisting of:



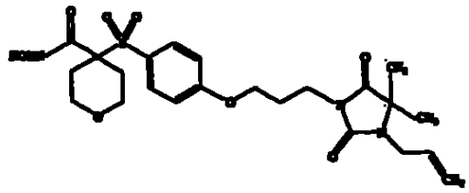
(290-1)



(290-2),



(290-3), and



(290-4).

291. A compound or salt thereof according to claim 285, wherein E^5 is fused-ring heterocyclyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, keto, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl.

292. A compound or salt thereof according to claim 291, wherein E^5 is selected from the group consisting of indolizinyl, pyrindinyl, pyranopyrrolyl, 4H-quinolizinyl,

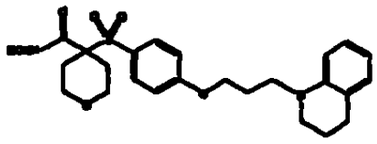
purinyl, naphthyridinyl, pyridopyridinyl, pteridinyl, indolyl, isoindolyl, indolenninyl, isoindazolyl, benzazinyl, phthalazinyl, quinoxalinyl, quinazolinyl, benzodiazinyl, benzopyranyl, benzothiopyranyl, benzoxazolyl, indoxazinyl, anthranilyl, benzodioxolyl, benzodioxanyl, benzoxadiazolyl, benzofuranyl, isobenzofuranyl, benzothienyl, isobenzothienyl, benzothiazolyl, benzothiadiazolyl, benzimidazolyl, benzotriazolyl, benzoxazinyl, benzisoxazinyl, tetrahydroisoquinolinyl, carbazolyl, xanthenyl, and acridinyl, wherein a member of such group:

optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, keto, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl.

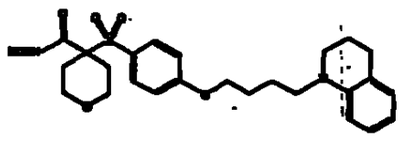
293. A compound or salt thereof according to claim 292, wherein E^5 is tetrahydroisoquinolinyl, which,

optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, keto, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl.

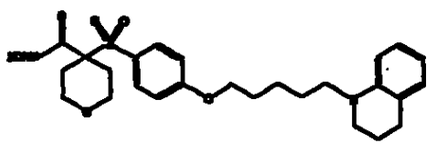
294. A compound or salt thereof according to claim 293, wherein the compound corresponds in structure to a formula selected from the group consisting of:



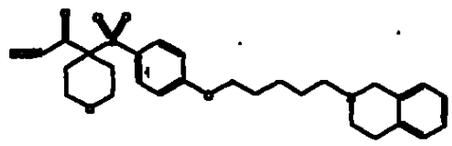
(294-1),



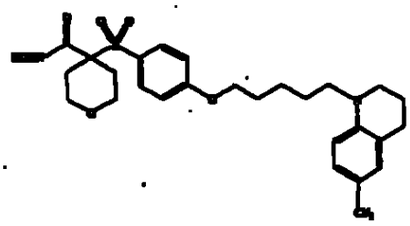
(294-2),



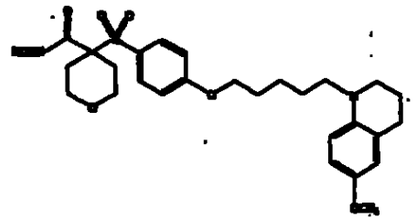
(294-3),



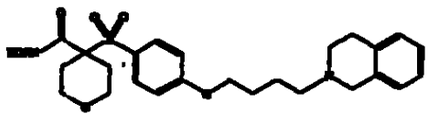
(294-4),



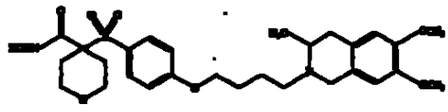
(294-5),



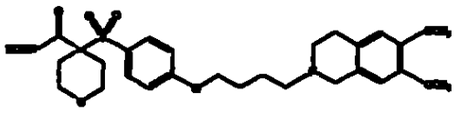
(294-6),



(294-7),

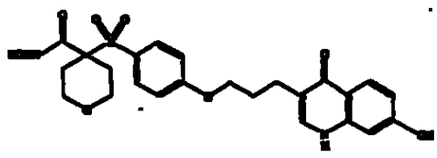


(294-8), and

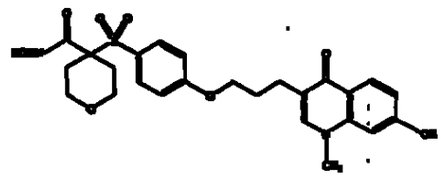


(294-9).

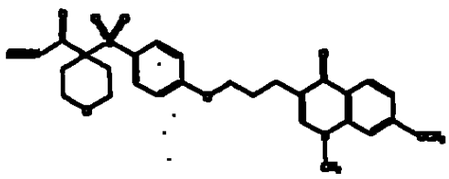
295: A compound or salt thereof according to claim 291, wherein the compound corresponds in structure to a formula selected from the group consisting of:



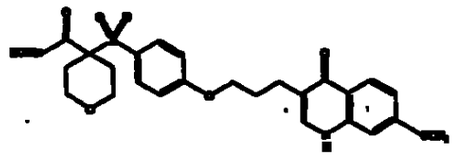
(295-1),



(295-2),

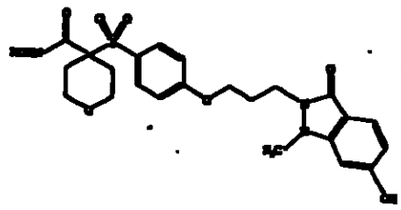


(295-3),

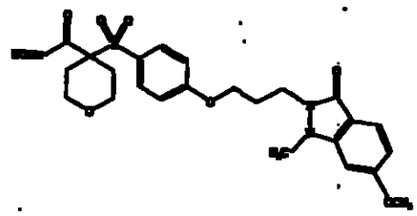


(295-4),

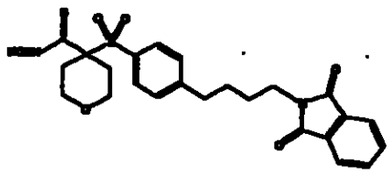
612



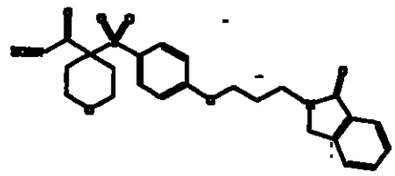
(295-5),



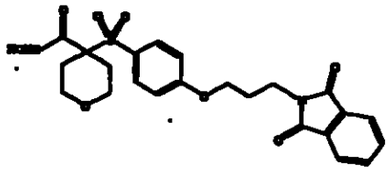
(295-6),



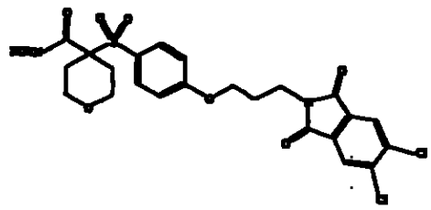
(295-7),



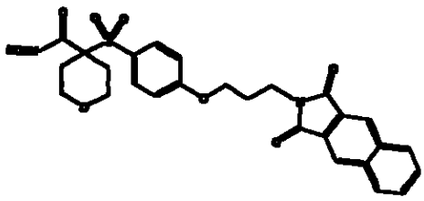
(295-8),



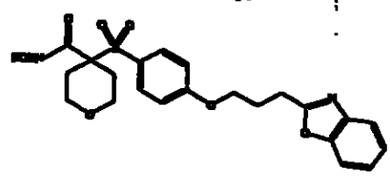
(295-9),



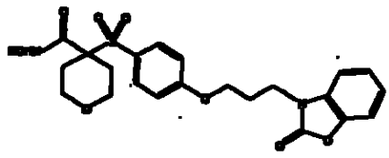
(295-10),



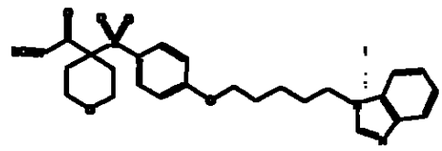
(295-11),



(295-12),



(295-13), and

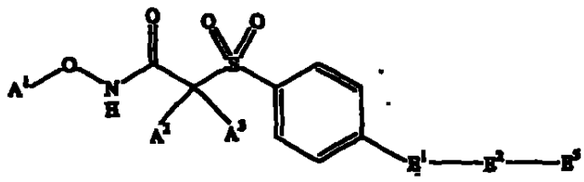


(295-14).

613

296. A compound or salt thereof, wherein:

the compound corresponds in structure to Formula 296-1:



(296-1); and

A^1 is selected from the group consisting of -H, alkylcarbonyl, alkoxycarbonyl, carbocyclylcarbonyl, carbocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclylalkylcarbonyl, carbocyclyloxycarbonyl, carbocyclylalkoxycarbonyl, aminoalkylcarbonyl, alkyl(thiocarbonyl), alkoxy(thiocarbonyl), carbocyclyl(thiocarbonyl), carbocyclylalkyl(thiocarbonyl), heterocyclyl(thiocarbonyl), heterocyclylalkyl(thiocarbonyl), carbocyclyloxy(thiocarbonyl), carbocyclylalkoxy(thiocarbonyl), and aminoalkyl(thiocarbonyl), wherein any member (except -H) of such group optionally is substituted; and

A^2 and A^3, together with the carbon atom to which they are both attached, form an optionally-substituted heterocyclyl containing from 5 to 8 ring members; and

E^1 is selected from the group consisting of -O-, $-S(O)_2-$, -S(O)-, $-N(R^1)-$, $-C(O)-N(R^1)-$, $-N(R^1)-C(O)-$, and $-C(R^1)(R^2)-$; and

R^1 and R^2 are independently selected from the group consisting of -H and alkyl, wherein the alkyl optionally is substituted; and

E^2 is selected from the group consisting of alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, and alkylcycloalkylalkyl, wherein any member of such group optionally is substituted; and

E^2 forms a link of at least 4 carbon atoms between E^1 and E^5; and

E^5 is selected from the group consisting of -OH and optionally-substituted carbocyclyl; and

neither R^1 nor R^2 forms a ring structure with E^5.

297. A compound or salt thereof according to claim 296, wherein:

A^1 is selected from the group consisting of -H, C_1-C_8-alkylcarbonyl, C_1-C_8-alkoxycarbonyl, carbocyclylcarbonyl, carbocyclyl-C_1-C_8-alkylcarbonyl,

heterocyclylcarbonyl, heterocyclyl-C_1-C_8-alkylcarbonyl, carbocyclyloxycarbonyl, carbocyclyl-C_1-C_8-alkoxycarbonyl, $N(R^3)(R^4)$-C_1-C_8-alkylcarbonyl, C_1-C_8-alkyl(thiocarbonyl), C_1-C_8-alkoxy(thiocarbonyl), carbocyclyl(thiocarbonyl), carbocyclyl-C_1-C_8-alkyl(thiocarbonyl), heterocyclyl(thiocarbonyl), heterocyclyl-C_1-C_8-alkyl(thiocarbonyl), carbocyclyloxy(thiocarbonyl), carbocyclyl-C_1-C_8-alkoxy(thiocarbonyl), and $N(R^3)(R^4)$-C_1-C_8-alkyl(thiocarbonyl); and

E^2 is selected from the group consisting of C_4-C_{20}-alkyl, cycloalkyl, C_1-C_{10}-alkyl-cycloalkyl, cycloalkyl-C_1-C_{10}-alkyl, and C_1-C_{10}-alkyl-cycloalkyl-C_1-C_{10}-alkyl, wherein the any member of such group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, C_1-C_6-alkyl, and halo-C_1-C_6-alkyl; and

E^5 is selected from the group consisting of -OH and carbocyclyl, wherein the carbocyclyl:

optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, keto, C_1-C_8-alkyl, halo-C_1-C_8-alkyl, C_1-C_8-alkoxy, halo-C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, halogen-substituted C_1-C_8-alkoxy-C_1-C_8-alkyl, $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_8-alkyl, and

optionally is substituted with two C_1-C_8-alkyl or halo-C_1-C_8-alkyl groups on the same atom that form a C_3-C_6-cycloalkyl or C_3-C_6-halocycloalkyl, and

R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_8-alkyl, and halo-C_1-C_8-alkyl; and

R^3 and R^4 are independently selected from the group consisting of -H, C_1-C_8-alkyl, C_1-C_8-alkoxycarbonyl, C_1-C_8-alkylcarbonyl, carbocyclyl-C_1-C_8-alkyl, and carbocyclyl-C_1-C_8-alkoxycarbonyl; and

R^5 and R^6 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl, wherein any member (except -H) of such group optionally is substituted with one or more halogen; and

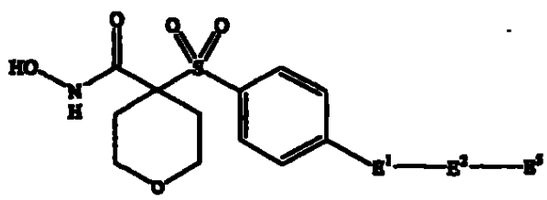
615

R^7 is selected from the group consisting of -H, C_1-C_8-alkyl, -O-R^8, -N(R^8)(R^9), carbocyclyl-C_1-C_8-alkyl, and heterocyclyl-C_1-C_8-alkyl, wherein the C_1-C_8-alkyl, carbocyclyl-C_1-C_8-alkyl, or heterocyclyl-C_1-C_8-alkyl optionally is substituted with one or more halogen; and

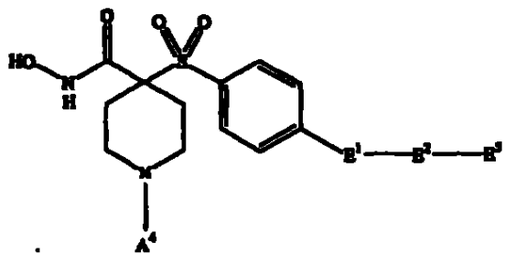
R^8 and R^9 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl, wherein any member (except -H) of such group optionally is substituted with one or more halogen.

298. A compound or salt thereof according to claim 297, wherein:

the compound corresponds in structure to a formula selected from the group consisting of:



(298-1) and



(298-2); and

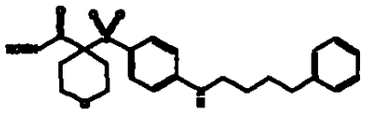
A^4 is selected from the group consisting of -H, alkyl, alkylcarbonyl, alkylcarbonylalkyl, alkylcarbonylalkylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkoxycarbonylalkylcarbonyl, alkylsulfonyl, alkyliminocarbonyl, alkenyl, alkynyl, alkoxyalkyl, alkylthioalkyl, alkylsulfonylalkyl, alkylsufoxidoalkyl, alkylthioalkenyl, alkylsulfoxidoalkenyl, alkylsulfonylalkenyl, carbocyclyl, carbocyclylalkyl, carbocyclylalkoxyalkyl, carbocyclylcarbonyl, carbocyclylsulfonyl, carbocyclyliminocarbonyl, carbocyclyloxycarbonyl, carbocylylthioalkyl, carbocylylsulfoxidoalkyl, carbocylylsulfonylalkyl, carbocyclylthioalkenyl,

carbocyclylsulfoxidoalkenyl, carbocyclylsulfonylalkenyl, heterocyclyl, heterocyclylalkyl, heterocyclylalkoxyalkyl, heterocyclylcarbonyl, heterocyclylthioalkyl, heterocyclylsulfoxidoalkyl, heterocyclylsulfonylalkyl, heterocyclylthioalkenyl, heterocyclylsulfoxidoalkenyl, heterocyclylsulfonylalkenyl, heterocyclylsulfonyl, heterocyclyliminocarbonyl, heterocyclylalkylcarbonyl, heterocyclylcarbonylalkylcarbonyl, heterocyclylsulfonyl, heterocyclylcarbonylalkyl, aminoalkylcarbonyl, aminocarbonyl, aminocarbonylalkylcarbonyl, aminosulfonyl, aminosulfonylalkyl, aminoalkyl, aminocarbonylalkyl, and aminoalkylsulfonyl, wherein:

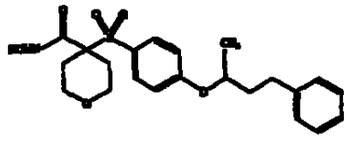
any member (except -H) of such group optionally is substituted.

299. A compound or salt thereof according to claim 298, wherein E^5 is phenyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, keto, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl.

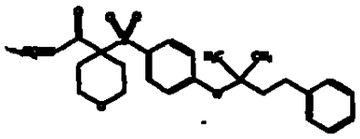
300. A compound or salt thereof according to claim 299, wherein the compound corresponds in structure to a formula selected from the group consisting of:



(300-1),



(300-2), and

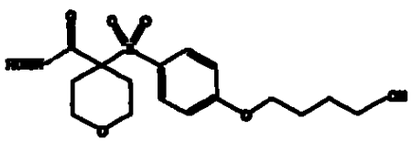


(300-3).

301. A compound or salt thereof according to claim 298, wherein E^5 is -OH.

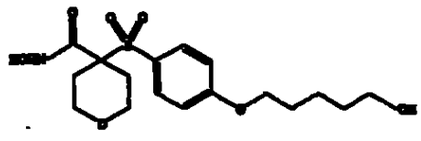
617

302. A compound or salt thereof according to claim 301, wherein the compound corresponds in structure to a formula selected from the group consisting of:



(302-1)

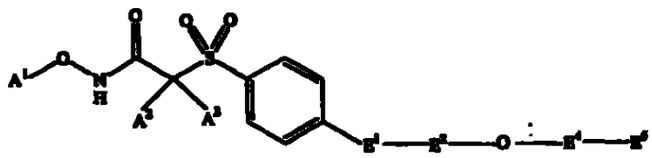
and



(302-2).

303. A compound or salt thereof, wherein:

the compound corresponds in structure to Formula 303-1:



(303-1); and

A^1 is selected from the group consisting of -H, alkylcarbonyl, alkoxycarbonyl, carbocyclylcarbonyl, carbocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclylalkylcarbonyl, carbocyclyloxycarbonyl, carbocyclylalkoxycarbonyl, aminoalkylcarbonyl, alkyl(thiocarbonyl), alkoxy(thiocarbonyl), carbocyclyl(thiocarbonyl), carbocyclylalkyl(thiocarbonyl), heterocyclyl(thiocarbonyl), heterocyclylalkyl(thiocarbonyl), carbocyclyloxy(thiocarbonyl), carbocyclylalkoxy(thiocarbonyl), and aminoalkyl(thiocarbonyl), wherein any member (except -H) of such group optionally is substituted; and

A^2 and A^3, together with the carbon atom to which they are both attached, form an optionally-substituted heterocyclyl containing from 5 to 8 ring members; and

E^1 is selected from the group consisting of $-S(O)_2-$, -S(O)-, $-N(R^1)-$, $-C(O)-N(R^1)-$, $-N(R^1)-C(O)-$, and $-C(R^1)(R^2)-$; and

E^2 is selected from the group consisting of alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, and alkylcycloalkylalkyl, wherein any member of such group optionally is substituted; and

E^4 is selected from the group consisting of a bond, alkyl, and alkenyl, wherein the alkyl or alkenyl optionally is substituted; and

618

E^5 is selected from the group consisting of alkyl, alkenyl, alkynyl, alkoxy, alkoxyalkyl, carbocyclyl, and heterocyclyl, wherein any member of such group optionally is substituted; and

R^1 and R^2 are independently selected from the group consisting of -H and alkyl, wherein the alkyl optionally is substituted; and

neither R^1 nor R^2 forms a ring structure with E^2, E^4, or E^5

304. A compound or salt thereof according to claim 303, wherein:

A^1 is selected from the group consisting of -H, C_1-C_8-alkylcarbonyl, C_1-C_8-alkoxycarbonyl, carbocyclylcarbonyl, carbocyclyl-C_1-C_8-alkylcarbonyl, heterocyclylcarbonyl, heterocyclyl-C_1-C_8-alkylcarbonyl, carbocyclyloxycarbonyl, carbocyclyl-C_1-C_8-alkoxycarbonyl, $N(R^3)(R^4)$-C_1-C_8-alkylcarbonyl, C_1-C_8-alkyl(thiocarbonyl), C_1-C_8-alkoxy(thiocarbonyl), carbocyclyl(thiocarbonyl), carbocyclyl-C_1-C_8-alkyl(thiocarbonyl), heterocyclyl(thiocarbonyl), heterocyclyl-C_1-C_8-alkyl(thiocarbonyl), carbocyclyloxy(thiocarbonyl), carbocyclyl-C_1-C_8-alkoxy(thiocarbonyl), and $N(R^3)(R^4)$-C_1-C_8-alkyl(thiocarbonyl); and

E^2 is selected from the group consisting of C_1-C_{20}-alkyl, cycloalkyl, C_1-C_{10}-alkylcycloalkyl, cycloalkyl-C_1-C_{10}-alkyl, and C_1-C_{10}-alkylcycloalkyl-C_1-C_{10}-alkyl, wherein any member of such group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, C_1-C_6-alkyl, C_1-C_6-halo-alkyl; and

E^4 is selected from the group consisting of a bond, C_1-C_{20}-alkyl, halo-C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, and halo-C_2-C_{20}-alkenyl; and

E^5 is selected from the group consisting of C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, C_1-C_{20}-alkoxy, C_1-C_{20}-alkoxy-C_1-C_{20}-alkyl, carbocyclyl, and heterocyclyl, wherein:

the C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, C_1-C_{20}-alkoxy, or C_1-C_{20}-alkoxy-C_1-C_{20}-alkyl optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, and -CN, and

the carbocyclyl or heterocyclyl optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH,

$-NO_2$, -CN, keto, C_1-C_8-alkyl, halo-C_1-C_8-alkyl, C_1-C_8-alkoxy, halo-C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, halogen-substituted C_1-C_8-alkoxy-C_1-C_8-alkyl, $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_8-alkyl, and halogen-substituted carbocyclyl-C_1-C_8-alkyl; and

R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_8-alkyl, and halo-C_1-C_8-alkyl; and

R^3 and R^4 are independently selected from the group consisting of -H, C_1-C_8-alkyl, C_1-C_8-alkoxycarbonyl, C_1-C_8-alkylcarbonyl, carbocyclyl-C_1-C_8-alkyl, and carbocyclyl-C_1-C_8-alkoxycarbonyl; and

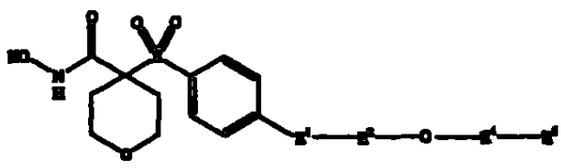
R^5 and R^6 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl, wherein any member (except -H) of such group optionally is substituted with one or more halogen; and

R^7 is selected from the group consisting of -H, C_1-C_6-alkyl, $-O-R^8$, $-N(R^8)(R^9)$, carbocyclyl-C_1-C_8-alkyl, and heterocyclyl-C_1-C_8-alkyl, wherein the C_1-C_8-alkyl, carbocyclyl-C_1-C_8-alkyl, or heterocyclyl-C_1-C_8-alkyl optionally is substituted with one or more halogen; and

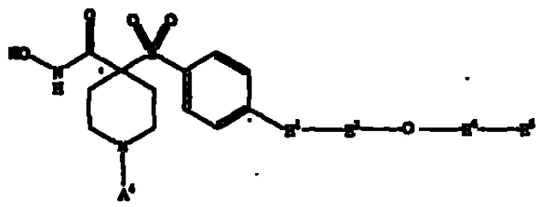
R^8 and R^9 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl, wherein any member (except -H) of such group optionally is substituted with one or more halogen.

305. A compound or salt thereof according to claim 304, wherein:

the compound corresponds in structure to a formula selected from the group consisting of:



(305-1) and



(305-2); and

A^4 is selected from the group consisting of -H, alkyl, alkylcarbonyl, alkylcarbonylalkyl, alkylcarbonylalkylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkoxycarbonylalkylcarbonyl, alkylsulfonyl, alkyliminocarbonyl, alkenyl, alkynyl, alkoxyalkyl, alkylthioalkyl, alkylsulfonylalkyl, alkylsulfoxidoalkyl, alkylthioalkenyl, alkylsulfoxidoalkenyl, alkylsulfonylalkenyl, carbocyclyl, carbocyclylalkyl, carbocyclylalkoxyalkyl, carbocyclylcarbonyl, carbocyclylsulfonyl, carbocyclyliminocarbonyl, carbocyclyloxycarbonyl, carbocylylthioalkyl, carbocylylsulfoxidoalkyl, carbocylylsulfonylalkyl, carbocyclylthioalkenyl, carbocyclylsulfoxidoalkenyl, carbocyclylsulfonylalkenyl, heterocyclyl, heterocyclylalkyl, heterocyclylalkoxyalkyl, heterocyclylcarbonyl, heterocyclylthioalkyl, heterocyclylsulfoxidoalkyl, heterocyclylsulfonylalkyl, heterocyclylthioalkenyl, heterocyclylsulfoxidoalkenyl, heterocyclylsulfonylalkenyl, heterocyclylsulfonyl, heterocyclyliminocarbonyl, heterocyclylalkylcarbonyl, heterocyclylcarbonylalkylcarbonyl, heterocyclylsulfonyl, heterocyclylcarbonylalkyl, aminoalkylcarbonyl, aminocarbonyl, aminocarbonylalkylcarbonyl, aminosulfonyl, aminosulfonylalkyl, aminoalkyl, aminocarbonylalkyl, and aminoalkylsulfonyl, wherein:

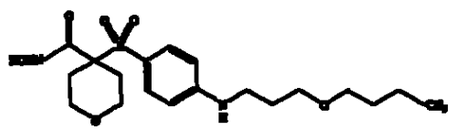
any member (except -H) of such group optionally is substituted.

306. A compound or salt thereof according to claim 305, wherein E^5 is selected from the group consisting of C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, C_1-C_8-alkoxy, and C_1-C_8-alkoxy-C_1-C_8-alkyl, wherein:

the C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, C_1-C_8-alkoxy, or C_1-C_8-alkoxy-C_1-C_8-alkyl optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, and -CN.

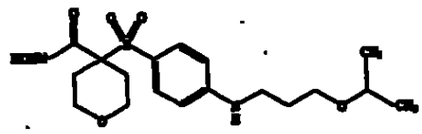
621

307. A compound or salt thereof according to claim 306, wherein the compound corresponds in structure to a formula selected from the group consisting of:



(307-1)

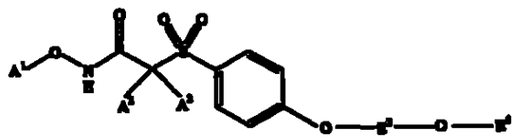
and



(307-2).

308. A compound or salt thereof, wherein:

the compound corresponds in structure to Formula 308-1:



(308-1); and

A^1 is selected from the group consisting of -H, alkylcarbonyl, alkoxycarbonyl, carbocyclylcarbonyl, carbocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclylalkylcarbonyl, carbocyclyloxycarbonyl, carbocyclylalkoxycarbonyl, aminoalkylcarbonyl, alkyl(thiocarbonyl), alkoxy(thiocarbonyl), carbocyclyl(thiocarbonyl), carbocyclylalkyl(thiocarbonyl), heterocyclyl(thiocarbonyl), heterocyclylalkyl(thiocarbonyl), carbocyclyloxy(thiocarbonyl), carbocyclylalkoxy(thiocarbonyl), and aminoalkyl(thiocarbonyl), wherein any member (except -H) of such group optionally is substituted; and

A^2 and A^3, together with the carbon atom to which they are both attached, form an optionally-substituted heterocyclyl containing from 5 to 8 ring members; and

E^2 is selected from the group consisting of alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, and alkylcycloalkylalkyl, wherein any member of such group optionally is substituted; and

E^2 comprises at least 3 carbon atoms; and

E^5 is selected from the group consisting of -H, alkyl, alkenyl, alkynyl, alkoxyalkyl, carbocyclyl, carbocyclylalkoxyalkyl, heterocyclyl, heterocyclylalkyl, and heterocyclylalkoxyalkyl, wherein:

622

the alkyl, alkenyl, alkynyl, or alkoxyalkyl optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, and -CN, and

the carbocyclyl, carbocyclylalkoxyalkyl, heterocyclyl, heterocyclylalkyl, or heterocyclylalkoxyalkyl optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, alkyl, haloalkyl, alkoxy, haloalkoxy, alkoxyalkyl, halogen-substituted alkoxyalkyl, $-N(R^5)(R^4)$, $-C(O)(R^5)$, $-S-R^3$, $-S(O)_2-R^3$, carbocyclyl, halocarbocyclyl, carbocyclylalkyl, and halogen-substituted carbocyclylalkyl; and

R^1 and R^2 are independently selected from the group consisting of -H, alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, and heterocyclylalkyl, wherein any member (except -H) of such group optionally is substituted with one or more halogen; and

R^3 is selected from the group consisting of -H, alkyl, $-O-R^4$, $-N(R^4)(R^5)$, carbocyclylalkyl, and heterocyclylalkyl, wherein the alkyl, carbocyclylalkyl, or heterocyclylalkyl optionally is substituted with one or more halogen; and

R^4 and R^5 are independently selected from the group consisting of -H, alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, and heterocyclylalkyl, wherein any member (except -H) of such group optionally is substituted with one or more halogen.

309. A compound or salt thereof according to claim 308, wherein:

A^1 is selected from the group consisting of -H, C_1-C_8-alkylcarbonyl, C_1-C_8-alkoxycarbonyl, carbocyclylcarbonyl, carbocyclyl-C_1-C_8-alkylcarbonyl, heterocyclylcarbonyl, heterocyclyl-C_1-C_8-alkylcarbonyl, carbocyclyloxycarbonyl, carbocyclyl-C_1-C_8-alkoxycarbonyl, $N(R^6)(R^7)$-C_1-C_8-alkylcarbonyl, C_1-C_8-alkyl(thiocarbonyl), C_1-C_8-alkoxy(thiocarbonyl), carbocyclyl(thiocarbonyl), carbocyclyl-C_1-C_8-alkyl(thiocarbonyl), heterocyclyl(thiocarbonyl), heterocyclyl-C_1-C_8-alkyl(thiocarbonyl), carbocyclyloxy(thiocarbonyl), carbocyclyl-C_1-C_8-alkoxy(thiocarbonyl), and $N(R^6)(R^7)$-C_1-C_8-alkyl(thiocarbonyl); and

E^2 is selected from the group consisting of C_3-C_{20}-alkyl, cycloalkyl, C_1-C_{10}-alkylcycloalkyl, cycloalkyl-C_1-C_{10}-alkyl, and C_1-C_{10}-alkylcycloalkyl-C_1-C_{10}-alkyl, wherein any member of such group optionally is substituted with one or more substituents

independently selected from the group consisting of halogen, C_1-C_6-alkyl, and halo-C_1-C_6-alkyl; and

E^5 is selected from the group consisting of -H, C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, C_1-C_{20}-alkoxy-C_1-C_{20}-alkyl, carbocyclyl, carbocyclyl-C_1-C_{10}-alkoxy-C_1-C_{10}-alkyl, heterocyclyl, heterocyclyl-C_1-C_{10}-alkyl, and heterocyclyl-C_1-C_{10}-alkoxy-C_1-C_{10}-alkyl, wherein:

the C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, or C_1-C_{20}-alkoxy-C_1-C_{20}-alkyl optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, and -CN, and

the carbocyclyl, carbocyclyl-C_1-C_{10}-alkoxy-C_1-C_{10}-alkyl, heterocyclyl, heterocyclyl-C_1-C_{10}-alkyl, or heterocyclyl-C_1-C_{10}-alkoxy-C_1-C_{10}-alkyl optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, keto, C_1-C_8-alkyl, halo-C_1-C_8-alkyl, C_1-C_8-alkoxy, halo-C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, halogen-substituted C_1-C_8-alkoxy-C_1-C_8-alkyl, -$N(R^3)(R^4)$, -$C(O)(R^5)$, -S-R^3, -$S(O)_2$-R^3, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_8-alkyl, and halogen-substituted carbocyclyl-C_1-C_8-alkyl; and

R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl, wherein any member (except -H) of such group optionally is substituted with one or more halogen; and

R^3 is selected from the group consisting of -H, C_1-C_8-alkyl, -O-R^4, -$N(R^4)(R^5)$, carbocyclyl-C_1-C_8-alkyl, and heterocyclyl-C_1-C_8-alkyl, wherein the C_1-C_8-alkyl, carbocyclyl-C_1-C_8-alkyl, or heterocyclyl-C_1-C_8-alkyl optionally is substituted with one or more halogen; and

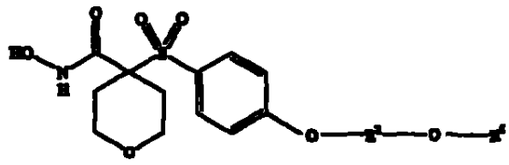
R^4 and R^5 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl, wherein any member (except -H) of such group optionally is substituted with one or more halogen; and

624

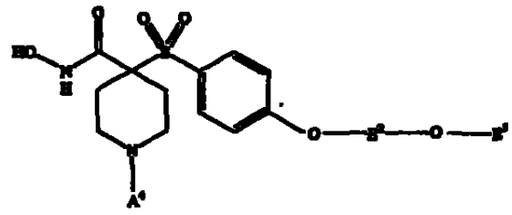
R^6 and R^7 are independently selected from the group consisting of -H, C_1-C_8-alkyl, C_1-C_8-alkoxycarbonyl, C_1-C_8-alkylcarbonyl, carbocyclyl-C_1-C_8-alkyl, and carbocyclyl-C_1-C_8-alkoxycarbonyl.

310. A compound or salt thereof according to claim 309, wherein:

the compound corresponds in structure to a formula selected from the group consisting of:



(310-1) and



(310-2); and

A^4 is selected from the group consisting of -H, alkyl, alkylcarbonyl, alkylcarbonylalkyl, alkylcarbonylalkylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkoxycarbonylalkylcarbonyl, alkylsulfonyl, alkyliminocarbonyl, alkenyl, alkynyl, alkoxyalkyl, alkylthioalkyl, alkylsulfonylalkyl, alkylsulfoxidoalkyl, alkylthioalkenyl, alkylsulfoxidoalkenyl, alkylsulfonylalkenyl, carbocyclyl, carbocyclylalkyl, carbocyclylalkoxyalkyl, carbocyclylcarbonyl, carbocyclylsulfonyl, carbocyclyliminocarbonyl, carbocyclyloxycarbonyl, carbocylylthioalkyl, carbocylylsulfoxidoalkyl, carbocylylsulfonylalkyl, carbocyclylthioalkenyl, carbocyclylsulfoxidoalkenyl, carbocyclylsulfonylalkenyl, heterocyclyl, heterocyclylalkyl, heterocyclylalkoxyalkyl, heterocyclylcarbonyl, heterocyclylthioalkyl, heterocyclylsulfoxidoalkyl, heterocyclylsulfonylalkyl, heterocylylthioalkenyl, heterocyclylsulfoxidoalkenyl, heterocyclylsulfonylalkenyl, heterocyclylsulfonyl, heterocyclyliminocarbonyl, heterocyclylalkylcarbonyl, heterocyclylcarbonylalkylcarbonyl, heterocyclylsulfonyl, heterocyclylcarbonylalkyl, aminoalkylcarbonyl, aminocarbonyl,

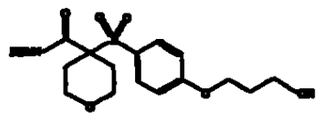
aminocarbonylalkylcarbonyl, aminosulfonyl, aminosulfonylalkyl, aminoalkyl, aminocarbonylalkyl, and aminoalkylsulfonyl, wherein:

any member (except -H) of such group optionally is substituted.

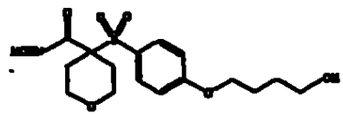
311. A compound or salt thereof according to claim 310, wherein E^5 is selected from the group consisting of -H, C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, and C_1-C_8-alkoxy-C_1-C_8-alkyl, wherein:

the C_1-C_8-alkyl, C_2-C_8-alkenyl, C_2-C_8-alkynyl, or C_1-C_8-alkoxy-C_1-C_8-alkyl optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, and -CN.

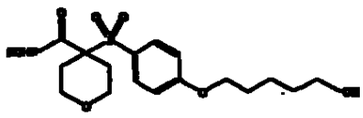
312. A compound or salt thereof according to claim 311, wherein the compound corresponds in structure to a formula selected from the group consisting of:



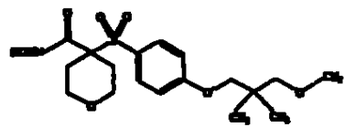
(312-1),



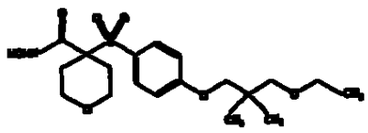
(312-2),



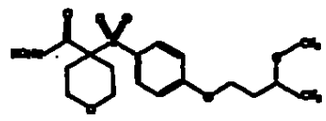
(312-3),



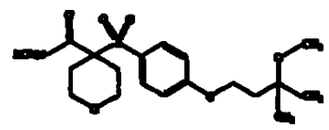
(312-4),



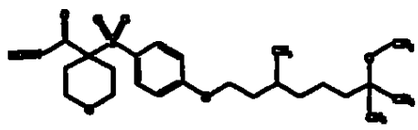
(312-5),



(312-6),



(312-7), and



(312-8).

313. A compound or salt thereof according to claim 310, wherein E^5 is selected from the group consisting of carbocyclyl, carbocyclyl-C_1-C_8-alkoxy-C_1-C_8-alkyl,

heterocyclyl, heterocyclyl-C_1-C_6-alkyl, and heterocyclyl-C_1-C_6-alkoxy-C_1-C_6-alkyl, wherein:

the carbocyclyl, carbocyclyl-C_1-C_6-alkoxy-C_1-C_6-alkyl, heterocyclyl, heterocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkoxy-C_1-C_6-alkyl optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, keto, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^3)(R^4)$, -$C(O)(R^5)$, -S-R^3, -$S(O)_2$-R^3, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl.

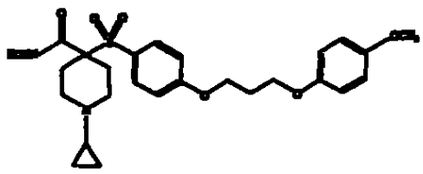
314. A compound or salt thereof according to claim 313, wherein E^5 is carbocyclyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^3)(R^4)$, -$C(O)(R^5)$, -S-R^3, -$S(O)_2$-R^3, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl.

315. A compound or salt thereof according to claim 314, wherein E^2 is C_3-C_5-alkyl optionally substituted with one or more halogen.

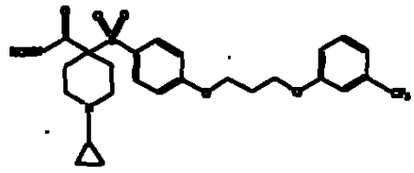
316. A compound or salt thereof according to claim 315, wherein E^5 is phenyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^3)(R^4)$, -$C(O)(R^5)$, -S-R^3, -$S(O)_2$-R^3, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl.

627

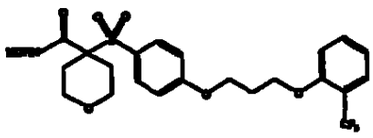
317. A compound or salt thereof according to claim 316, wherein the compound corresponds in structure to a formula selected from the group consisting of:



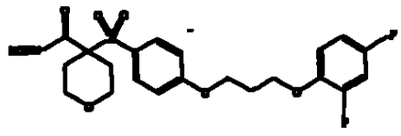
(317-1),



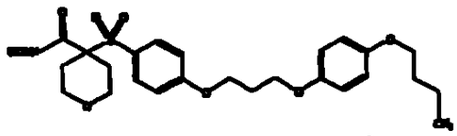
(317-2),



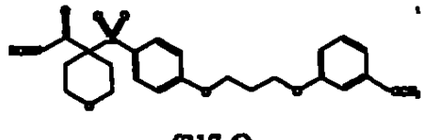
(317-3),



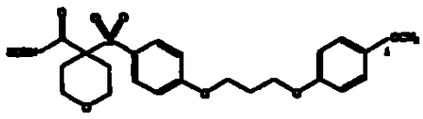
(317-4),



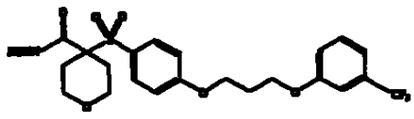
(317-5),



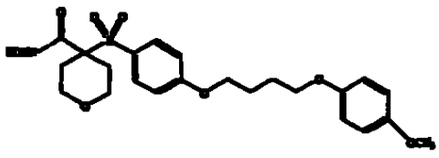
(317-6),



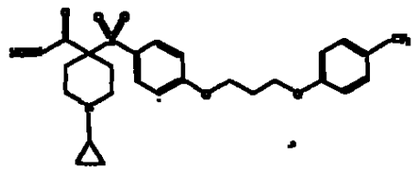
(317-7),



(317-8),



(317-9), and

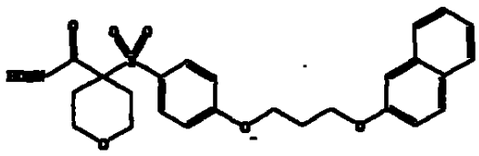


(317-10).

318. A compound or salt thereof according to claim 315, wherein E^5 is naphthalenyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^3)(R^4)$, -$C(O)(R^5)$, -S-R^3, -$S(O)_2$-R^3, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl.

628

319. A compound or salt thereof according to claim 318, wherein the compound corresponds in structure to the following formula:

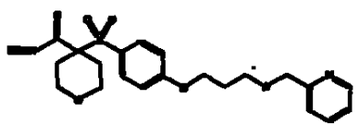


(319-1).

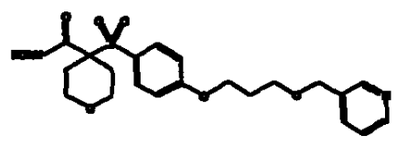
320. A compound or salt thereof according to claim 310, wherein R^5 is selected from the group consisting of heterocyclyl and heterocyclyl-C_1-C_6-alkyl, wherein:

the heterocyclyl and heterocyclyl-C_1-C_6-alkyl optionally are substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, keto, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^3)(R^4)$, -$C(O)(R^5)$, -S-R^3, -$S(O)_2$-R^3, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl.

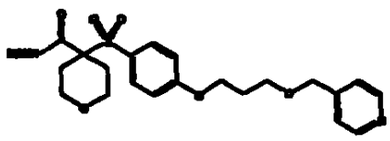
321. A compound or salt thereof according to claim 320, wherein the compound corresponds in structure to a formula selected from the group consisting of:



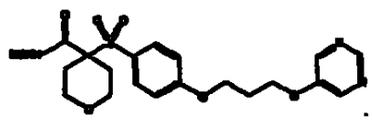
(321-1),



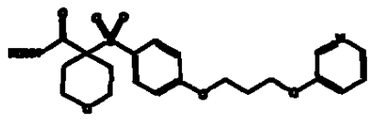
(321-2),



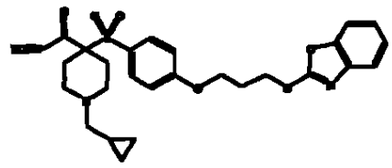
(321-3),



(321-4),



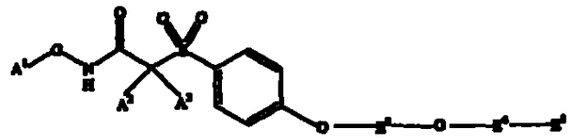
(321-5), and



(321-6).

322. A compound or salt thereof, wherein:

the compound corresponds in structure to Formula 322-1:



(322-1); and

A^1 is selected from the group consisting of -H, alkylcarbonyl, alkoxycarbonyl, carbocyclylcarbonyl, carbocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclylalkylcarbonyl, carbocyclyloxycarbonyl, carbocyclylalkoxycarbonyl, aminoalkylcarbonyl, alkyl(thiocarbonyl), alkoxy(thiocarbonyl), carbocyclyl(thiocarbonyl), carbocyclylalkyl(thiocarbonyl), heterocyclyl(thiocarbonyl), heterocyclylalkyl(thiocarbonyl), carbocyclyloxy(thiocarbonyl), carbocyclylalkoxy(thiocarbonyl), and aminoalkyl(thiocarbonyl), wherein any member (except -H) of such group optionally is substituted; and

A^2 and A^3, together with the carbon atom to which they are both attached, form an optionally-substituted heterocyclyl containing from 5 to 8 ring members; and

E^2 is selected from the group consisting of alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, and alkylcycloalkylalkyl, wherein any member of such group optionally is substituted; and

E^4 is selected from the group consisting of a bond, alkyl, and alkenyl, wherein the alkyl or alkenyl optionally is substituted; and

E^5 is selected from the group consisting of:

optionally-substituted alkenyl, and

optionally-substituted alkynyl, and

optionally-substituted alkoxy, and

optionally-substituted alkoxyalkyl, and

single-ring carbocyclyl substituted with one or more substituents independently selected from the group consisting of -OH, -NO_2, -CN, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbocyclyl, halocarbocyclyl, carbocyclylalkyl, halogen-substituted carbocyclylalkyl, heterocyclyl, haloheterocyclyl, heterocyclylalkyl, and halogen-substituted heterocyclylalkyl, and

single-ring carbocyclyl having multiple substitutions, and

optionally-substituted fused-ring carbocyclyl, and

optionally-substituted heterocyclyl; and

R^1 and R^2 are independently selected from the group consisting of -H, alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, and heterocyclylalkyl, wherein any member (except -H) of such group optionally is substituted with one or more halogen; and

R^3 is selected from the group consisting of -H, alkyl, -O-R^4, -$N(R^4)(R^5)$, carbocyclylalkyl, and heterocyclylalkyl, wherein the alkyl, carbocyclylalkyl, or heterocyclylalkyl optionally is substituted with one or more halogen; and

R^4 and R^5 are independently selected from the group consisting of -H, alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, and heterocyclylalkyl, wherein any member (except -H) of such group optionally is substituted with one or more halogen; and

an atom in E^2 optionally is bound to an atom in R^5 to form a ring.

323. A compound or salt thereof according to claim 322, wherein:

A^1 is selected from the group consisting of -H, C_1-C_8-alkylcarbonyl, C_1-C_8-alkoxycarbonyl, carbocyclylcarbonyl, carbocyclyl-C_1-C_8-alkylcarbonyl, heterocyclylcarbonyl, heterocyclyl-C_1-C_8-alkylcarbonyl, carbocyclyloxycarbonyl, carbocyclyl-C_1-C_8-alkoxycarbonyl, $N(R^6)(R^7)$-C_1-C_8-alkylcarbonyl, C_1-C_8-alkyl(thiocarbonyl), C_1-C_8-alkoxy(thiocarbonyl), carbocyclyl(thiocarbonyl), carbocyclyl-C_1-C_8-alkyl(thiocarbonyl), heterocyclyl(thiocarbonyl), heterocyclyl-C_1-C_8-alkyl(thiocarbonyl), carbocyclyloxy(thiocarbonyl), carbocyclyl-C_1-C_8-alkoxy(thiocarbonyl), and $N(R^6)(R^7)$-C_1-C_8-alkyl(thiocarbonyl); and

E^2 is selected from the group consisting of C_1-C_{20}-alkyl, cycloalkyl, C_1-C_{10}-alkylcycloalkyl, cycloalkyl-C_1-C_{10}-alkyl, and C_1-C_{10}-alkylcycloalkyl-C_1-C_{10}-alkyl,

631

wherein any member of such group optionally is substituted with one or more substituents selected from the group consisting of halogen, C_1-C_6-alkyl, halo-C_1-C_6-alkyl; and

E^4 is selected from the group consisting of a bond, C_1-C_{20}-alkyl, halo-C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, and halo-C_2-C_{20}-alkenyl; and

E^5 is selected from the group consisting of C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, C_1-C_{20}-alkoxy, C_1-C_{20}-alkoxy-C_1-C_{20}-alkyl, heterocyclyl, single-ring carbocyclyl, and fused-ring carbocyclyl, wherein:

the C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, C_1-C_{20}-alkoxy, or C_1-C_{20}-alkoxy-C_1-C_{20}-alkyl optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, and -CN, and

the heterocyclyl or fused-ring carbocyclyl optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, halogen-substituted carbocyclyl-C_1-C_6-alkyl, heterocyclyl, haloheterocyclyl, heterocyclyl-C_1-C_6-alkyl, and halogen-substituted heterocyclyl-C_1-C_6-alkyl, and

the single-ring carbocyclyl is either:

substituted with one or more substituents independently selected from the group consisting of -OH, -NO_2, -CN, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, halogen-substituted carbocyclyl-C_1-C_6-alkyl, heterocyclyl, haloheterocyclyl, heterocyclyl-C_1-C_6-alkyl, and halogen-substituted heterocyclyl-C_1-C_6-alkyl, or

substituted with 2 or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5,

632

carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_8-alkyl, halogen-substituted carbocyclyl-C_1-C_8-alkyl, heterocyclyl, haloheterocyclyl, heterocyclyl-C_1-C_8-alkyl, and halogen-substituted heterocyclyl-C_1-C_8-alkyl; and

R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl, wherein any member (except -H) of such group optionally is substituted with one or more halogen; and

R^3 is selected from the group consisting of -H, C_1-C_8-alkyl, -O-R^4, -N(R^4)(R^5), carbocyclyl-C_1-C_8-alkyl, and heterocyclyl-C_1-C_8-alkyl, wherein the C_1-C_8-alkyl, carbocyclyl-C_1-C_8-alkyl, or heterocyclyl-C_1-C_8-alkyl optionally is substituted with one or more halogen; and

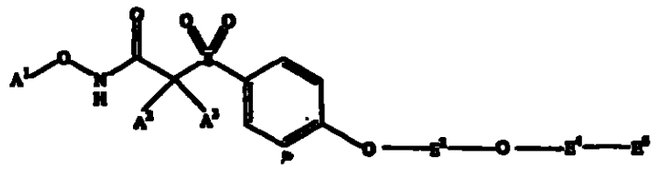
R^4 and R^5 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl, wherein any member (except -H) of such group optionally is substituted with one or more halogen; and

R^6 and R^7 are independently selected from the group consisting of -H, C_1-C_8-alkyl, C_1-C_8-alkoxycarbonyl, C_1-C_8-alkylcarbonyl, carbocyclyl-C_1-C_8-alkyl, and carbocyclyl-C_1-C_8-alkoxycarbonyl; and

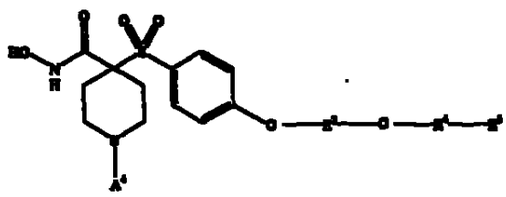
an atom in E^2 optionally is bound to an atom in E^5 to form a ring.

324. A compound or salt thereof according to claim 323, wherein:

the compound corresponds in structure to a formula selected from the group consisting of:



(324-1) and



(324-2); and

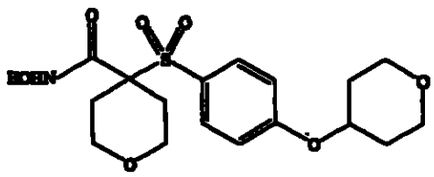
A^4 is selected from the group consisting of -H, alkyl, alkylcarbonyl, alkylcarbonylalkyl, alkylcarbonylalkylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkoxycarbonylalkylcarbonyl, alkylsulfonyl, alkyliminocarbonyl, alkenyl, alkynyl, alkoxyalkyl, alkylthioalkyl, alkylsulfonylalkyl, alkylsuloxidoalkyl, alkylthioalkenyl, alkylsulfoxidoalkenyl, alkylsulfonylalkenyl, carbocyclyl, carbocyclylalkyl, carbocyclylalkoxyalkyl, carbocyclylcarbonyl, carbocyclylsulfonyl, carbocyclyliminocarbonyl, carbocyclyloxycarbonyl, carbocylylthioalkyl, carbocylylsulfoxidoalkyl, carbocylylsulfonylalkyl, carbocyclylthioalkenyl, carbocyclylsulfoxidoalkenyl, carbocyclylsulfonylalkenyl, heterocyclyl, heterocyclylalkyl, heterocyclylalkoxyalkyl, heterocyclylcarbonyl, heterocyclylthioalkyl, heterocyclylsulfoxidoalkyl, heterocyclylsulfonylalkyl, heterocyclylthioalkenyl, heterocyclylsulfoxidoalkenyl, heterocyclylsulfonylalkenyl, heterocyclylsulfonyl, heterocyclyliminocarbonyl, heterocyclylalkylcarbonyl, heterocyclylcarbonylalkylcarbonyl, heterocyclylsulfonyl, heterocyclylcarbonylalkyl, aminoalkylcarbonyl, aminocarbonyl, aminocarbonylalkylcarbonyl, aminosulfonyl, aminosulfonylalkyl, aminoalkyl, aminocarbonylalkyl, and aminoalkylsulfonyl, wherein:

any member (except -H) of such group optionally is substituted.

325. A compound or salt thereof according to claim 324, wherein an atom of E^2 is bound to an atom of E^5 to form a ring.

634

326. A compound or salt thereof according to claim 325, wherein the compound corresponds in structure to the following formula:



(326-1).

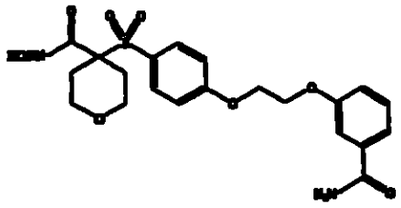
327. A compound or salt thereof according to claim 324, wherein:

E^5 is phenyl substituted with one or more substituents independently selected from the group consisting of -OH, $-NO_2$, -CN, $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, halogen-substituted carbocyclyl-C_1-C_6-alkyl, heterocyclyl, haloheterocyclyl, heterocyclyl-C_1-C_6-alkyl, and halogen-substituted heterocyclyl-C_1-C_6-alkyl; and

E^2 is not bound to an atom of E^5 to form a ring.

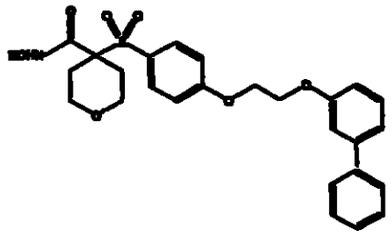
328. A compound or salt thereof according to claim 327, wherein E^4 is a bond.

329. A compound or salt thereof according to claim 328, wherein the compound corresponds in structure to a formula selected from the group consisting of:



(329-1)

and



(329-2).

330. A compound or salt thereof according to claim 324, wherein:

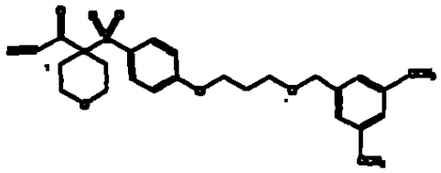
E^5 is phenyl substituted with 2 or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbocyclyl,

halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, halogen-substituted carbocyclyl-C_1-C_6-alkyl, heterocyclyl, haloheterocyclyl, heterocyclyl-C_1-C_6-alkyl, and halogen-substituted heterocyclyl-C_1-C_6-alkyl; and

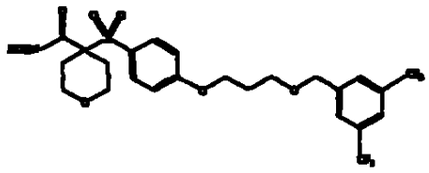
E^2 is not bound to an atom of E^5 to form a ring.

331. A compound or salt thereof according to claim 330, wherein E^4 is methyl.

332. A compound or salt thereof according to claim 331, wherein the compound corresponds in structure to a formula selected from the group consisting of:



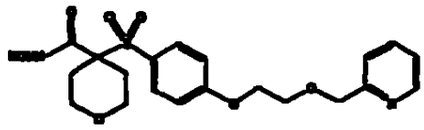
and

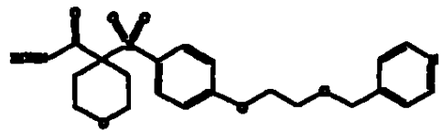


(332-1) (332-2).

333. A compound or salt thereof according to claim 324, wherein E^5 is heterocyclyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, halogen-substituted carbocyclyl-C_1-C_6-alkyl, heterocyclyl, haloheterocyclyl, heterocyclyl-C_1-C_6-alkyl, and halogen-substituted heterocyclyl-C_1-C_6-alkyl.

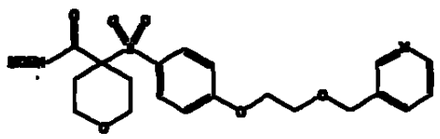
334. A compound or salt thereof according to claim 333, wherein the compound corresponds in structure to a formula selected from the group consisting of:



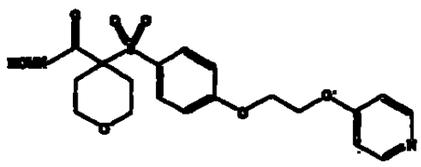


(334-1), (334-2),

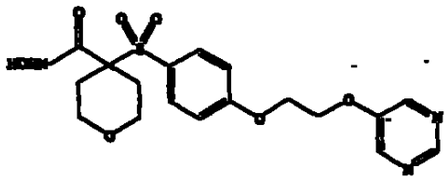
636



(334-3),



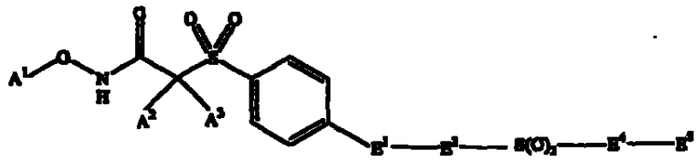
(334-4), and



(334-5).

335. A compound or salt thereof, wherein:

the compound corresponds in structure to Formula 335-1:



(335-1); and

A^1 is selected from the group consisting of -H, alkylcarbonyl, alkoxycarbonyl, carbocyclylcarbonyl, carbocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclylalkylcarbonyl, carbocyclyloxycarbonyl, carbocyclylalkoxycarbonyl, aminoalkylcarbonyl, alkyl(thiocarbonyl), alkoxy(thiocarbonyl), carbocyclyl(thiocarbonyl), carbocyclylalkyl(thiocarbonyl), heterocyclyl(thiocarbonyl), heterocyclylalkyl(thiocarbonyl), carbocyclyloxy(thiocarbonyl), carbocyclylalkoxy(thiocarbonyl), and aminoalkyl(thiocarbonyl), wherein any member (except -H) of such group optionally is substituted; and

A^2 and A^3, together with the carbon atom to which they are both attached, form an optionally-substituted heterocyclyl containing from 5 to 8 ring members; and

E^1 is selected from the group consisting of $-S(O)_2-$, $-S(O)-$, $-N(R^1)-$, $-C(O)-N(R^1)-$, $-N(R^1)-C(O)-$, and $-C(R^1)(R^2)-$; and

637

E^2 is selected from the group consisting of alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, and alkylcycloalkylalkyl, wherein any member of such group optionally is substituted; and

E^4 is selected from the group consisting of a bond, alkyl, and alkenyl, wherein the alkyl or alkenyl optionally is substituted; and

E^5 is selected from the group consisting of alkyl, alkenyl, alkynyl, alkoxy, alkoxyalkyl, carbocyclyl, and heterocyclyl, wherein any member of such group optionally is substituted; and

R^1 and R^2 are independently selected from the group consisting of -H and alkyl, wherein the alkyl optionally is substituted; and

neither R^1 nor R^2 forms a ring structure with E^2, E^4, or E^5

336. A compound or salt thereof according to claim 335, wherein:

A^1 is selected from the group consisting of -H, C_1-C_8-alkylcarbonyl, C_1-C_8-alkoxycarbonyl, carbocyclylcarbonyl, carbocyclyl-C_1-C_8-alkylcarbonyl, heterocyclylcarbonyl, heterocyclyl-C_1-C_8-alkylcarbonyl, carbocyclyloxycarbonyl, carbocyclyl-C_1-C_8-alkoxycarbonyl, $N(R^3)(R^4)$-C_1-C_8-alkylcarbonyl, C_1-C_8-alkyl(thiocarbonyl), C_1-C_8-alkoxy(thiocarbonyl), carbocyclyl(thiocarbonyl), carbocyclyl-C_1-C_8-alkyl(thiocarbonyl), heterocyclyl(thiocarbonyl), heterocyclyl-C_1-C_8-alkyl(thiocarbonyl), carbocyclyloxy(thiocarbonyl), carbocyclyl-C_1-C_8-alkoxy(thiocarbonyl), and $N(R^3)(R^4)$-C_1-C_8-alkyl(thiocarbonyl); and

E^2 is selected from the group consisting of C_1-C_{20}-alkyl, cycloalkyl, C_1-C_{10}-alkylcycloalkyl, cycloalkyl-C_1-C_{10}-alkyl, and C_1-C_{10}-alkylcycloalkyl-C_1-C_{10}-alkyl, wherein any member of such group optionally is substituted with one or more substituents selected from the group consisting of halogen, C_1-C_6-alkyl, and halo-C_1-C_6-alkyl; and

E^4 is selected from the group consisting of a bond, C_1-C_{20}-alkyl, halo-C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, and halo-C_2-C_{20}-alkenyl; and

E^5 is selected from the group consisting of C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, C_1-C_{20}-alkoxy, C_1-C_{20}-alkoxy-C_1-C_{20}-alkyl, carbocyclyl, and heterocyclyl, wherein:

the C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, C_1-C_{20}-alkoxy, or C_1-C_{20}-alkoxy-C_1-C_{20}-alkyl optionally is substituted with one or more substituents

638

independently selected from the group consisting of halogen, -OH, $-NO_2$, and -CN, and

the carbocyclyl or heterocyclyl optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_8-alkyl, halo-C_1-C_8-alkyl, C_1-C_8-alkoxy, halo-C_1-C_8-alkoxy, $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_8-alkyl, and halogen-substituted carbocyclyl-C_1-C_8-alkyl; and

R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_8-alkyl, and halo-C_1-C_8-alkyl; and

R^3 and R^4 are independently selected from the group consisting of -H, C_1-C_8-alkyl, C_1-C_8-alkoxycarbonyl, C_1-C_8-alkylcarbonyl, carbocyclyl-C_1-C_8-alkyl, and carbocyclyl-C_1-C_8-alkoxycarbonyl; and

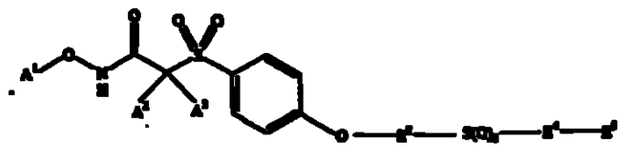
R^5 and R^6 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl, wherein any member (except -H) of such group optionally is substituted with one or more halogen; and

R^7 is selected from the group consisting of -H, C_1-C_6-alkyl, $-O-R^8$, $-N(R^8)(R^9)$, carbocyclyl-C_1-C_8-alkyl, and heterocyclyl-C_1-C_8-alkyl, wherein the C_1-C_8-alkyl, carbocyclyl-C_1-C_8-alkyl, or heterocyclyl-C_1-C_8-alkyl optionally is substituted with one or more halogen; and

R^8 and R^9 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl, wherein any member (except -H) of such group optionally is substituted with one or more halogen.

337. A compound or salt thereof, wherein:

the compound corresponds in structure to Formula 337-1:



(337-1); and

A^1 is selected from the group consisting of -H, alkylcarbonyl, alkoxycarbonyl, carbocyclylcarbonyl, carbocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclylalkylcarbonyl, carbocyclyloxycarbonyl, carbocyclylalkoxycarbonyl, aminoalkylcarbonyl, alkyl(thiocarbonyl), alkoxy(thiocarbonyl), carbocyclyl(thiocarbonyl), carbocyclylalkyl(thiocarbonyl), heterocyclyl(thiocarbonyl), heterocyclylalkyl(thiocarbonyl), carbocyclyloxy(thiocarbonyl), carbocyclylalkoxy(thiocarbonyl), and aminoalkyl(thiocarbonyl), wherein any member (except -H) of such group optionally is substituted; and

A^2 and A^3, together with the carbon atom to which they are both attached, form an optionally-substituted heterocyclyl containing from 5 to 8 ring members; and

E^3 is selected from the group consisting of alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, and alkylcycloalkylalkyl, wherein any member of such group optionally is substituted; and

E^4 is selected from the group consisting of alkyl and alkenyl, wherein the alkyl or alkenyl optionally is substituted; and

E^5 is selected from the group consisting of -H, alkyl, alkenyl, alkynyl, alkoxy, carbocyclyl, and heterocyclyl, wherein any member of such group optionally is substituted.

338. A compound or salt thereof according to claim 337, wherein:

A^1 is selected from the group consisting of -H, C_1-C_8-alkylcarbonyl, C_1-C_8-alkoxycarbonyl, carbocyclylcarbonyl, carbocyclyl-C_1-C_8-alkylcarbonyl, heterocyclylcarbonyl, heterocyclyl-C_1-C_8-alkylcarbonyl, carbocyclyloxycarbonyl, carbocyclyl-C_1-C_8-alkoxycarbonyl, $N(R^1)(R^2)$-C_1-C_8-alkylcarbonyl, C_1-C_8-alkyl(thiocarbonyl), C_1-C_8-alkoxy(thiocarbonyl), carbocyclyl(thiocarbonyl), carbocyclyl-C_1-C_8-alkyl(thiocarbonyl), heterocyclyl(thiocarbonyl), heterocyclyl-C_1-C_8-alkyl(thiocarbonyl), carbocyclyloxy(thiocarbonyl), carbocyclyl-C_1-C_8-alkoxy(thiocarbonyl), and $N(R^1)(R^2)$-C_1-C_8-alkyl(thiocarbonyl); and

E^2 is selected from the group consisting of C_1-C_{20}-alkyl, cycloalkyl, C_1-C_{10}-alkylcycloalkyl, cycloalkyl-C_1-C_{10}-alkyl, and C_1-C_{10}-alkylcycloalkyl-C_1-C_{10}-alkyl, wherein any member of such group optionally is substituted with one or more substituents

640

independently selected from the group consisting of halogen, C_1-C_6-alkyl, and halo-C_1-C_6-alkyl; and

E^4 is selected from the group consisting of C_1-C_{20}-alkyl, halo-C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, and halo-C_2-C_{20}-alkenyl; and

E^5 is selected from the group consisting of -H, C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, C_1-C_{20}-alkoxy, carbocyclyl, and heterocyclyl, wherein:

the C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, or C_1-C_{20}-alkoxy optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, and -CN, and

the carbocyclyl or heterocyclyl optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, $-N(R^3)(R^4)$, $-C(O)(R^5)$, $-S-R^3$, $-S(O)_2-R^3$, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl; and

R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_6-alkyl, C_1-C_6-alkoxycarbonyl, C_1-C_6-alkylcarbonyl, carbocyclyl-C_1-C_6-alkyl, and carbocyclyl-C_1-C_6-alkoxycarbonyl; and

R^3 and R^4 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl, wherein any member (except -H) of such group optionally is substituted with one or more halogen; and

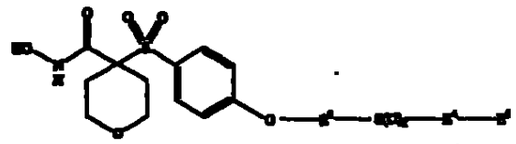
R^5 is selected from the group consisting of -H, C_1-C_6-alkyl, $-O-R^6$, $-N(R^6)(R^7)$, carbocyclyl-C_1-C_6-alkyl, and heterocyclyl-C_1-C_6-alkyl, wherein the C_1-C_6-alkyl, carbocyclyl-C_1-C_6-alkyl, or heterocyclyl-C_1-C_6-alkyl optionally is substituted with one or more halogen; and

R^6 and R^7 are independently selected from the group consisting of -H, C_1-C_6-alkyl, carbocyclyl, carbocyclyl-C_1-C_6-alkyl, heterocyclyl, and heterocyclyl-C_1-C_6-alkyl, wherein any member (except -H) of such group optionally is substituted with one or more halogen.

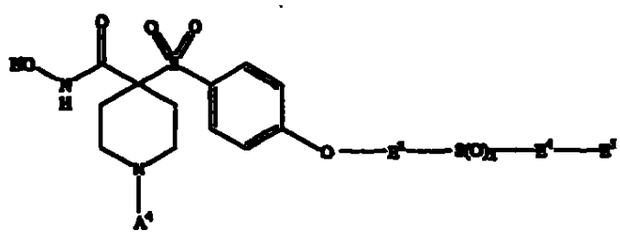
641

339. A compound or salt thereof according to claim 338, wherein:

the compound corresponds in structure to a formula selected from the group consisting of:



(339-1) and



(339-2); and

A^4 is selected from the group consisting of -H, alkyl, alkylcarbonyl, alkylcarbonylalkyl, alkylcarbonylalkylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkoxycarbonylalkylcarbonyl, alkylsulfonyl, alkyliminocarbonyl, alkenyl, alkynyl, alkoxyalkyl, alkylthioalkyl, alkylsulfonylalkyl, alkylsufoxidoalkyl, alkylthioalkenyl, alkylsulfoxidoalkenyl, alkylsulfonylalkenyl, carbocyclyl, carbocyclylalkyl, carbocyclylalkoxyalkyl, carbocyclylcarbonyl, carbocyclylsulfonyl, carbocyclyliminocarbonyl, carbocyclyloxycarbonyl, carbocylylthioalkyl, carbocylylsulfoxidoalkyl, carbocylylsulfonylalkyl, carbocyclylthioalkenyl, carbocyclylsulfoxidoalkenyl, carbocyclylsulfonylalkenyl, heterocyclyl, heterocyclylalkyl, heterocyclylalkoxyalkyl, heterocyclylcarbonyl, heterocylylthioalkyl, heterocylylsulfoxidoalkyl, heterocyclylsulfonylalkyl, heterocylylthioalkenyl, heterocylylsulfoxidoalkenyl, heterocyclylsulfonylalkenyl, heterocylylsulfonyl, heterocyclyliminocarbonyl, heterocylylalkylcarbonyl, heterocylylcarbonylalkylcarbonyl, heterocylylsulfonyl, heterocyclylcarbonylalkyl, aminoalkylcarbonyl, aminocarbonyl, aminocarbonylalkylcarbonyl, aminosulfonyl, aminosulfonylalkyl, aminoalkyl, aminocarbonylalkyl, and aminoalkylsulfonyl, wherein:

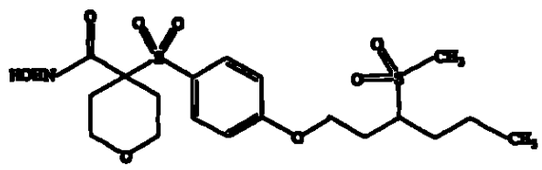
any member (except -H) of such group optionally is substituted.

642

340. A compound or salt thereof according to claim 339, wherein E^5 is selected from the group consisting of -H, C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, and C_1-C_6-alkoxy, wherein:

the C_1-C_6-alkyl, C_2-C_6-alkenyl, C_2-C_6-alkynyl, or C_1-C_6-alkoxy optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, and -CN.

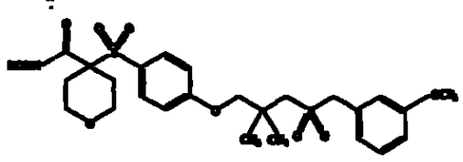
341. A compound or salt thereof according to claim 340, wherein the compound corresponds in structure to the following formula:



(341-1).

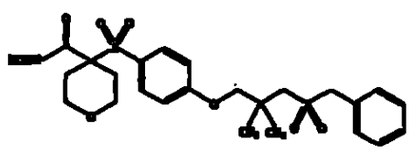
342. A compound or salt thereof according to claim 339, wherein E^5 is phenyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, $-N(R^3)(R^4)$, $-C(O)(R^5)$, $-S-R^3$, $-S(O)_2-R^3$, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl.

343. A compound or salt thereof according to claim 342, wherein the compound corresponds in structure to a formula selected from the group consisting of:



(343-1)

and

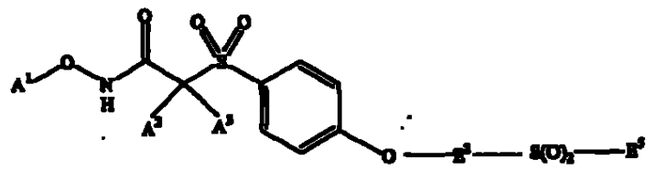


(343-2).

643

344. A compound or salt thereof, wherein:

the compound corresponds in structure to Formula 344-1:



-(344-1); and

A^1 is selected from the group consisting of -H, alkylcarbonyl, alkoxycarbonyl, carbocyclylcarbonyl, carbocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclylalkylcarbonyl, carbocyclyloxycarbonyl, carbocyclylalkoxycarbonyl, aminoalkylcarbonyl, alkyl(thiocarbonyl), alkoxy(thiocarbonyl), carbocyclyl(thiocarbonyl), carbocyclylalkyl(thiocarbonyl), heterocyclyl(thiocarbonyl), heterocyclylalkyl(thiocarbonyl), carbocyclyloxy(thiocarbonyl), carbocyclylalkoxy(thiocarbonyl), and aminoalkyl(thiocarbonyl), wherein any member (except -H) of such group optionally is substituted; and

A^2 and A^3, together with the carbon atom to which they are both attached, form an optionally-substituted heterocyclyl containing from 5 to 8 ring members; and

E^2 is selected from the group consisting of alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, and alkylcycloalkylalkyl, wherein any member of such group optionally is substituted; and

E^2 contains less than 5 carbon atoms; and

E^5 is selected from the group consisting of alkyl, alkenyl, alkynyl, alkoxyalkyl, carbocyclyl, and heterocyclyl, wherein any member of such group optionally is substituted.

345. A compound or salt thereof according to claim 344, wherein:

A^1 is selected from the group consisting of -H, C_1-C_8-alkylcarbonyl, C_1-C_8-alkoxycarbonyl, carbocyclylcarbonyl, carbocyclyl-C_1-C_8-alkylcarbonyl, heterocyclylcarbonyl, heterocyclyl-C_1-C_8-alkylcarbonyl, carbocyclyloxycarbonyl, carbocyclyl-C_1-C_8-alkoxycarbonyl, $N(R^1)(R^2)$-C_1-C_8-alkylcarbonyl, C_1-C_8-alkyl(thiocarbonyl), C_1-C_8-alkoxy(thiocarbonyl), carbocyclyl(thiocarbonyl), carbocyclyl-C_1-C_8-alkyl(thiocarbonyl), heterocyclyl(thiocarbonyl),

heterocyclyl-C_1-C_8-alkyl(thiocarbonyl), carbocyclyloxy(thiocarbonyl), carbocyclyl-C_1-C_8-alkoxy(thiocarbonyl), and N(R^1)(R^2)-C_1-C_8-alkyl(thiocarbonyl); and

E^5 is selected from the group consisting of C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, C_1-C_{20}-alkoxy-C_1-C_{20}-alkyl, carbocyclyl, and heterocyclyl, wherein:

the C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, or C_1-C_{20}-alkoxy-C_1-C_{20}-alkyl optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, and -CN, and

the carbocyclyl or heterocyclyl optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, keto, C_1-C_8-alkyl, halo-C_1-C_8-alkyl, C_1-C_8-alkoxy, halo-C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, halogen-substituted C_1-C_8-alkoxy-C_1-C_8-alkyl, -N(R^3)(R^4), -C(O)(R^5), -S-R^3, -S(O)$_2$-R^3, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_8-alkyl, halogen-substituted carbocyclyl-C_1-C_8-alkyl, C_1-C_8-alkylcarbocyclyloxy, and halogen-substituted C_1-C_8-alkylcarbocyclyloxy; and

R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_8-alkyl, C_1-C_8-alkoxycarbonyl, C_1-C_8-alkylcarbonyl, carbocyclyl-C_1-C_8-alkyl, and carbocyclyl-C_1-C_8-alkoxycarbonyl; and

R^3 and R^4 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl, wherein any member (except -H) of such group optionally is substituted with one or more halogen; and

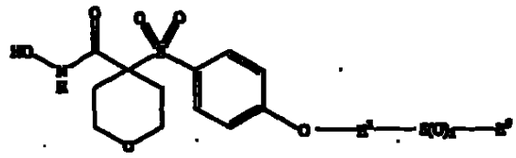
R^5 is selected from the group consisting of -H, C_1-C_8-alkyl, -O-R^6, -N(R^6)(R^7), carbocyclyl-C_1-C_8-alkyl, and heterocyclyl-C_1-C_8-alkyl, wherein the C_1-C_8-alkyl, carbocyclyl-C_1-C_8-alkyl, or heterocyclyl-C_1-C_8-alkyl optionally is substituted with one or more halogen; and

R^6 and R^7 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl, wherein any member (except -H) of such group optionally is substituted with one or more halogen.

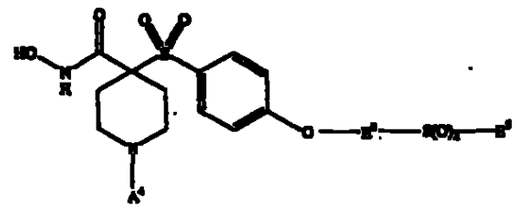
645

346. A compound or salt thereof according to claim 345, wherein:

the compound corresponds in structure to a formula selected from the group consisting of:



(346-1) and



(346-2); and

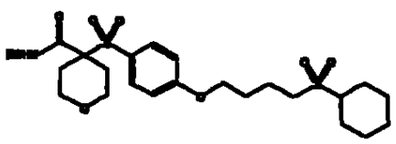
A^4 is selected from the group consisting of -H, alkyl, alkylcarbonyl, alkylcarbonylalkyl, alkylcarbonylalkylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkoxycarbonylalkylcarbonyl, alkylsulfonyl, alkyliminocarbonyl, alkenyl, alkynyl, alkoxyalkyl, alkylthioalkyl, alkylsulfonylalkyl, alkylsufoxidoalkyl, alkylthioalkenyl, alkylsulfoxidoalkenyl, alkylsulfonylalkenyl, carbocyclyl, carbocyclylalkyl, carbocyclylalkoxyalkyl, carbocyclylcarbonyl, carbocyclylsulfonyl, carbocyclyliminocarbonyl, carbocyclyloxycarbonyl, carbocylylthioalkyl, carbocylylsulfoxidoalkyl, carbocylylsulfonylalkyl, carbocyclylthioalkenyl, carbocyclylsulfoxidoalkenyl, carbocyclylsulfonylalkenyl, heterocyclyl, heterocyclylalkyl, heterocyclylalkoxyalkyl, heterocyclylcarbonyl, heterocyclylthioalkyl, heterocyclylsulfoxidoalkyl, heterocyclylsulfonylalkyl, heterocylylthioalkenyl, heterocylylsulfoxidoalkenyl, heterocylylsulfonylalkenyl, heterocylylsulfonyl, heterocyclyliminocarbonyl, heterocyclylalkylcarbonyl, heterocyclylcarbonylalkylcarbonyl, heterocylylsulfonyl, heterocyclylcarbonylalkyl, aminoalkylcarbonyl, aminocarbonyl, aminocarbonylalkylcarbonyl, aminosulfonyl, aminosulfonylalkyl, aminoalkyl, aminocarbonylalkyl, and aminoalkylsulfonyl, wherein:

any member (except -H) of such group optionally is substituted.

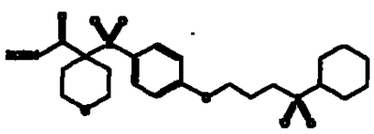
646

347. A compound or salt thereof according to claim 346, wherein E^5 is C_3-C_6-cycloalkyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, keto, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^3)(R^4)$, -$C(O)(R^5)$, -S-R^3, -$S(O)_2$-R^3, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, halogen-substituted carbocyclyl-C_1-C_6-alkyl, C_1-C_6-alkylcarbocyclyloxy, and halogen-substituted C_1-C_6-alkylcarbocyclyloxy.

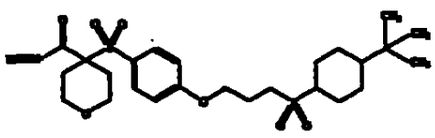
348. A compound or salt thereof according to claim 347, wherein the compound corresponds in structure to a formula selected from the group consisting of:



(348-1), and



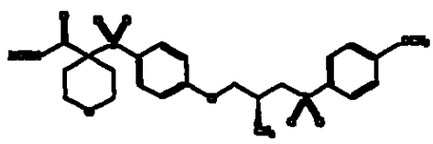
(348-2),



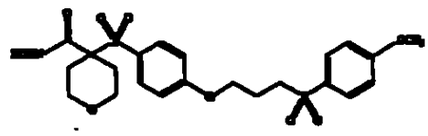
(348-3).

349. A compound or salt thereof according to claim 346, wherein E^5 is phenyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^3)(R^4)$, -$C(O)(R^5)$, -S-R^3, -$S(O)_2$-R^3, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, halogen-substituted carbocyclyl-C_1-C_6-alkyl, C_1-C_6-alkylcarbocyclyloxy, and halogen-substituted C_1-C_6-alkylcarbocyclyloxy.

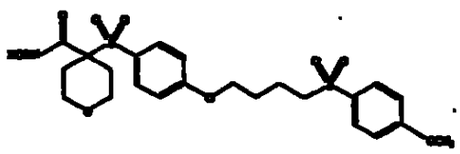
350. A compound or salt thereof according to claim 349, wherein the compound corresponds in structure to a formula selected from the group consisting of:



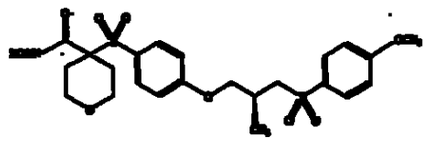
(350-1),



(350-2),



(350-3), and



(350-4).

351. A compound or salt thereof according to claim 346, wherein E^5 is selected from the group consisting of furanyl, tetrahydropyranyl, dihydrofuranyl, tetrahydrofuranyl, thiophenyl, dihydrothiophenyl, tetrahydrothiophenyl, pyrrolyl, isopyrrolyl, pyrrolinyl, pyrrolidinyl, imidazolyl, isoimidazolyl, imidazolinyl, imidazolidinyl, pyrazolyl, pyrazolinyl, pyrazolidinyl, triazolyl, tetrazolyl, dithiolyl, oxathiolyl, oxazolyl, isoxazolyl, oxazolidinyl, isoxazolidinyl, thiazolyl, isothiazolyl, thiazolinyl, isothiazolinyl, thiazolidinyl, isothiazolidinyl, thiodiazolyl, oxathiazolyl, oxadiazolyl, oxatriazolyl, dioxazolyl, oxathiazolyl, oxathiolyl, oxathiolanyl, pyranyl, dihydropyranyl, pyridinyl, piperidinyl, diazinyl, piperazinyl, triazinyl, oxazinyl, isoxazinyl, oxathiazinyl, oxadiazinyl, morpholinyl, azepinyl, oxepinyl, thiepinyl, diazepinyl, indolizinyl, pyrindinyl, pyranopyrrolyl, 4H-quinolizinyl, purinyl, naphthyridinyl, pyridopyridinyl, pteridinyl, indolyl, isoindolyl, indoleninyl, isoindazolyl, benzazinyl, phthalazinyl, quinoxalinyl, quinazolinyl, benzodiazinyl, benzopyranyl, benzothiopyranyl, benzoxazolyl, indoxazinyl, anthranilyl, benzodioxolyl, benzodioxanyl, benzoxadiazolyl, benzofuranyl, isobenzofuranyl, benzothienyl, isobenzothienyl, benzothiazolyl, benzothiadiazolyl, benzimidazolyl, benzotriazolyl, benzoxazinyl, benzisoxazinyl, tetrahydroisoquinolinyl, carbazolyl, xanthenyl, and acridinyl, wherein a member of such group:

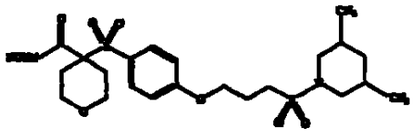
optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, keto, C_1-C_6-alkyl,

halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^3)(R^4)$, -$C(O)(R^5)$, -S-R^3, -$S(O)_2$-R^3, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, halogen-substituted carbocyclyl-C_1-C_6-alkyl, C_1-C_6-alkylcarbocyclyloxy, and halogen-substituted C_1-C_6-alkylcarbocyclyloxy.

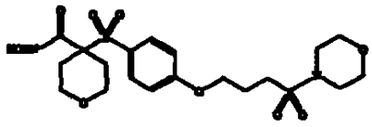
352. A compound or salt thereof according to claim 351, wherein E^5 is selected from the group consisting of piperidinyl, morpholinyl, and tetrahydroisoquinolinyl, wherein a member of such group:

optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, keto, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^3)(R^4)$, -$C(O)(R^5)$, -S-R^3, -$S(O)_2$-R^3, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, halogen-substituted carbocyclyl-C_1-C_6-alkyl, C_1-C_6-alkylcarbocyclyloxy, and halogen-substituted C_1-C_6-alkylcarbocyclyloxy.

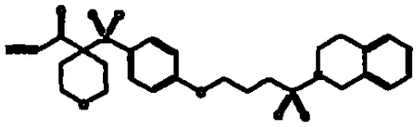
353. A compound or salt thereof according to claim 352, wherein the compound corresponds in structure to a formula selected from the group consisting of:



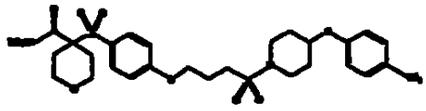
(353-1)



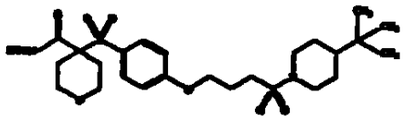
(353-2),



(353-3),



(353-4), and

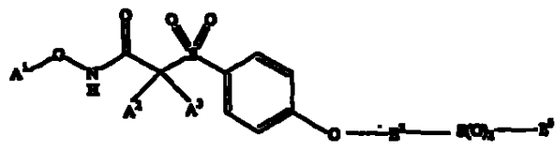


(353-5).

649

354. A compound or salt thereof, wherein:

the compound corresponds in structure to Formula 354-1:



(354-1); and

A^1 is selected from the group consisting of -H, alkylcarbonyl, alkoxycarbonyl, carbocyclylcarbonyl, carbocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclylalkylcarbonyl, carbocyclyloxycarbonyl, carbocyclylalkoxycarbonyl, aminoalkylcarbonyl, alkyl(thiocarbonyl), alkoxy(thiocarbonyl), carbocyclyl(thiocarbonyl), carbocyclylalkyl(thiocarbonyl), heterocyclyl(thiocarbonyl), heterocyclylalkyl(thiocarbonyl), carbocyclyloxy(thiocarbonyl), carbocyclylalkoxy(thiocarbonyl), and aminoalkyl(thiocarbonyl), wherein any member (except -H) of such group optionally is substituted; and

A^2 and A^3, together with the carbon atom to which they are both attached, form an optionally-substituted heterocyclyl containing from 5 to 8 ring members; and

E^2 is selected from the group consisting of alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, and alkylcycloalkylalkyl, wherein any member of such group optionally is substituted; and

E^5 is selected from the group consisting of alkyl, alkenyl, alkynyl, alkoxyalkyl, saturated carbocyclyl, partially saturated carbocyclyl, and heterocyclyl, wherein any member of such group optionally is substituted.

355. A compound or salt thereof according to claim 354, wherein:

A^1 is selected from the group consisting of -H, C_1-C_8-alkylcarbonyl, C_1-C_8-alkoxycarbonyl, carbocyclylcarbonyl, carbocyclyl-C_1-C_8-alkylcarbonyl, heterocyclylcarbonyl, heterocyclyl-C_1-C_8-alkylcarbonyl, carbocyclyloxycarbonyl, carbocyclyl-C_1-C_8-alkoxycarbonyl, $N(R^1)(R^2)$-C_1-C_8-alkylcarbonyl, C_1-C_8-alkyl(thiocarbonyl), C_1-C_8-alkoxy(thiocarbonyl), carbocyclyl(thiocarbonyl), carbocyclyl-C_1-C_8-alkyl(thiocarbonyl), heterocyclyl(thiocarbonyl),

650

heterocyclyl-C_1-C_8-alkyl(thiocarbonyl), carbocyclyloxy(thiocarbonyl), carbocyclyl-C_1-C_8-alkoxy(thiocarbonyl), and $N(R^1)(R^2)$-C_1-C_8-alkyl(thiocarbonyl); and

E^2 is selected from the group consisting of C_1-C_{20}-alkyl, cycloalkyl, C_1-C_{10}-alkylcycloalkyl, cycloalkyl-C_1-C_{10}-alkyl, and C_1-C_{10}-alkylcycloalkyl-C_1-C_{10}-alkyl, wherein any member of such group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, C_1-C_8-alkyl, halo-C_1-C_8-alkyl; and

E^5 is selected from the group consisting of C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, C_1-C_{20}-alkoxy-C_1-C_{20}-alkyl, saturated carbocyclyl, partially saturated carbocyclyl, and heterocyclyl, wherein:

the C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, or C_1-C_{20}-alkoxy-C_1-C_{20}-alkyl optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, and -CN, and

the saturated carbocyclyl, partially saturated carbocyclyl, or heterocyclyl optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_8-alkoxy, halo-C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, halogen-substituted C_1-C_8-alkoxy-C_1-C_8-alkyl, $-N(R^3)(R^4)$, $-C(O)(R^5)$, $-S-R^3$, $-S(O)_2-R^3$, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, halogen-substituted carbocyclyl-C_1-C_8-alkyl, C_1-C_8-alkylcarbocyclyloxy, and halogen-substituted C_1-C_8-alkylcarbocyclyloxy; and

R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_8-alkyl, C_1-C_8-alkoxycarbonyl, C_1-C_8-alkylcarbonyl, carbocyclyl-C_1-C_8-alkyl, and carbocyclyl-C_1-C_8-alkoxycarbonyl; and

R^3 and R^4 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl, wherein any member (except -H) of such group optionally is substituted with one or more halogen; and

R^5 is selected from the group consisting of -H, C_1-C_8-alkyl, $-O-R^6$, $-N(R^6)(R^7)$, carbocyclyl-C_1-C_8-alkyl, and heterocyclyl-C_1-C_8-alkyl, wherein the C_1-C_8-alkyl,

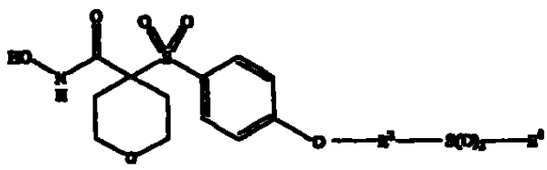
651

carbocyclyl-C_1-C_8-alkyl, or heterocyclyl-C_1-C_8-alkyl optionally is substituted with one or more halogen; and

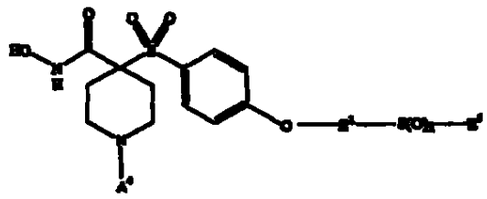
R^6 and R^7 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl, wherein any member (except -H) of such group optionally is substituted with one or more halogen.

356. A compound or salt thereof according to claim 355, wherein:

the compound corresponds in structure to a formula selected from the group consisting of:



(356-1) and



(356-2); and

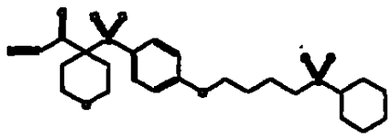
A^4 is selected from the group consisting of -H, alkyl, alkylcarbonyl, alkylcarbonylalkyl, alkylcarbonylalkylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkoxycarbonylalkylcarbonyl, alkylsulfonyl, alkyliminocarbonyl, alkenyl, alkynyl, alkoxyalkyl, alkylthioalkyl, alkylsulfonylalkyl, alkylsulfoxidoalkyl, alkylthioalkenyl, alkylsulfoxidoalkenyl, alkylsulfonylalkenyl, carbocyclyl, carbocyclylalkyl, carbocyclylalkoxyalkyl, carbocyclylcarbonyl, carbocyclylsulfonyl, carbocyclyliminocarbonyl, carbocyclyloxycarbonyl, carbocylylthioalkyl, carbocylylsulfoxidoalkyl, carbocylylsulfonylalkyl, carbocyclylthioalkenyl, carbocyclylsulfoxidoalkenyl, carbocyclylsulfonylalkenyl, heterocyclyl, heterocyclylalkyl, heterocyclylalkoxyalkyl, heterocyclylcarbonyl, heterocyclylthioalkyl, heterocyclylsulfoxidoalkyl, heterocyclylsulfonylalkyl, heterocyclylthioalkenyl, heterocyclylsulfoxidoalkenyl, heterocyclylsulfonylalkenyl, heterocyclylsulfonyl,

heterocyclyliminocarbonyl, heterocyclylalkylcarbonyl, heterocyclylcarbonylalkylcarbonyl, heterocyclylsulfonyl, heterocyclylcarbonylalkyl, aminoalkylcarbonyl, aminocarbonyl, aminocarbonylalkylcarbonyl, aminosulfonyl, aminosulfonylalkyl, aminoalkyl, aminocarbonylalkyl, and aminoalkylsulfonyl, wherein:

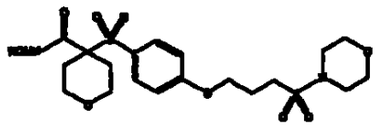
any member (except -H) of such group optionally is substituted.

357. A compound or salt thereof according to claim 356, wherein E^5 is heterocyclyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^3)(R^4)$, -$C(O)(R^5)$, -S-R^3, -$S(O)_2$-R^3, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, halogen-substituted carbocyclyl-C_1-C_6-alkyl, C_1-C_6-alkylcarbocyclyloxy, and halogen-substituted C_1-C_6-alkylcarbocyclyloxy.

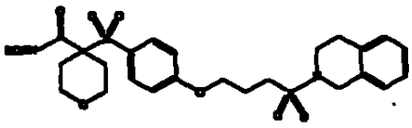
358. A compound or salt thereof according to claim 357, wherein the compound corresponds in structure to a formula selected from the group consisting of:



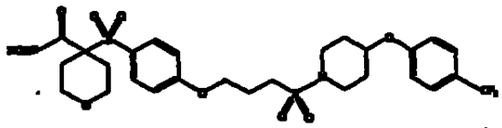
(358-1),



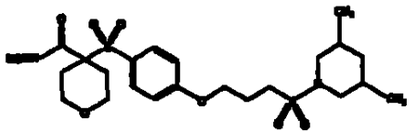
(358-2),



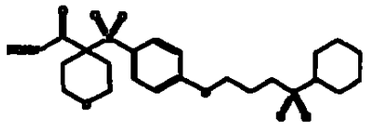
(358-3),



(358-4),

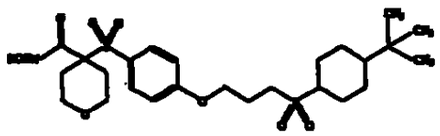


(358-5),



(358-6), and

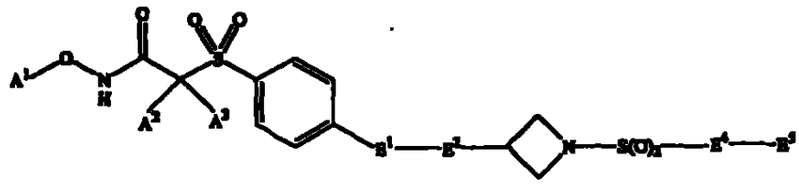
653



(358-7).

359. A compound or salt thereof, wherein:

the compound corresponds in structure to Formula 359-1:



(359-1); and

A^1 is selected from the group consisting of -H, alkylcarbonyl, alkoxycarbonyl, carbocyclylcarbonyl, carbocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclylalkylcarbonyl, carbocyclyloxycarbonyl, carbocyclylalkoxycarbonyl, aminoalkylcarbonyl, alkyl(thiocarbonyl), alkoxy(thiocarbonyl), carbocyclyl(thiocarbonyl), carbocyclylalkyl(thiocarbonyl), heterocyclyl(thiocarbonyl), heterocyclylalkyl(thiocarbonyl), carbocyclyloxy(thiocarbonyl), carbocyclylalkoxy(thiocarbonyl), and aminoalkyl(thiocarbonyl), wherein any member (except -H) of such group optionally is substituted; and

A^2 and A^3, together with the carbon atom to which they are both attached, form an optionally-substituted heterocyclyl containing from 5 to 8 ring members; and

E^1 is selected from the group consisting of $-S(O)_2-$, -S(O)-, $-N(R^1)-$, $-C(O)-N(R^1)-$, $-N(R^1)-C(O)-$, and $-C(R^1)(R^2)-$; and

E^2 is selected from the group consisting of alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, and alkylcycloalkylalkyl, wherein any member of such group optionally is substituted; and

E^4 is selected from the group consisting of a bond, alkyl, and alkenyl, wherein the alkyl or alkenyl optionally is substituted; and

E^5 is selected from the group consisting of alkyl, alkenyl, alkynyl, alkoxy, alkoxyalkyl, carbocyclyl, and heterocyclyl, wherein any member of such group optionally is substituted; and

R^1 and R^2 are independently selected from the group consisting of -H and alkyl, wherein the alkyl optionally is substituted; and

neither R^1 nor R^2 forms a ring structure with E^2, E^4, or E^5.

360. A compound or salt thereof according to claim 359, wherein:

A^1 is selected from the group consisting of -H, C_1-C_8-alkylcarbonyl, C_1-C_8-alkoxycarbonyl, carbocyclylcarbonyl, carbocyclyl-C_1-C_8-alkylcarbonyl, heterocyclylcarbonyl, heterocyclyl-C_1-C_8-alkylcarbonyl, carbocyclyloxycarbonyl, carbocyclyl-C_1-C_8-alkoxycarbonyl, $N(R^3)(R^4)$-C_1-C_8-alkylcarbonyl, C_1-C_8-alkyl(thiocarbonyl), C_1-C_8-alkoxy(thiocarbonyl), carbocyclyl(thiocarbonyl), carbocyclyl-C_1-C_8-alkyl(thiocarbonyl), heterocyclyl(thiocarbonyl), heterocyclyl-C_1-C_8-alkyl(thiocarbonyl), carbocyclyloxy(thiocarbonyl), carbocyclyl-C_1-C_8-alkoxy(thiocarbonyl), and $N(R^3)(R^4)$-C_1-C_8-alkyl(thiocarbonyl); and

E^2 is selected from the group consisting of C_1-C_{20}-alkyl, cycloalkyl, C_1-C_{10}-alkylcycloalkyl, cycloalkyl-C_1-C_{10}-alkyl, and C_1-C_{10}-alkylcycloalkyl-C_1-C_{10}-alkyl, wherein any member of such group optionally is substituted with one or more halogen; and

E^4 is selected from the group consisting of a bond, C_1-C_{20}-alkyl, halo-C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, and halo-C_2-C_{20}-alkenyl; and

E^5 is selected from the group consisting of C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, C_1-C_{20}-alkoxy, C_1-C_{20}-alkoxy-C_1-C_{20}-alkyl, carbocyclyl, and heterocyclyl, wherein:

the C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, C_2-C_{20}-alkynyl, C_1-C_{20}-alkoxy, or C_1-C_{20}-alkoxy-C_1-C_{20}-alkyl optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, and -CN, and

the carbocyclyl or heterocyclyl optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_8-alkyl, halo-C_1-C_8-alkyl, C_1-C_8-alkoxy, halo-C_1-C_8-alkoxy,

C_1-C_8-alkoxy-C_1-C_8-alkyl, halogen-substituted C_1-C_8-alkoxy-C_1-C_8-alkyl, $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_8-alkyl, and halogen-substituted carbocyclyl-C_1-C_8-alkyl; and

R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_8-alkyl, and halo-C_1-C_8-alkyl; and

R^3 and R^4 are independently selected from the group consisting of -H, C_1-C_8-alkyl, C_1-C_8-alkoxycarbonyl, C_1-C_8-alkylcarbonyl, carbocyclyl-C_1-C_8-alkyl, and carbocyclyl-C_1-C_8-alkoxycarbonyl; and

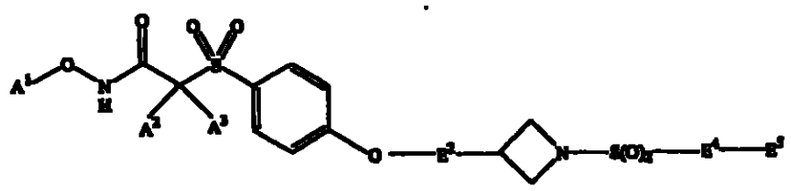
R^5 and R^6 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl, wherein any member (except -H) of such group optionally is substituted with one or more halogen; and

R^7 is selected from the group consisting of -H, C_1-C_8-alkyl, $-O-R^8$, $-N(R^8)(R^5)$, carbocyclyl-C_1-C_8-alkyl, and heterocyclyl-C_1-C_8-alkyl, wherein the C_1-C_8-alkyl, carbocyclyl-C_1-C_8-alkyl, or heterocyclyl-C_1-C_8-alkyl optionally is substituted with one or more halogen; and

R^8 and R^9 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl, wherein any member (except -H) of such group optionally is substituted with one or more halogen.

361. A compound or salt thereof, wherein:

the compound corresponds in structure to Formula 361-1:



(361-1); and

A^1 is selected from the group consisting of -H, alkylcarbonyl, alkoxycarbonyl, carbocyclylcarbonyl, carbocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclylalkylcarbonyl, carbocyclyloxycarbonyl, carbocyclylalkoxycarbonyl, aminoalkylcarbonyl, alkyl(thiocarbonyl), alkoxy(thiocarbonyl), carbocyclyl(thiocarbonyl),

carbocyclylalkyl(thiocarbonyl), heterocyclyl(thiocarbonyl), heterocyclylalkyl(thiocarbonyl), carbocyclyloxy(thiocarbonyl), carbocyclylalkoxy(thiocarbonyl), and aminoalkyl(thiocarbonyl), wherein any member (except -H) of such group optionally is substituted; and

A^2 and A^3, together with the carbon atom to which they are both attached, form an optionally-substituted heterocyclyl containing from 5 to 8 ring members; and

E^2 is selected from the group consisting of a bond, alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, and alkylcycloalkylalkyl, wherein any member of such group optionally is substituted; and

E^4 is selected from the group consisting of a bond, alkyl, and alkenyl, wherein the alkyl or alkenyl optionally is substituted; and

E^5 is selected from the group consisting of substituted carbocyclyl and optionally-substituted heterocyclyl, wherein:

the carbocyclyl is substituted with:

2 or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, alkyl, haloalkyl, alkoxy, haloalkoxy, alkoxyalkyl, halogen-substituted alkoxyalkyl, $-N(R^3)(R^4)$, $-C(O)(R^5)$, $-S-R^3$, $-S(O)_2-R^3$, carbocyclyl, halocarbocyclyl, carbocyclylalkyl, and halogen-substituted carbocyclylalkyl, or

a substituent selected from the group consisting of halogen, -OH, $-NO_2$, -CN, $-C(O)-O-R^3$, $-S-R^3$, $-S(O)_2-R^3$, carbocyclyl, halocarbocyclyl, carbocyclylalkyl, and halogen-substituted carbocyclylalkyl, and

the heterocyclyl optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, alkyl, haloalkyl, alkoxy, haloalkoxy, alkoxyalkyl, halogen-substituted alkoxyalkyl, $-N(R^3)(R^4)$, $-C(O)(R^5)$, $-S-R^3$, $-S(O)_2-R^3$, carbocyclyl, halocarbocyclyl, carbocyclylalkyl, and halogen-substituted carbocyclylalkyl; and

R^3 and R^4 are independently selected from the group consisting of -H, alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, and heterocyclylalkyl, wherein any member (except -H) of such group optionally is substituted with one or more halogen; and

R^5 is selected from the group consisting of -H, alkyl, -O-R^6, -N(R^6)(R^7), carbocyclylalkyl, and heterocyclylalkyl, wherein the alkyl, carbocyclylalkyl, or heterocyclylalkyl optionally is substituted with one or more halogen; and

R^6 and R^7 are independently selected from the group consisting of -H, alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, and heterocyclylalkyl, wherein any member (except -H) of such group optionally is substituted with one or more halogen.

362. A compound or salt thereof according to claim 361, wherein:

A^1 is selected from the group consisting of -H, C_1-C_8-alkylcarbonyl, C_1-C_8-alkoxycarbonyl, carbocyclylcarbonyl, carbocyclyl-C_1-C_8-alkylcarbonyl, heterocyclylcarbonyl, heterocyclyl-C_1-C_8-alkylcarbonyl, carbocyclyloxycarbonyl, carbocyclyl-C_1-C_8-alkoxycarbonyl, N(R^5)(R^5)-C_1-C_8-alkylcarbonyl, C_1-C_8-alkyl(thiocarbonyl), C_1-C_8-alkoxy(thiocarbonyl), carbocyclyl(thiocarbonyl), carbocyclyl-C_1-C_8-alkyl(thiocarbonyl), heterocyclyl(thiocarbonyl), heterocyclyl-C_1-C_8-alkyl(thiocarbonyl), carbocyclyloxy(thiocarbonyl), carbocyclyl-C_1-C_8-alkoxy(thiocarbonyl), and N(R^5)(R^5)-C_1-C_8-alkyl(thiocarbonyl); and

E^2 is selected from the group consisting of a bond, C_1-C_{20}-alkyl, cycloalkyl, C_1-C_{10}-alkylcycloalkyl, cycloalkyl-C_1-C_{10}-alkyl, and C_1-C_{10}-alkylcycloalkyl-C_1-C_{10}-alkyl, wherein any member of such group optionally is substituted with one or more halogen; and

E^4 is selected from the group consisting of a bond, C_1-C_{20}-alkyl, halo-C_1-C_{20}-alkyl, C_2-C_{20}-alkenyl, and halo-C_2-C_{20}-alkenyl; and

E^5 is selected from the group consisting of substituted carbocyclyl and optionally-substituted heterocyclyl, wherein:

the carbocyclyl is substituted with:

2 or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_8-alkyl, halo-C_1-C_8-alkyl, C_1-C_8-alkoxy, halo-C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, halogen-substituted

C_1-C_8-alkoxy-C_1-C_8-alkyl, -$N(R^3)(R^4)$, -$C(O)(R^5)$, -S-R^3, -$S(O)_2$-R^3, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_8-alkyl, and halogen-substituted carbocyclyl-C_1-C_8-alkyl, or

a substituent selected from the group consisting of halogen, -OH, -NO_2, -CN, -C(O)-O-R^3, -S-R^3, -$S(O)_2$-R^3, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_8-alkyl, and halogen-substituted carbocyclyl-C_1-C_8-alkyl, and

the heterocyclyl optionally is substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_8-alkyl, halo-C_1-C_8-alkyl, C_1-C_8-alkoxy, halo-C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, halogen-substituted C_1-C_8-alkoxy-C_1-C_8-alkyl, -$N(R^3)(R^4)$, -$C(O)(R^5)$, -S-R^3, -$S(O)_2$-R^3, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_8-alkyl, and halogen-substituted carbocyclyl-C_1-C_8-alkyl; and

R^3 and R^4 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl, wherein any member (except -H) of such group optionally is substituted with one or more halogen; and

R^5 is selected from the group consisting of -H, C_1-C_8-alkyl, -O-R^6, -$N(R^6)(R^7)$, carbocyclyl-C_1-C_8-alkyl, and heterocyclyl-C_1-C_8-alkyl, wherein the C_1-C_8-alkyl, carbocyclyl-C_1-C_8-alkyl, or heterocyclyl-C_1-C_8-alkyl optionally is substituted with one or more halogen; and

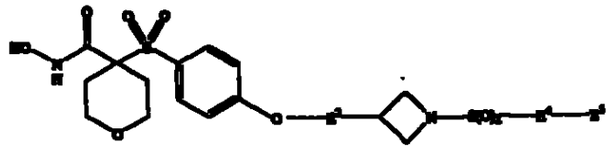
R^6 and R^7 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl, wherein any member (except -H) of such group optionally is substituted with one or more halogen; and

R^8 and R^9 are independently selected from the group consisting of -H, C_1-C_8-alkyl, C_1-C_8-alkoxycarbonyl, C_1-C_8-alkylcarbonyl, carbocyclyl-C_1-C_8-alkyl, and carbocyclyl-C_1-C_8-alkoxycarbonyl.

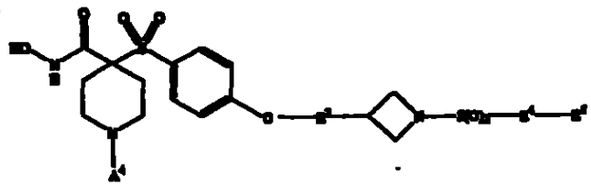
659

363. A compound or salt thereof according to claim 362, wherein:

the compound corresponds in structure to a formula selected from the group consisting of:



(363-1) and



(363-2); and

A^4 is selected from the group consisting of -H, alkyl, alkylcarbonyl, alkylcarbonylalkyl, alkylcarbonylalkylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkoxycarbonylalkylcarbonyl, alkylsulfonyl, alkyliminocarbonyl, alkenyl, alkynyl, alkoxyalkyl, alkylthioalkyl, alkylsulfonylalkyl, alkylsufoxidoalkyl, alkylthioalkenyl, alkylsulfoxidoalkenyl, alkylsulfonylalkenyl, carbocyclyl, carbocyclylalkyl, carbocyclylalkoxyalkyl, carbocyclylcarbonyl, carbocyclylsulfonyl, carbocyclyliminocarbonyl, carbocyclyloxycarbonyl, carbocylylthioalkyl, carbocylylsulfoxidoalkyl, carbocylylsulfonylalkyl, carbocyclylthioalkenyl, carbocyclylsulfoxidoalkenyl, carbocyclylsulfonylalkenyl, heterocyclyl, heterocyclylalkyl, heterocyclylalkoxyalkyl, heterocyclylcarbonyl, heterocyclylthioalkyl, heterocyclylsulfoxidoalkyl, heterocyclylsulfonylalkyl, heterocyclylthioalkenyl, heterocyclylsulfoxidoalkenyl, heterocyclylsulfonylalkenyl, heterocyclylsulfonyl, heterocyclyliminocarbonyl, heterocyclylalkylcarbonyl, heterocyclylcarbonylalkylcarbonyl, heterocyclylsulfonyl, heterocyclylcarbonylalkyl, aminoalkylcarbonyl, aminocarbonyl, aminocarbonylalkylcarbonyl, aminosulfonyl, aminosulfonylalkyl, aminoalkyl, aminocarbonylalkyl, and aminoalkylsulfonyl, wherein:

any member (except -H) of such group optionally is substituted.

364. A compound or salt thereof according to claim 363, wherein E^5 is phenyl substituted with:

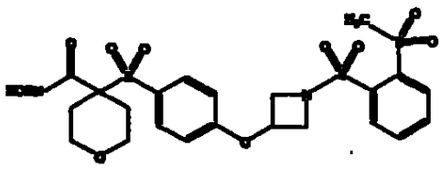
2 or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_6-alkyl, halo-C_1-C_6-alkyl, C_1-C_6-alkoxy, halo-C_1-C_6-alkoxy, C_1-C_6-alkoxy-C_1-C_6-alkyl, halogen-substituted C_1-C_6-alkoxy-C_1-C_6-alkyl, -$N(R^3)(R^4)$, -$C(O)(R^5)$, -S-R^3, -$S(O)_2$-R^3, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl, or

a substituent selected from the group consisting of halogen, -OH, -NO_2, -CN, -C(O)-O-R^3, -S-R^3, -$S(O)_2$-R^3, carbocyclyl, halocarbocyclyl, carbocyclyl-C_1-C_6-alkyl, and halogen-substituted carbocyclyl-C_1-C_6-alkyl.

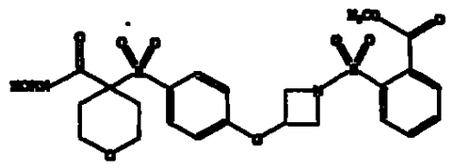
365. A compound or salt thereof according to claim 364, wherein E^2 is a bond.

366. A compound or salt thereof according to claim 365, wherein E^4 is a bond.

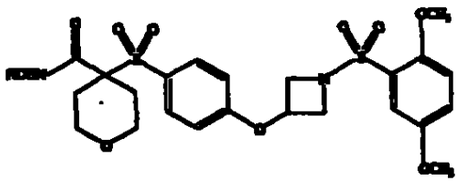
367. A compound or salt thereof according to claim 366, wherein the compound corresponds in structure to a formula selected from the group consisting of:



(367-1),



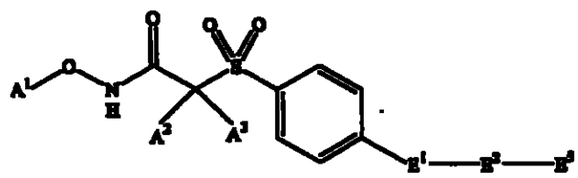
(367-2), and



(367-3).

368. A compound or salt thereof, wherein:

the compound corresponds in structure to Formula 368-1:



(368-1); and

A^1 is selected from the group consisting of -H, alkylcarbonyl, alkoxycarbonyl, carbocyclylcarbonyl, carbocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclylalkylcarbonyl, carbocyclyloxycarbonyl, carbocyclylalkoxycarbonyl, aminoalkylcarbonyl, alkyl(thiocarbonyl), alkoxy(thiocarbonyl), carbocyclyl(thiocarbonyl), carbocyclylalkyl(thiocarbonyl), heterocyclyl(thiocarbonyl), heterocyclylalkyl(thiocarbonyl), carbocyclyloxy(thiocarbonyl), carbocyclylalkoxy(thiocarbonyl), and aminoalkyl(thiocarbonyl), wherein any member (except -H) of such group optionally is substituted; and

A^2 and A^3, together with the carbon atom to which they are both attached, form an optionally-substituted heterocyclyl containing from 5 to 8 ring members; and

E^1 is selected from the group consisting of -O-, $-S(O)_2-$, -S(O)-, -S-, $-N(R^1)-$, $-C(O)-N(R^1)-$, $-N(R^1)-C(O)-$, and $-C(R^1)(R^2)-$; and

E^2 is selected from the group consisting of alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, and alkylcycloalkylalkyl, wherein any member of such group optionally is substituted; and

E^3 is substituted heterocyclyl; and

R^1 and R^2 are independently selected from the group consisting of -H and alkyl, wherein the alkyl optionally is substituted; and

neither R^1 nor R^2 forms a ring structure with E^3.

369. A compound or salt thereof according to claim 368, wherein:

A^1 is selected from the group consisting of -H, C_1-C_8-alkylcarbonyl, C_1-C_8-alkoxycarbonyl, carbocyclylcarbonyl, carbocyclyl-C_1-C_8-alkylcarbonyl, heterocyclylcarbonyl, heterocyclyl-C_1-C_8-alkylcarbonyl, carbocyclyloxycarbonyl, carbocyclyl-C_1-C_8-alkoxycarbonyl, $N(R^3)(R^4)$-C_1-C_8-alkylcarbonyl,

C_1-C_8-alkyl(thiocarbonyl), C_1-C_8-alkoxy(thiocarbonyl), carbocyclyl(thiocarbonyl), carbocyclyl-C_1-C_8-alkyl(thiocarbonyl), heterocyclyl(thiocarbonyl), heterocyclyl-C_1-C_8-alkyl(thiocarbonyl), carbocyclyloxy(thiocarbonyl), carbocyclyl-C_1-C_8-alkoxy(thiocarbonyl), and $N(R^3)(R^4)$-C_1-C_8-alkyl(thiocarbonyl); and

E^2 is selected from the group consisting of C_1-C_{20}-alkyl, cycloalkyl, C_1-C_{10}-alkyl-cycloalkyl, cycloalkyl-C_1-C_{10}-alkyl, and C_1-C_{10}-alkyl-cycloalkyl-C_1-C_{10}-alkyl, wherein the any member of such group optionally is substituted with one or more halogen; and

E^5 is heterocyclyl that is:

substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, keto, C_1-C_8-alkyl, halo-C_1-C_8-alkyl, C_1-C_8-alkoxy, halo-C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, halogen-substituted C_1-C_8-alkoxy-C_1-C_8-alkyl, $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbocyclyl, halocarbocyclyl, and carbocyclyl-C_1-C_8-alkyl, and/or

substituted on the same atom with two substituents independently selected from the group consisting of alkyl and haloalkyl, the two substituents together forming C_3-C_6-cycloalkyl or halo-C_3-C_6-cycloalkyl; and

R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_8-alkyl, and halo-C_1-C_8-alkyl; and

R^3 and R^4 are independently selected from the group consisting of -H, C_1-C_8-alkyl, C_1-C_8-alkoxycarbonyl, C_1-C_8-alkylcarbonyl, carbocyclyl-C_1-C_8-alkyl, and carbocyclyl-C_1-C_8-alkoxycarbonyl; and

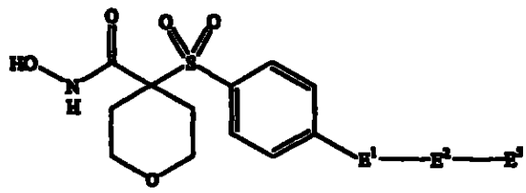
R^5 and R^6 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl, wherein any member (except -H) of such group optionally is substituted with one or more halogen; and

R^7 is selected from the group consisting of -H, C_1-C_8-alkyl, $-O-R^5$, $-N(R^5)(R^5)$, carbocyclyl-C_1-C_8-alkyl, and heterocyclyl-C_1-C_8-alkyl, wherein the C_1-C_8-alkyl, carbocyclyl-C_1-C_8-alkyl, or heterocyclyl-C_1-C_8-alkyl optionally is substituted with one or more halogen; and

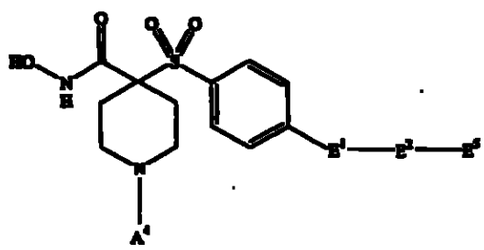
R^8 and R^9 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl, wherein any member (except -H) of such group optionally is substituted with one or more halogen.

370. A compound or salt thereof according to claim 369, wherein:

the compound corresponds in structure to a formula selected from the group consisting of:



(370-1) and



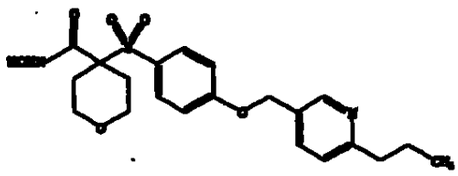
(370-2); and

A^4 is selected from the group consisting of -H, alkyl, alkylcarbonyl, alkylcarbonylalkyl, alkylcarbonylalkylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkoxycarbonylalkylcarbonyl, alkylsulfonyl, alkyliminocarbonyl, alkenyl, alkynyl, alkoxyalkyl, alkylthioalkyl, alkylsulfonylalkyl, alkylsufoxidoalkyl, alkylthioalkenyl, alkylsulfoxidoalkenyl, alkylsulfonylalkenyl, carbocyclyl, carbocyclylalkyl, carbocyclylalkoxyalkyl, carbocyclylcarbonyl, carbocyclylsulfonyl, carbocyclyliminocarbonyl, carbocyclyloxycarbonyl, carbocylylthioalkyl, carbocylylsulfoxidoalkyl, carbocylylsulfonylalkyl, carbocyclylthioalkenyl, carbocyclylsulfoxidoalkenyl, carbocyclylsulfonylalkenyl, heterocyclyl, heterocyclylalkyl, heterocyclylalkoxyalkyl, heterocyclylcarbonyl, heterocyclylthioalkyl, heterocyclylsulfoxidoalkyl, heterocyclylsulfonylalkyl, heterocyclylthioalkenyl, heterocyclylsulfoxidoalkenyl, heterocyclylsulfonylalkenyl, heterocyclylsulfonyl, heterocyclyliminocarbonyl, heterocyclylalkylcarbonyl, heterocyclylcarbonylalkylcarbonyl,

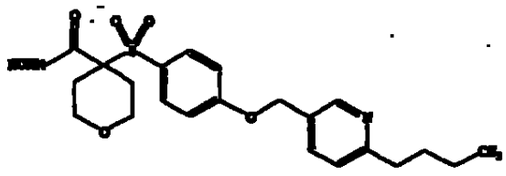
heterocyclylsulfonyl, heterocyclylcarbonylalkyl, aminoalkylcarbonyl, aminocarbonyl, aminocarbonylalkylcarbonyl, aminosulfonyl, aminosulfonylalkyl, aminoalkyl, aminocarbonylalkyl, and aminoalkylsulfonyl, wherein:

any member (except -H) of such group optionally is substituted.

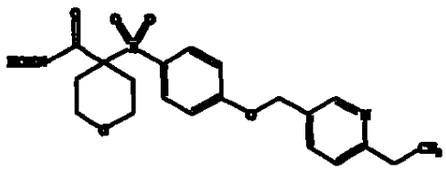
371. A compound or salt thereof according to claim 370, wherein the compound corresponds in structure to a formula selected from the group consisting of:



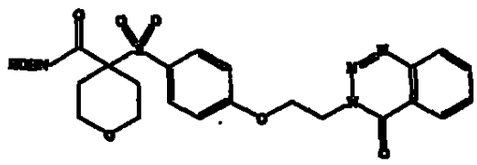
(371-1),



(371-2),



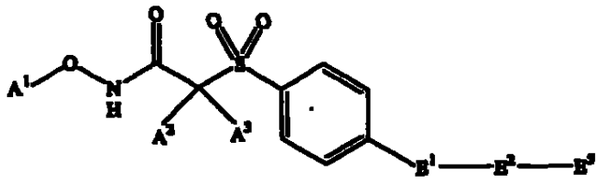
(371-3), and



(371-4).

372. A compound or salt thereof, wherein:

the compound corresponds in structure to Formula 372-1:



(372-1); and

A^1 is selected from the group consisting of -H, alkylcarbonyl, alkoxycarbonyl, carbocyclylcarbonyl, carbocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclylalkylcarbonyl, carbocyclyloxycarbonyl, carbocyclylalkoxycarbonyl, aminoalkylcarbonyl, alkyl(thiocarbonyl), alkoxy(thiocarbonyl), carbocyclyl(thiocarbonyl), carbocyclylalkyl(thiocarbonyl), heterocyclyl(thiocarbonyl), heterocyclylalkyl(thiocarbonyl), carbocyclyloxy(thiocarbonyl),

665

carbocyclylalkoxy(thiocarbonyl), and aminoalkyl(thiocarbonyl), wherein any member (except -H) of such group optionally is substituted; and

A^2 and A^3, together with the carbon atom to which they are both attached, form an optionally-substituted heterocyclyl containing from 5 to 8 ring members; and

E^1 is selected from the group consisting of -O-, $-S(O)_2-$, -S(O)-, $-N(R^1)-$, $-C(O)-N(R^1)-$, $-N(R^1)-C(O)-$, and $-C(R^1)(R^2)-$; and

E^2 is selected from the group consisting of alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, and alkylcycloalkylalkyl, wherein any member of such group optionally is substituted; and

E^2 comprises at least two carbon atoms; and

E^5 is optionally-substituted heterocyclyl; and

R^1 and R^2 are independently selected from the group consisting of -H and alkyl, wherein the alkyl optionally is substituted; and

neither R^1 nor R^2 forms a ring structure with E^5.

373. A compound or salt thereof according to claim 372, wherein:

A^1 is selected from the group consisting of -H, C_1-C_8-alkylcarbonyl, C_1-C_8-alkoxycarbonyl, carbocyclylcarbonyl, carbocyclyl-C_1-C_8-alkylcarbonyl, heterocyclylcarbonyl, heterocyclyl-C_1-C_8-alkylcarbonyl, carbocyclyloxycarbonyl, carbocyclyl-C_1-C_8-alkoxycarbonyl, $N(R^3)(R^4)$-C_1-C_8-alkylcarbonyl, C_1-C_8-alkyl(thiocarbonyl), C_1-C_8-alkoxy(thiocarbonyl), carbocyclyl(thiocarbonyl), carbocyclyl-C_1-C_8-alkyl(thiocarbonyl), heterocyclyl(thiocarbonyl), heterocyclyl-C_1-C_8-alkyl(thiocarbonyl), carbocyclyloxy(thiocarbonyl), carbocyclyl-C_1-C_8-alkoxy(thiocarbonyl), and $N(R^3)(R^4)$-C_1-C_8-alkyl(thiocarbonyl); and

E^2 is selected from the group consisting of C_2-C_{20}-alkyl, cycloalkyl, C_1-C_{10}-alkyl-cycloalkyl, cycloalkyl-C_1-C_{10}-alkyl, and C_1-C_{10}-alkyl-cycloalkyl-C_1-C_{10}-alkyl, wherein the any member of such group optionally is substituted with one or more halogen; and

E^5 is heterocyclyl that is:

optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, keto, C_1-C_8-alkyl, halo-C_1-C_8-alkyl, C_1-C_8-alkoxy, halo-C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl,

halogen-substituted C_1-C_8-alkoxy-C_1-C_8-alkyl, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbocyclyl, halocarbocyclyl, and carbocyclyl-C_1-C_8-alkyl, and/or optionally substituted on the same atom with two substituents independently selected from the group consisting of alkyl and haloalkyl, the two substituents together forming C_3-C_6-cycloalkyl or halo-C_3-C_6-cycloalkyl; and

R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_8-alkyl, and halo-C_1-C_8-alkyl; and

R^3 and R^4 are independently selected from the group consisting of -H, C_1-C_8-alkyl, C_1-C_8-alkoxycarbonyl, C_1-C_8-alkylcarbonyl, carbocyclyl-C_1-C_8-alkyl, and carbocyclyl-C_1-C_8-alkoxycarbonyl; and

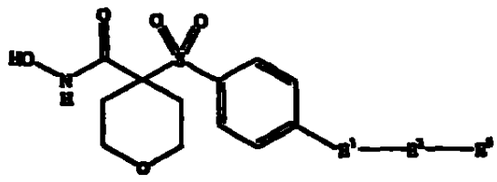
R^5 and R^6 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl, wherein any member (except -H) of such group optionally is substituted with one or more halogen; and

R^7 is selected from the group consisting of -H, C_1-C_8-alkyl, -O-R^8, -$N(R^8)(R^9)$, carbocyclyl-C_1-C_8-alkyl, and heterocyclyl-C_1-C_8-alkyl, wherein the C_1-C_8-alkyl, carbocyclyl-C_1-C_8-alkyl, or heterocyclyl-C_1-C_8-alkyl optionally is substituted with one or more halogen; and

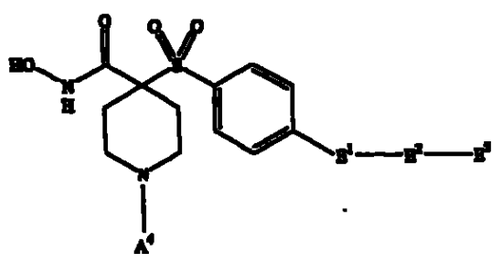
R^8 and R^9 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl, wherein any member (except -H) of such group optionally is substituted with one or more halogen.

374. A compound or salt thereof according to claim 373, wherein:

the compound corresponds in structure to a formula selected from the group consisting of:



(374-1) and

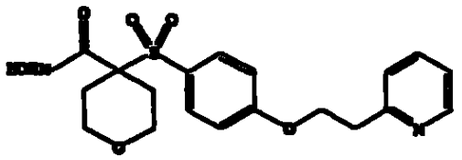


(374-2); and

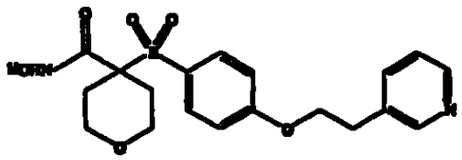
A^4 is selected from the group consisting of -H, alkyl, alkylcarbonyl, alkylcarbonylalkyl, alkylcarbonylalkylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkoxycarbonylalkylcarbonyl, alkylsulfonyl, alkyliminocarbonyl, alkenyl, alkynyl, alkoxyalkyl, alkylthioalkyl, alkylsulfonylalkyl, alkylsufoxidoalkyl, alkylthioalkenyl, alkylsulfoxidoalkenyl, alkylsulfonylalkenyl, carbocyclyl, carbocyclylalkyl, carbocyclylalkoxyalkyl, carbocyclylcarbonyl, carbocyclylsulfonyl, carbocyclyliminocarbonyl, carbocyclyloxycarbonyl, carbocylylthioalkyl, carbocylylsulfoxidoalkyl, carbocylylsulfonylalkyl, carbocyclylthioalkenyl, carbocyclylsulfoxidoalkenyl, carbocyclylsulfonylalkenyl, heterocyclyl, heterocyclylalkyl, heterocyclylalkoxyalkyl, heterocyclylcarbonyl, heterocyclylthioalkyl, heterocyclylsulfoxidoalkyl, heterocyclylsulfonylalkyl, heterocyclylthioalkenyl, heterocyclylsulfoxidoalkenyl, heterocyclylsulfonylalkenyl, heterocyclylsulfonyl, heterocyclyliminocarbonyl, heterocyclylalkylcarbonyl, heterocyclylcarbonylalkylcarbonyl, heterocyclylsulfonyl, heterocyclylcarbonylalkyl, aminoalkylcarbonyl, aminocarbonyl, aminocarbonylalkylcarbonyl, aminosulfonyl, aminosulfonylalkyl, aminoalkyl, aminocarbonylalkyl, and aminoalkylsulfonyl, wherein:

any member (except -H) of such group optionally is substituted.

375. A compound or salt thereof according to claim 374, wherein the compound corresponds in structure to a formula selected from the group consisting of:



and

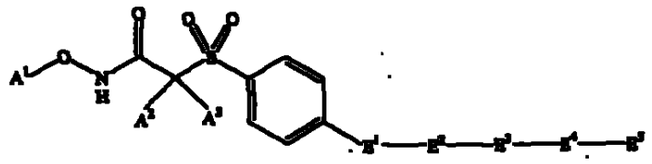


(375-1) (375-2).

668

376. A compound or salt thereof, wherein:

the compound corresponds in structure to Formula 376-1:



(376-1); and

A^1 is selected from the group consisting of -H, alkylcarbonyl, alkoxycarbonyl, carbocyclylcarbonyl, carbocyclylalkylcarbonyl, heterocyclylcarbonyl, heterocyclylalkylcarbonyl, carbocyclyloxycarbonyl, carbocyclylalkoxycarbonyl, aminoalkylcarbonyl, alkyl(thiocarbonyl), alkoxy(thiocarbonyl), carbocyclyl(thiocarbonyl), carbocyclylalkyl(thiocarbonyl), heterocyclyl(thiocarbonyl), heterocyclylalkyl(thiocarbonyl), carbocyclyloxy(thiocarbonyl), carbocyclylalkoxy(thiocarbonyl), and aminoalkyl(thiocarbonyl), wherein any member (except -H) of such group optionally is substituted; and

A^2 and A^3, together with the carbon atom to which they are both attached, form an optionally-substituted heterocyclyl containing from 5 to 8 ring members; and

E^1 is selected from the group consisting of -O-, $-S(O)_2-$, -S(O)-, -S-, $-N(R^1)-$, $-C(O)-N(R^1)-$, $-N(R^1)-C(O)-$, and $-C(R^1)(R^2)-$; and

E^2 is selected from the group consisting of alkyl, cycloalkyl, alkylcycloalkyl, cycloalkylalkyl, and alkylcycloalkylalkyl, wherein any member of such group optionally is substituted; and

E^3 is selected from the group consisting of -C(O)-, -O-(CO)-, -C(O)-O-, $-C(NR^3)-$, $-N(R^4)-$, $-N(R^4)-C(NR^3)-$, $-C(NR^3)-N(R^4)-$, $-C(O)-N(R^4)-$, $-N(R^4)-C(O)-$, $-N(R^4)-C(O)-N(R^5)-$, -S-, -S(O)-, $-N(R^4)-S(O)_2-$, $-S(O)_2-N(R^4)-$, $-C(O)-N(R^4)-N(R^5)-C(O)-$, $-C(R^4)(R^5)-C(O)-$, and $-C(R^7)(R^8)-$; and

E^4 is selected from the group consisting of a bond, alkyl, and alkenyl, wherein the alkyl or alkenyl optionally is substituted; and

E^5 is selected from the group consisting of carbocyclyl and heterocyclyl, wherein the carbocyclyl and heterocyclyl are:

substituted with a substituent selected from the group consisting of optionally-substituted carbocyclyl, optionally-substituted carbocyclylalkyl, optionally-substituted heterocyclyl, and optionally-substituted heterocyclylalkyl, and

optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, alkyl, alkoxy, alkoxyalkyl, $-N(R^{11})(R^{12})$, $-C(O)(R^{13})$, $-S-R^{11}$, $-S(O)_2-R^{11}$, carbocyclyl, carbocyclylalkyl, haloalkyl, haloalkoxy, halogen-substituted alkoxyalkyl, halocarbocyclyl, halogen-substituted carbocyclylalkyl, hydroxycarbocyclyl, and heteroaryl; and

R^1 and R^2 are independently selected from the group consisting of -H and alkyl, wherein the alkyl optionally is substituted; and

R^3 is selected from the group consisting of -H and -OH; and

R^4 and R^5 are independently selected from the group consisting of -H, alkyl, carbocyclyl, carbocyclylalkyl, heterocyclyl, and heterocyclylalkyl, wherein any member (except -H) of such group optionally is substituted; and

R^6 is selected from the group consisting of -CN and -OH; and

R^7 is selected from the group consisting of -H, halogen, -OH, alkyl, alkoxy, and alkoxyalkyl, wherein the alkyl, alkoxy, or alkoxyalkyl optionally is substituted; and

R^8 is selected from the group consisting of -OH and alkoxy, wherein the alkoxy optionally is substituted; and

R^{11} and R^{12} are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl, wherein any member (except -H) of such group optionally is substituted with one or more halogen; and

R^{13} is selected from the group consisting of -H, C_1-C_8-alkyl, $-O-R^{14}$, $-N(R^{14})(R^{15})$, carbocyclyl-C_1-C_8-alkyl, heterocyclyl-C_1-C_8-alkyl, halo-C_1-C_8-alkyl, halogen-substituted carbocyclyl-C_1-C_8-alkyl, and halogen-substituted heterocyclyl-C_1-C_8-alkyl; and

R^{14} and R^{15} are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl, wherein any member (except -H) of such group optionally is substituted with one or more halogen; and

neither R^1 nor R^2 forms a ring structure with E^2, E^3, E^4, or E^5; and

neither R^4 nor R^5 forms a ring structure with E^2, E^4, or E^5.

377. A compound or salt thereof according to claim 376, wherein:

A^1 is selected from the group consisting of -H, C_1-C_8-alkylcarbonyl, C_1-C_8-alkoxycarbonyl, carbocyclylcarbonyl, carbocyclyl-C_1-C_8-alkylcarbonyl, heterocyclylcarbonyl, heterocyclyl-C_1-C_8-alkylcarbonyl, carbocyclyloxycarbonyl, carbocyclyl-C_1-C_8-alkoxycarbonyl, $N(R^9)(R^{10})$-C_1-C_8-alkylcarbonyl, C_1-C_8-alkyl(thiocarbonyl), C_1-C_8-alkoxy(thiocarbonyl), carbocyclyl(thiocarbonyl), carbocyclyl-C_1-C_8-alkyl(thiocarbonyl), heterocyclyl(thiocarbonyl), heterocyclyl-C_1-C_8-alkyl(thiocarbonyl), carbocyclyloxy(thiocarbonyl), carbocyclyl-C_1-C_8-alkoxy(thiocarbonyl), and $N(R^9)(R^{10})$-C_1-C_8-alkyl(thiocarbonyl); and

E^2 is selected from the group consisting of C_2-C_{20}-alkyl, cycloalkyl, C_1-C_{10}-alkylcycloalkyl, cycloalkyl-C_1-C_{10}-alkyl, and C_1-C_{10}-alkylcycloalkyl-C_1-C_{10}-alkyl, wherein any member of such group optionally is substituted with one or more substituents independently selected from the group consisting of halogen, C_1-C_8-alkyl, and halo-C_1-C_8-alkyl; and

E^4 is selected from the group consisting of a bond, C_1-C_{20}-alkyl, and C_2-C_{20}-alkenyl, wherein the C_1-C_{20}-alkyl or C_2-C_{20}-alkenyl optionally is substituted with one or more substituents independently selected from the group consisting of:

halogen, and

carbocyclyl optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, $-NO_2$, -CN, C_1-C_8-alkyl, C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, halo-C_1-C_8-alkyl, halo-C_1-C_8-alkoxy, halogen-substituted C_1-C_8-alkoxy-C_1-C_8-alkyl, halocarbocyclyl, and halogen-substituted carbocyclyl-C_1-C_8-alkyl; and

E^5 is selected from the group consisting of carbocyclyl and heterocyclyl, wherein the carbocyclyl and heterocyclyl are:

substituted with a substituent selected from the group consisting of optionally-substituted carbocyclyl, optionally-substituted carbocyclyl-C_1-C_8-alkyl, optionally-substituted heterocyclyl, and optionally-substituted heterocyclyl-C_1-C_8-alkyl, and

optionally substituted with one or more substituents independently selected from the group consisting of halogen, -OH, -NO_2, -CN, C_1-C_8-alkyl, C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, -$N(R^{11})(R^{12})$, -$C(O)(R^{13})$, -S-R^{11}, -$S(O)_2$-R^{11}, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, halo-C_1-C_8-alkyl, halo-C_1-C_8-alkoxy, halogen-substituted C_1-C_8-alkoxy-C_1-C_8-alkyl, halocarbocyclyl, halogen-substituted carbocyclyl-C_1-C_8-alkyl, hydroxycarbocyclyl, and heteroaryl; and

R^1 and R^2 are independently selected from the group consisting of -H, C_1-C_8-alkyl, and halo-C_1-C_8-alkyl; and

R^4 and R^5 are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl, wherein any member (except -H) of such group optionally is substituted with one or more halogen; and

R^7 is selected from the group consisting of -H, halogen, -OH, C_1-C_8-alkyl, C_1-C_8-alkoxy, C_1-C_8-alkoxy-C_1-C_8-alkyl, halo-C_1-C_8-alkyl, halo-C_1-C_8-alkoxy, and halogen-substituted C_1-C_8-alkoxy-C_1-C_8-alkyl; and

R^8 is selected from the group consisting of -OH, C_1-C_8-alkoxy, and halo-C_1-C_8-alkoxy; and

R^9 and R^{10} are independently selected from the group consisting of -H, C_1-C_8-alkyl, C_1-C_8-alkoxycarbonyl, C_1-C_8-alkylcarbonyl, carbocyclyl-C_1-C_8-alkyl, and carbocyclyl-C_1-C_8-alkoxycarbonyl; and

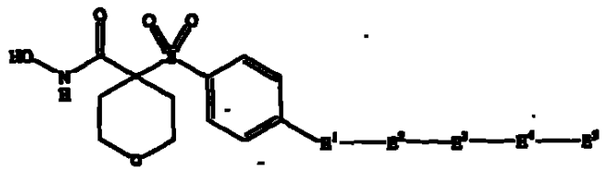
R^{11} and R^{12} are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl, wherein any member (except -H) of such group optionally is substituted with one or more halogen; and

R^{13} is selected from the group consisting of -H, C_1-C_8-alkyl, -O-R^{14}, -$N(R^{14})(R^{15})$, carbocyclyl-C_1-C_8-alkyl, heterocyclyl-C_1-C_8-alkyl, halo-C_1-C_8-alkyl, halogen-substituted carbocyclyl-C_1-C_8-alkyl, and halogen-substituted heterocyclyl-C_1-C_8-alkyl; and

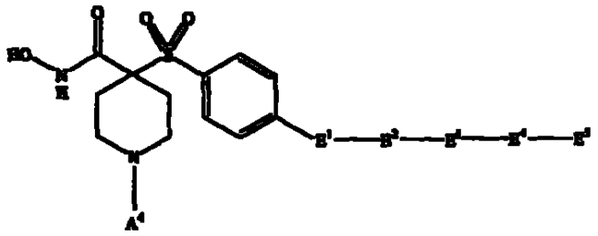
R^{14} and R^{15} are independently selected from the group consisting of -H, C_1-C_8-alkyl, carbocyclyl, carbocyclyl-C_1-C_8-alkyl, heterocyclyl, and heterocyclyl-C_1-C_8-alkyl, wherein any member (except -H) of such group optionally is substituted with one or more halogen.

378. A compound or salt thereof according to claim 377, wherein:

the compound corresponds in structure to a formula selected from the group consisting of:



(378-1) and

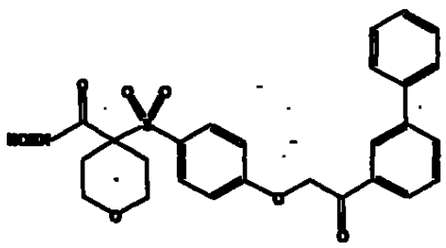


(378-2); and

A^4 is selected from the group consisting of -H, alkyl, alkylcarbonyl, alkylcarbonylalkyl, alkylcarbonylalkylcarbonyl, alkoxycarbonyl, alkoxycarbonylalkyl, alkoxycarbonylalkylcarbonyl, alkylsulfonyl, alkyliminocarbonyl, alkenyl, alkynyl, alkoxyalkyl, alkylthioalkyl, alkylsulfonylalkyl, alkylsuloxidoalkyl, alkylthioalkenyl, alkylsulfoxidoalkenyl, alkylsulfonylalkenyl, carbocyclyl, carbocyclylalkyl, carbocyclylalkoxyalkyl, carbocyclylcarbonyl, carbocyclylsulfonyl, carbocyclyliminocarbonyl, carbocyclyloxycarbonyl, carbocylylthioalkyl, carbocylylsulfoxidoalkyl, carbocylylsulfonylalkyl, carbocyclylthioalkenyl, carbocyclylsulfoxidoalkenyl, carbocyclylsulfonylalkenyl, heterocyclyl, heterocyclylalkyl, heterocyclylalkoxyalkyl, heterocyclylcarbonyl, heterocyclylthioalkyl, heterocyclylsulfoxidoalkyl, heterocyclylsulfonylalkyl, heterocyclylthioalkenyl, heterocyclylsulfoxidoalkenyl, heterocyclylsulfonylalkenyl, heterocyclylsulfonyl, heterocyclyliminocarbonyl, heterocyclylalkylcarbonyl, heterocyclylcarbonylalkylcarbonyl, heterocyclylsulfonyl, heterocyclylcarbonylalkyl, aminoalkylcarbonyl, aminocarbonyl, aminocarbonylalkylcarbonyl, aminosulfonyl, aminosulfonylalkyl, aminoalkyl, aminocarbonylalkyl, and aminoalkylsulfonyl, wherein:

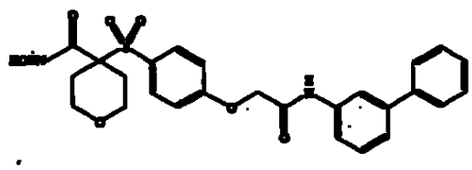
any member (except -H) of such group optionally is substituted.

379. A compound or salt thereof according to claim 378, wherein the compound corresponds in structure to a formula selected from the group consisting of:



(379-1)

and



(379-2).

380. A method for preventing or treating a condition associated with pathological matrix metalloprotease activity in a mammal having the condition or predisposed to having the condition, wherein:

the method comprises administering a compound or a pharmaceutically acceptable salt thereof in a therapeutically-effective amount to the mammal; and

the compound is selected from the group of compounds recited in claims 1, 122, 225, 235, 250, 260, 267, 296, 303, 308, 322, 335, 337, 344, 354, 359, 361, 368, 372, and 376.

381. A method according to claim 380, wherein the compound or salt inhibits the activity of one or more of MMP-2, MMP-9, and MMP-13, while exhibiting substantially less inhibitory activity against both MMP-1 and MMP-14.

382. A method according to claim 381, wherein the compound or salt inhibits the activity of MMP-13, while exhibiting substantially less inhibitory activity against both MMP-1 and MMP-14.

383. A method according to claim 382, wherein the pathological condition comprises arthritis or a cardiovascular condition.

384. A method according to claim 381, wherein the compound or salt inhibits the activity of both MMP-2 and MMP-9, while exhibiting substantially less inhibitory activity against both MMP-1 and MMP-14.

385. A method according to claim 384, wherein the pathological condition comprises cancer, an opthalmologic condition, or a cardiovascular condition.

386. A method for preventing or treating a pathological condition in a mammal having the pathological condition or predisposed to having the pathological condition, wherein:

the method comprises administering a compound or a pharmaceutically acceptable salt thereof in a therapeutically-effective amount to the mammal; and

the compound is selected from the group of compounds recited in claims 1, 122, 225, 235, 250, 260, 267, 296, 303, 308, 322, 335, 337, 344, 354, 359, 361, 368, 372, and 376; and

the pathological condition is selected from the group consisting of tissue destruction, a fibrotic disease, matrix weakening, defective injury repair, a cardiovascular disease, a pulmonary disease, a kidney disease, a liver disease, an ophthalmologic disease, and a central nervous system disease.

387. A method for preventing or treating a pathological condition in a mammal having the pathological condition or predisposed to having the pathological condition, wherein:

the method comprises administering a compound or a pharmaceutically acceptable salt thereof in a therapeutically-effective amount to the mammal; and

the compound is selected from the group of compounds recited in claims 1, 122, 225, 235, 250, 260, 267, 296, 303, 308, 322, 335, 337, 344, 354, 359, 361, 368, 372, and 376; and

the pathological condition is selected from the group consisting of osteoarthritis, rheumatoid arthritis, septic arthritis, tumor invasion, tumor metastasis, tumor angiogenesis, a decubitis ulcer, a gastric ulcer, a corneal ulcer, periodontal disease, liver

cirrhosis, fibrotic lung disease, otosclerosis, atherosclerosis, multiple sclerosis, dilated cardiomyopathy, epidermal ulceration, epidermolysis bullosa, aortic aneurysm, defective injury repair, an adhesion, scarring, congestive heart failure, post myocardial infarction, coronary thrombosis, emphysema, proteinuria, Alzheimer's disease, bone disease, and chronic obstructive pulmonary disease.

388. A method according to claim 387, wherein the condition comprises arthritis.

389. A method according to claim 387, wherein the condition comprises tumor invasion, tumor metastasis, or tumor angiogenesis.

390. A method according to claim 387, wherein the condition comprises periodontal disease.

391. A method according to claim 387, wherein the condition comprises atherosclerosis.

392. A method according to claim 387, wherein the condition comprises multiple sclerosis.

393. A method according to claim 387, wherein the condition comprises dilated cardiomyopathy.

394. A method according to claim 387, wherein the condition comprises post myocardial infarction.

395. A method according to claim 387, wherein the condition comprises congestive heart failure.

396. A method according to claim 387, wherein the condition comprises chronic obstructive pulmonary disease.

397. A method for preventing or treating a pathological condition associated with pathological TNF-α convertase activity in a mammal having the pathological condition or predisposed to having the condition, wherein:

the method comprises administering a compound or a pharmaceutically acceptable salt thereof in a therapeutically-effective amount to the mammal; and

the compound is selected from the group of compounds recited in claims 1, 122, 225, 235, 250, 260, 267, 296, 303, 308, 322, 335, 337, 344, 354, 359, 361, 368, 372, and 376.

398. A method according to claim 397, wherein the pathological condition is selected from the group consisting of inflammation, a pulmonary disease, a cardiovascular disease, an autoimmune disease, graft rejection, a fibrotic disease, multiple sclerosis, cancer, an infectious disease, fever, psoriasis, hemorrhage, coagulation, radiation damage, acute-phase responses of shock and sepsis, anorexia, and cachexia.

399. A method for preventing or treating a pathological condition associated with pathological aggrecanase activity in a mammal having the pathological condition or predisposed to having the condition, wherein:

the method comprises administering a compound or a pharmaceutically acceptable salt thereof in a therapeutically-effective amount to the mammal; and

the compound is selected from the group of compounds recited in claims 1, 122, 225, 235, 250, 260, 267, 296, 303, 308, 322, 335, 337, 344, 354, 359, 361, 368, 372, and 376.

400. A method according to claim 399, wherein the condition comprises an inflammation condition or cancer.

401. A method according to claim 399, wherein the method further comprises administering the compound or salt thereof to prevent or treat a condition associated with matrix metalloprotease activity.

402. A pharmaceutical composition comprising a therapeutically-effective amount of a compound or a pharmaceutically-acceptable salt thereof, wherein the compound is selected from the group of compounds recited in claims 1, 122, 225, 235, 250, 260, 267, 296, 303, 308, 322, 335, 337, 344, 354, 359, 361, 368, 372, and 376.

403. A use of a compound or a pharmaceutically acceptable salt thereof to prepare a medicament for treating a condition associated with pathological matrix metalloprotease activity, wherein the compound is selected from the group of compounds recited in claims 1, 122, 225, 235, 250, 260, 267, 296, 303, 308, 322, 335, 337, 344, 354, 359, 361, 368, 372, and 376.

404. A use of a compound or a pharmaceutically acceptable salt thereof to prepare a medicament for treating a condition associated with pathological TNF-α convertase activity, wherein the compound is selected from the group of compounds recited in claims 1, 122, 225, 235, 250, 260, 267, 296, 303, 308, 322, 335, 337, 344, 354, 359, 361, 368, 372, and 376.

405. A use of a compound or a pharmaceutically acceptable salt thereof to prepare a medicament for treating a condition associated with pathological aggrecanase activity, wherein the compound is selected from the group of compounds recited in claims 1, 122, 225, 235, 250, 260, 267, 296, 303, 308, 322, 335, 337, 344, 354, 359, 361, 368, 372, and 376.

678

SULFONA-HIDROXAMATOS AROMÁTICOS Y SU USO COMO INHIBIDORES DE PROTEASAS

PRIORIDAD DE SOLICITUD DE PATENTE RELACIONADA

[1] La presente solicitud reivindica el beneficio de prioridad de la Solicitud de Patente Provisional de los Estados Unidos Nro. 60/290,375 (presentada el 11 de mayo de 2001). El texto completo de dicha Solicitud de Patente Provisional de los Estados Unidos Nro. 60/290,375 se incorpora a la presente a modo de referencia.

CAMPO DE LA INVENCIÓN

[2] La presente Invención tiene como objeto inhibidores de proteinasas (también conocidas como proteasas), y más particularmente con sulfona-hidroxamatos aromáticos (también conocidos como "ácidos sulfona hidroxámicos aromáticos") que, entre otras cosas, son inhibidores de la actividad de las metaloproteinasas de matriz (también conocidas como "metaloproteasas de matriz"o MMP") y/o de la agrecanasa. Esta invención también tiene como objeto composiciones de tales inhibidores, intermediarios para la síntesis de tales inhibidores, métodos para preparar tales inhibidores y métodos para impedir o tratar condiciones asociadas con la actividad de MPP y/o la actividad de agrecanasa, particularmente en condiciones patológicas.

ANTECEDENTES DE LA INVENCIÓN

[3] El tejido conectivo es un componente necesario en todos los mamíferos. Estos compuestos son los materiales biológicos que proveen rigidez, diferenciación, uniones y, en algunos casos, elasticidad. Los componentes de los tejidos conectivos incluyen, por ejemplo, colágeno, elastina, proteoglicanos, fibronectina y laminina. Estos compuestos bioquímicos constituyen (o son componentes de) estructuras, tales como piel,

679

hueso, dientes, tendones, cartílagos, membranas basales, vasos sanguíneos, córnea y humor vítreo.

[4] Bajo condiciones normales, los procesos de recambio y/o reparación están controlados y en equilibrio con la producción de tejido conectivo. La degradación del tejido conectivo tiene lugar por la acción de las proteinasas liberadas por los tejidos celulares residentes y/o células invasoras inflamatorias o tumorales.

[5] Las metaloproteinasas de matriz, una familia de proteinasas dependientes de zinc, constituyen una de las clases de enzimas más importantes involucradas en la degradación del tejido conectivo. Las metaloproteinasas de matriz se dividen en clases, donde algunos miembros tienen distintos nombres de uso común. Algunos ejemplos son: MMP-1 (también conocida como colagenasa 1, colagenasa de fibroblastos, o EC 3.4.24.3); MMP-2 (también conocida como gelatinasa A, 72kDa gelatinasa, colagenasa de la membrana basal, o EC 3.4.24.24), MMP-3 (también conocida como estromelisina 1 o EC 3.4.24.17), proteoglicanasa, MMP-7 (también conocida como matrilisina), MMP-8 (también conocida como colagenasa II, neutrófilo colagenasa, o EC 3.4.24.34), MMP-9 (también conocida como gelatinasa B, 92kDa gelatinasa, o EC 3.4.24.35), MMP-10 (también conocida como estromelisina 2 o EC 3.4.24.22), MMP-1 I (también conocida como estromelisina 3), MMP-12 (también conocida como metaloelastasa, elastasa de macrófagos humanos o HME), MMP- 13 (también conocida como colagenasa 111), y MMP- 14 (también conocida como MT1-MMP o MMP de la membrana). Véase , en general, Woessner, J.F., "The Matrix Metalloprotease Family" en Matrix Metalloproteases , pp.1-14 (Editado Parks, W.C. & Mecham, R.P., Academic Press, San Diego, CA 1998).

[6] La degradación excesiva del tejido conectivo por parte de las metaloproteinasas es una característica de muchas condiciones patológicas. La inhibición de las MMP por lo tanto provee un mecanismo de control para la descomposición de tejidos para impedir y/o tratar estas condiciones patológicas. Tales condiciones patológicas generalmente incluyen, por ejemplo, la destrucción de tejidos, enfermedades fibróticas, debilitación patológica de la matriz, reparación deficiente de heridas, enfermedades cardiovasculares, enfermedades pulmonares, enfermedades renales, enfermedades hepáticas, enfermedades oftalmológicas y enfermedades del sistema nervioso central. Algunos ejemplos específicos de tales condiciones incluyen, por ejemplo, artritis reumatoidea, osteoartritis, artritis séptica, esclerosis múltiple, una úlcera de decubitus, ulceración de la córnea, ulceración epidérmica, úlcera gástrica, metástasis tumoral, invasión tumoral, angiogénesis tumoral, enfermedad periodontal, cirrosis hepática, enfermedad fibrótica pulmonar, enfisema, otoesclerosis, ateroesclerosis, proteinuria, trombosis coronaria, cardiomiopatía dilatada, deficiencia cardiaca congestiva, aneurisma aórtico, epidermólisis ampollar, enfermedad ósea, mal de Alzheimer, reparación deficiente de heridas (por ejemplo, reparación deficiente de heridas, adherencias, tales como adherencias pos-quirúrgicas y escarificación), infarto pos-miocardial, enfermedad de los huesos y enfermedad pulmonar obstructiva crónica.

[7] Las metaloproteinasas también están involucradas en la biosíntesis del factor de necrosis tumoral (TNF). Los factores de necrosis tumoral intervienen en numerosas condiciones patológicas. Por ejemplo, se considera actualmente que el TNF-α, una citoquina, es producida inicialmente como una molécula de 28 kD asociada a células. Es liberado como una forma

681

activa de 17 kD que puede mediar una gran cantidad de efectos deletéreos in vitro e in vivo. Por ejemplo, el TNF α puede causar y/o contribuir con los efectos de inflamación, (por ejemplo, artritis reumatoidea), enfermedades autoinmunes, rechazo de injertos, esclerosis múltiple, enfermedades fibróticas, cáncer, enfermedades infecciosas (por ejemplo, malaria, infecciones microbacterianas, meningitis, etc.), fiebre, psoriasis, trastornos cardiovasculares (por ejemplo, lesiones por reperfusión post-isquémica e insuficiencia cardiaca congestiva), enfermedades pulmonares, hemorragia, coagulación, lesiones alveolares hiperóxicas, daños por radiación y respuestas de fase aguda, como aquéllas que se observan con infecciones y sepsias y durante estados de shock, (por ejemplo, shock séptico y shock hemodinámico). La liberación crónica de TNF α activo puede causar caquexia y anorexia. El TNF α puede ser letal.

[8] La inhibición de la producción y acción del TNF (y compuestos relacionados) es un tratamiento clínico importante. Un mecanismo que se puede usar es la inhibición de las metaloproteinasas de matriz. Se ha demostrado que los compuestos que inhiben MMP, tales como colagenasa, estromelisina y gelatinasa, inhiben la liberación del TNF α (Gearing et al. Nature 376, 555-557 (1994); McGeehan et al., Nature 376, 558-561 (1994)). También se ha informado que los inhibidores de MMP inhiben la TNF-α convertasa, una metaloproteinasa involucrada en la formación de TNF-α activa. Véase, por ejemplo, Publ. Int. OMPI. No. WO 94/24140. Véase también, Publ. Int. OMPI. No. WO 94/02466. Véase también, Publ. Int. OMPI. No. WO 97/20824.

[9] Las metaloproteinasas de matriz también están involucradas en otros procesos bioquímicos en mamíferos. Entre ellos se puede incluir el

682

control de la ovulación, la involución uterina post-parto, posiblemente implantes, clivaje de APP (Proteína Precursora □-Amiloide) de la placa amiloide e inactivación de inhibidores α_1-proteasas (α_1-PI). La inhibición de estas MMP permite el control de la fertilidad. Además, el aumento y mantenimiento de los niveles de una inhibidor de serina endógeno o administrado (por ejemplo, α_1 -PI) colabora con el tratamiento y prevención de condiciones patológicas tales como enfisema, enfermedades pulmonares, enfermedades inflamatorias, y enfermedades del envejecimiento (por ejemplo, pérdida de piel o estiramiento y resillencia de órganos.

[10] Se conocen numerosos inhibidores de metaloproteinasas. Véase en general, Brown, P.D., "Syntetic Inhibitors de Metaloproteinasas de matriz," en Metaloproteinasas de matriz, pp. 243-61 (Editado por Parks, W.C. & Mecham, R.P., Academic Press, San Diego, CA 1998).

[11] Los inhibidores de las metaloproteinasas incluyen sustancias bioquímicas naturales tales como inhibidores tisulares de metaloproteinasas (TIMP), α_2-macroglobulina y sus análogos o derivados. Estas son moléculas proteicas de alto peso molecular que forman complejos inactivos con las metaloproteinasas

[12] Se han descripto una cantidad de compuestos más pequeños de tipo peptídico, que inhiben las metaloproteinasas. Los derivados mercaptoamidapeptidilo han mostrado inhibición de la enzima convertidora de angiotensina (también conocida como ACE) in vitro e in vivo. La ACE ayuda en la producción de angiotensina II, una potente sustancia vasopresora en mamíferos y la inhibición de esta enzima conduce a la disminución de la presión sanguínea

683

[13] Se ha informado una amplia variedad de compuestos tiol que inhiben las MMP. Véase, por ejemplo, W095/12389. Véase también, W096/11209. Véase también, la Patente de los Estados Unidos Nro. 4,595,700. Véase también, la Patente de los Estados Unidos Nro. 6.013,649.

[14] También se han informado una amplia variedad de hidroxamatos que inhiben las MMP. Tales compuestos informados incluyen hidroxamatos con una estructura de carbonos. Véase, por ejemplo, Publ. Int. OMPI. No. WO 95/29892. Véase también, Publ. Int. OMPI. No. WO 97/24117. Véase también, Publ. Int. OMPI. No. WO 97/49679. Véase también, Patente Europea Nro. EP 0 780 386. Tales compuestos también incluyen hidroxamatos que tienen estructuras básicas de peptidilo o peptidomiméticas.. Véase, por ejemplo, Publ. Int. OMPI. No. WO 90/05719. Véase también, Publ. Int. OMPI. No. WO 93/20047. Véase también, Publ. Int. OMPI. No. WO 95/09841. Véase también, Publ. Int. OMPI. No. WO 96/06074. Véase también, Schwartz et al., Progr. Med. Chem., 29:271-334(1992). Véase también, Rasmussen et al., PharmacoL Ther., 75(I): 69-75 (1997). Véase también, Denis et al., Invest New Drugs, 15(3): 175-185 (1997). También se han informado diversos piperazinilsulfonilmetil-hidroxamatos y piperidinilsulfonilmetil-hidroxamatos que inhiben MMP. Véase, Publ. Int. OMPI. No. WO 00/46221. y se ha informado sobre distintos sulfona hidroxamatos aromáticos que inhiben MMPs. Véase, Publ. Int. OMPI. No. WO 99/25687. Véase también, Publ. Int. OMPI. No. WO 00/50396. Véase también, Publ. Int. OMPI. No. WO 00/69821.

[15] En general es ventajoso que una droga inhibidora de MMP se dirija a una o más MMP con preferencia a otras MMP. Por ejemplo, típicamente se prefiere inhibir las MMP-2, MMP-3, MMP-9, y/o MMP-13 (particularmente la MMP-13) para el tratamiento y/o prevención del cáncer,

para inhibir la metástasis e inhibir la angiogénesis. También es típicamente preferido que se desee inhibir la MMP-13 para prevenir y/o tratar la osteoartritis. Véase, por ejemplo, Mitchell et al., J Clin. Invest., 97:761-768 (1996). Véase también, Reboul et al., J Clin. Invest., 97:2011-2019 (1996). Normalmente, sin embargo, se prefiere usar una droga que tenga poco o ningún efecto inhibidor sobre las MMP-1 y MMP-14. Esta preferencia se basa en el hecho de que ambas MMP-1 y MMP-14 participan en varios procesos homeostáticos, y la inhibición de la MMP-1 y/o MMP-14 en consecuencia tiende a interferir con dichos procesos.

[16] Muchos inhibidores de MMP conocidos a menudo exhiben los mismos efectos inhibitorios, o efectos similares, contra cada una de las enzimas MMP. Por ejemplo, se ha informado que el hidroxamato peptidomimético conocido como batimastato exhibe valores IC_{50} de aproximadamente 1 a 20 nanomolar (nM) contra cada una de MMP-1, MMP-2, MMP-3, MMP-7 y MMP-9. El Marimastato, (otro hidroxamato peptidomimético) se ha descripto como otro inhibidor de MMP de amplio espectro, con un espectro inhibidor de enzimas muy similar al del batimastato, excepto que el Marimastato exhibe un valor IC_{50} contra MMP-3 de 230 nM. Véase Rasmussen et al., Pharmacol. Ther., 75(I): 69-75 (1997).

[17] Un análisis profundo de los datos de los estudios de Fase I/II utilizando Marimastato en pacientes con tumores cancerosos sólidos avanzados, refractarios a tratamiento y rápidamente progresivos (colorrectales, pancreáticos, ováricos, prostáticos) indicaron una reducción relacionada con la dosis en el aumento de los antígenos específicos de cáncer utilizados como marcadores substitutos para la actividad biológica. Si bien el Marimastato presentaba en alguna medida cierta eficacia por medio de estos marcadores,

se observaron efectos colaterales tóxicos. La toxicidad relacionada con la droga más común del Marimastato en dichos ensayos clínicos eran rigidez y dolor musculoesqueletario, a menudo comenzando en las pequeñas articulaciones de las manos con difusión posterior hacia brazos y hombros. Un corto paréntesis en la dosificación de 1-3 semanas seguido de una reducción en la misma, permite continuar con el tratamiento. Rasmussen et al., Pharmacol. Ther., 75(I): 69-75 (1997). Se cree que la falta de especificidad del efecto inhibitorio entre los MMP puede ser la causa de dicho efecto.

[18] Otra enzima involucrada en las condiciones patológicas asociadas con la degradación excesiva del tejido conectivo es la agrecanasa, particularmente la agrecanasa-1 (también conocida como ADAMTS-4). Específicamente, el cartílago articular contiene grandes cantidades de proteoglicano agrecano. El proteoglicano agrecano provee propiedades mecánicas que ayudan al cartílago articular a soportar las deformaciones compresivas durante la articulación. La pérdida de fragmentos de agrecano y su liberación en el fluido sinovial provocada por la separación proteolítica es un evento patofisiológico central en la osteoartritis y artritis reumatoidea. Se ha informado sobre la existencia de dos sitios de clivado importantes en los dominios interglobulares proteolíticamente sensibles en la región N-terminal de la proteína madre de la agrecanasa. Se ha informado que uno de dichos sitios es clivado por diversas metaloproteinasas de matriz. El otro sitio, sin embargo, es clivado por agrecanasa-1. Por lo tanto, al inhibir la actividad excesiva de la agrecanasa se provee una prevención o tratamiento adicional y/o alternativo para los trastornos inflamatorios. Véase en general, Tang, B. L., "ADAMTS: A Novel Family of Extracellular Matrix Proteases," Int'l Journal of Biochemistry & Cell Biology, 33, pp. 33-44 (2001). Tales enfermedades incluyen, por ejemplo,

osteoartritis, artritis reumatoidea, lesiones articulares, artritis reactiva, artritis pirofosfática aguda, y artritis psoriática. Véase, por ejemplo, Public. de Patente Europea No. EP 1 081 137 A1.

[19] Además de los trastornos inflamatorios, también existe evidencia de que la inhibición de la agrecanasa puede ser usada para prevenir o tratar el cáncer. Por ejemplo, se han observado niveles excesivos de agrecanasa-1 con una línea de células ghoma. También se ha postulado que la naturaleza enzimática de la agrecanasa y sus similitudes con las MMP constituiría un soporte para la invasión tumoral, la metástasis y la angiogénesis. Véase Tang, Int'l Journal de Biochemistry & Cell Biology, 33, pp. 33-44 (2001).

[20] Se han informado diversos compuestos que inhiben la agrecanasa-1. Dichos compuestos incluyen, por ejemplo, los descritos en la Public. de Patente Europea No. EP 1 081 137 A1. Tales compuestos también incluyen, por ejemplo, los de Public. de PCT Int. OMPI No. WO 00/09000. Tales compuestos también incluyen, por ejemplo, los descritos en la Public. de PCT Int. OMPI No. WO 00/59874.

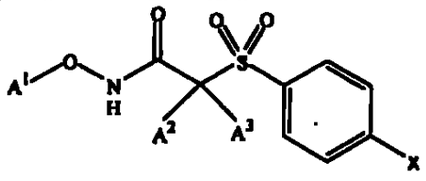
[21] En vista de la importancia de los compuestos de hidroxamato en la prevención o tratamiento de diversas condiciones patológicas y la ausencia de especificidad enzimática demostrada por dos de las drogas inhibidoras de MMP más potentes que han sido objeto de pruebas clínicas, continúa existiendo la necesidad de contar con hidroxamatos con mayor especificidad enzimática (preferentemente contra la MMP-2, MMP-9, MMP-13, y/o agrecanasa (en algunos casos particularmente contra la MMP-13, y en otros casos contra la MMP-2 y la MMP-9, y agrecanasa en aun otros casos), y que al mismo tiempo presenten poca o ninguna inhibición de la MMP-1 y/o MMP-

14. La siguiente memoria describe compuestos de hidroxamato que tienden a exhibir dichas actividades deseables.

RESUMEN DE LA INVENCIÓN

[22] Esta invención tiene como objeto compuestos de hidroxamato (y sus sales) que inhiben la actividad patológica de las proteasas (particularmente compuestos que inhiben la actividad de MMP-2, MMP-9, MMP- 13, y/o agrecanasa), y al mismo tiempo exhiben en general poca o ninguna inhibición de la actividad de la MMP-1 y MMP-14. Esta invención también tiene como objeto un método para inhibir la actividad de MMP y/o agrecanasa, particularmente la actividad patológica de MMP y/o agrecanasa. Dicho método es particularmente adecuado para ser usado con mamíferos, tales como seres humanos, otros primates (por ejemplo, monos, chimpancés, etc.), animales domésticos (por ejemplo, perros, gatos, caballos etc.), ganado (por ejemplo, caprino, ovino, porcino, vacuno, etc.), animales de laboratorio (por ejemplo, ratones, ratas, etc.), y animales salvajes o en cautiverio (por ejemplo, lobos, osos, ciervos, etc.).

[23] En resumen, por lo tanto, la invención tiene como objeto parcialmente un compuesto o sal del mismo. El compuesto tiene una estructura que corresponde a la Fórmula I:



I

donde:

A^1 es -H, alquilcarbonilo, alcoxicarbonilo, carbociclilcarbonilo, carbociclilalquilcarbonilo, heterociclilcarbonilo, heterociclilalquilcarbonilo,

688

carbociclilloxicarbonilo, carbociclilalcoxicarbonilo, aminoalquilcarbonilo, alquil(tiocarbonilo), alcoxi(tiocarbonilo), carbociclil(tiocarbonilo), carbociclilalquil(tiocarbonilo), heterociclil(tiocarbonilo), heterociclilalquil(tiocarbonilo), carbocicliloxi(tiocarbonilo), carbociclilalcoxi(tiocarbonilo), o aminoalquil(tiocarbonilo). Salvo cuando A^1 es -H, cualquier miembro de este grupo es optativamente sustituido (es decir, puede estar sustituido o insustituido).

A^2 y A^3, junto con el átomo de carbono al cual ambos están unidos, forman un heterociclilo optativamente sustituido que contiene entre 5 y 8 miembros en el anillo.

[24] En una realización preferida de la invención, X es $-E^1-E^2-E^3-E^4-E^5$. En esta realización:

E^1 es -O-, $-S(O)_2-$, -S(O)-, -S-, $-N(R^1)-$, $-C(O)-N(R^1)-$, $-N(R^1)-C(O)-$, o $-C(R^1)(R^2)-$.

E^2 forma un enlace de al menos 2 átomos de carbono entre E^1 y E^3. E^2 es alquilo, cicloalquilo, alquilcicloalquilo, cicloalquilalquilo, o alquilcicloalquilalquilo. Cualquier miembro de este grupo es optativamente sustituido.

E^3 es $-C(O)-$, $-O-(CO)-$, $-C(O)-O-$, $-C(NR^3)-$, $-N(R^4)-$, $-C(O)-N(R^4)-$, $-N(R^4)-C(O)-$, $-N(R^4)-C(O)-N(R^5)-$, -S-, -S(O)-, $-N(R^4)-S(O)_2-$, $-S(O)_2-N(R^4)-$, $-C(O)-N(R^4)-N(R^5)-C(O)-$, $-C(R^4)(R^6)-C(O)-$, o $-C(R^7)(R^8)-$.

E^4 es un enlace, alquilo, y alquenilo. El alquilo y alquenilo son optativamente sustituidos.

E^5 es -H, -OH, alquilo, alquenilo, alquinilo, alcoxi, alcoxialquilo, carbociclilo, o heterociclilo. Salvo cuando E^5 es excepto -H o -OH, cualquier

669

miembro de este grupo es optativamente sustituido. E^5 no es -H cuando E^3 es $-C(R^7)(R^8)-$ y E^4 es un enlace.

R^1 y R^2 se seleccionan independientemente del grupo formado por -H y alquilo. El alquilo es optativamente sustituido. Ni R^1 ni R^2 forman una estructura de anillo con E^2, E^3, E^4, o E^5.

R^3 es -H o -OH.

R^4 y R^5 se seleccionan independientemente del grupo formado por -H, alquilo, carbociclilo, carbociclilalquilo, heterociclilo, y heterociclilalquilo. Con la excepción de -H, cualquier miembro de este grupo es optativamente sustituido. Ni R^4 ni R^5 forman una estructura de anillo con E^2, E^4, o E^5.

R^6 es -CN o -OH.

R^7 es -H, halógeno, -OH, alquilo, alcoxi, o alcoxialquilo. El alquilo, alcoxi, y alcoxialquilo son optativamente sustituidos.

R^8 es -OH o alcoxi. El alcoxi es optativamente sustituido.

[25] En otra realización preferida de la invención, X es $-E^1-E^2-E^3-E^4-E^5$. En esta realización:

E^1 es -O-, $-S(O)_2-$, -S(O)-, -S-, $-N(R^1)-$, $-C(O)-N(R^1)-$, $-N(R^1)-C(O)-$, o $-C(R^1)(R^2)-$.

E^2 forma un enlace de al menos 2 átomos de carbono entre E^1 y E3. E^2 es alquilo, cicloalquilo, alquilcicloalquilo, cicloalquilalquilo, o alquilcicloalquilalquilo. Cualquier miembro de este grupo es optativamente sustituido.

E^3 es carbociclilo o heterociclilo. El carbociclilo y heterociclilo tienen 5 ó 6 miembros en el anillo y es optativamente sustituido.

E^4 es un enlace, alquilo, alquenilo, -O-, o $-N(R^3)-$. El alquilo o alquenilo son optativamente sustituidos.

1690

E^5 es carbociclilo o heterociclilo. El carbociclilo o heterociclilo son optativamente sustituidos.

R^1 y R^2 se seleccionan independientemente del grupo formado por -H y alquilo. El alquilo es optativamente sustituido. Ni R^1 ni R^2 forman una estructura de anillo con E^2, E^3, E^4, o E^5.

R^3 es -H o alquilo. El alquilo es optativamente sustituido.

[26] En otra realización preferida de la invención, X es $-E^1-E^2-C(E^6)=C(E^7)-E^3-E^4-E^5$. En esta realización:

E^1 es -O-, $-S(O)_2-$, -S(O)-, $-N(R^1)-$, $-C(O)-N(R^1)-$, $-N(R^1)-C(O)-$, o $-C(R^1)(R^2)-$.

E^2 es alquilo, cicloalquilo, alquilcicloalquilo, cicloalquilalquilo, o alquilcicloalquilalquilo. Cualquier miembro de este grupo es optativamente sustituido.

E^4 es un enlace y alquilo. El alquilo es optativamente sustituido.

E^5 es alquilo, alquenilo, alquinilo, alcoxi, alcoxialquilo, carbociclilo, o heterociclilo. Cualquier miembro de este grupo es optativamente sustituido.

E^6 es -H, halógeno, o alquilo. El alquilo es optativamente sustituido.

E^7 es -H, alquilo, alquenilo, alquinilo, $-S(O)_2-R^3$, $-NO_2$, $-C(O)-N(R^3)(R^4)$, $-(C)(OR^3)$, carbociclilo, carbociclilalquilo, alcoxicarbociclilo, -CN, -C=N-OH, o -C=NH. El alquilo, alquenilo, alquinilo, carbociclilo, carbociclilalquilo, o alcoxicarbociclilo son optativamente sustituidos.

R^1 y R^2 se seleccionan independientemente del grupo formado por -H y alquilo. El alquilo es optativamente sustituido. Ni R^1 ni R^2 forman una estructura de anillo con E^2, E^4, E^5, E^6, o E^7.

R^3 y R^4 se seleccionan independientemente del grupo formado por -H, alquilo, carbociclilo, carbociclilalquilo, heterociclilo, heterociclilalquilo. Salvo

691

cuando el miembro es -H, cualquier miembro de este grupo es optativamente sustituido.

[27] En otra realización preferida de la invención, X es $-E^1-E^2-E^3-E^4-E^5$. En esta realización:

E^1 es -O-, $-S(O)_2-$, -S(O)-, $-N(R^3)-$, $-C(O)-N(R^3)-$, $-N(R^3)-C(O)-$, o $-C(R^1)(R^2)-$.

E^2 es un enlace, alquilo, cicloalquilo, alquilcicloalquilo, cicloalquilalquilo, o alquilcicloalquilalquilo. Salvo cuando el miembro es un enlace, cualquier miembro de dicho grupo es optativamente sustituido.

E^3 es carbonilpirrolidinilo. El carbonilpirrolidinilo es optativamente sustituido.

E^4 es un enlace, alquilo, o alquenilo. El alquilo y alquenilo son optativamente sustituidos.

E^5 es alquilo, alquenilo, alquinilo, alcoxi, alcoxialquilo, carbociclilo, o heterociclilo. Cualquier miembro de este grupo es optativamente sustituido.

R^1 y R^2 se seleccionan independientemente del grupo formado por -H y alquilo. El alquilo es optativamente sustituido. Ni R^1 ni R^2 forman una estructura de anillo con E^2, E^3, E^4, o E^5.

[28] En otra realización preferida de la invención, X es $-E^1-E^2-E^5$. En esta realización:

E^1 es -O-, $-S(O)_2-$, -S(O)-, $-N(R^1)-$, $-C(O)-N(R^1)-$, $-N(R^1)-C(O)-$, o $-C(R^1)(R^2)-$.

E^2 es alquilo, cicloalquilo, alquilcicloalquilo, cicloalquilalquilo, o alquilcicloalquilalquilo. Cualquier miembro de este grupo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, alquilo, y haloalquilo.

E^5 es alquilo, alquenilo, alquinilo, cicloalquilo, ciclopentenilo, ciclopentadienilo, ciclohexenilo, o ciclohexadienilo. El cicloalquilo, ciclopentenilo, ciclopentadienilo, ciclohexenilo, y ciclohexadienilo son optativamente sustituidos. El alquilo, alquenilo, y alquinilo (a) contienen al menos 4 átomos de carbono, y (b) son optativamente sustituidos con uno o más sustituyentes seleccionados del grupo formado por -OH, $-NO_2$, -CN, y halógeno.

R^1 y R^2 se seleccionan independientemente del grupo formado por -H y alquilo. El alquilo es optativamente sustituido. Ni R^1 ni R^2 forman una estructura de anillo con E^5.

[29] En otra realización preferida de la invención, X es $-E^1-E^2-E^3-E^4-E^5$. En esta realización:

E^1 es -O-, $-S(O)_2-$, -S(O)-, $-N(R^1)-$, $-C(O)-N(R^1)-$, $-N(R^1)-C(O)-$, o $-C(R^1)(R^2)-$.

E^2 es alquilo, cicloalquilo, alquilcicloalquilo, cicloalquilalquilo, o alquilcicloalquilalquilo. Cualquier miembro de este grupo es optativamente sustituido.

E^3 es carbonilpiperidinilo. El carbonilpiperidinilo es optativamente sustituido.

E^4 es un enlace, alquilo, y alquenilo. El alquilo y alquenilo son optativamente sustituidos.

E^5 es alquilo, alquenilo, alquinilo, alcoxi, alcoxialquilo, carbociclilo, o heterociclilo. Cualquier miembro de este grupo es optativamente sustituido.

R^1 y R^2 se seleccionan independientemente del grupo formado por -H y alquilo. El alquilo es optativamente sustituido. Ni R^1 ni R^2 forman una estructura de anillo con E^2, E^3, E^4, o E^5.

693

[30] En otra realización preferida de la invención, X es $-E^1-E^2-E^5$. En esta realización:

E^1 es -O-, $-S(O)_2-$, -S(O)-, $-N(R^1)-$, $-C(O)-N(R^1)-$, $-N(R^1)-C(O)-$, o $-C(R^1)(R^2)-$.

E^2 forma un enlace de al menos 3 átomos de carbono entre E^1 y E^5. E^2 es alquilo, cicloalquilo, alquilcicloalquilo, cicloalquilalquilo, o alquilcicloalquilalquilo. Cualquier miembro de este grupo es optativamente sustituido.

E^5 es heterociclilo optativamente sustituido, carbociclilo de anillos fusionados optativamente sustituido, o carbociclilo de anillo único sustituido.

R^1 y R^2 se seleccionan independientemente del grupo formado por -H y alquilo. El alquilo es optativamente sustituido. Ni R^1 ni R^2 forman una estructura de anillo con E^5.

[31] En otra realización preferida de la invención, X es $-E^1-E^2-E^5$. En esta realización:

E^1 es -O-, $-S(O)_2-$, -S(O)-, $-N(R^1)-$, $-C(O)-N(R^1)-$, $-N(R^1)-C(O)-$, o $-C(R^1)(R^2)-$.

E^2 forma un enlace de al menos 4 átomos de carbono entre E^1 y E^5. E^2 es alquilo, cicloalquilo, alquilcicloalquilo, cicloalquilalquilo, o alquilcicloalquilalquilo. Cualquier miembro de este grupo es optativamente sustituido.

E^5 es -OH o carbociclilo optativamente sustituido.

R^1 y R^2 se seleccionan independientemente del grupo formado por -H y alquilo. El alquilo es optativamente sustituido. Ni R^1 ni R^2 forman una estructura de anillo con E^5.

694

[32] En otra realización preferida de la invención, X es $-E^1-E^2-O-E^4-E^5$. En esta realización:

E^1 es $-S(O)_2-$, $-S(O)-$, $-N(R^1)-$, $-C(O)-N(R^1)-$, $-N(R^1)-C(O)-$, o $-C(R^1)(R^2)-$.

E^2 es alquilo, cicloalquilo, alquilcicloalquilo, cicloalquilalquilo, o alquilcicloalquilalquilo. Cualquier miembro de este grupo es optativamente sustituido.

E^4 es un enlace, alquilo, o alquenilo. El alquilo y alquenilo son optativamente sustituidos.

E^5 es alquilo, alquenilo, alquinilo, alcoxi, alcoxialquilo, carbociclilo, o heterociclilo. Cualquier miembro de este grupo es optativamente sustituido.

R^1 y R^2 se seleccionan independientemente del grupo formado por -H y alquilo. El alquilo es optativamente sustituido. Ni R^1 ni R^2 forman una estructura de anillo con E^2, E^4, o E^5.

[33] En otra realización preferida de la invención, X es $-O-E^2-O-E^5$. En esta realización:

E^2 comprende al menos 3 átomos de carbono. E^2 es alquilo, cicloalquilo, alquilcicloalquilo, cicloalquilalquilo, o alquilcicloalquilalquilo. Cualquier miembro de este grupo es optativamente sustituido.

E^5 es -H, alquilo, alquenilo, alquinilo, alcoxialquilo, carbociclilo, carbociclilalcoxialquilo, heterociclilo, heterociclilalquilo, o heterociclilalcoxialquilo. El alquilo, alquenilo, alquinilo, y alcoxialquilo son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, y -CN. el carbociclilo, carbociclilalcoxialquilo, heterociclilo, heterociclilalquilo, y heterociclilalcoxialquilo son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por

695

halógeno, -OH, -NO_2, -CN, alquilo, haloalquilo, alcoxi, haloalcoxi, alcoxialquilo, alcoxialquilo sustituido con halógeno, -$N(R^3)(R^4)$, -$C(O)(R^5)$, -$S-R^3$, -$S(O)_2-R^3$, carbociclilo, halocarbociclilo, carbociclilalquilo, y carbociclilalquilo sustituido con halógeno.

R^1 y R^2 se seleccionan independientemente del grupo formado por -H, alquilo, carbociclilo, carbociclilalquilo, heterociclilo, y heterociclilalquilo. Salvo cuando el miembro es -H., cualquier miembro de este grupo es optativamente sustituido con uno o más halógenos.

R^3 es -H, alquilo, -$O-R^4$, -$N(R^4)(R^5)$, carbociclilalquilo, o heterociclilalquilo. El alquilo, carbociclilalquilo, y heterociclilalquilo son optativamente sustituidos con uno o más halógenos.

R^4 y R^5 se seleccionan independientemente del grupo formado por -H, alquilo, carbociclilo, carbociclilalquilo, heterociclilo, y heterociclilalquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo es optativamente sustituido con uno o más halógenos.

[34] En otra realización preferida de la invención, X es -$O-E^2-O-E^4-E^5$. En esta realización:

E^2 es alquilo, cicloalquilo, alquilcicloalquilo, cicloalquilalquilo, o alquilcicloalquilalquilo. Cualquier miembro de este grupo es optativamente sustituido. Un átomo en E^2 optativamente está unido a un átomo en E^5 para formar un anillo.

E^4 es un enlace, alquilo, o alquenilo. El alquilo y alquenilo son optativamente sustituidos.

E^5 es:

696

un radical optativamente sustituido seleccionado del grupo formado por alquenilo, alquinilo, alcoxi, alcoxialquilo, carbociclilo de anillos fusionados, y heterociclilo;

carbociclilo de anillo único sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por -OH, $-NO_2$, -CN, $-N(R^6)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbociclilo, halocarbociclilo, carbociclilalquilo, carbociclilalquilo sustituido con halógeno, heterociclilo, haloheterociclilo, heterociclilalquilo, y heterociclilalquilo sustituido con halógeno; o

carbociclilo de anillo único con sustituciones múltiples.

R^1 y R^2 se seleccionan independientemente del grupo formado por -H, alquilo, carbociclilo, carbociclilalquilo, heterociclilo, y heterociclilalquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo es optativamente sustituido con uno o más halógenos.

R^3 es -H, alquilo, $-O-R^4$, $-N(R^4)(R^5)$, carbociclilalquilo, o heterociclilalquilo. El alquilo, carbociclilalquilo, y heterociclilalquilo son optativamente sustituidos con uno o más halógenos.

R^4 y R^5 se seleccionan independientemente del grupo formado por -H, alquilo, carbociclilo, carbociclilalquilo, heterociclilo, y heterociclilalquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo es optativamente sustituido con uno o más halógenos.

[35] En otra realización preferida de la invención, X es $-E^1-E^2-S(O)_2-E^4-E^5$. En esta realización:

E^1 es $-S(O)_2-$, -S(O)-, $-N(R^1)-$, $-C(O)-N(R^1)-$, $-N(R^1)-C(O)-$, o $-C(R^1)(R^2)-$.

697

E^2 es alquilo, cicloalquilo, alquilcicloalquilo, cicloalquilalquilo, o alquilcicloalquilalquilo. Cualquier miembro de este grupo es optativamente sustituido.

E^4 es un enlace, alquilo, o alquenilo. El alquilo y alquenilo son optativamente sustituidos.

E^5 es alquilo, alquenilo, alquinilo, alcoxi, alcoxialquilo, carbociclilo, o heterociclilo. Cualquier miembro de este grupo es optativamente sustituido.

R^1 y R^2 se seleccionan independientemente del grupo formado por -H y alquilo. El alquilo es optativamente sustituido. Ni R^1 ni R^2 forman una estructura de anillo con E^2, E^4, o E^5.

[36] En otra realización preferida de la invención, X es $-O-E^2-S(O)_2-E^4-E^5$. En esta realización:

E^2 es alquilo, cicloalquilo, alquilcicloalquilo, cicloalquilalquilo, o alquilcicloalquilalquilo. Cualquier miembro de este grupo es optativamente sustituido.

E^4 es alquilo o alquenilo. El alquilo y alquenilo son optativamente sustituidos.

E^5 es -H, alquilo, alquenilo, alquinilo, alcoxi, carbociclilo, o heterociclilo. Cualquier miembro de este grupo es optativamente sustituido.

[37] En otra realización preferida de la invención, X es $-O-E^2-S(O)_2-E^5$. En esta realización:

E^2 comprende menos de 5 átomos de carbono. E^2 es alquilo, cicloalquilo, alquilcicloalquilo, cicloalquilalquilo, o alquilcicloalquilalquilo. Cualquier miembro de este grupo es optativamente sustituido.

E^5 es alquilo, alquenilo, alquinilo, alcoxialquilo, carbociclilo, o heterociclilo. Cualquier miembro de este grupo es optativamente sustituido.

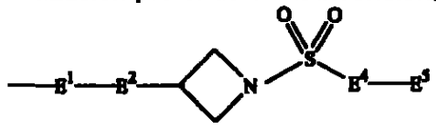
698

[38] En otra realización preferida de la invención, X es $-O-E^2-S(O)_2-E^5$. En esta realización:

E^2 es alquilo, cicloalquilo, alquilcicloalquilo, cicloalquilalquilo, o alquilcicloalquilalquilo. Cualquier miembro de este grupo es optativamente sustituido.

E^5 es alquilo, alquenilo, alquinilo, alcoxialquilo, carbociclilo saturado, carbociclilo parcialmente saturado, o heterociclilo. Cualquier miembro de este grupo es optativamente sustituido.

[39] En otra realización preferida de la invención, X es:



En esta realización:

E^1 es $-S(O)_2-$, $-S(O)-$, $-N(R^1)-$, $-C(O)-N(R^1)-$, $-N(R^1)-C(O)-$, o $-C(R^1)(R^2)-$.

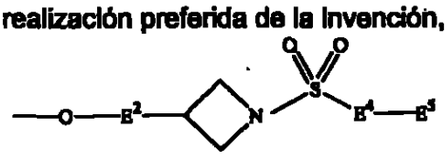
E^2 es alquilo, cicloalquilo, alquilcicloalquilo, cicloalquilalquilo, o alquilcicloalquilalquilo. Cualquier miembro de este grupo es optativamente sustituido.

E^4 es un enlace, alquilo, o alquenilo, El alquilo y alquenilo son optativamente sustituidos.

E^5 es alquilo, alquenilo, alquinilo, alcoxi, alcoxialquilo, carbociclilo, o heterociclilo. Cualquier miembro de este grupo es optativamente sustituido.

R^1 y R^2 se seleccionan independientemente del grupo formado por -H y alquilo. El alquilo es optativamente sustituido. Ni R^1 ni R^2 forman una estructura de anillo con E^2, E^4, o E^5.

[40] En otra realización preferida de la invención, X es:



699

En esta realización:

E^2 es un enlace, alquilo, cicloalquilo, alquilcicloalquilo, cicloalquilalquilo, o alquilcicloalquilalquilo. Cualquier miembro de este grupo es optativamente sustituido.

E^4 es un enlace, alquilo, o alquenilo. El alquilo y alquenilo son optativamente sustituidos.

E^5 es carbociclilo sustituido o heterociclilo optativamente sustituido. El carbociclilo es sustituido con:

dos o más sustituyentes seleccionados independientemente del grupo formado por halógeno, -OH, $-NO_2$, -CN, alquilo, haloalquilo, alcoxi, haloalcoxi, alcoxialquilo, alcoxialquilo sustituido con halógeno, $-N(R^3)(R^4)$, $-C(O)(R^5)$, $-S-R^3$, $-S(O)_2-R^3$, carbociclilo, halocarbociclilo, carbociclilalquilo, y carbociclilalquilo sustituido con halógeno; o

un sustituyente seleccionado del grupo formado por halógeno, -OH, $-NO_2$, -CN, $-C(O)-O-R^3$, $-S-R^3$, $-S(O)_2-R^3$, carbociclilo, halocarbociclilo, carbociclilalquilo, y carbociclilalquilo sustituido con halógeno.

El heterociclilo, por otra parte, es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, -CN, alquilo, haloalquilo, alcoxi, haloalcoxi, alcoxialquilo, alcoxialquilo sustituido con halógeno, $-N(R^3)(R^4)$, $-C(O)(R^5)$, $-S-R^3$, $-S(O)_2-R^3$, carbociclilo, halocarbociclilo, carbociclilalquilo, y carbociclilalquilo sustituido con halógeno.

R^3 y R^4 se seleccionan independientemente del grupo formado por -H, alquilo, carbociclilo, carbociclilalquilo, heterociclilo, y heterociclilalquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo es optativamente sustituido con uno o más halógenos.

R^5 es -H, alquilo, -O-R^6, -N(R^6)(R^7), carbociclilalquilo, o heterociclilalquilo. El alquilo, carbociclilalquilo, y heterociclilalquilo son optativamente sustituidos con uno o más halógenos.

R^6 y R^7 se seleccionan independientemente del grupo formado por -H, alquilo, carbociclilo, carbociclilalquilo, heterociclilo, y heterociclilalquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo es optativamente sustituido con uno o más halógenos.

[41] En otra realización preferida de la invención, X es -E^1-E^2-E^5. En esta realización:

E^1 es -O-, -$S(O)_2$-, -S(O)-, -S-, -N(R^1)-, -C(O)-N(R^1)-, -N(R^1)-C(O)-, o -C(R^1)(R^2)-

E^2 es alquilo, cicloalquilo, alquilcicloalquilo, cicloalquilalquilo, o alquilcicloalquilalquilo. Cualquier miembro de dicho grupo es optativamente sustituido.

E^5 es sustituido heterociclilo.

R^1 y R^2 se seleccionan independientemente del grupo formado por -H y alquilo. El alquilo es optativamente sustituido.

Ni R^1 ni R^2 forman una estructura de anillo con E^5.

[42] En otra realización preferida de la invención, X es -E^1-E^2-E^5. En esta realización:

E^1 es -O-, -$S(O)_2$-, -S(O)-, -N(R^1)-, -C(O)-N(R^1)-, -N(R^1)-C(O)-, o -C(R^1)(R^2)-.

E^2 es alquilo, cicloalquilo, alquilcicloalquilo, cicloalquilalquilo, o alquilcicloalquilalquilo. Cualquier miembro de dicho grupo es optativamente sustituido. Además, E^2 comprende al menos dos átomos de carbono.

E^5 es heterociclilo optativamente sustituido.

R^1 y R^2 se seleccionan independientemente del grupo formado por -H y alquilo. El alquilo es optativamente sustituido.

Ni R^1 ni R^2 forman una estructura de anillo con E^5.

[43] En otra realización preferida de la invención, X es $-E^1-E^2-E^3-E^4-E^5$. En esta realización:

E^1 es -O-, $-S(O)_2-$, -S(O)-, -S-, $-N(R^1)-$, $-C(O)-N(R^1)-$, $-N(R^1)-C(O)-$, o $-C(R^1)(R^2)-$

E^2 es alquilo, cicloalquilo, alquilcicloalquilo, cicloalquilalquilo, o alquilcicloalquilalquilo. Cualquier miembro de dicho grupo es optativamente sustituido.

E^3 es $-C(O)-$, $-O-(CO)-$, $-C(O)-O-$, $-C(NR^3)-$, $-N(R^4)-$, $-N(R^4)-C(NR^3)-$, $-C(NR^3)-N(R^4)-$, $-C(O)-N(R^4)-$, $-N(R^4)-C(O)-$, $-N(R^4)-C(O)-N(R^5)-$, -S-, -S(O)-, $-N(R^4)-S(O)_2-$, $-S(O)_2-N(R^4)-$, $-C(O)-N(R^4)-N(R^5)-C(O)-$, $-C(R^4)(R^6)-C(O)-$, o $-C(R^7)(R^8)-$.

E^4 es un enlace, alquilo, o alquenilo. El alquilo y alquenilo son optativamente sustituidos.

E^5 es carbociclilo o heterociclilo. El carbociclilo y heterociclilo son:

sustituido con un sustituyente seleccionado del grupo formado por carbociclilo optativamente sustituido, carbociclilalquilo optativamente sustituido, heterociclilo optativamente sustituido, y heterociclilalquilo optativamente sustituido; y

optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, -CN, alquilo, alcoxi, alcoxialquilo, $-N(R^{11})(R^{12})$, $-C(O)(R^{13})$, $-S-R^{11}$, $-S(O)_2-R^{11}$, carbociclilo, carbociclilalquilo, haloalquilo, haloalcoxi,

alcoxialquilo sustituido con halógeno, halocarbociclilo, carbociclilalquilo sustituido con halógeno, hidroxicarbociclilo, y heteroarilo.

R^1 y R^2 se seleccionan independientemente del grupo formado por -H y alquilo, donde el alquilo es optativamente sustituido.

R^3 es -H o -OH.

R^4 y R^5 se seleccionan independientemente del grupo formado por -H, alquilo, carbociclilo, carbociclilalquilo, heterociclilo, y heterociclilalquilo, donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido.

R^6 es -CN o -OH.

R^7 es -H, halógeno, -OH, alquilo, alcoxi, o alcoxialquilo. El alquilo, alcoxi, y alcoxialquilo son optativamente sustituidos.

R^8 es -OH o alcoxi. El alcoxi es optativamente sustituido.

R^{11} y R^{12} se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, carbociclilo, carbociclil-C_1-C_8-alquilo, heterociclilo, y heterociclil-C_1-C_8-alquilo. Cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido con uno o más halógenos.

R^{13} es -H, C_1-C_8-alquilo, -O-R^{14}, -N(R^{14})(R^{15}), carbociclil-C_1-C_8-alquilo, heterociclil-C_1-C_8-alquilo, halo-C_1-C_8-alquilo, carbociclil-C_1-C_8-alquilo sustituido con halógeno, o heterociclil-C_1-C_8-alquilo sustituido con halógeno.

R^{14} y R^{15} se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, carbociclilo, carbociclil-C_1-C_8-alquilo, heterociclilo, y heterociclil-C_1-C_8-alquilo. Cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido con uno o más halógenos.

Ni R^1 ni R^2 forman una estructura de anillo con E^2, E^3, E^4, o E^5.

Ni R^4 ni R^5 forman una estructura de anillo con E^2, E^4, o E^5.

[44] Esta invención también tiene como objeto, en parte, un método para prevenir o tratar una condición vinculada con actividad patológica de la metaloproteinasa de matriz en un mamífero afectado por dicha condición o predispuesto a adquirir dicha condición. El método comprende administrar un compuesto de la invención o una sal aceptable para uso farmacéutico del mismo al mamífero en una cantidad que es eficaz en términos terapéuticos para prevenir o tratar la condición.

[45] Esta invención también tiene como objeto, en parte, un método para prevenir o tratar una condición patológica en un mamífero afectado por dicha condición o predispuesto a adquirir dicha condición. El método comprende administrar un compuesto de la invención o una sal aceptable para uso farmacéutico del mismo al mamífero en una cantidad que es eficaz en términos terapéuticos para prevenir o tratar la condición. En esta realización, la condición patológica comprende destrucción de tejidos, una enfermedad fibrótica, debilitación patológica de la matriz, reparación deficiente de heridas, una enfermedad cardiovascular, una enfermedad pulmonar, una enfermedad renal, una enfermedad hepática, una enfermedad oftalmológica, y una enfermedad del sistema nervioso central.

[46] Esta invención también tiene como objeto, en parte, un método para prevenir o tratar una condición patológica en un mamífero afectado por dicha condición o predispuesto a adquirir dicha condición. El método comprende administrar un compuesto de la invención o una sal aceptable para uso farmacéutico del mismo al mamífero en una cantidad que es eficaz en términos terapéuticos para prevenir o tratar la condición. En esta realización, la condición patológica comprende osteoartritis, artritis reumatoidea, artritis séptica, invasión tumoral, metástasis tumoral, angiogénesis tumoral, una

704

úlcera de decubitus, una úlcera gástrica, una úlcera de córnea, enfermedad periodontal, cirrosis hepática, enfermedad fibrótica pulmonar, otoesclerosis, ateroesclerosis, esclerosis múltiple, cardiomiopatía dilatada, ulceración epidérmica, epidermólisis ampollar, aneurisma aórtico, reparación deficiente de heridas, una adherencia , escarificación, deficiencia cardiaca congestiva, infarto pos-miocardial, trombosis coronaria, enfisema, proteinuria, mal de Alzheimer, enfermedad ósea, y obstrucción pulmonar crónica.

[47] Esta invención también tiene como objeto, en parte, un método para prevenir o tratar una condición vinculada con actividad patológica de TNF-α convertasa en un mamífero afectado por dicha condición o predispuesto a adquirir dicha condición. El método comprende administrar un compuesto de la invención o una sal aceptable para uso farmacéutico del mismo al mamífero en una cantidad que es eficaz en términos terapéuticos para prevenir o tratar la condición.

[48] Esta invención también tiene como objeto, en parte, un método para prevenir o tratar una condición vinculada con actividad patológica agrecanasa en un mamífero afectado por dicha condición o predispuesto a adquirir dicha condición. El método comprende administrar un compuesto de la invención o una sal aceptable para uso farmacéutico del mismo al mamífero en una cantidad que es eficaz en términos terapéuticos para prevenir o tratar la condición.

[49] Esta invención también tiene como objeto, en parte, composiciones farmacéuticas que comprenden una cantidad eficaz en términos terapéuticos de un compuesto de la invención o una sal aceptable para uso farmacéutico del mismo.

[50] Esta invención también tiene como objeto, en parte, un uso de un compuesto de la invención o una sal aceptable para uso farmacéutico del mismo para preparar un medicamento para tratar una condición vinculada con actividad patológica de la metaloproteinasa de matriz.

[51] Esta invención también tiene como objeto, en parte, un uso de un compuesto de la invención o una sal aceptable para uso farmacéutico del mismo para preparar un medicamento para tratar una condición vinculada con actividad patológica de TNF-α convertasa .

[52] Esta invención también tiene como objeto, en parte, un uso de un compuesto de la invención o una sal aceptable para uso farmacéutico del mismo para preparar un medicamento para tratar una condición vinculada con actividad patológica de agrecanasa.

[53] Otros beneficios de la invención serán evidentes para los expertos en la materia a partir de la presente memoria descriptiva.

DESCRIPCIÓN DETALLADA DE LAS REALIZACIONES PREFERIDAS

[54] La presente descripción detallada de las realizaciones preferidas de la invención tiene como objeto simplemente familiarizar a los especialistas con la invención, sus principios y aplicaciones prácticas, de modo que estos puedan adaptar y aplicar la invención en sus numerosas formas, según resulte más adecuado para los requerimientos de un uso específico. Esta invención, por lo tanto, no se limita a las realizaciones preferidas descritas en esta patente, y puede ser modificada de diversas formas.

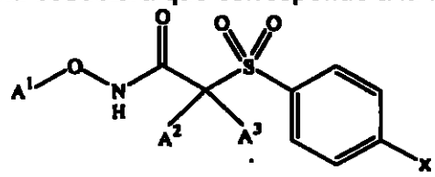
a. Compuestos de la invención

[55] De acuerdo con la presente invención, se ha encontrado que determinados sulfona hidroxamatos aromáticos tienden a ser eficaces para inhibir las MMP, particularmente aquéllas asociadas con una descomposición

excesiva (o patológica de alguna otra manera) del tejido conectivo: En forma más específica, los solicitantes hemos descubierto que estos hidroxamatos tienden a ser eficaces para inhibir proteasas (particularmente las MMP-2, MMP-9, MMP- 13, otras MMP asociadas con condiciones patológicas, y/o agrecanasa) que frecuentemente son particularmente destructivas de los tejidos si se encuentran presentes o se generan en cantidades o concentraciones excesivas anormales. Además, los solicitantes han descubierto que estos hidroxamatos tienden a ser selectivos respecto de la inhibición de la actividad patológica de la proteasa, mientras evitan una inhibición excesiva de otras proteasas (particularmente MMP-1 y/o MMP-14) que son típicamente esenciales para la función corporal normal (por ejemplo, renovación y reparación de tejidos).

A-1. Estructuras de compuestos preferidos

[56] Como se ha indicado, el compuesto de esta invención generalmente tiene una estructura que corresponde a la Fórmula I:



I.

[57] A^1 es -H, alquilcarbonilo, alcoxicarbonilo, carbociclilcarbonilo, carbociclilalquilcarbonilo, heterociclilcarbonilo, heterociclilalquilcarbonilo, carbocicliloxicarbonilo, carbociclilalcoxicarbonilo, aminoalquilcarbonilo, alquil(tiocarbonilo), alcoxi(tiocarbonilo), carbociclil(tiocarbonilo), carbociclilalquil(tiocarbonilo), heterociclil(tiocarbonilo), heterociclilalquil(tiocarbonilo), carbociclíloxi(tiocarbonilo),

carbociclilalcoxi(tiocarbonilo), o aminoalquil(tiocarbonilo). Salvo cuando el miembro es -H, cualquier miembro de este grupo es optativamente sustituido.

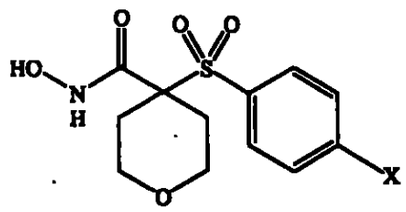
[58] En algunas realizaciones preferidas, A^1 es -H, C_1-C_8-alquilcarbonilo, C_1-C_8-alcoxicarbonilo, carbociclilcarbonilo, carbociclil-C_1-C_8-alquilcarbonilo, heterociclilcarbonilo, heterociclil-C_1-C_8-alquilcarbonilo, carbociclíloxicarbonilo, carbociclil-C_1-C_8-alcoxicarbonilo, $N(R^A)(R^B)$-C_1-C_8-alquilcarbonilo, C_1-C_8-alquil(tiocarbonilo), C_1-C_8-alcoxi(tiocarbonilo), carbociclil(tiocarbonilo), carbociclil-C_1-C_8-alquil(tiocarbonilo), heterociclil(tiocarbonilo), heterociclil-C_1-C_8-alquil(tiocarbonilo), carbociclíloxi(tiocarbonilo), carbociclil-C_1-C_8-alcoxi(tiocarbonilo), o $N(R^A)(R^B)$-C_1-C_8-alquil(tiocarbonilo). R^A y R^B se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, C_1-C_8-alcoxicarbonilo, C_1-C_8-alquilcarbonilo, carbociclil-C_1-C_8-alquilo, y carbociclil-C_1-C_8-alcoxicarbonilo.

[59] En realizaciones en general más preferidas, A^1 es -H.

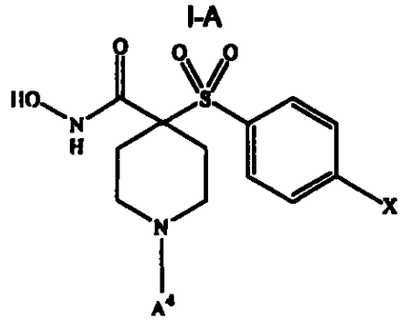
[60] A^2 y A^3, junto con el átomo de carbono al cual ambos están unidos, forman un heterociclilo optativamente sustituido que contiene entre 5 y 8 miembros en el anillo (es decir, entre 5 y 8 átomos se unen para formar el anillo (o anillos) del heterociclilo).

[61] En algunas realizaciones preferidas, A^2 y A^3, junto con el átomo de carbono al cual están ambos unidos, forman un heterociclilo optativamente sustituido que contiene ya sea 5 o 6 miembros en el anillo.

[62] En algunas realizaciones preferidas, el compuesto corresponde en estructura a una de las siguientes fórmula:



I-A



I-B

[63] A^4 es -H, alquilo, alquilcarbonilo, alquilcarbonilalquilo, alquilcarbonilalquilcarbonilo, alcoxicarbonilo, alcoxicarbonilalquilo, alcoxicarbonilalquilcarbonilo, alquilsulfonilo, alquiliminocarbonilo, alquenilo, alquinilo, alcoxialquilo, alquiltioalquilo, alquilsulfonilalquilo, alquilsufoxidoalquilo, alquiltioalquenilo, alquilsulfoxidoalquenilo, alquilsulfonilalquenilo, carbociclilo, carbociclilalquilo, carbociclilalcoxialquilo, carbociclilcarbonilo, carbociclilsulfonilo, carbociclliminocarbonilo, carbociclioxicarbonilo, carbocililtioalquilo, carbocililsulfoxidoalquilo, carbociclilsulfonilalquilo, carbociclitioalquenilo, carbociclilsulfoxidoalquenilo, carbociclilsulfonilalquenilo, heterociclilo, heterociclilalquilo, heterociclilalcoxialquilo, heterociclilcarbonilo, heterocicliltioalquilo, heterociclilsulfoxidoalquilo, heterociclilsulfonilalquilo, heterocicliltioalquenilo, heterociclilsulfoxidoalquenilo, heterociclilsulfonilalquenilo, heterociclilsulfonilo, heterociclliminocarbonilo, heterociclilalquilcarbonilo, heterociclilcarbonilalquilcarbonilo, heterociclilsulfonilo, heterociclilcarbonilalquilo, aminoalquilcarbonilo, aminocarbonilo, aminocarbonilalquilcarbonilo, aminosulfonilo,

aminosulfonilalquilo, aminoalquilo, aminocarbonilalquilo, o aminoalquilsulfonilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo es optativamente sustituido.

[64] En algunas realizaciones preferidas, A^4 es -H, C_1-C_8-alquilo, C_1-C_8-alquilcarbonilo, C_1-C_8-alquilcarbonil-C_1-C_8-alquilo, C_1-C_8-alquilcarbonil-C_1-C_8-alquilcarbonilo, C_1-C_8-alcoxicarbonilo, C_1-C_8-alcoxicarbonil-C_1-C_8-alquilo, C_1-C_8-alcoxicarbonil-C_1-C_8-alquilcarbonilo, C_1-C_8-alquilsulfonilo, C_1-C_8-alquiliminocarbonilo, C_2-C_8-alquenilo, C_2-C_8-alquinilo, C_1-C_8-alcoxi-C_1-C_8-alquilo, C_1-C_8-alquiltio-C_1-C_8-alquilo, C_1-C_8-alquiltio-C_2-C_8-alquenilo, C_1-C_8-alquilsulfoxido-C_1-C_8-alquilo, C_1-C_8-alquilsulfoxido-C_2-C_8-alquenilo, C_1-C_8-alquilsulfonil-C_1-C_8-alquilo, C_1-C_8-alquilsulfonil-C_2-C_8-alquenilo, carbociclilo, carbociclil-C_1-C_8-alquilo, carbociclil-C_1-C_8-alcoxi-C_1-C_8-alquilo, carbociclilcarbonilo, carbociclilsulfonilo, carbociclliminocarbonilo, carbociclioxicarbonilo, carbociclitio-C_1-C_8-alquilo, carbociclitio-C_2-C_8-alquenilo, carbociclilsulfoxido-C_1-C_8-alquilo, carbociclilsulfoxido-C_2-C_8-alquenilo, carbociclilsulfonil-C_1-C_8-alquilo, carbociclilsulfonil-C_2-C_8-alquenilo, heterociclilo, heterociclil-C_1-C_8-alquilo, heterociclil-C_1-C_8-alcoxi-C_1-C_8-alquilo, heterociclilcarbonilo, heterociclitio-C_1-C_8-alquilo, heterociclilsulfoxido-C_1-C_8-alquilo, heterociclilsulfonil-C_1-C_8-alquilo, heterociclitio-C_2-C_8-alquenilo, heterociclilsulfoxido-C_2-C_8-alquenilo, heterociclilsulfonil-C_2-C_8-alquenilo, heterociclilsulfonilo, heterociclliminocarbonilo, heterociclil-C_1-C_8-alquilcarbonilo, heterociclilcarbonil-C_1-C_8-alquilcarbonilo, heterociclilsulfonilo, heterociclilcarbonil-C_1-C_8-alquilo, $N(R^C)(R^D)$-C_1-C_8-alquilcarbonilo, $N(R^C)(R^D)$-carbonilo, $N(R^C)(R^D)$-carbonil-C_1-C_8-alquilcarbonilo, $N(R^C)(R^D)$-sulfonilo, $N(R^C)(R^D)$-sulfonil-C_1-C_8-alquilo, $N(R^C)(R^D)$-C_1-C_8-alquilo, $N(R^C)(R^D)$-carbonil-C_1-C_8-alquilo, o $N(R^C)(R^D)$-C_1-C_8-alquilsulfonilo. Cualquier miembro

710

adecuado de este grupo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -CN, -C(O)-OH, -SH, $-SO_3H$, y NO_2.

[65] R^C y R^D se seleccionan independientemente del grupo formado por -H, -OH, C_1-C_8-alquilo, C_1-C_8-alquil-carbonilo, C_1-C_8-alcoxi-C_1-C_8-alquilo, C_2-C_8-alquenilo, C_2-C_8-alquinilo, C_1-C_8-alquil-tio-C_1-C_8-alquilo, C_1-C_8-alquil-sulfoxido-C_1-C_8-alquilo, C_1-C_8-alquil-sulfonil-C_1-C_8-alquilo, carbociclilo, carbociclil-C_1-C_8-alquilo, carbociclilcarbonilo, carbociclil-C_1-C_8-alcoxi-C_1-C_8-alquilo, carbocicliltio-C_1-C_8-alquilo, carbociclilsulfoxido-C_1-C_8-alquilo, carbociclilsulfonil-C_1-C_8-alquilo, heterociclilo, heterociclil-C_1-C_8-alquilo, heterociclil-C_1-C_8-alcoxi-C_1-C_8-alquilo, heterociclilcarbonilo, heterocicliltio-C_1-C_8-alquilo, heterociclilsulfoxido-C_1-C_8-alquilo, heterociclilsulfonil-C_1-C_8-alquilo, aminocarbonil-C_1-C_8-alquilo, C_1-C_8-alquiloxicarbonilamino-C_1-C_8-alquilo, y amino-C_1-C_8-alquilo. Salvo cuando el miembro es -H o OH, cualquier miembro de este grupo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -CN, -C(O)-OH, -SH, $-SO_3H$, y NO_2. El nitrógeno del amino -C_1-C_8-alquilo es optativamente sustituido con 1 o 2 sustituyentes seleccionados independientemente del grupo formado por C_1-C_8-alquilo, C_1-C_8-alquilcarbonilo, carbociclilo, y carbociclil-C_1-C_8-alquilo. No más de uno de R^C o R^D es -OH.

[66] En algunas realizaciones preferidas, A^4 es -H, C_1-C_8-alquilo (generalmente preferentemente C_1-C_4-alquilo, y más preferentemente etilo), C_1-C_8-alcoxi-C_1-C_8-alquilo (generalmente preferentemente C_1-C_2-alcoxi-C_1-C_3-alquilo, y más preferentemente metoxietilo), carbociclilo (generalmente preferentemente C_3-C_8-cicloalquilo o fenilo, y más preferentemente

711

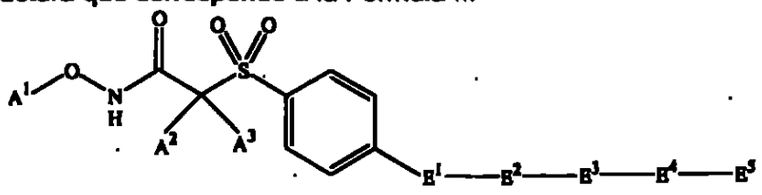
ciclopropilo), carbociclil-C_1-C_6-alquilo (generalmente preferentemente C_3-C_6-cicloalquil-C_1-C_3-alquilo o fenil-C_1-C_3-alquilo, y más preferentemente ciclopropilmetilo o bencilo), C_1-C_6-alquilsulfonilo (generalmente preferentemente C_1-C_2-alquilsulfonilo, y más preferentemente metilsulfonilo), C_3-C_6-alquenilo (generalmente preferentemente C_3-C_4-alquenilo, y más preferentemente C_3-alquenilo), C_3-C_6-alquinilo (generalmente preferentemente C_3-C_4-alquinilo, y más preferentemente C_3-alquinilo). Salvo cuando el miembro es -H, cualquier miembro de estos grupos es optativamente sustituido con halógeno, pero más típicamente es preferentemente no sustituido con halógeno.

[67] En algunas realizaciones preferidas, A^4 es -H, etilo, metoxietilo, ciclopropilo, ciclopropilmetilo, o bencilo.

[68] X se puede seleccionar a partir de un amplio rango de sustituyentes. A continuación se describen varias realizaciones específicas preferidas que comprenden los sustituyentes que los solicitantes han descubierto que son los preferidos en general.

Realización preferida Nro. 1

[69] En algunas realizaciones de esta invención, el compuesto tiene una estructura que corresponde a la Fórmula II:



II.

[70] A^1, A^2, y A^3 tienen los valores definidos anteriormente para la Fórmula I.

[71] E^1 es -O-, -$S(O)_2$-, -S(O)-, -$N(R^1)$-, -C(O)-$N(R^1)$-, -$N(R^1)$-C(O)-, o -$C(R^1)(R^2)$-. E^1 como alternativa puede ser -S-.

[72] E^2 forma un enlace de al menos 2 átomos de carbono entre E^1 y E^3. E^2 es alquilo, cicloalquilo, alquilcicloalquilo, cicloalquilalquilo, o alquilcicloalquilalquilo. Cualquier miembro de este grupo es optativamente sustituido.

[73] En algunas realizaciones preferidas, E^2 es C_2-C_{20}-alquilo, cicloalquilo, C_1-C_{10}-alquilcicloalquilo, cicloalquil-C_1-C_{10}-alquilo, o C_1-C_{10}-alquilcicloalquil-C_1-C_{10}-alquilo. Cualquier miembro de este grupo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, C_1-C_6-alquilo, y halo-C_1-C_6-alquilo.

[74] En algunas realizaciones preferidas, E^2 es C_2-C_6-alquilo optativamente sustituido con uno o más halógenos.

[75] En algunas realizaciones preferidas, E^2 es C_2-C_6-alquilo.

[76] En algunas realizaciones preferidas, E^2 es C_2-C_6-alquilo.

[77] E^3 es -C(O)-, -O-(CO)-, -C(O)-O-, -$C(NR^3)$-, -$N(R^4)$-, -C(O)-$N(R^4)$-, -$N(R^4)$-C(O)-, -$N(R^4)$-C(O)-$N(R^5)$-, -S-, -S(O)-, -$N(R^4)$-$S(O)_2$-, -$S(O)_2$-$N(R^4)$-, -C(O)-$N(R^4)$-$N(R^5)$-C(O)-, -$C(R^4)(R^6)$-C(O)-, o -$C(R^7)(R^8)$-.

[78] E^4 es un enlace, alquilo, o alquenilo. El alquilo y alquenilo son optativamente sustituidos.

[79] En algunas realizaciones preferidas, E^4 es un enlace, C_1-C_{20}-alquilo, o C_2-C_{20}-alquenilo. El C_1-C_{20}-alquilo y C_2-C_{20}-alquenilo son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno y carbociclilo. Este carbociclilo, a su vez, es optativamente sustituido con uno o más sustituyentes

independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_8-alquilo, C_1-C_8-alcoxi, C_1-C_8-alcoxi-C_1-C_8-alquilo, carbociclilo, carbociclil-C_1-C_8-alquilo, halo-C_1-C_8-alquilo, halo-C_1-C_8-alcoxi, C_1-C_8-alcoxi-C_1-C_8-alquilo sustituido con halógeno , halocarbociclilo, y carbociclil-C_1-C_8-alquilo sustituido con halógeno.

[80] En algunas realizaciones preferidas, E^4 un enlace, C_1-C_3-alquilo, o C_2-C_3-alquenilo. El C_1-C_3-alquilo, y C_2-C_3-alquenilo optativamente son sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno y carbociclilo. Este carbociclilo, a su vez, es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_8-alquilo, C_1-C_8-alcoxi, C_1-C_8-alcoxi-C_1-C_8-alquilo, carbociclilo, carbociclil-C_1-C_8-alquilo, halo-C_1-C_8-alquilo, halo-C_1-C_8-alcoxi, C_1-C_8-alcoxi-C_1-C_8-alquilo sustituido con halógeno, halocarbociclilo, y carbociclil-C_1-C_8-alquilo sustituido con halógeno.

[81] En algunas realizaciones preferidas, E^4 es un enlace, C_1-C_3-alquilo, o C_2-C_3-alquenilo.

[82] E^5 es -H, -OH, alquilo, alquenilo, alquinilo, alcoxi, alcoxialquilo, carbociclilo, o heterociclilo. Salvo cuando E^5 es -H o -OH, cualquier miembro de este grupo es optativamente sustituido. E^5 no es -H cuando E^3 es -$C(R^7)(R^8)$- y E^4 es un enlace.

[83] En algunas realizaciones preferidas, E^5 es -H, -OH, C_1-C_{20}-alquilo, C_2-C_{20}-alquenilo, C_2-C_{20}-alquinilo, C_1-C_{20}-alcoxi, C_1-C_{20}-alcoxi-C_1-C_{20}-alquilo, carbociclilo, o heterociclilo. El C_1-C_{20}-alquilo, C_2-C_{20}-alquenilo, C_2-C_{20}-alquinilo, C_1-C_{20}-alcoxi, y C_1-C_{20}-alcoxi-C_1-C_{20}-alquilo son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, y -CN. El carbociclilo y

714

heterociclilo son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, -$N(R^{11})(R^{12})$, -$C(O)(R^{13})$, -S-R^{11}, -$S(O)_2$-R^{11}, carbociclilo, carbociclil-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno , halocarbociclilo, y carbociclil-C_1-C_6-alquilo sustituido con halógeno. El carbociclilo y heterociclilo también son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por C_1-C_6-alquilcarbociclilo, C_1-C_6-alquilcarbociclilo sustituido con halógeno, hidroxicarbociclilo, y heterociclilo.

[84] En algunas realizaciones preferidas, E^5 es -H, -OH, C_1-C_6-alquilo, C_2-C_6-alquenilo, C_2-C_6-alquinilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, carbociclilo, o heterociclilo. El C_1-C_6-alquilo, C_2-C_6-alquenilo, C_2-C_6-alquinilo, C_1-C_6-alcoxi, y C_1-C_6-alcoxi-C_1-C_6-alquilo son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, y -CN. El carbociclilo y heterociclilo son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, -$N(R^{11})(R^{12})$, -$C(O)(R^{13})$, -S-R^{11}, -$S(O)_2$-R^{11}, carbociclilo, carbociclil-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, halocarbociclilo, carbociclil-C_1-C_6-alquilo sustituido con halógeno, C_1-C_6-alquilcarbociclilo, halógeno-sustituido C_1-C_6-alquilcarbociclilo, hidroxicarbociclilo, y heteroarilo.

[85] En algunas realizaciones preferidas, E^5 es furanilo, tetrahidropiranilo, dihidrofuranilo, tetrahidrofuranilo, tiofenilo, dihidrotiofenilo, tetrahidrotiofenilo, pirrolilo, isopirrolilo, pirrolinilo, pirrolidinilo, imidazolilo,

715

isoimidazolilo, imidazolinilo, imidazolidinilo, pirazolilo, pirazolinilo, pirazolidinilo, triazolilo, tetrazolilo, ditiolilo, oxatiolilo, oxazolilo, isoxazolilo, oxazolidinilo, isoxazolidinilo, tiazolilo, isotiazolilo, tiazolinilo, isotiazolinilo, tiazolidinilo, isotiazolidinilo, tiodiazolilo, oxatiazolilo, oxadiazolilo, oxatriazolilo, dioxazolilo, oxatiazolilo, oxatiolilo, oxatiolanilo, piranilo, dihidropiranilo, piridinilo, piperidinilo, diazinilo, piperazinilo, triazinilo, oxazinilo, isoxazinilo, oxatiazinilo, oxadiazinilo, morfolinilo, azepinilo, oxepinilo, tiepinilo, diazepinilo, indolizinilo, pirindinilo, piranopirrolilo, 4H-quinolizinilo, purinilo, naftiridinilo, piridopiridinilo, pteridinilo, indolilo, isoindolilo, indoleninilo, isoindazolilo, benzacinilo, ftalazinilo, quinoxalinilo, quinazolinilo, benzodiazinilo, benzopiranilo, benzotiopiranilo, benzoxazolilo, indoxazinilo, antranililo, benzodioxolilo, benzodioxanilo, benzoxadiazolilo, benzofuranilo, isobenzofuranilo, benzotienilo, isobenzotienilo, benzotiazolilo, benzotiadiazolilo, bencimidazolilo, benzotriazolilo, benzoxacinilo, bencisoxacinilo, tetrahidroisoquinolinilo, carbazolilo, xantenilo, o acridinilo. Tal sustituyente es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, -CN, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, $-N(R^{11})(R^{12})$, $-C(O)(R^{13})$, $-S-R^{11}$, $-S(O)_2-R^{11}$, arilo, aril-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, haloarilo, y C_1-C_6-alquilo sustituido con halógeno. Cualquier miembro de dicho grupo también es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por C_1-C_6-alquilarilo, C_1-C_6-alquilarilo sustituido con halógeno, hidroxiarilo, y heteroarilo.

[86] En algunas realizaciones preferidas, E^5 es indolizinilo, pirindinilo, piranopirrolilo, 4H-quinolizinilo, purinilo, naftiridinilo, piridopiridinilo, pteridinilo, indolilo, isoindolilo, indoleninilo, isoindazolilo, benzazinilo, ftalazinilo,

quinoxalinilo, quinazolinilo, benzodiazinilo, benzopiranilo, benzotiopiranilo, benzoxazolilo, indoxazinilo, antranililo, benzodioxolilo, benzodioxanilo, benzoxadiazolilo, benzofuranilo, isobenzofuranilo, benzotienilo, isobenzotienilo, benzotiazolilo, benzotiadiazolilo, bencimidazolilo, benzotriazolilo, benzoxazinilo, bencisoxazinilo, tetrahidroisoquinolinilo, o piridofuranilo. Tal sustituyente es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, -$N(R^{11})(R^{12})$, -$C(O)(R^{13})$, -S-R^{11}, -$S(O)_2$-R^{11}, arilo, aril-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, haloarilo, C_1-C_6-alquilo sustituido con halógeno. Tal sustituyente también es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por C_1-C_6-alquilarilo, C_1-C_6-alquilarilo sustituido con halógeno, hidroxiarilo, y heteroarilo.

[87] En algunas realizaciones preferidas, E^5 es benzazinilo, benzofuranilo, o tetrahidroisoquinolinilo. Tal sustituyente es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, -$N(R^{11})(R^{12})$, -$C(O)(R^{13})$, -S-R^{11}, -$S(O)_2$-R^{11}, arilo, aril-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, haloarilo, y C_1-C_6-alquilo sustituido con halógeno. Tal sustituyente también es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por C_1-C_6-alquilarilo, C_1-C_6-alquilarilo sustituido con halógeno, hidroxiarilo, y heteroarilo.

[88] En algunas realizaciones preferidas, E^5 es indolilo, benzoxazolilo, benzotienilo, benzotiazolilo, o piridofuranilo. Tal sustituyente cualquier

717

miembro de dicho grupo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, -CN, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, $-N(R^{11})(R^{12})$, $-C(O)(R^{13})$, $-S-R^{11}$, $-S(O)_2-R^{11}$, arilo, aril-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, haloarilo, y C_1-C_6-alquilo sustituido con halógeno. Tal sustituyente también es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por C_1-C_6-alquilarilo, C_1-C_6-alquilarilo sustituido con halógeno, hidroxiarilo, y heteroarilo.

[89] R^1 y R^2 se seleccionan independientemente del grupo formado por -H y alquilo. El alquilo es optativamente sustituido. Ni R^1 ni R^2 forman una estructura de anillo con E^2, E^3, E^4, o E^5.

[90] En algunas realizaciones preferidas, R^1 y R^2 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, y halo-C_1-C_6-alquilo.

[91] En algunas realizaciones preferidas, R^1 y R^2 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, y halo-C_1-C_6-alquilo.

[92] En algunas realizaciones preferidas, R^1 y R^2 se seleccionan independientemente del grupo formado por -H, y C_1-C_6-alquilo.

[93] R^3 es -H o -OH.

[94] R^4 y R^5 se seleccionan independientemente del grupo formado por -H, alquilo, carbociclilo, carbociclilalquilo, heterociclilo, y heterociclilalquilo. Con la excepción de -H, cualquier miembro de este grupo es optativamente sustituido. Ni R^4 ni R^5 forman una estructura de anillo con E^2, E^4, o E^5.

[95] En algunas realizaciones preferidas, R^4 y R^5 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[96] En algunas realizaciones preferidas, R^4 y R^5 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo es optativamente sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[97] R^6 es -CN o -OH.

[98] R^7 es -H, halógeno, -OH, alquilo, alcoxi, o alcoxialquilo. El alquilo, alcoxi y alcoxialquilo son optativamente sustituidos.

[99] En algunas realizaciones preferidas, R^7 es -H, halógeno, -OH, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, o C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno .

[100] En algunas realizaciones preferidas, R^7 es -H, halógeno, -OH, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, o C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno.

[101] En algunas realizaciones preferidas, R^7 es -H, halógeno, -OH, C_1-C_6-alquilo, C_1-C_6-alcoxi, o C_1-C_6-alcoxi-C_1-C_6-alquilo.

[102] R^8 es -OH o alcoxi. El alcoxi es optativamente sustituido.

[103] En algunas realizaciones preferidas, R^8 es -OH, C_1-C_6-alcoxi, o halo-C_1-C_6-alcoxi.

[104] En algunas realizaciones preferidas, R^8 es -OH, C_1-C_6-alcoxi, o halo-C_1-C_6-alcoxi.

[105] En algunas realizaciones preferidas, R^8 es -OH o C_1-C_6-alcoxi.

[106] R^{11} y R^{12} se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[107] En algunas realizaciones preferidas, R^{11} y R^{12} se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[108] R^{13} es -H, C_1-C_6-alquilo, -O-R^{14}, -N(R^{14})(R^{15}), carbociclil-C_1-C_6-alquilo, heterociclil-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, carbociclil-C_1-C_6-alquilo sustituido con halógeno, o heterociclil-C_1-C_6-alquilo sustituido con halógeno.

[109] En algunas realizaciones preferidas, R^{13} es -H, C_1-C_6-alquilo, -O-R^{14}, -N(R^{14})(R^{15}), carbociclil-C_1-C_6-alquilo, heterociclil-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, carbociclil-C_1-C_6-alquilo sustituido con halógeno, o heterociclil-C_1-C_6-alquilo sustituido con halógeno.

[110] En algunas realizaciones preferidas, R^{13} es -H, C_1-C_6-alquilo, -O-R^{14}, -N(R^{14})(R^{15}), carbociclil-C_1-C_6-alquilo, o heterociclil-C_1-C_6-alquilo.

[111] R^{14} y R^{15} se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es -H, cualquier miembro

de este grupo puede ser sustituido con uno o más halógenos, pero típicamente es preferentemente no sustituido con halógeno.

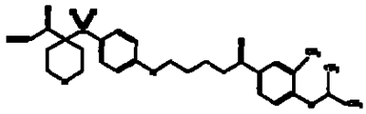
[112] En algunas realizaciones preferidas, R^{14} y R^{15} se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo puede ser sustituido con uno o más halógenos, pero típicamente es preferentemente no sustituido con halógeno.

Realización preferida Nro. 1-a: E^3 es -C(O)-

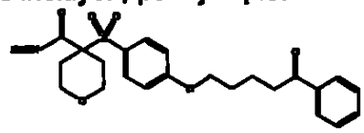
[113] En algunas realizaciones, E^3 es -C(O)-.

[114] En algunas de dichas realizaciones, E^5 es carbociclilo optativamente sustituido, y generalmente preferentemente cicloalquilo optativamente sustituido o arilo optativamente sustituido.

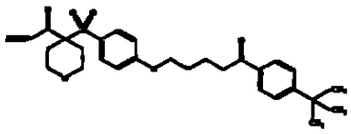
[115] En algunas realizaciones preferidas, por ejemplo, E^5 es fenilo optativamente sustituido. Dichos compuestos incluyen, por ejemplo:



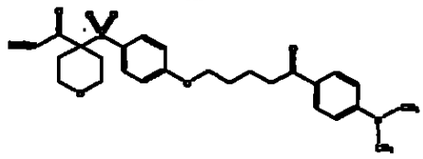
IIA-1



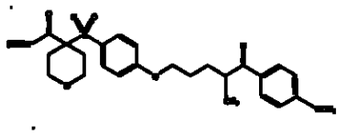
IIA-2



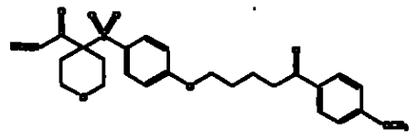
IIA-3



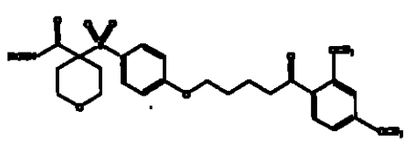
IIA-4



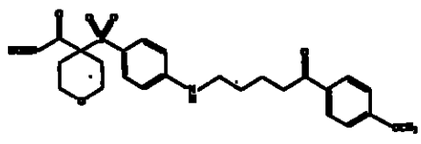
IIA-5



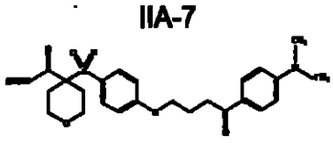
IIA-6



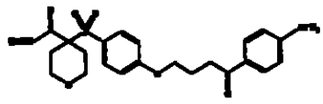
IIA-7



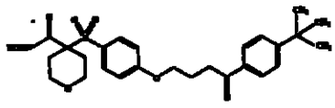
IIA-8



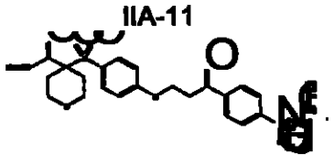
IIA-9



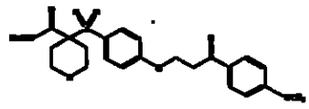
IIA-10



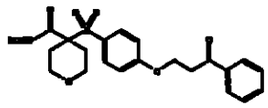
IIA-11



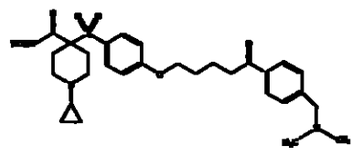
IIA-12



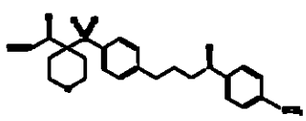
IIA-13



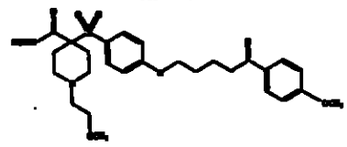
IIA-14



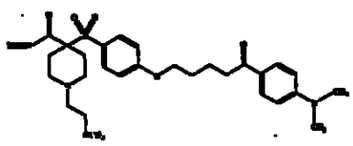
IIA-15



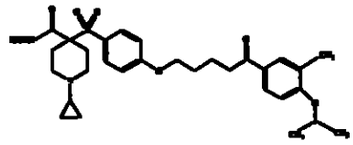
IIA-16



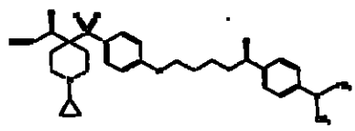
IIA-17



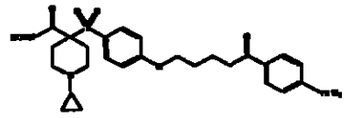
IIA-18



IIA-19

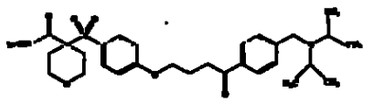


IIA-20

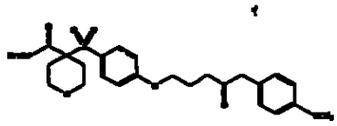


IIA-21

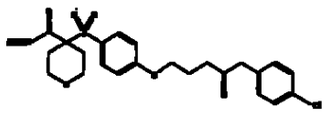
IIA-22



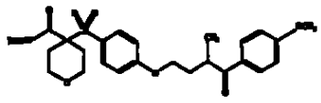
IIA-23



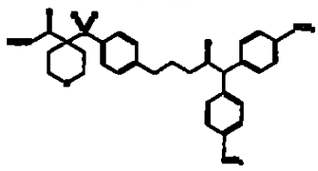
IIA-24



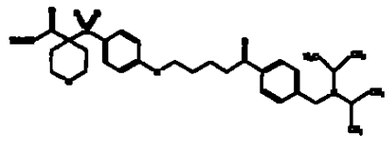
IIA-25



IIA-26

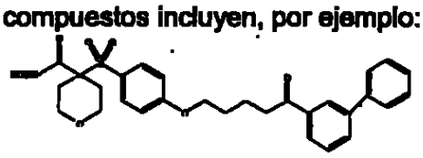


IIA-27

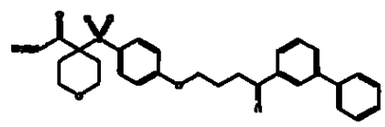


IIA-28

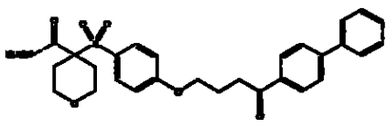
Dichos compuestos también incluyen compuestos donde E^5 es fenilo sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por arilo, haloarilo, aril-C_1-C_6-alquilo, y C_1-C_6-alquilo sustituido con halógeno. En este caso, el fenilo también es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, -$N(R^{11})(R^{12})$, -$C(O)(R^{13})$, -S-R^{11}, -$S(O)_2$-R^{11}, arilo, aril-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, haloarilo, C_1-C_6-alquilo sustituido con halógeno, C_1-C_6-alquilarilo, C_1-C_6-alquilarilo sustituido con halógeno, hidroxiarilo, y heteroarilo. Dichos compuestos incluyen, por ejemplo:



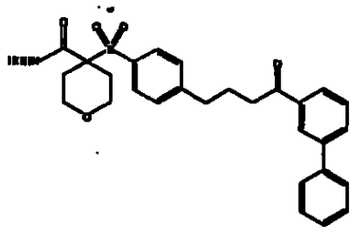
IIA-29



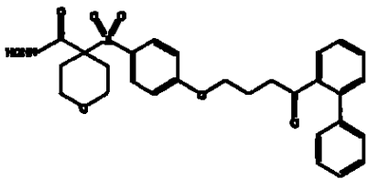
IIA-30



IIA-31

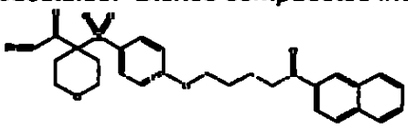


IIA-32

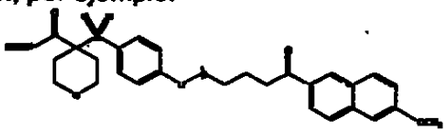


IIA-33

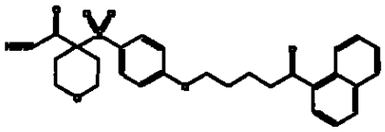
[116] En otras realizaciones preferidas, E^5 es naftalenilo optativamente sustituido. Dichos compuestos incluyen, por ejemplo:



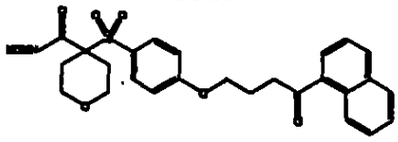
IIA-34



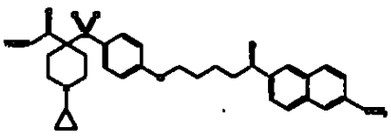
IIA-35



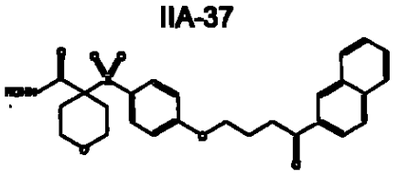
IIA-36



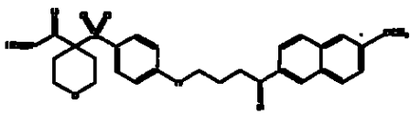
IIA-37



IIA-38



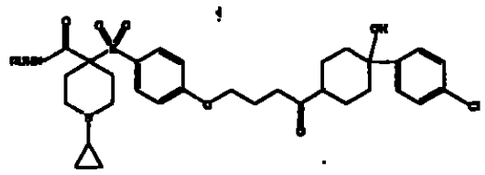
IIA-39



IIA-40

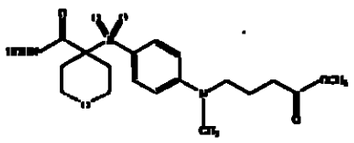
[117] En aún otras realizaciones preferidas, E^5 es C_3-C_6-cicloalquilo optativamente sustituido. Dichos compuestos incluyen, por ejemplo:

724

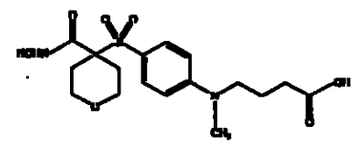


IIA-41.

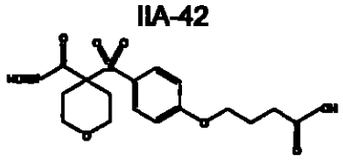
[118] En algunas realizaciones preferidas, E^5 es -H, -OH, C_1-C_6-alquilo, C_2-C_6-alquenilo, C_2-C_6-alquinilo, C_1-C_6-alcoxi, o C_1-C_6-alcoxi-C_1-C_6-alquilo. El C_1-C_6-alquilo, C_2-C_6-alquenilo, C_2-C_6-alquinilo, C_1-C_6-alcoxi, y C_1-C_6-alcoxi-C_1-C_6-alquilo son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, y -CN. Dichos compuestos incluyen, por ejemplo:



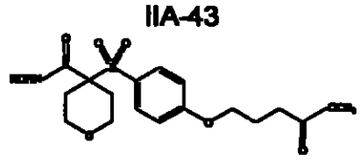
IIA-42



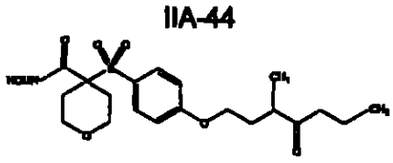
IIA-43



IIA-44

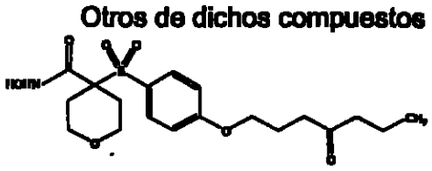


IIA-45

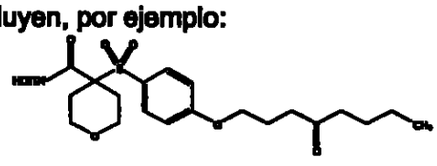


IIA-46

Otros de dichos compuestos incluyen, por ejemplo:

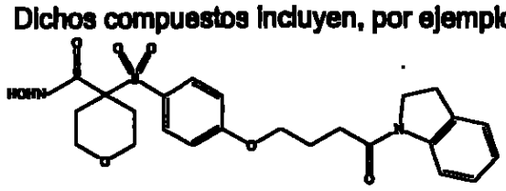


IIA-47



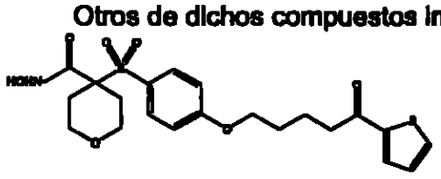
IIA-48

[119] En otras realizaciones preferidas, E^5 es heterociclilo optativamente sustituido. En una de tales realizaciones, E^5 es optativamente-sustituido tiofenilo. Dichos compuestos incluyen, por ejemplo:

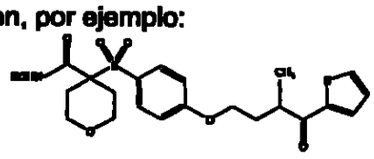


IIA-49

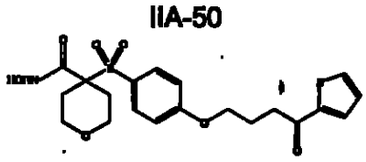
Otros de dichos compuestos incluyen, por ejemplo:



IIA-50



IIA-51

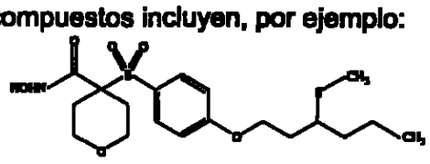


IIA-52

Realización preferida Nro. 1-b: E^3 es -S-

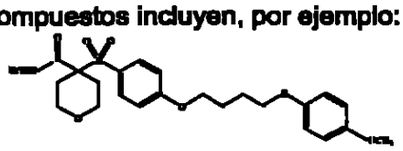
[120] En algunas realizaciones, E^3 es -S-.

[121] En algunas de dichas realizaciones, E^5 es -H, -OH, C_1-C_8-alquilo, C_2-C_8-alquenilo, C_2-C_8-alquinilo, C_1-C_8-alcoxi, o C_1-C_8-alcoxi-C_1-C_8-alquilo. El C_1-C_8-alquilo, C_2-C_8-alquenilo, C_2-C_8-alquinilo, C_1-C_8-alcoxi, y C_1-C_8-alcoxi-C_1-C_8-alquilo son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, y -CN. Dichos compuestos incluyen, por ejemplo:

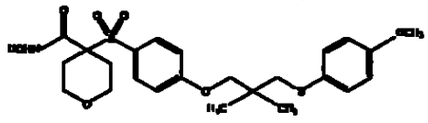


IIB-1

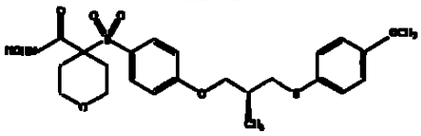
[122] En algunas realizaciones preferidas, E^5 es carbociclilo optativamente sustituido, generalmente preferentemente arilo optativamente sustituido, y más preferentemente fenilo optativamente sustituido. Dichos compuestos incluyen, por ejemplo:



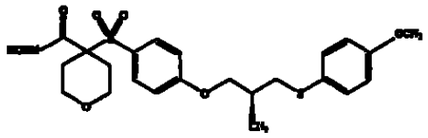
IIB-2



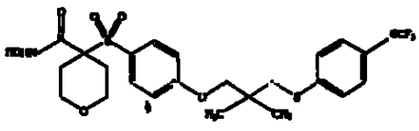
IIB-3



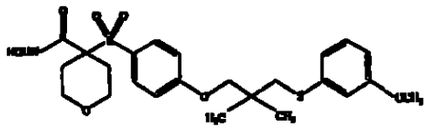
IIB-4



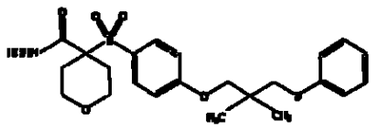
IIB-5



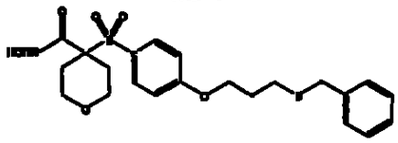
IIB-6



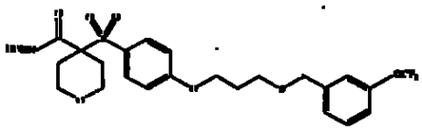
IIB-7



IIB-8

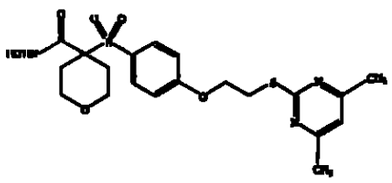


IIB-9

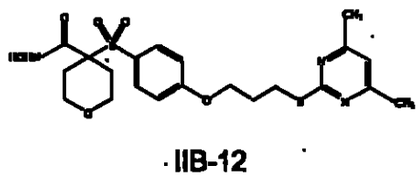


IIB-10

[123] En algunas realizaciones preferidas, E^5 es heterociclilo optativamente sustituido. En una de tales realizaciones, E^5 es pirimidilo optativamente sustituido. Dichos compuestos incluyen, por ejemplo:

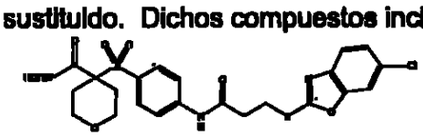


IIB-11

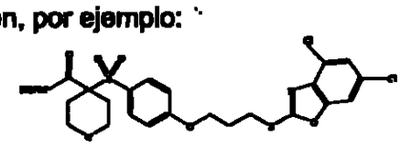


IIB-12

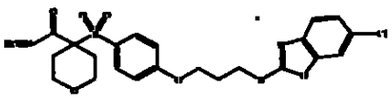
En otra de estas realizaciones, E^5 es heterocicilo de 2 anillos fusionados optativamente sustituido. En algunas realizaciones preferidas, E^5 es benzoxazolilo optativamente sustituido o benzotiazolilo optativamente sustituido. Dichos compuestos incluyen, por ejemplo:



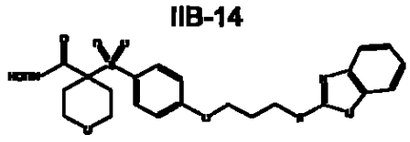
IIB-13



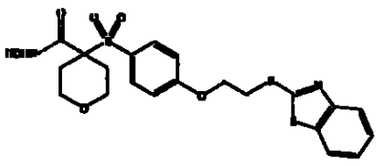
IIB-14



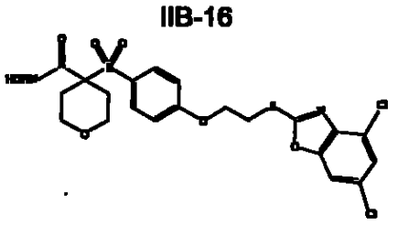
IIB-15



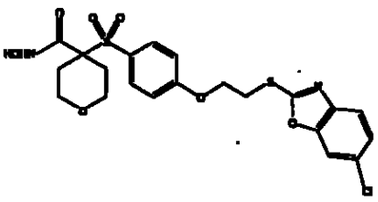
IIB-16



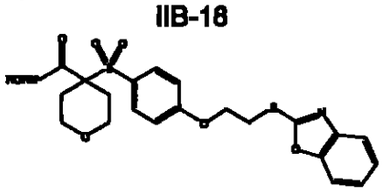
IIB-17



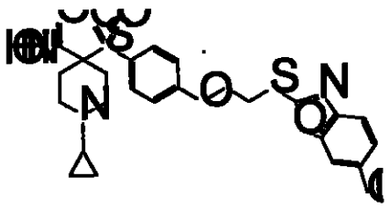
IIB-18



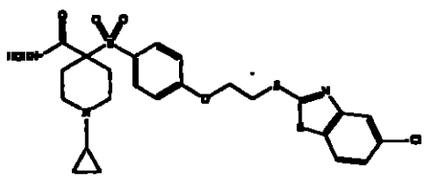
IIB-19



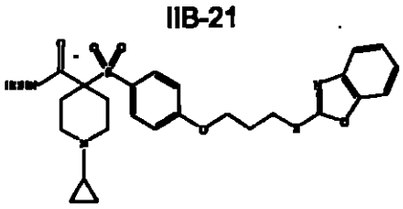
IIB-20



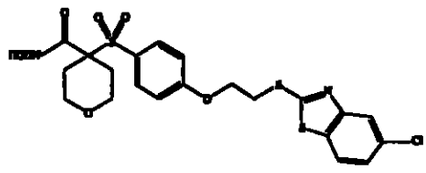
IIB-21



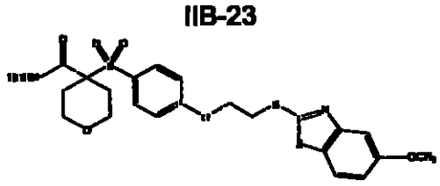
IIB-22



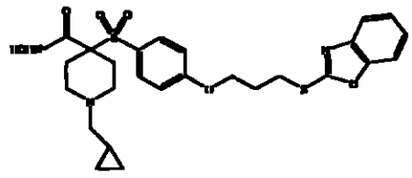
IIB-23



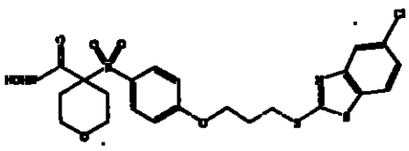
IIB-24



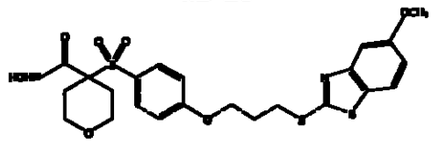
IIB-25



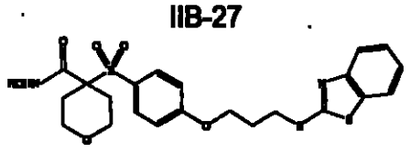
IIB-26



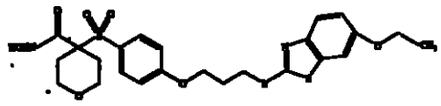
IIB-27



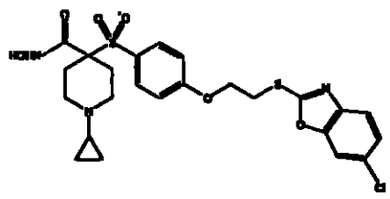
IIB-28



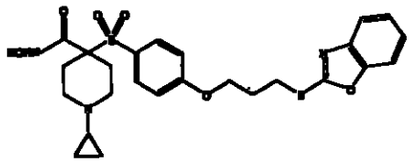
IIB-29



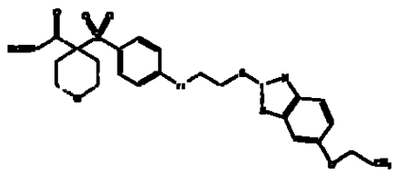
IIB-30



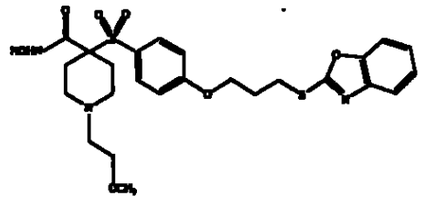
IIB-31



IIB-32

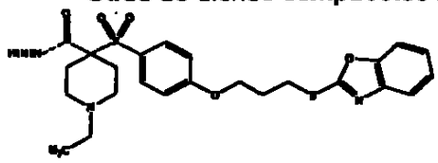


IIB-33

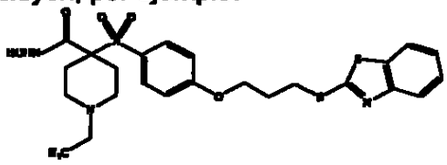


IIB-34

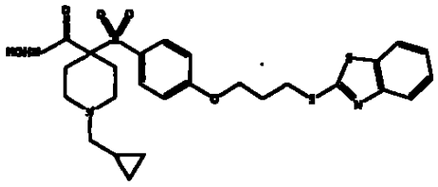
Otros de dichos compuestos incluyen, por ejemplo:



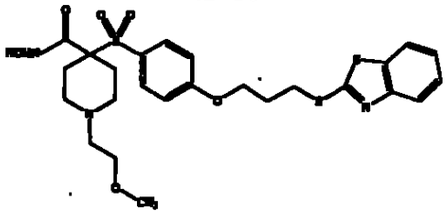
IIB-35



IIB-36



IIB-37

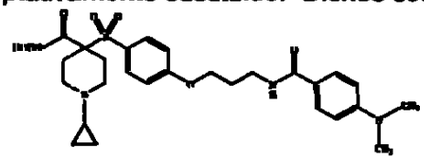


IIB-38

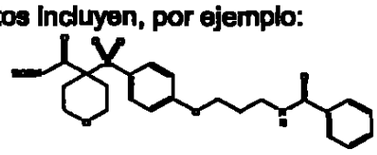
Realización preferida Nro. 1-c: E^3 es $-N(R^4)-C(O)-$

[124] En algunas realizaciones, E^3 es $-N(R^4)-C(O)-$.

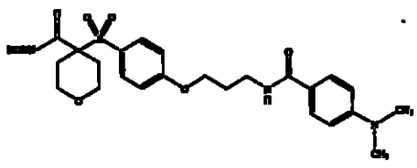
[125] En algunas de dichas realizaciones, E^5 es carbociclilo optativamente sustituido. En algunas realizaciones preferidas, E^5 es fenilo optativamente sustituido. Dichos compuestos incluyen, por ejemplo:



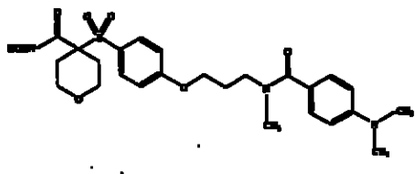
IIC-1



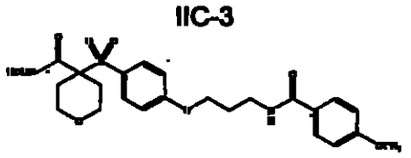
IIC-2



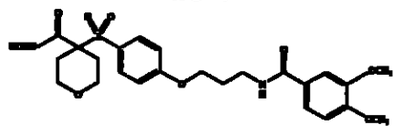
IIC-3



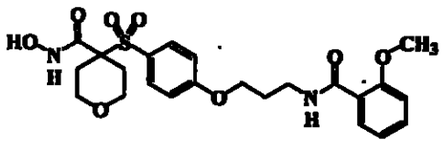
IIC-4



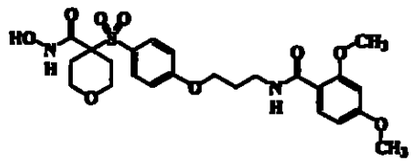
IIC-5



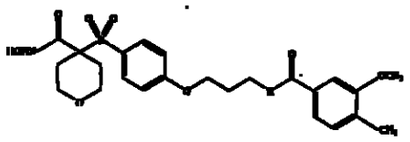
IIC-6



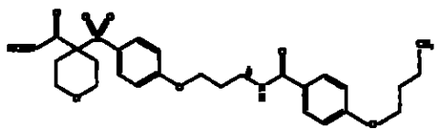
IIC-7



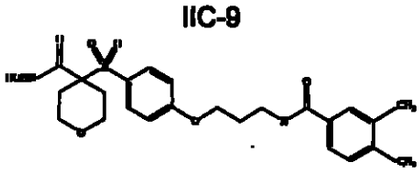
IIC-8



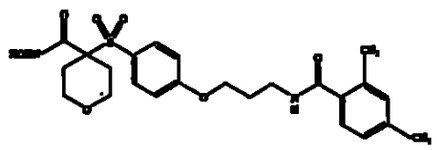
IIC-9



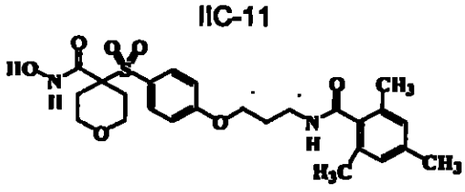
IIC-10



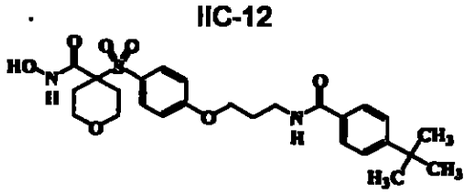
IIC-11



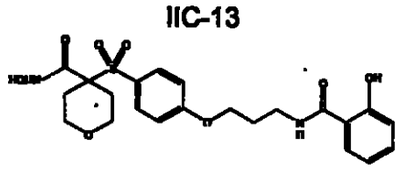
IIC-12



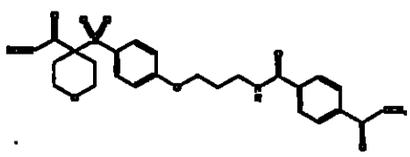
IIC-13



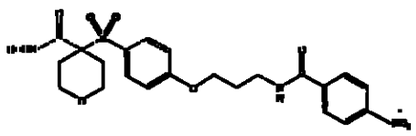
IIC-14



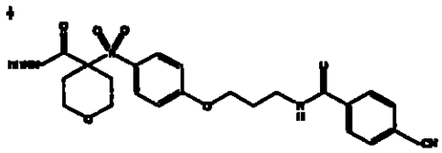
IIC-15



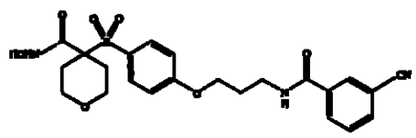
IIC-16



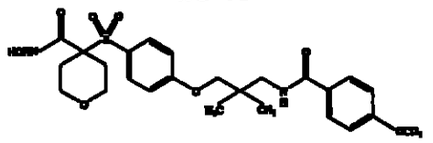
IIC-17



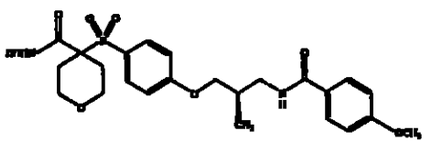
IIC-18



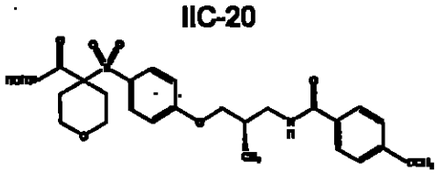
IIC-19



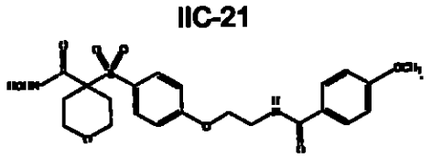
IIC-20



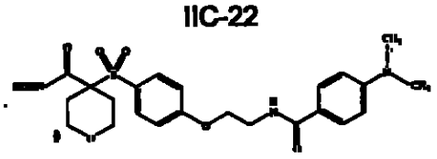
IIC-21



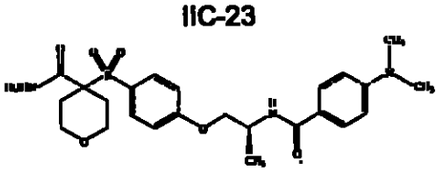
IIC-22



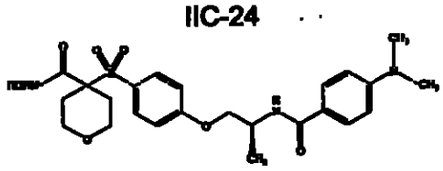
IIC-23



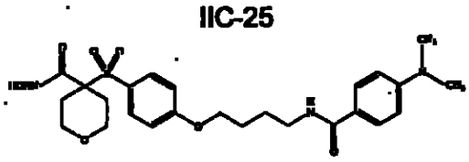
IIC-24



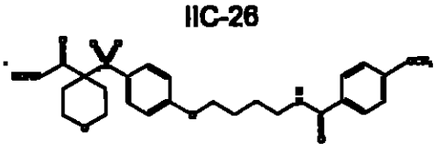
IIC-25



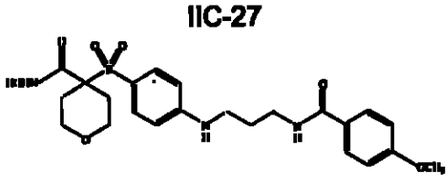
IIC-26



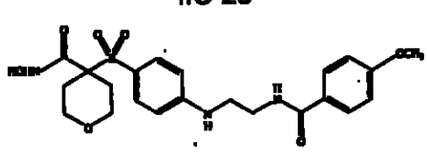
IIC-27



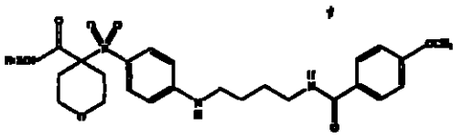
IIC-28



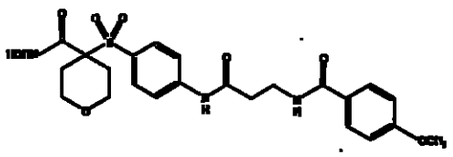
IIC-29



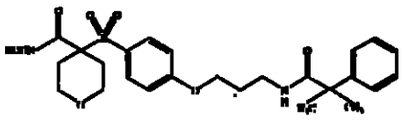
IIC-30



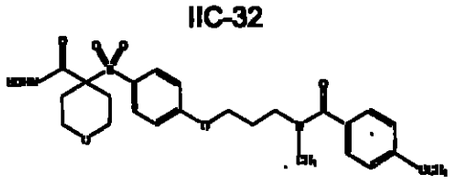
IIC-31



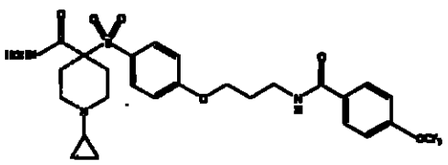
IIC-32



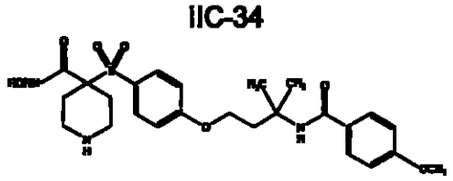
IIC-33



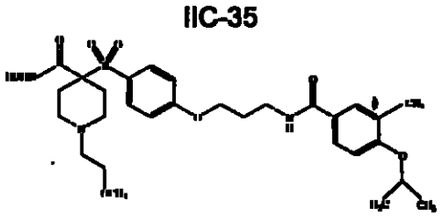
IIC-34



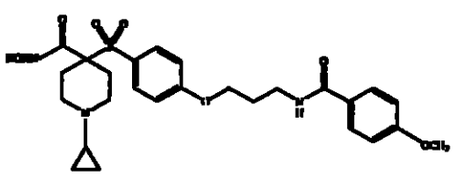
IIC-35



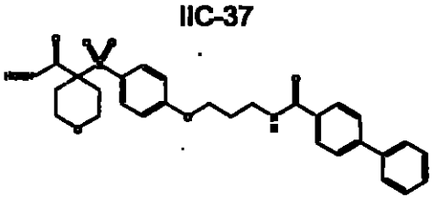
IIC-36



IIC-37

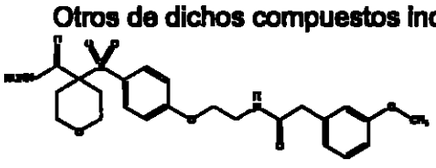


IIC-38

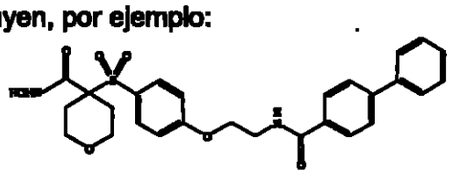


IIC-39

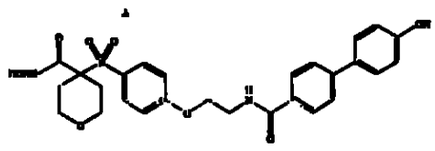
Otros de dichos compuestos incluyen, por ejemplo:



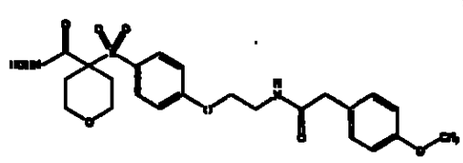
IIC-40



IIC-41

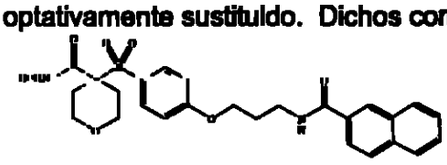


IIC-42

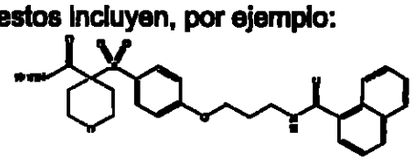


IIC-43

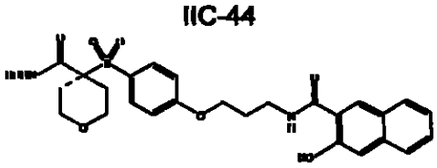
[126] En algunas realizaciones preferidas, E^5 es naftalenilo optativamente sustituido. Dichos compuestos incluyen, por ejemplo:



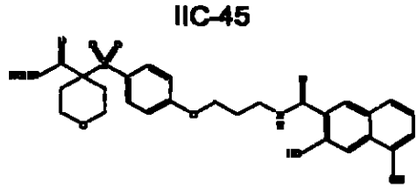
IIC-44



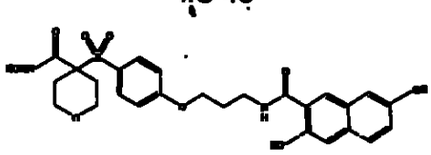
IIC-45



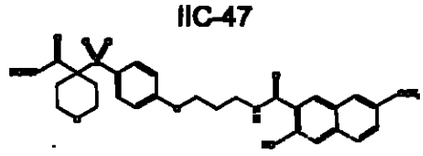
IIC-46



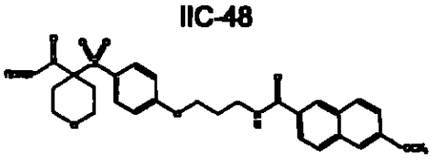
IIC-47



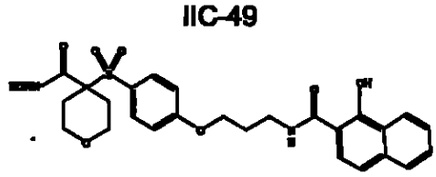
IIC-48



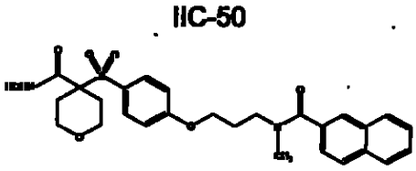
IIC-49



IIC-50

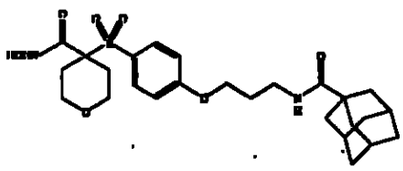


IIC-51



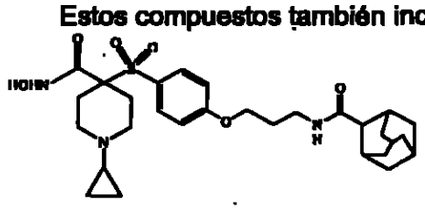
IIC-52

[127] En algunas realizaciones preferidas, E^5 es cicloalquilo optativamente sustituido. Dichos compuestos incluyen, por ejemplo, cicloalquilos de anillos fusionados. Estos compuestos incluyen, por ejemplo:

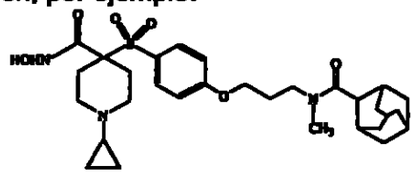


IIC-53

Estos compuestos también incluyen, por ejemplo:

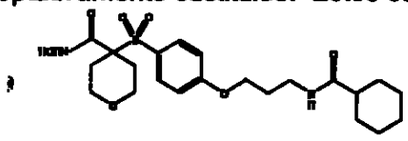


IIC-54

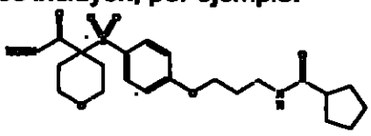


IIC-55

[128] En algunas realizaciones preferidas, E^5 es C_5-C_8-cicloalquilo optativamente sustituido. Estos compuestos incluyen, por ejemplo:

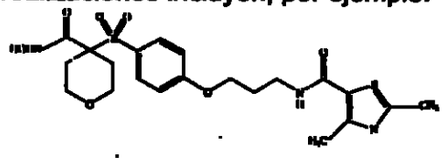


IIC-56

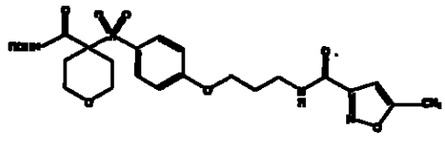


IIC-57

[129] En algunas realizaciones preferidas, E^5 es heterociclilo optativamente sustituido. En una de tales realizaciones, E^5 es un heterociclo optativamente sustituido seleccionado del grupo formado por piridinilo, pirrolilo, isopirrolilo, oxazolilo, isoxazol, tiazolilo, furanilo, y morfolinilo. En otra de estas realizaciones, E^5 es un heterociclo optativamente sustituido seleccionado del grupo formado por tetrazolilo, imidazolilo, y tienilo. Compuestos de estas realizaciones incluyen, por ejemplo:

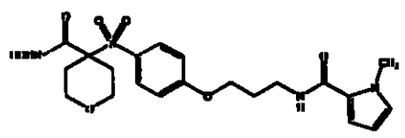


IIC-58

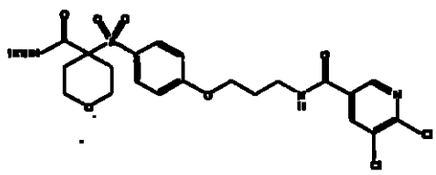


IIC-59

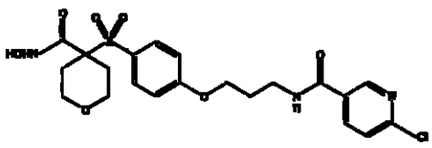
735



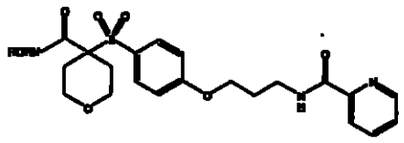
IIC-60



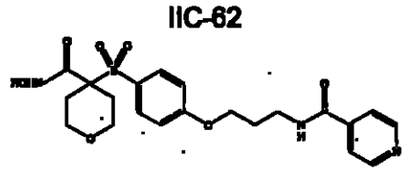
IIC-61



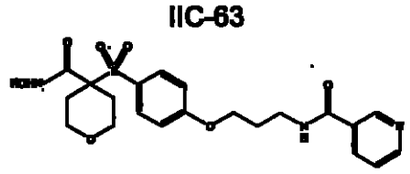
IIC-62



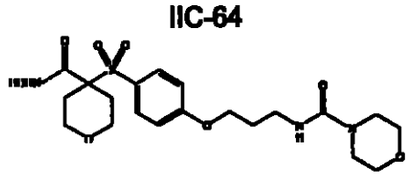
IIC-63



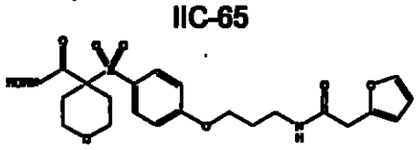
IIC-64



IIC-65

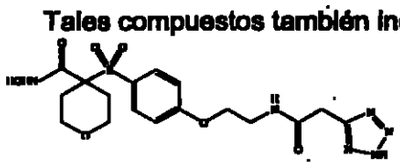


IIC-66

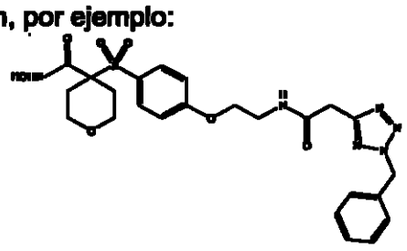


IIC-67

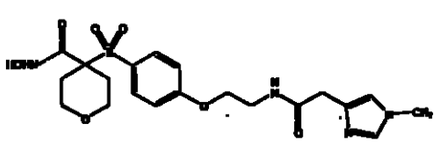
Tales compuestos también incluyen, por ejemplo:



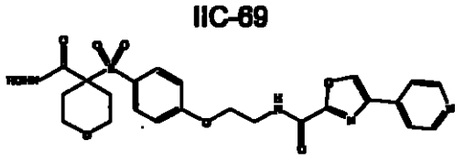
IIC-68



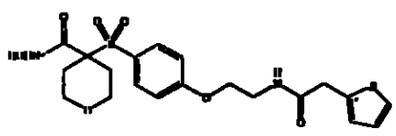
IIC-69



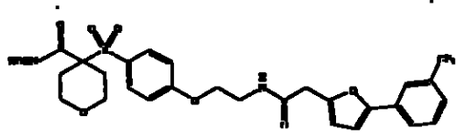
IIC-70



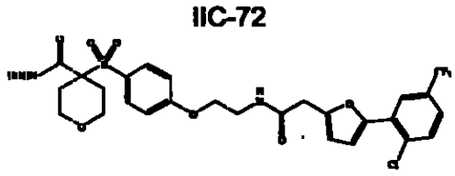
IIC-71



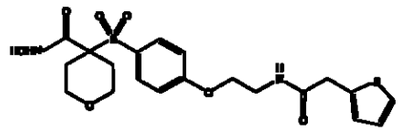
IIC-72



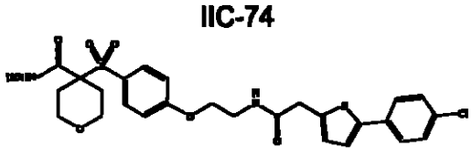
IIC-73



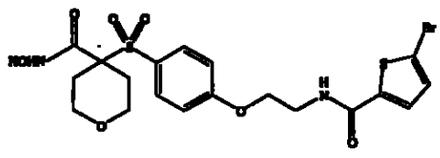
IIC-74



IIC-75

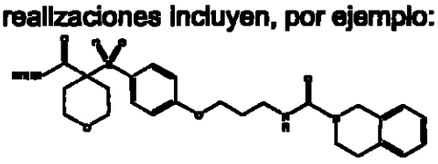


IIC-76

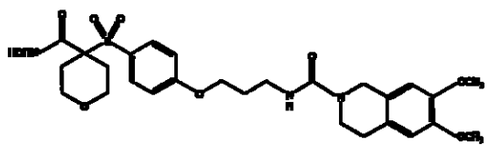


IIC-77

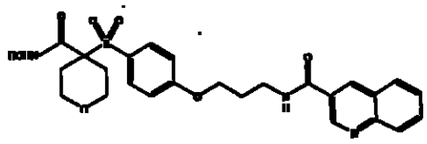
[130] En algunas realizaciones preferidas, E^5 es heterociclilo de 2 anillos fusionados optativamente sustituidos. En algunas realizaciones más preferidas, E^5 es un heterociclo optativamente sustituido seleccionado del grupo formado por benzazinilo, benzofuranilo, tetrahidroisoquinolinilo o piridofuranilo. En algunas otras realizaciones más preferidas, E^5 es un heterociclo optativamente sustituido seleccionado del grupo formado por indolilo, benzoxazolilo, benzotienilo, y benzotiazolilo. Compuestos de tales realizaciones incluyen, por ejemplo:



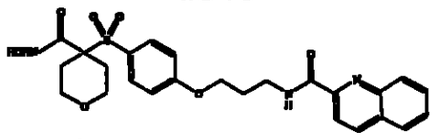
IIC-78



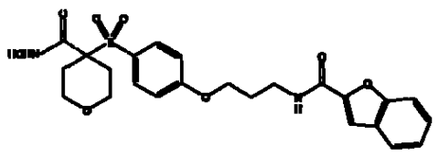
IIC-79



IIC-80

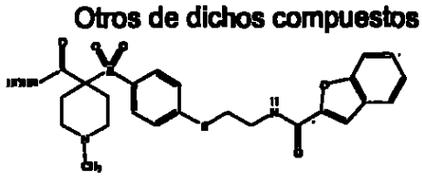


IIC-81

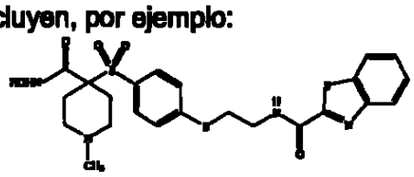


IIC-82

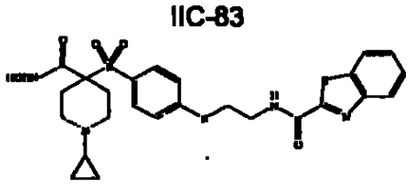
Otros de dichos compuestos incluyen, por ejemplo:



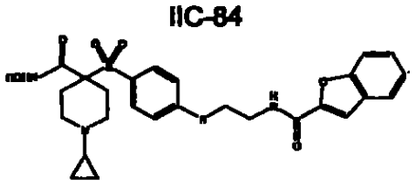
IIC-83



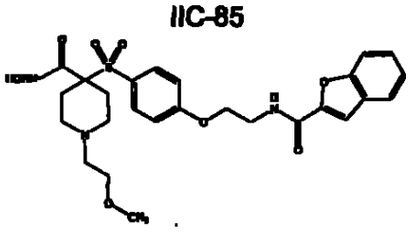
IIC-84



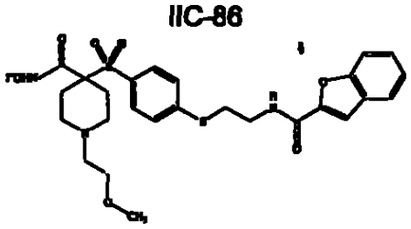
IIC-85



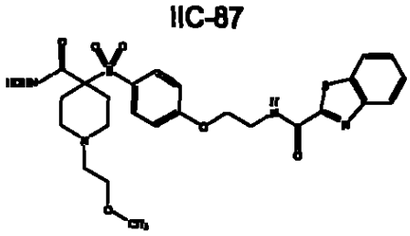
IIC-86



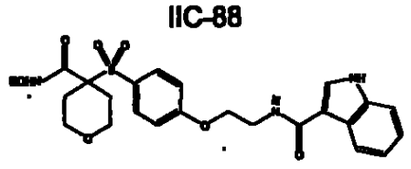
IIC-87



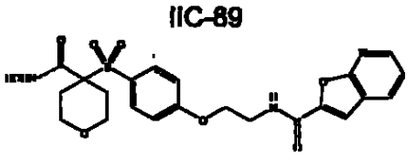
IIC-88



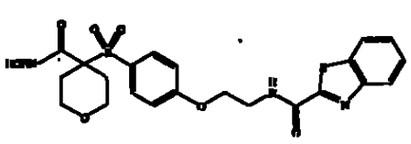
IIC-89



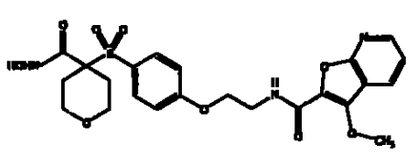
IIC-90



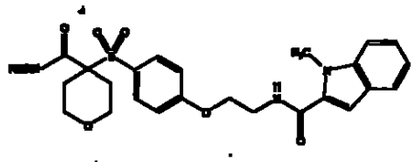
IIC-91



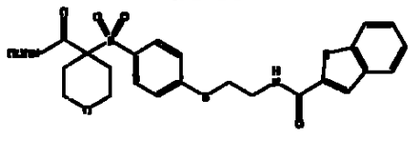
IIC-92



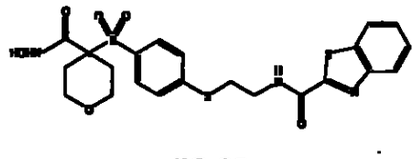
IIC-93



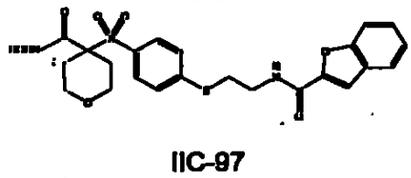
IIC-94



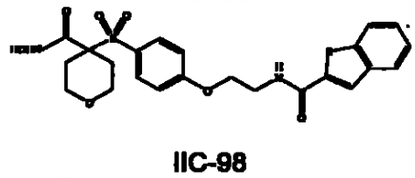
IIC-95



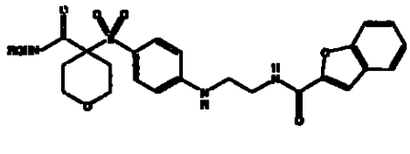
IIC-96



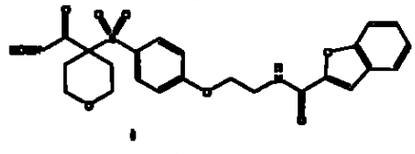
IIC-97



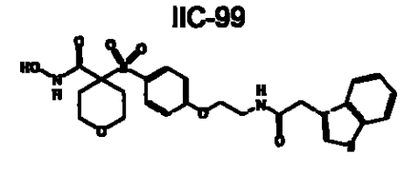
IIC-98



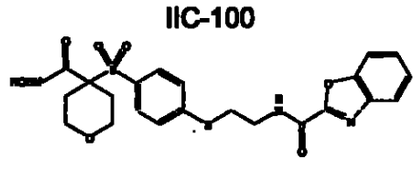
IIC-99



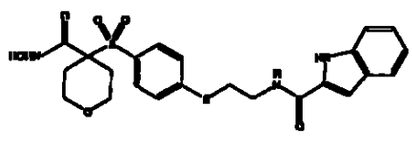
IIC-100



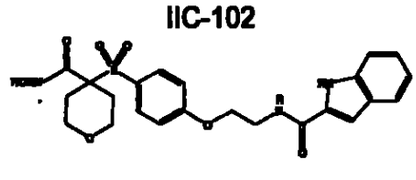
IIC-101



IIC-102

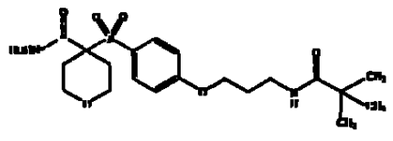


IIC-103

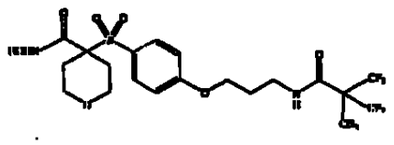


IIC-104

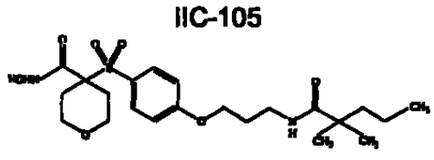
[131] En algunas realizaciones preferidas, E^5 es -OH, C_1-C_6-alquilo, C_2-C_6-alquenilo, C_2-C_6-alquinilo, C_1-C_6-alcoxi, o C_1-C_6-alcoxil-C_1-C_6-alquilo. Salvo cuando el miembro es -OH, cualquier miembro de este grupo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, y -CN. Dichos compuestos incluyen, por ejemplo:



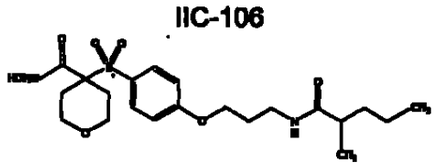
IIC-105



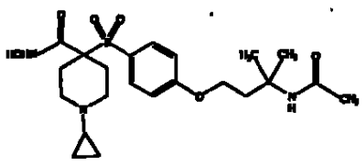
IIC-106



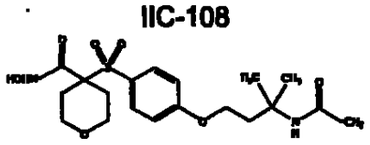
IIC-107



IIC-108



IIC-109



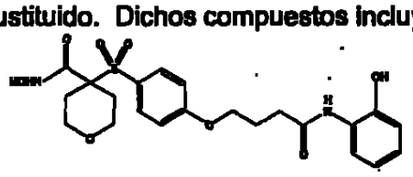
IIC-110

Realización preferida Nro. 1-d: E^3 es -C(O)-N(R^4)-

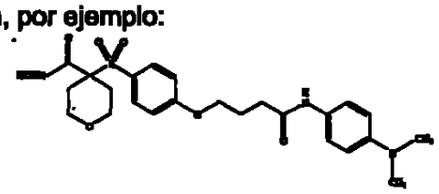
[132] En algunas realizaciones, E^3 es -C(O)-N(R^4)-.

[133] En algunas de dichas realizaciones, por ejemplo, E^5 es carbociclilo optativamente sustituido, generalmente preferentemente arilo optativamente sustituido.

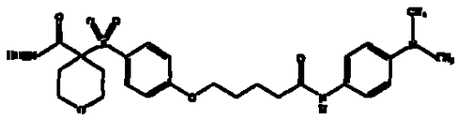
[134] En algunas realizaciones preferidas, E^5 es fenilo optativamente sustituido. Dichos compuestos incluyen, por ejemplo:



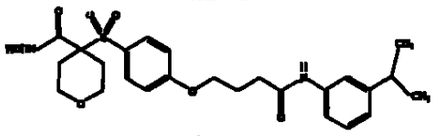
IID-1



IID-2

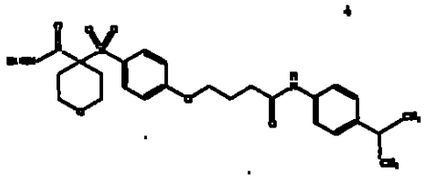


IID-3

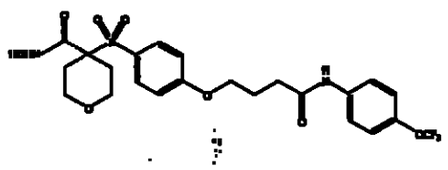


IID-4

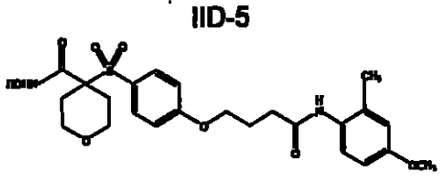
740



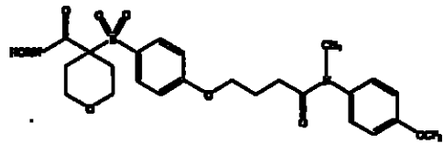
IID-5



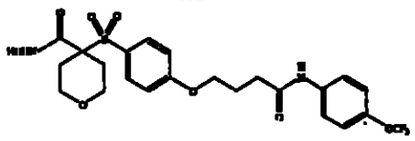
IID-6



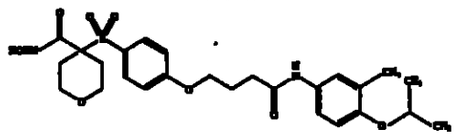
IID-7



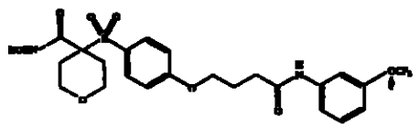
IID-8



IID-9

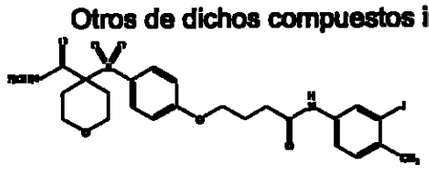


IID-10

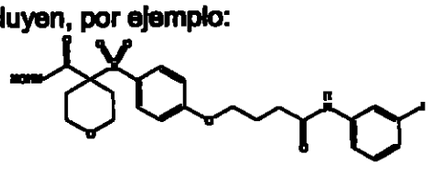


IID-11

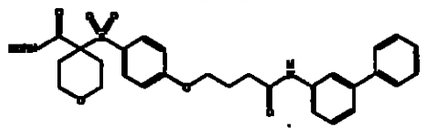
Otros de dichos compuestos incluyen, por ejemplo:



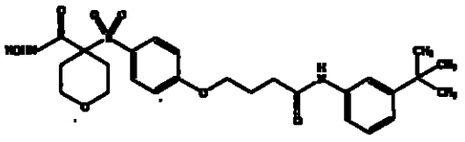
IID-12



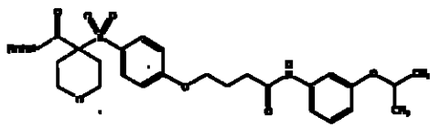
IID-13



IID-14



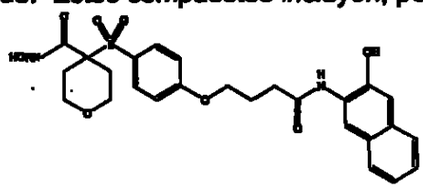
IID-15



IID-16

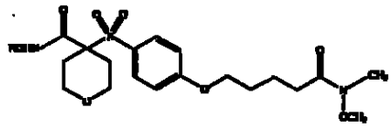
741

[135] En algunas realizaciones preferidas, E^5 es naftalenilo optativamente sustituido. Estos compuestos incluyen, por ejemplo:



IID-17

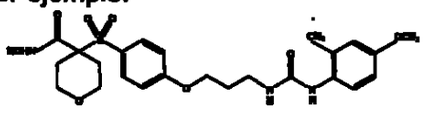
[136] En algunas realizaciones preferidas, E^5 es -OH, C_1-C_6-alquilo, C_2-C_6-alquenilo, C_2-C_6-alquinilo, C_1-C_6-alcoxi, o C_1-C_6-alcoxi-C_1-C_6-alquilo. Salvo cuando el miembro es -OH, cualquier miembro de este grupo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, y -CN. Dichos compuestos incluyen, por ejemplo:



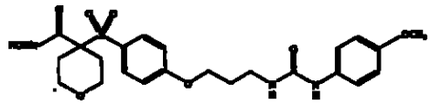
IID-18

Realización preferida Nro. 1-e: E^3 es $-N(R^4)-C(O)-N(R^5)-$

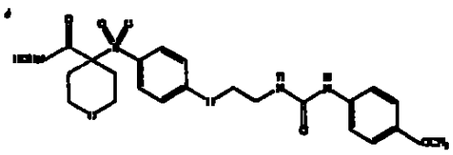
[137] En algunas realizaciones, E^3 es $-N(R^4)-C(O)-N(R^5)-$. En algunas de dichas realizaciones, por ejemplo, E^5 es carbociclilo optativamente sustituido, generalmente preferentemente arilo optativamente sustituido, y más preferentemente fenilo optativamente sustituido. Dichos compuestos incluyen, por ejemplo:



IIE-1



IIE-2

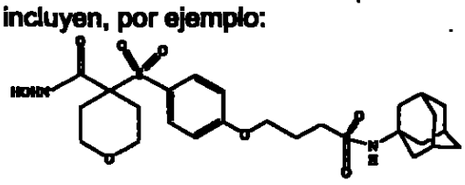


IIE-3

Realización preferida Nro. 1-f: E^3 es $-S(O)_2-N(R^4)-$

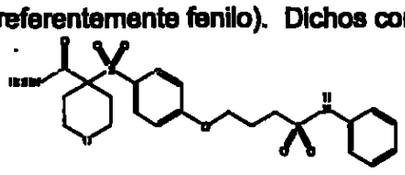
[138] En algunas realizaciones, E^3 es $-S(O)_2-N(R^4)-$.

[139] En algunas de dichas realizaciones, E^5 es carbociclilo optativamente sustituido. El carbociclilo puede ser, por ejemplo, cicloalquilo. Dichos compuestos incluyen, por ejemplo:

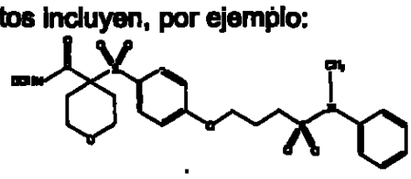


IIF-1

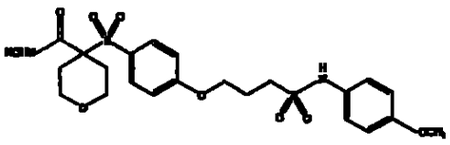
En algunas realizaciones preferidas, el carbociclilo es arilo (preferentemente fenilo). Dichos compuestos incluyen, por ejemplo:



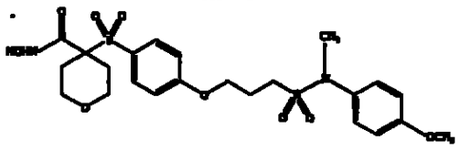
IIF-2



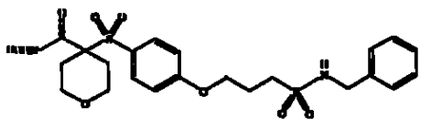
IIF-3



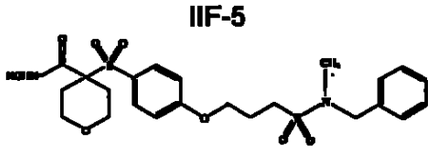
IIF-4



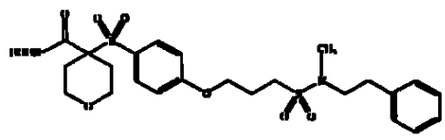
IIF-5



IIF-6

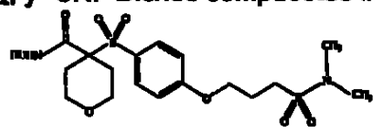


IIF-7

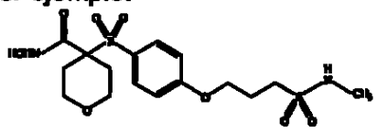


IIF-8

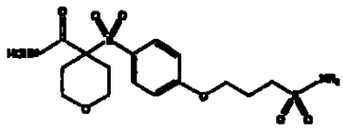
[140] En algunas realizaciones preferidas, E^5 es -H, -OH, C_1-C_6-alquilo, C_2-C_6-alquenilo, C_2-C_6-alquinilo, C_1-C_6-alcoxi, o C_1-C_6-alcoxi-C_1-C_6-alquilo. Salvo cuando el miembro es -H o -OH, cualquier miembro de este grupo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, y -CN. Dichos compuestos incluyen, por ejemplo:



IIF-9



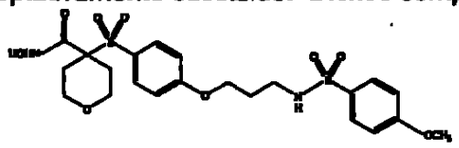
IIF-10



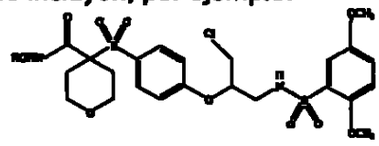
IIF-11

Realización preferida Nro. 1-g: E^3 es -$N(R^4)$-$S(O)_2$-

[141] En algunas realizaciones, E^3 es -$N(R^4)$-$S(O)_2$-. En algunas de dichas realizaciones, E^5 es carbociclilo optativamente sustituido, generalmente preferentemente arilo optativamente sustituido, y más preferentemente fenilo optativamente sustituido. Dichos compuestos incluyen, por ejemplo:



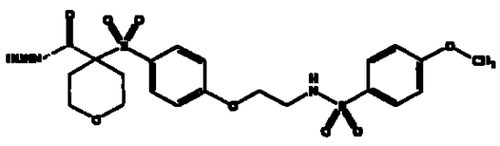
IIG-1



IIG-2

Otros de dichos compuestos incluyen, por ejemplo:

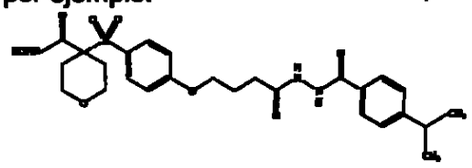
744



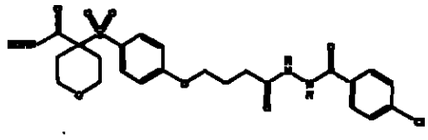
IIG-3

Realización preferida Nro. 1-h: E^3 es -C(O)-N(R^4)-N(R^5)-C(O)-

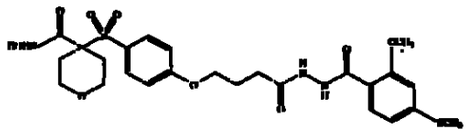
[142] En algunas realizaciones, E^3 es -C(O)-N(R^4)-N(R^5)-C(O)-. En algunas de dichas realizaciones, E^5 es carbociclilo optativamente sustituido, generalmente preferentemente arilo optativamente sustituido, y más preferentemente fenilo optativamente sustituido. Dichos compuestos incluyen, por ejemplo:



IIH-1



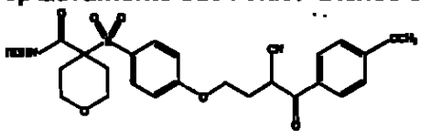
IIH-2



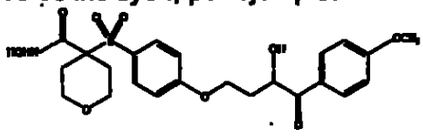
IIH-3

Realización preferida Nro. 1-i: E^3 es -C(R^4)(R^6)-C(O)-

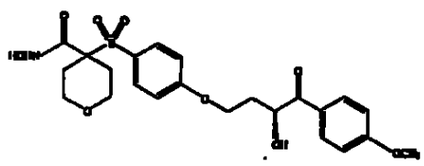
[143] En algunas realizaciones, E^3 es -C(R^4)(R^6)-C(O)-. En algunas de dichas realizaciones, E^5 es carbociclilo optativamente sustituido, generalmente preferentemente arilo optativamente sustituido, y más preferentemente fenilo optativamente sustituido. Dichos compuestos incluyen, por ejemplo:



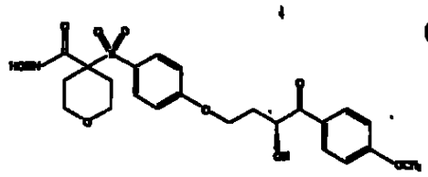
III-1



III-2



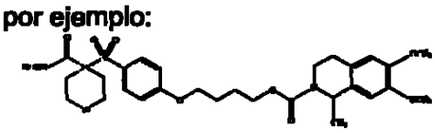
III-3



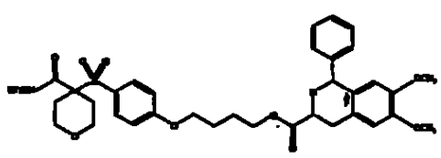
III-4

Realización preferida Nro. 1-j: E^3 es -O-C(O)-

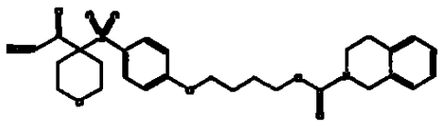
[144] En algunas realizaciones, E^3 es -O-C(O)-. En algunas de dichas realizaciones, E^5 es heterociclilo optativamente sustituido. En algunas realizaciones preferidas, E^5 es un heterociclo de 2 anillos fusionados optativamente sustituido. En algunas realizaciones, por ejemplo, E^5 es tetrahidroisoquinolinilo optativamente-sustituido. Dichos compuestos incluyen, por ejemplo:



IIJ-1



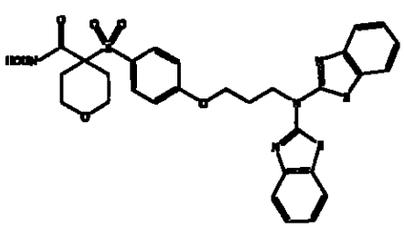
IIJ-2



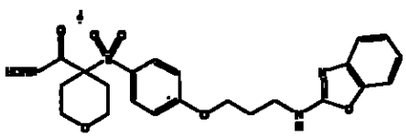
IIJ-3

Realización preferida Nro. 1-k: E^3 es -N(R^4)-

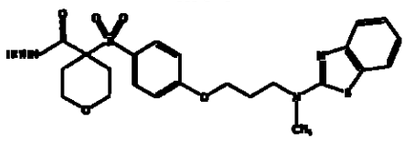
[145] En algunas realizaciones, E^3 es -N(R^4)-. En algunas de dichas realizaciones, E^5 es heterociclilo optativamente sustituido. En algunas realizaciones preferidas, E^5 es heterociclilo de 2 anillos fusionados optativamente sustituido. En algunas realizaciones, por ejemplo, E^5 es benzoxazolilo optativamente sustituido, benzotiazolilo, o bencimidazolilo. Dichos compuestos incluyen, por ejemplo:



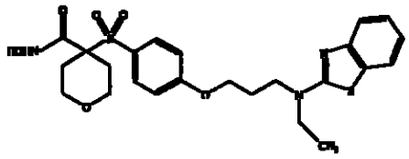
IIK-1



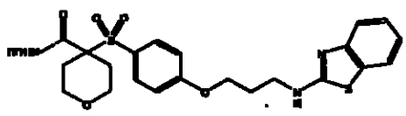
IIK-2



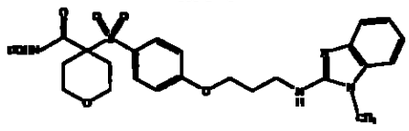
IIK-3



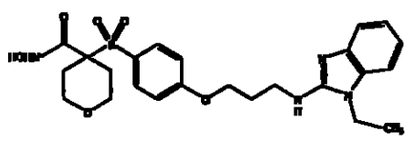
IIK-4



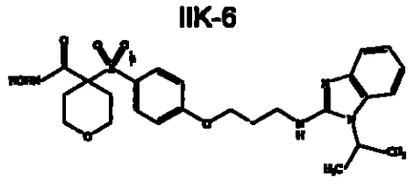
IIK-5



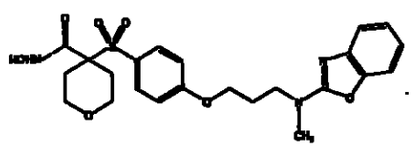
IIK-6



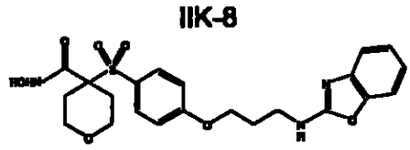
IIK-7



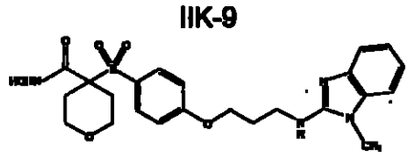
IIK-8



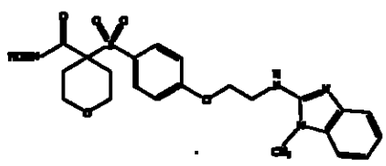
IIK-9



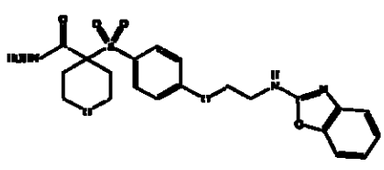
IIK-10



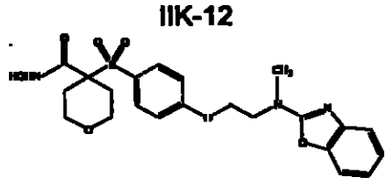
IIK-11



IIK-12



IIK-13

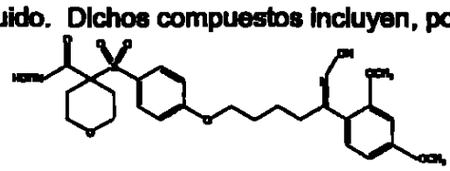


IIK-14

747

Realización preferida Nro. 1-l: E^3 es $-C(NR^3)-$

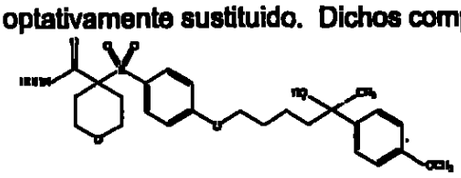
[146] En algunas realizaciones, E^3 es $-C(NR^3)-$. En algunas de dichas realizaciones, E^5 es carbociclilo optativamente sustituido, generalmente preferentemente arilo optativamente sustituido, y más preferentemente fenilo optativamente sustituido. Dichos compuestos incluyen, por ejemplo:



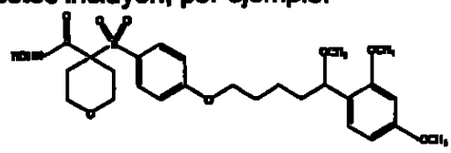
IIL-1

Realización preferida Nro. 1-m: E^3 es $-C(R^7)(R^8)-$

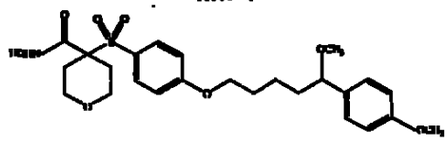
[147] En algunas realizaciones, E^3 es $-C(R^7)(R^8)-$. En algunas de dichas realizaciones, E^5 es carbociclilo optativamente sustituido, generalmente preferentemente arilo optativamente sustituido, y más preferentemente fenilo optativamente sustituido. Dichos compuestos incluyen, por ejemplo:



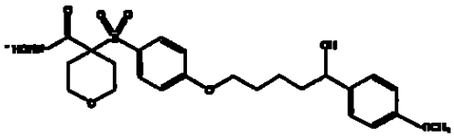
IIM-1



IIM-2



IIM-3

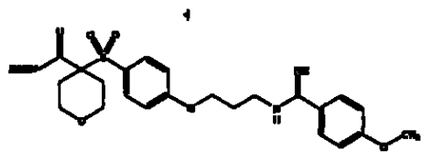


IIM-4

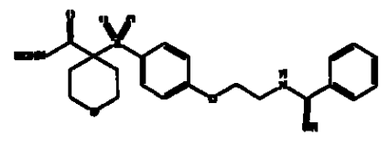
Realización preferida Nro. 1-n: E^3 es $-N(R^4)-C(NR^3)-$

[148] En algunas realizaciones, E^3 es $-N(R^4)-C(NR^3)-$. En algunas de dichas realizaciones, E^5 es carbociclilo optativamente sustituido, generalmente preferentemente arilo optativamente sustituido, y más preferentemente fenilo optativamente sustituido. Dichos compuestos incluyen, por ejemplo:

748



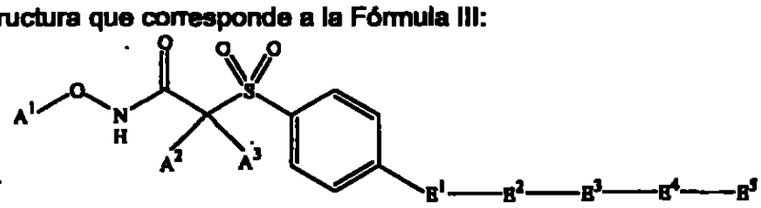
IIN-1



IIN-2

Realización preferida Nro. 2

[149] En algunas realizaciones de esta invención, el compuesto tiene una estructura que corresponde a la Fórmula III:



III

[150] A^1, A^2, y A^3 tienen los valores definidos anteriormente para la Fórmula I.

[151] E^1 es -O-, -$S(O)_2$-, -S(O)-, -$N(R^1)$-, -$C(O)$-$N(R^1)$-, -$N(R^1)$-$C(O)$-, o -$C(R^1)(R^2)$-. E^1 como alternativa puede ser -S-.

[152] E^2 forma un enlace de al menos 2 átomos de carbono entre E^1 y E^3. E^2 es alquilo, cicloalquilo, alquilcicloalquilo, cicloalquilalquilo, o alquilcicloalquilalquilo. Cualquier miembro de este grupo es optativamente sustituido.

[153] En algunas realizaciones preferidas, E^2 es C_2-C_{20}-alquilo, cicloalquilo, C_1-C_{10}-alquilcicloalquilo, cicloalquil-C_1-C_{10}-alquilo, o C_1-C_{10}-alquilcicloalquil-C_1-C_{10}-alquilo. Cualquier miembro de este grupo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, C_1-C_6-alquilo, y halo-C_1-C_6-alquilo.

[154] En algunas realizaciones preferidas, E^2 es C_2-C_8-alquilo optativamente sustituido con uno o más halógenos.

749

[155] En algunas realizaciones preferidas, E^2 es C_2-C_5-alquilo optativamente sustituido con uno o más halógenos.

[156] En algunas realizaciones preferidas, E^2 es C_2-C_5-alquilo.

[157] En algunas realizaciones preferidas, E^2 es $-(CH_2)_m-$, donde m es entre 2 y 5.

[158] E^3 es carbociclilo o heterociclilo. Estos carbociclilo y heterociclilo tienen 5 ó 6 miembros en el anillo y son optativamente sustituidos.

[159] En algunas realizaciones preferidas, E^3 es carbociclilo o heterociclilo donde el carbociclilo y heterociclilo tiene 5 ó 6 miembros en el anillo y son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, ceto, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el sustituyente es halógeno, -OH, o ceto, cualquiera de estos sustituyentes es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alquiltio, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, halo-C_1-C_6-alquiltio, y C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno.

[160] En algunas realizaciones preferidas, E^3 es carbociclilo o heterociclilo donde el carbociclilo y heterociclilo tienen 5 ó 6 miembros en el anillo y son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, ceto, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el sustituyente es halógeno, -OH, o ceto, cualquier sustituyente de este grupo

es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alquiltio, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, y halo-C_1-C_6-alquiltio.

[161] E^4 es un enlace, alquilo, alquenilo, -O-, o -N(R^3)-. El alquilo y alquenilo son optativamente sustituidos.

[162] En algunas realizaciones preferidas, E^4 es un enlace, -O-, -N(R^3)-, C_1-C_{20}-alquilo, o C_2-C_{20}-alquenilo. El C_1-C_{20}-alquilo y C_2-C_{20}-alquenilo son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno y carbociclilo optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, halocarbociclilo, carbociclil-C_1-C_6-alquilo sustituido con halógeno, y C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno .

[163] En algunas realizaciones preferidas, E^4 es un enlace, -O-, -N(R^3)-, C_1-C_3-alquilo, o C_2-C_3-alquenilo. El C_1-C_3-alquilo y C_2-C_3-alquenilo son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno y carbociclilo optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, halocarbociclilo, y carbociclil-C_1-C_6-alquilo sustituido con halógeno.

[164] En algunas realizaciones preferidas, E^4 es un enlace, -O-, -N(R^3)-, C_1-C_3-alquilo, o C_2-C_3-alquenilo.

[165] En algunas realizaciones preferidas, E^4 es un enlace.

[166] E^5 es carbociclilo o heterociclilo. El carbociclilo y heterociclilo es optativamente sustituido. En algunas realizaciones preferidas, el carbociclilo o heterociclilo son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, ceto, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, -N(R^8)(R^7), -C(O)(R^5), -S-R^6, -S(O)$_2$-R^6, carbociclilo, carbociclil-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno , halocarbociclilo, y carbociclil-C_1-C_6-alquilo sustituido con halógeno. El carbociclilo y heterociclilo también son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por C_2-C_6-alquenilo y C_2-C_6-alquinilo.

[167] En algunas realizaciones preferidas, E^5 es piridinilo optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, -N(R^8)(R^7), -C(O)(R^5), -S-R^6, -S(O)$_2$-R^6, fenilo, fenil-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, halofenilo, y fenil-C_1-C_6-alquilo sustituido con halógeno. el piridinilo también es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por C_2-C_6-alquenilo y C_2-C_6-alquinilo.

[168] En algunas realizaciones preferidas, E^5 es piperidinilo, piperazinilo, imidazolilo, furanilo, tienilo, pirimidilo, benzodioxolilo, benzodioxanilo, benzofurilo, o benzotienilo. Tal sustituyente es optativamente

752

sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, -CN, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, $-N(R^6)(R^7)$, $-C(O)(R^6)$, $-S-R^6$, $-S(O)_2-R^6$, fenilo, fenil-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, halofenilo, y fenil-C_1-C_6-alquilo sustituido con halógeno. Tal sustituyente también es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por C_2-C_6-alquenilo y C_2-C_6-alquinilo.

[169] En algunas realizaciones preferidas, E^5 es fenilo optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, -CN, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, $-N(R^6)(R^7)$, $-C(O)(R^6)$, $-S-R^6$, $-S(O)_2-R^6$, fenilo, fenil-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, halofenilo, y fenil-C_1-C_6-alquilo sustituido con halógeno. El fenilo también es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por C_2-C_6-alquenilo y C_2-C_6-alquinilo.

[170] En algunas realizaciones preferidas, E^5 es naftalenilo optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, -CN, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, $-N(R^6)(R^7)$, $-C(O)(R^6)$, $-S-R^6$, $-S(O)_2-R^6$, fenilo, fenil-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, halofenilo, y fenil-C_1-C_6-alquilo sustituido con halógeno. El naftalenilo también es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por C_2-C_6-alquenilo y C_2-C_6-alquinilo.

753

[171] R^1 y R^2 se seleccionan independientemente del grupo formado por -H y alquilo. El alquilo es optativamente sustituido. Ni R^1 ni R^2 forman una estructura de anillo con E^2, E^3, E^4, o E^5.

[172] En algunas realizaciones preferidas, R^1 y R^2 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, y halo-C_1-C_6-alquilo.

[173] En algunas realizaciones preferidas, R^1 y R^2 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, y halo-C_1-C_6-alquilo.

[174] En algunas realizaciones preferidas, R^1 y R^2 se seleccionan independientemente del grupo formado por -H y C_1-C_6-alquilo.

[175] R^3 es -H o alquilo. El alquilo es optativamente sustituido.

[176] En algunas realizaciones preferidas, R^3 es -H, C_1-C_6-alquilo, o halo-C_1-C_6-alquilo.

[177] En algunas realizaciones preferidas, R^3 es -H, C_1-C_6-alquilo, o halo-C_1-C_6-alquilo.

[178] En algunas realizaciones preferidas, R^3 es -H o C_1-C_6-alquilo.

[179] R^6 y R^7 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, heterociclil-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo sustituido con halógeno, haloheterociclilo, y heterociclil-C_1-C_6-alquilo sustituido con halógeno.

[180] En algunas realizaciones preferidas, R^6 y R^7 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo puede ser

754

sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[181] R^8 es -H, C_1-C_6-alquilo, -O-R^9, -N(R^9)(R^{10}), carbociclil-C_1-C_6-alquilo, heterociclil-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, carbociclil-C_1-C_6-alquilo sustituido con halógeno, o heterociclil-C_1-C_6-alquilo sustituido con halógeno.

[182] En algunas realizaciones preferidas, R^8 es -H, C_1-C_6-alquilo, -O-R^9, -N(R^9)(R^{10}), carbociclil-C_1-C_6-alquilo, heterociclil-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, carbociclil-C_1-C_6-alquilo sustituido con halógeno, o heterociclil-C_1-C_6-alquilo sustituido con halógeno.

[183] En algunas realizaciones preferidas, R^8 es -H, C_1-C_6-alquilo, -O-R^9, -N(R^9)(R^{10}), carbociclil-C_1-C_6-alquilo, o heterociclil-C_1-C_6-alquilo.

[184] R^9 y R^{10} se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, heterociclil-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo sustituido con halógeno, haloheterociclilo, y heterociclil-C_1-C_6-alquilo sustituido con halógeno.

[185] En algunas realizaciones preferidas, R^9 y R^{10} se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, heterociclil-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo sustituido con halógeno, haloheterociclilo, y heterociclil-C_1-C_6-alquilo sustituido con halógeno.

[186] En algunas realizaciones preferidas, R^9 y R^{10} se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, y heterociclilo, heterociclil-C_1-C_6-alquilo.

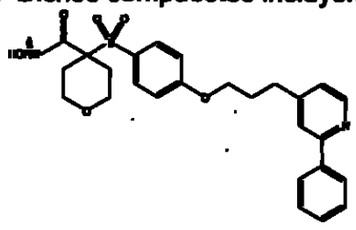
755

Realización preferida Nro. 2-a: E^3 es heterociclilo optativamente sustituido

[187] En algunas realizaciones, E^3 es heterociclilo optativamente sustituido.

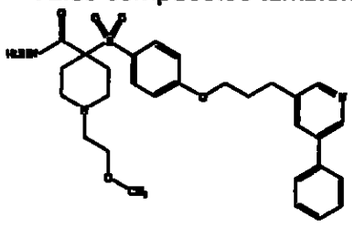
[188] En algunas realizaciones preferidas E^3 es un heterociclo optativamente sustituido que contiene solamente un miembro heteroátomo en el anillo. Ejemplos de heterociclilos generalmente adecuados incluyen furanilo, tetrahidropiranilo, dihidrofuranilo, tetrahidrofuranilo, tiofenilo, dihidrotiofenilo, tetrahidrotiofenilo, pirrolinilo, pirrolilo, isopirrolilo, pirrolidinilo, piridinilo, piperidinilo, piranilo, dihidropiranilo, y tetrahidropiranilo.

[189] En algunas realizaciones preferidas, E^3 es piridinilo optativamente sustituido. En algunas de dichas realizaciones, E^5 es fenilo optativamente sustituido. Dichos compuestos incluyen, por ejemplo:

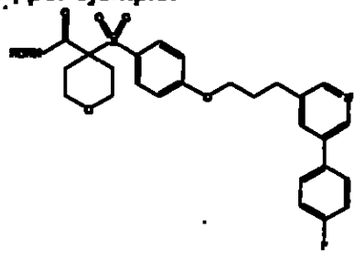


IIIA-1

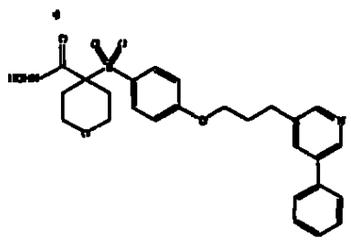
Tales compuestos también incluyen, por ejemplo:



IIIA-2

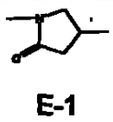


IIIA-3

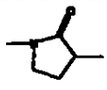


IIIA-4

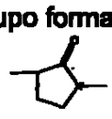
[190] En algunas realizaciones preferidas, E^3 es un heterociclo optativamente sustituido seleccionado del grupo formado por:



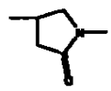
E-1



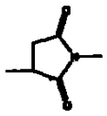
E-2



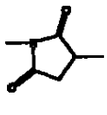
E-3



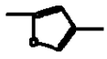
E-4



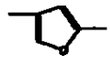
E-5



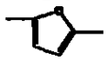
E-6



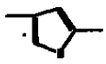
E-7



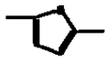
E-8.



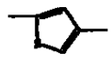
E-9



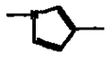
E-10



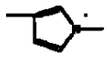
E-11



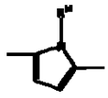
E-12



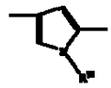
E-13



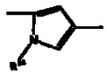
E-14



E-15



E-16

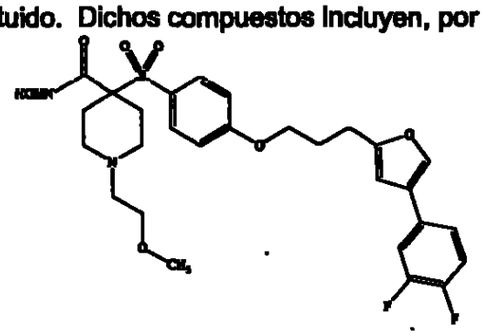


E-17

Cualquier miembro de este grupo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el sustituyente es halógeno o -OH, cualquier sustituyente de este grupo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, C_1-

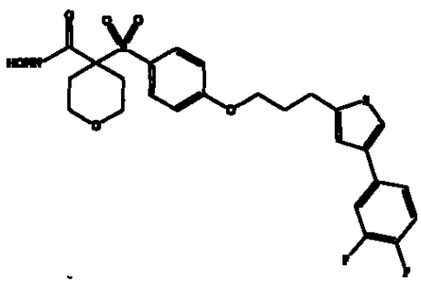
C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alquiltio, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, y halo-C_1-C_6-alquiltio. R^{14} se selecciona del grupo formado por halógeno, -OH, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es halógeno o -OH, cualquier miembro de este grupo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alquiltio, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, y halo-C_1-C_6-alquiltio.

[191] En algunas realizaciones preferidas, E^3 es furanilo optativamente sustituido. En una de tales realizaciones, por ejemplo, E^5 es fenilo optativamente sustituido. Dichos compuestos incluyen, por ejemplo:

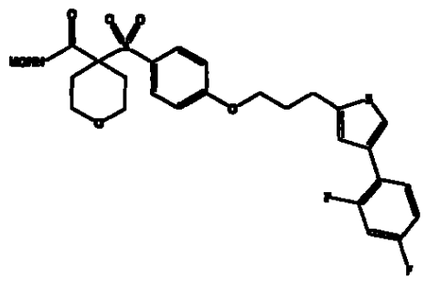


IIIA-5

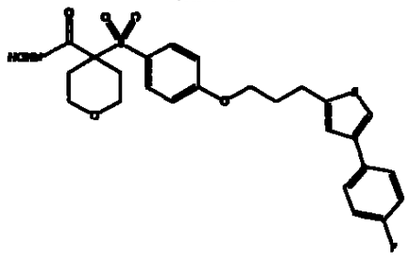
[192] En algunas realizaciones preferidas, E^3 es tienilo optativamente sustituido. En algunas de dichas realizaciones, E^5 es fenilo optativamente sustituido. Dichos compuestos incluyen, por ejemplo:



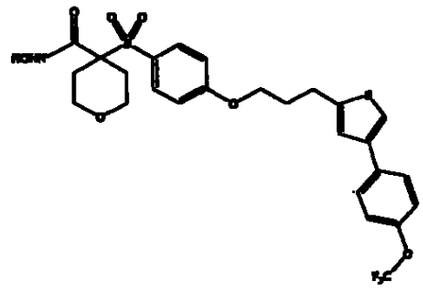
IIIA-6



IIIA-7

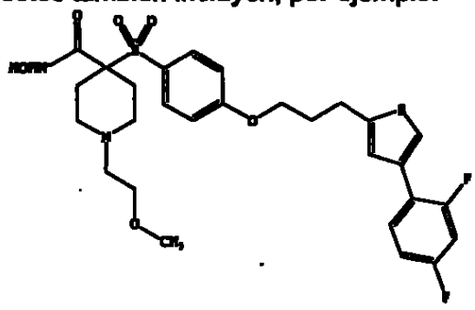


IIIA-8



IIIA-9

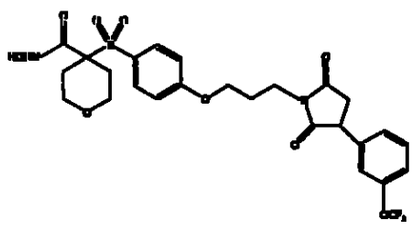
Tales compuestos también incluyen, por ejemplo:



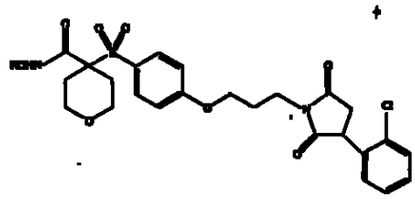
IIIA-10

[193] En algunas realizaciones preferidas, E^3 es pirrolidinilo optativamente sustituido. En algunas de dichas realizaciones, por ejemplo, E^5 es fenilo optativamente sustituido. Dichos compuestos incluyen, por ejemplo:

759



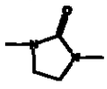
IIIA-11



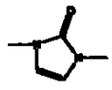
IIIA-12

[194] E^3 también puede ser, por ejemplo, un heterociclo optativamente sustituido que contiene no más y no menos de dos miembros heteroatómicos en el anillo. Los heterociclos adecuados incluyen, por ejemplo, pirazolilo, pirazolinilo, pirazolidinilo, imidazolilo, isoimidazolilo, imidazolinilo, imidazolidinilo, ditiolilo, tiazolilo, isotiazolilo, tiazolinilo, isotiazolinilo, tiazolidinilo, isotiazolidinilo, oxatiolilo, oxatiolanilo, oxazolilo, isoxazolilo, oxazolidinilo, isoxazolidinilo, pirazinilo, piperazinilo, pirimidinilo, piridazinilo, oxazinilo, y morfolinilo.

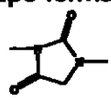
[195] En algunas realizaciones preferidas, E^3 es un heterociclo optativamente sustituido seleccionado del grupo formado por:



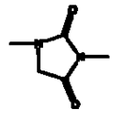
E-18



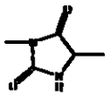
E-19



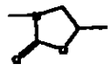
E-20



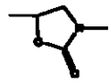
E-21



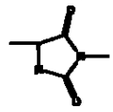
E-22



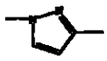
E-23



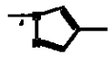
E-24



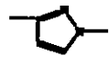
E-25



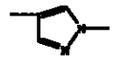
E-1



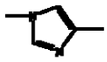
E-1



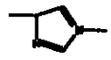
E-1



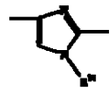
E-1



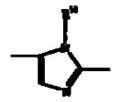
E-26



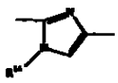
E-27



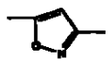
E-28



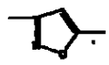
E-29



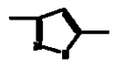
E-30



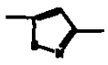
E-31



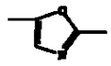
E-32



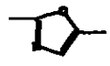
E-33



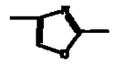
E-34



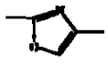
E-35



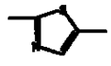
E-36



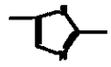
E-37



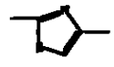
E-38



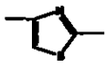
E-39



E-40



E-41



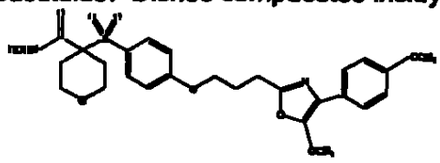
E-42

Cualquier miembro de este grupo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el sustituyente es halógeno o -OH, cualquier sustituyente de este grupo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alquiltio, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, y halo-C_1-C_6-alquiltio. Tales sustituyentes también optativamente son sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por C_2-C_6-alquenilo y C_2-C_6-alquinilo. R^{14} tiene los valores definidos anteriormente donde E^3 contiene solamente un heteroátomo en su anillo.

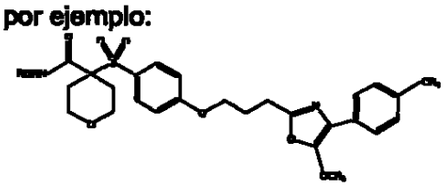
[196] En algunas realizaciones particularmente preferidas, E^3 es un heterociclo optativamente sustituido seleccionado del grupo formado por oxazolilo y isoxazolilo. En algunas de dichas realizaciones, por ejemplo, E^5 es carbociclilo optativamente sustituido, generalmente preferentemente arilo

761

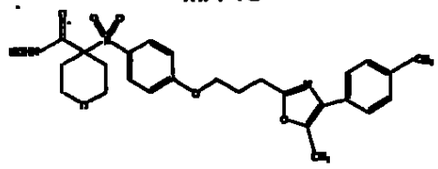
optativamente sustituido, y más preferentemente fenilo optativamente sustituido. Dichos compuestos incluyen, por ejemplo:



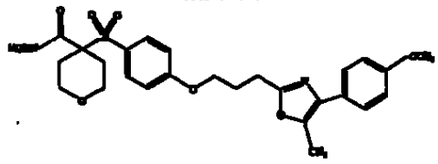
IIIA-13



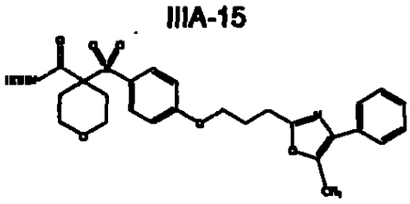
IIIA-14



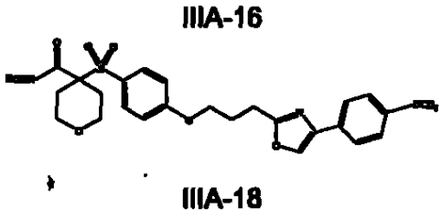
IIIA-15



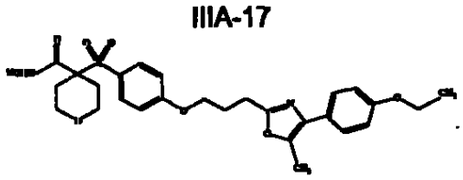
IIIA-16



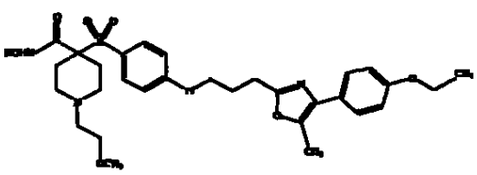
IIIA-17



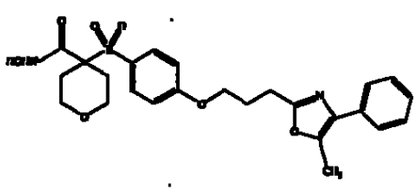
IIIA-18



IIIA-19



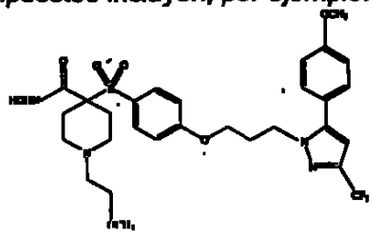
IIIA-20



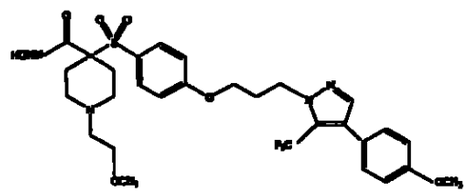
IIIA-21

[197] En algunas realizaciones preferidas, E^3 es un heteroarilo optativamente sustituido seleccionado del grupo formado por pirazolilo y isoimidazolilo. En algunas de dichas realizaciones, E^5 es carbociclilo optativamente sustituido, generalmente preferentemente arilo optativamente

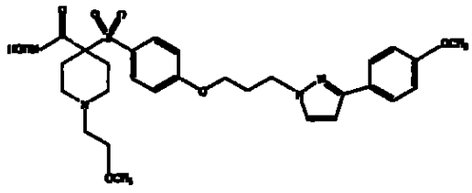
sustituido, y más preferentemente fenilo optativamente sustituido. Dichos compuestos incluyen, por ejemplo:



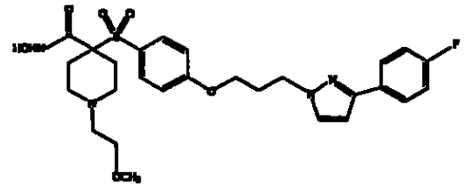
IIIA-22



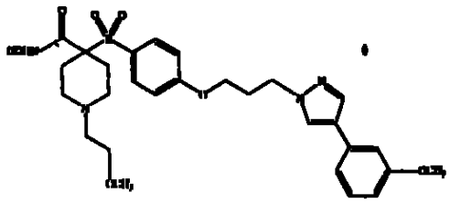
IIIA-23



IIIA-24

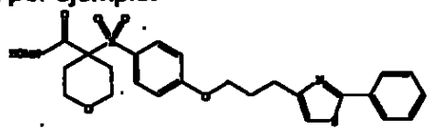


IIIA-25



IIIA-26

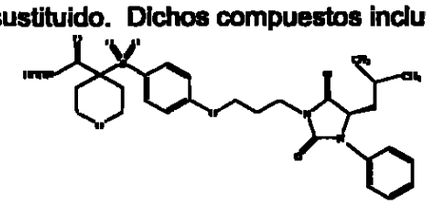
[198] En algunas realizaciones preferidas, E^3 es un heteroarilo optativamente sustituido seleccionado del grupo formado por tiazolilo y isotiazolilo. En una de tales realizaciones, por ejemplo, E^5 es carbociclilo optativamente sustituido, generalmente preferentemente arilo optativamente sustituido, y más preferentemente fenilo optativamente sustituido. Dichos compuestos incluyen, por ejemplo:



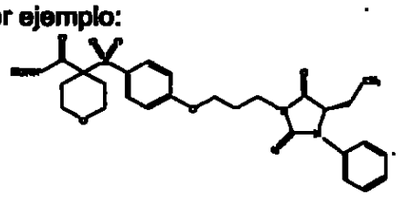
IIIA-27

763

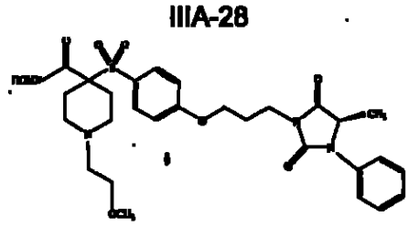
[199] En algunas realizaciones preferidas, E^3 es un heteroarilo optativamente sustituido seleccionado del grupo formado por pirazolidinilo y imidazolidinilo. En algunas de dichas realizaciones, E^5 es carbociclilo optativamente sustituido. En algunas realizaciones preferidas, E^5 es arilo optativamente sustituido, generalmente preferentemente fenilo optativamente sustituido. Dichos compuestos incluyen, por ejemplo:



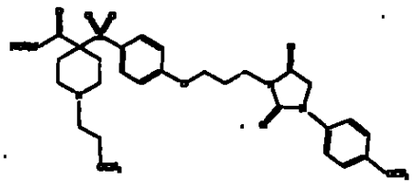
IIIA-28



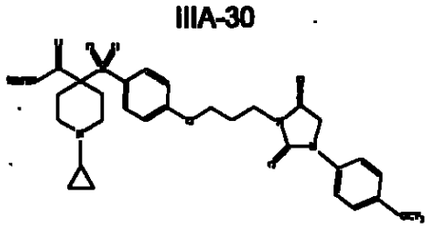
IIIA-29



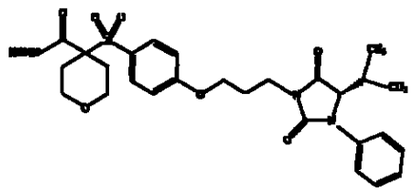
IIIA-30



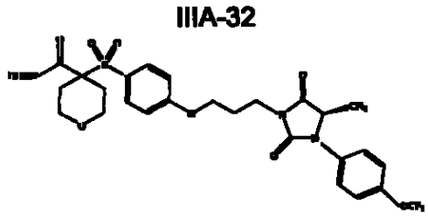
IIIA-31



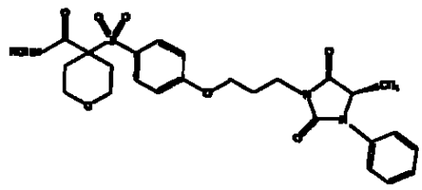
IIIA-32



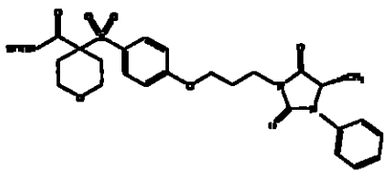
IIIA-33



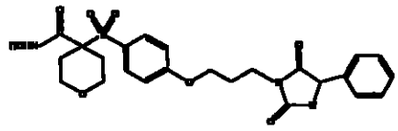
IIIA-34



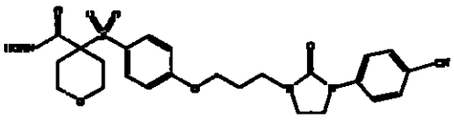
IIIA-35



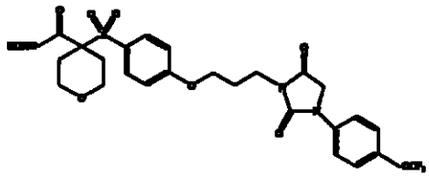
IIIA-36



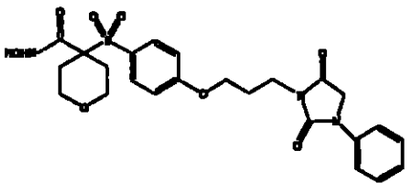
IIIA-37



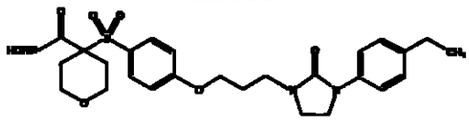
IIIA-38



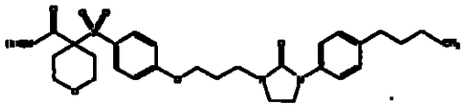
IIIA-39



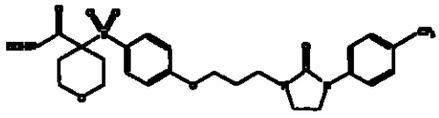
IIIA-40



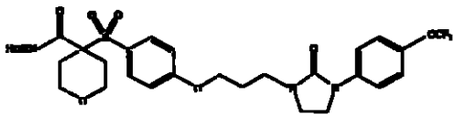
IIIA-41



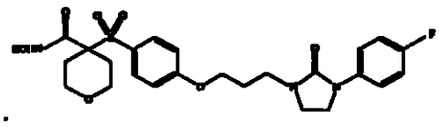
IIIA-42



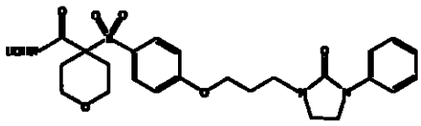
IIIA-43



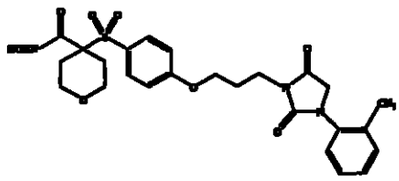
IIIA-44



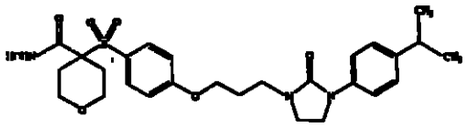
IIIA-45



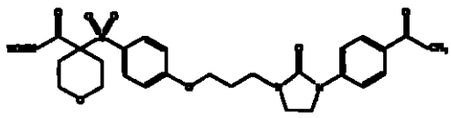
IIIA-46



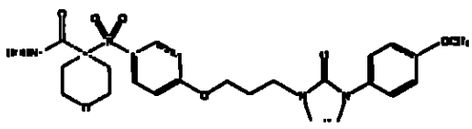
IIIA-47



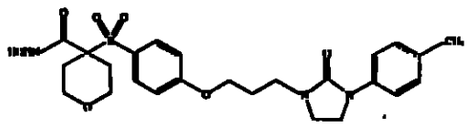
IIIA-48



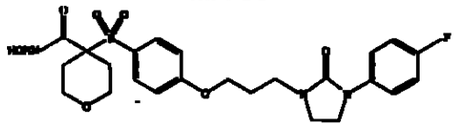
IIIA-49



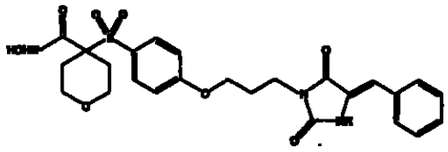
IIIA-50



IIIA-51

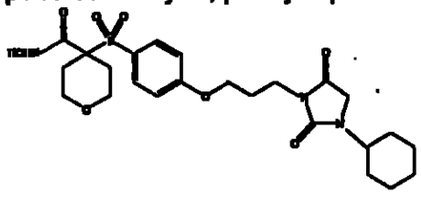


IIIA-52



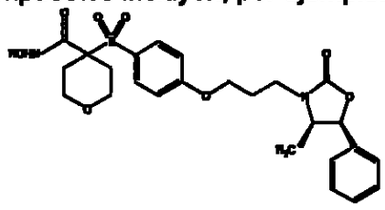
IIIA-53

En otras realizaciones preferidas, E^5 es C_5-C_8-cicloalquilo optativamente sustituido. Dichos compuestos incluyen, por ejemplo:

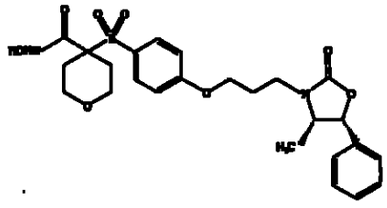


IIIA-54

[200] En algunas realizaciones preferidas, E^3 es optativamente-sustituido oxazolidinilo. En algunas de dichas realizaciones, E^5 es carbociclilo optativamente sustituido, generalmente preferentemente arilo optativamente sustituido, y más preferentemente fenilo optativamente sustituido. Dichos compuestos incluyen, por ejemplo:

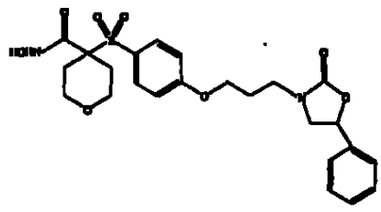


IIIA-55

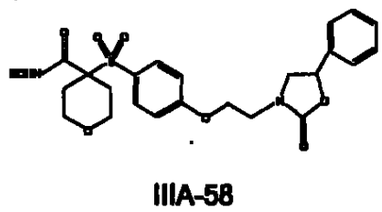


IIIA-56

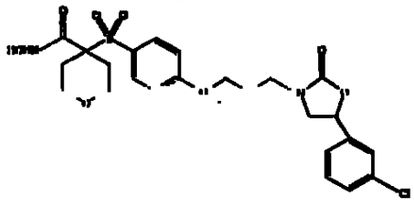
766



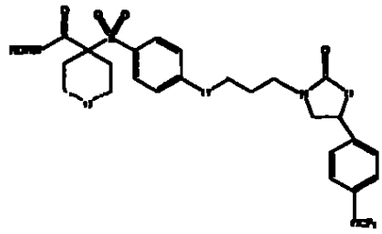
IIIA-57



IIIA-58



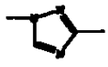
IIIA-59



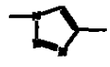
IIIA-60

[201] E^3 también puede ser, por ejemplo, un heterociclo optativamente sustituido que contiene no más y no menos de 3 miembros heteroátomos en el anillo. Heterociclilos generalmente adecuados incluyen, por ejemplo, oxadiazolilo, tiadiazolilo, y triazolilo. En este caso, el triazolilo es optativamente sustituido.

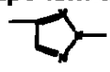
[202] En algunas realizaciones preferidas, E^3 es un heteroarilo optativamente sustituido seleccionado del grupo formado por:



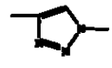
E-43



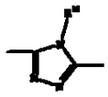
E-44



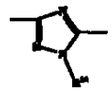
E-45



E-46



E-47



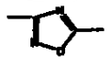
E-48



E-49



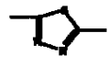
E-50



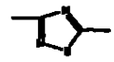
E-51



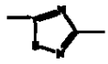
E-52



E-53



E-54



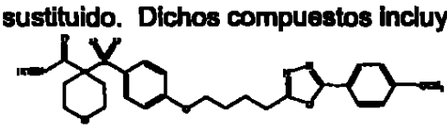
E-55

767

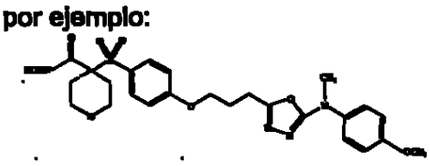
Cualquier miembro de este grupo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el sustituyente es halógeno o -OH, cualquier sustituyente de este grupo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alquiltio, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, y halo-C_1-C_6-alquiltio. R^{14} tiene los valores definidos anteriormente para heterociclilos que contienen 1 o 2 miembros heteroatómicos en el anillo.

[203] En algunas realizaciones preferidas, E^3 es oxadiazolilo.

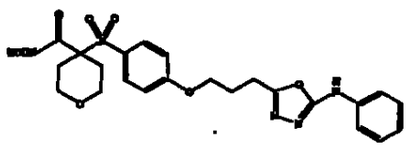
[204] En algunas de tales realizaciones, E^5 es fenilo optativamente sustituido. Dichos compuestos incluyen, por ejemplo:



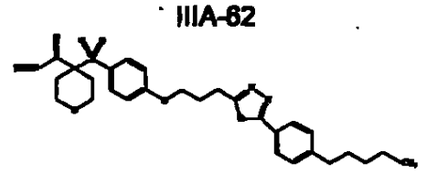
IIIA-61



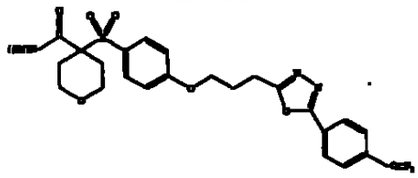
IIIA-62



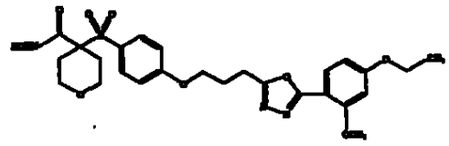
IIIA-63



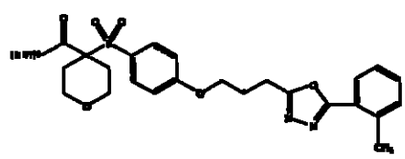
IIIA-64



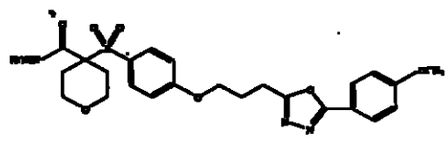
IIIA-65



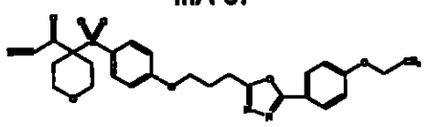
IIIA-66



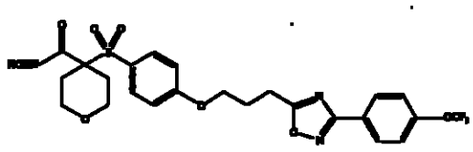
IIIA-67



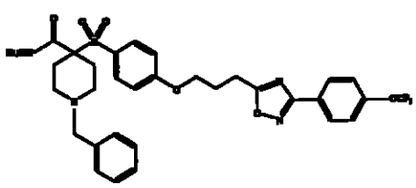
IIIA-68



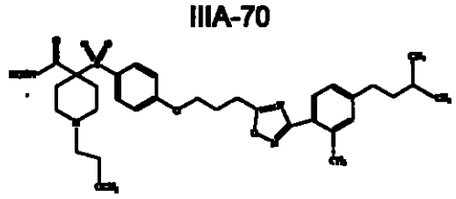
IIIA-69



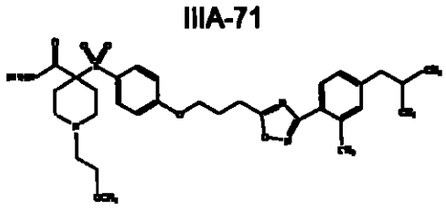
IIIA-70



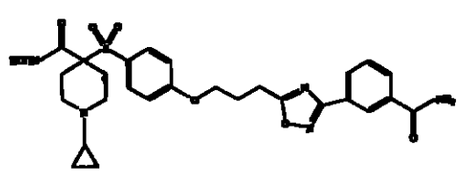
IIIA-71



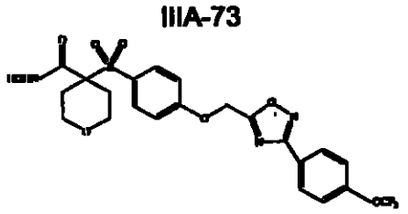
IIIA-72



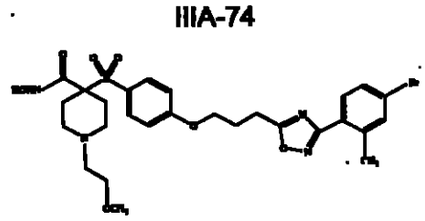
IIIA-73



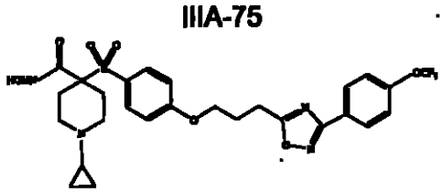
IIIA-74



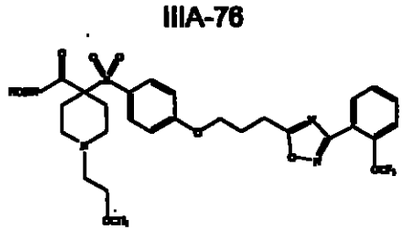
IIIA-75



IIIA-76

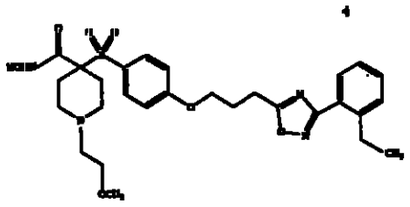


IIIA-77

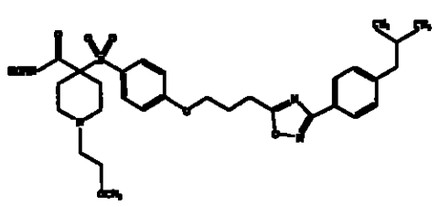


IIIA-78

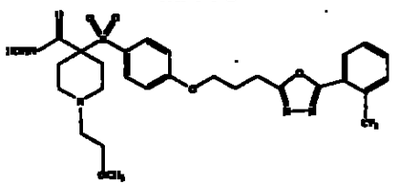
769



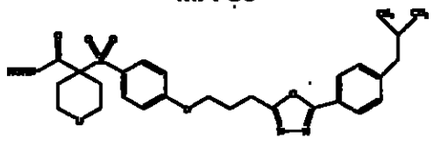
IIIA-79



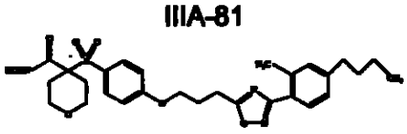
IIIA-80



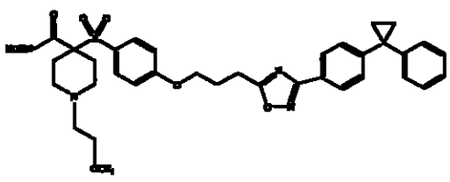
IIIA-81



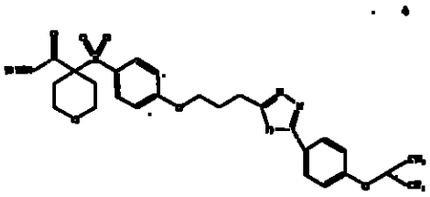
IIIA-82



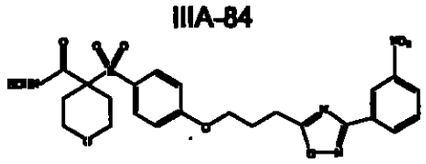
IIIA-83



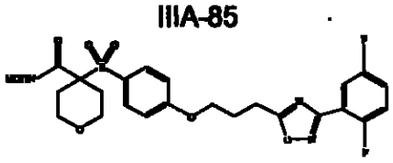
IIIA-84



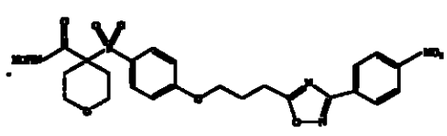
IIIA-85



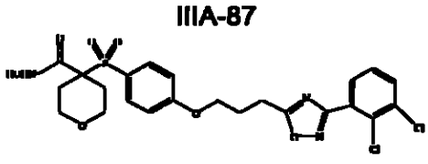
IIIA-86



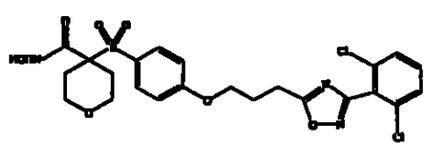
IIIA-87



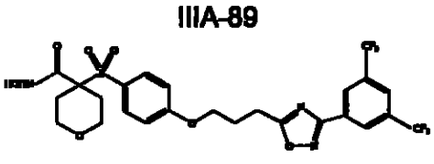
IIIA-88



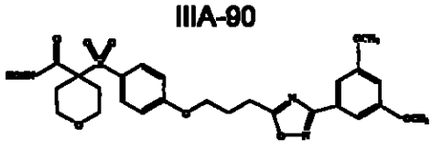
IIIA-89



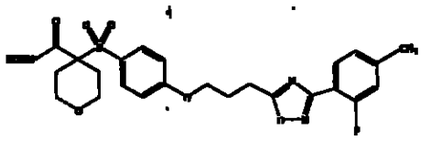
IIIA-90



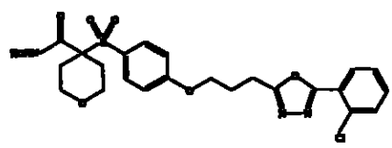
IIIA-91



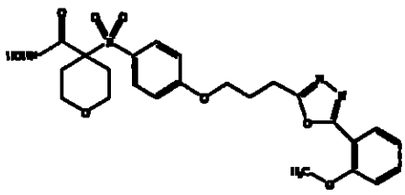
IIIA-92



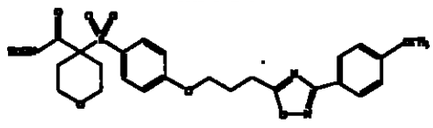
IIIA-93



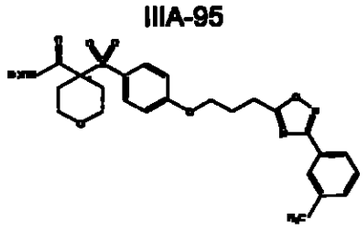
IIIA-94



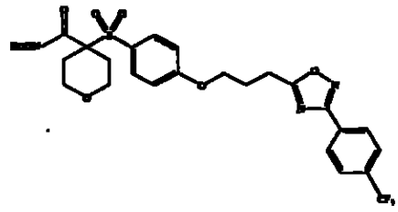
IIIA-95



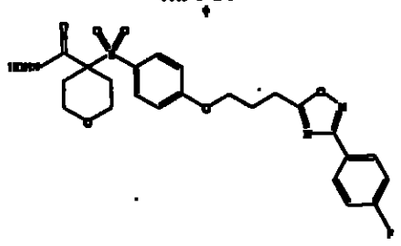
IIIA-96



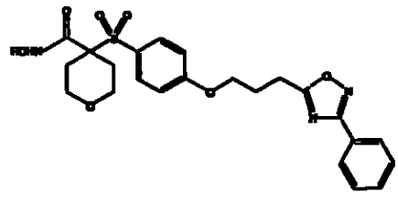
IIIA-97



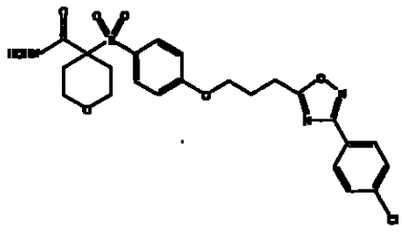
IIIA-98



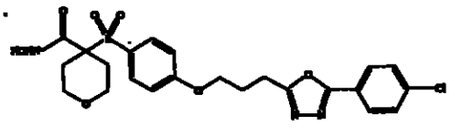
IIIA-99



IIIA-100

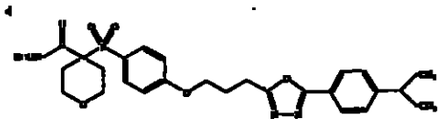


IIIA-101

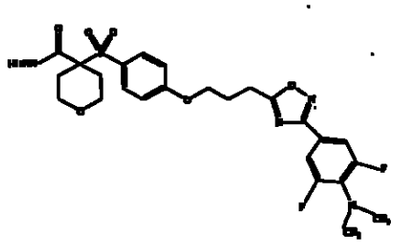


IIIA-102

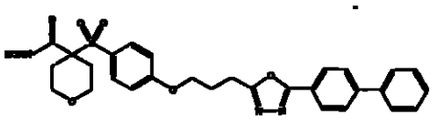
771



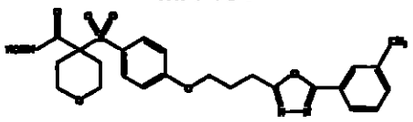
IIIA-103



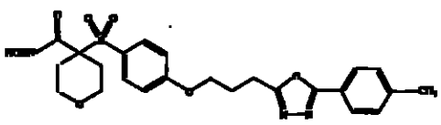
IIIA-104



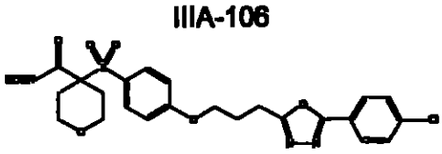
IIIA-105



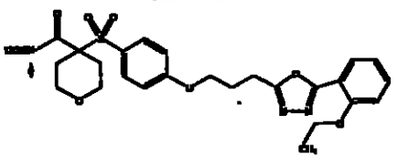
IIIA-106



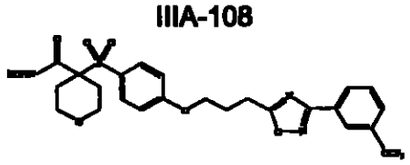
IIIA-107



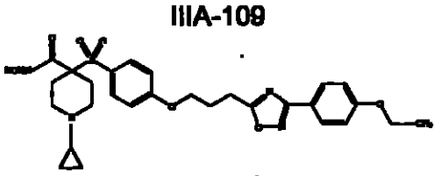
IIIA-108



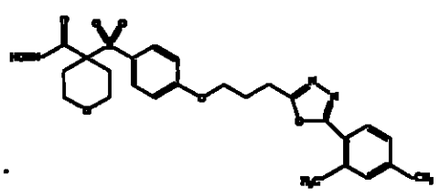
IIIA-109



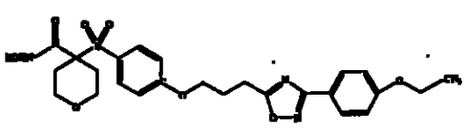
IIIA-110



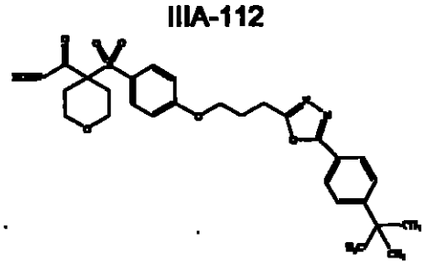
IIIA-111



IIIA-112

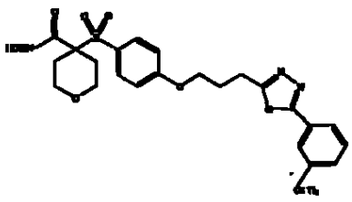


IIIA-113

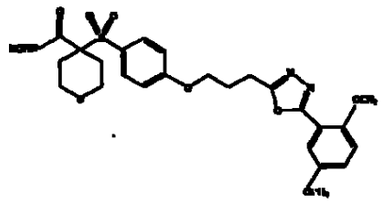


IIIA-114

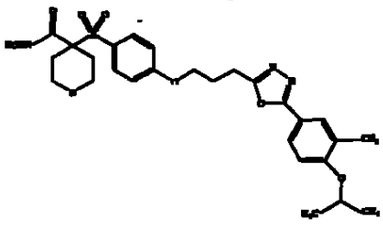
772



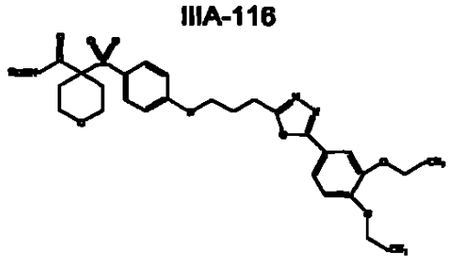
IIIA-115



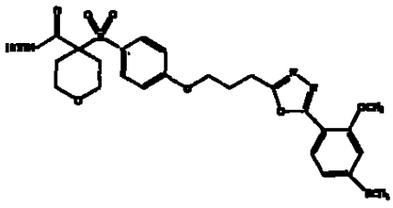
IIIA-116



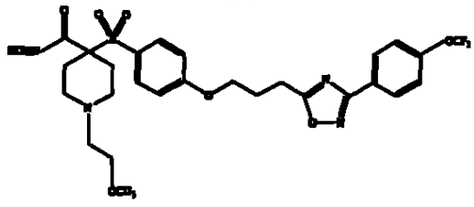
IIIA-117



IIIA-118

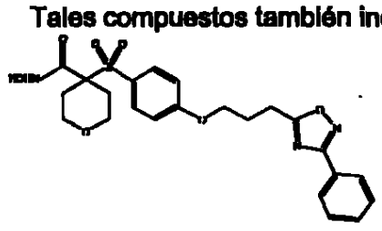


IIIA-119

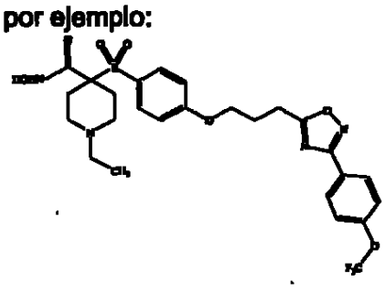


IIIA-120

Tales compuestos también incluyen, por ejemplo:

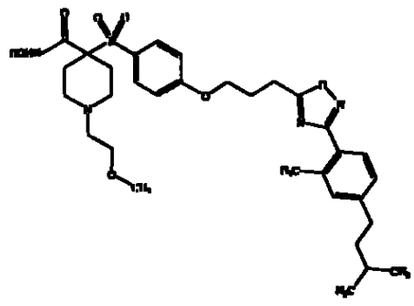


IIIA-121



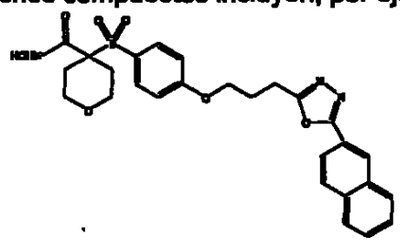
IIIA-122

773

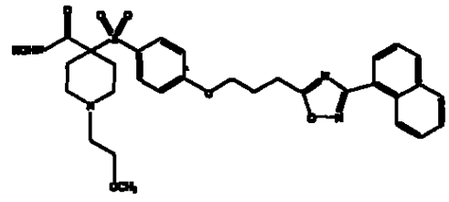


IIIA-123

[205] En otras realizaciones, E^5 es naftalenilo optativamente sustituido. Dichos compuestos incluyen, por ejemplo:

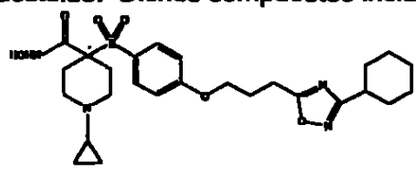


IIIA-124

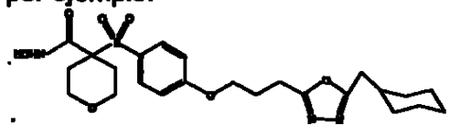


IIIA-125

[206] En otras realizaciones, E^5 es C_5-C_8-cicloalquilo optativamente sustituido. Dichos compuestos incluyen, por ejemplo:

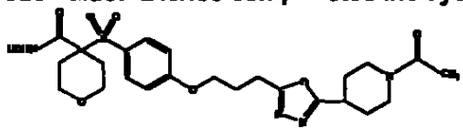


IIIA-126

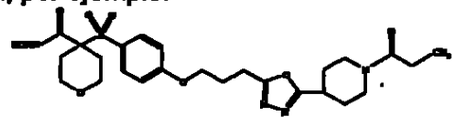


IIIA-127

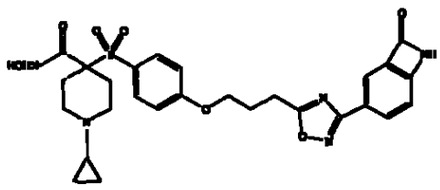
[207] En aún otras realizaciones, E^5 es heterociclilo optativamente sustituido. Dichos compuestos incluyen, por ejemplo:



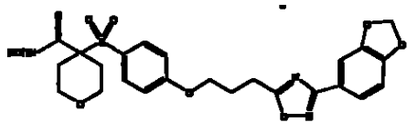
IIIA-128



IIIA-129

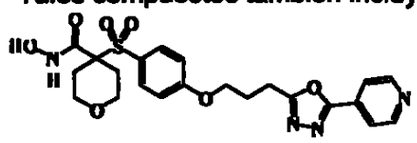


IIIA-130

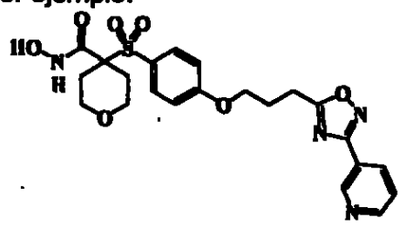


IIIA-131

Tales compuestos también incluyen, por ejemplo:



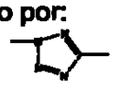
IIIA-132



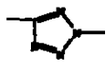
IIIA-133

[208] E^3 también puede ser, por ejemplo, un heterociclo optativamente sustituido que contiene al menos 4 miembros heteroatómicos en el anillo.

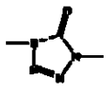
[209] En algunas realizaciones preferidas, E^3 se selecciona del grupo formado por:



E-56

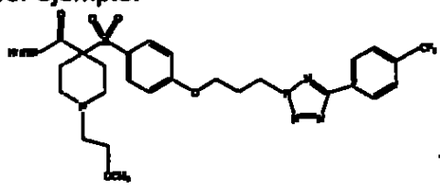


E-57

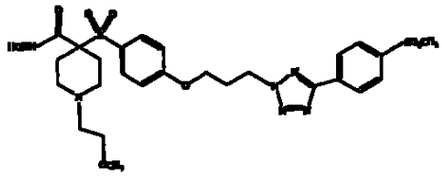


E-58

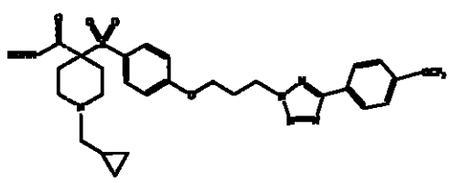
En algunas de dichas realizaciones, E^5 es carbociclilo optativamente sustituido, generalmente preferentemente arilo optativamente sustituido, y más preferentemente fenilo optativamente sustituido. Dichos compuestos incluyen, por ejemplo:



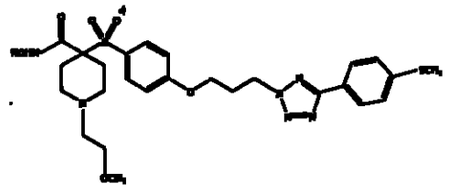
IIIA-134



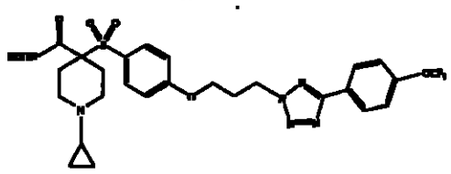
IIIA-135



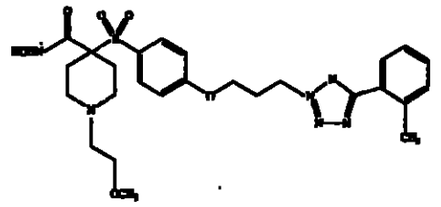
IIIA-136



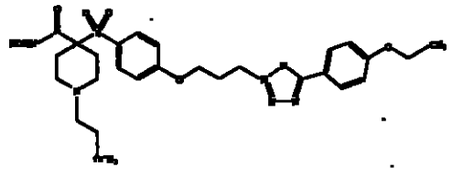
IIIA-137



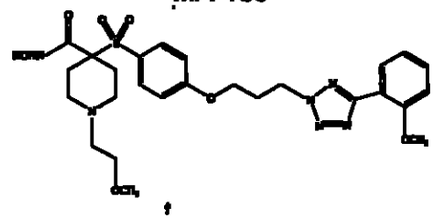
IIIA-138



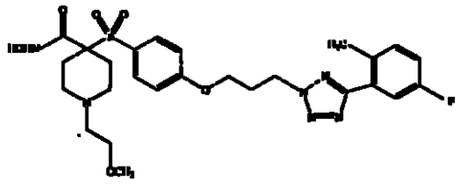
IIIA-139



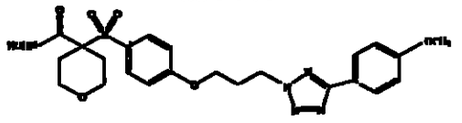
IIIA-140



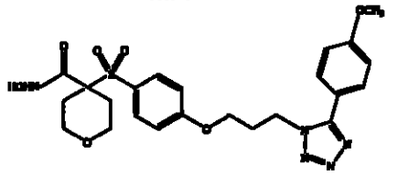
IIIA-141



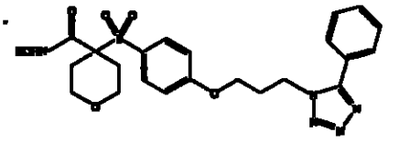
IIIA-142



IIIA-143

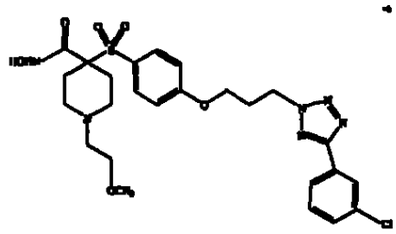


IIIA-144

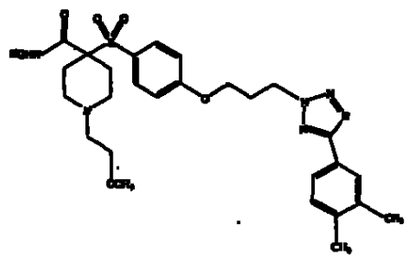


IIIA-145

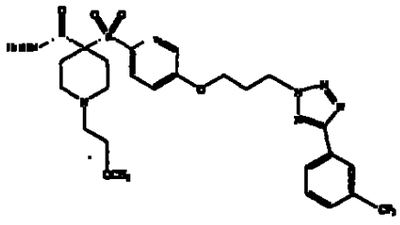
776



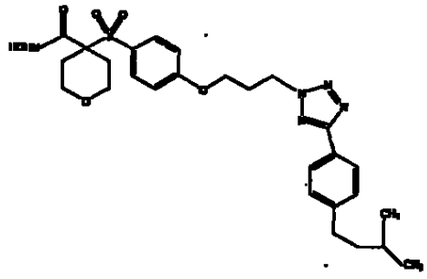
IIIA-146



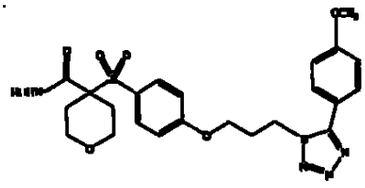
IIIA-147



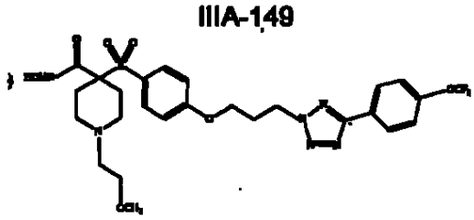
IIIA-148



IIIA-149

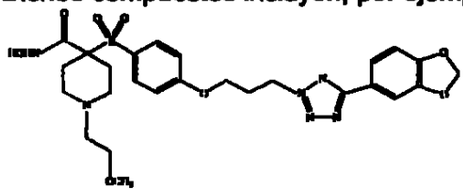


IIIA-150

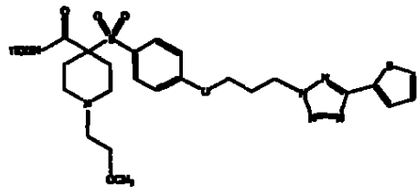


IIIA-151

En otras tales realizaciones, E^5 es heterociclilo optativamente sustituido. Dichos compuestos incluyen, por ejemplo:



IIIA-152



IIIA-153

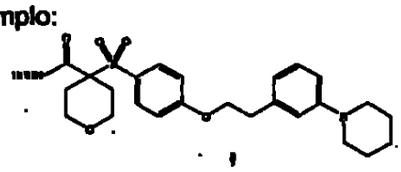
Realización preferida Nro. 2-b: E^3 es carbociclilo optativamente sustituido

[210] En algunas realizaciones, E^3 es un carbociclilo optativamente sustituido. E^3 puede ser, por ejemplo, un carbociclilo optativamente sustituido seleccionado del grupo formado por ciclopropilo, ciclobutilo, ciclopentilo,

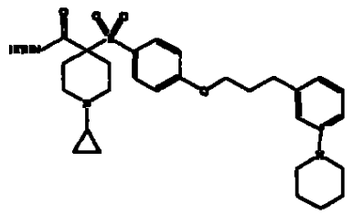
ciclopentenilo, ciclopentadienilo, ciclohexilo, ciclohexenilo, ciclohexadienilo, fenilo, naftalenilo, tetrahidronaftalenilo, indenilo, isoindenilo, indanilo, biciclodecanilo, antracenilo, fenantreno, benzonaftenilo, fluorenelio, decalinilo, y norpinanilo.

[211] En algunas realizaciones preferidas, E^3 es fenilo optativamente sustituido. En una de tales realizaciones, por ejemplo, E^5 es heterociclilo optativamente sustituido.

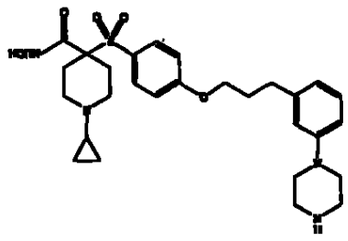
[212] En algunas de dichas realizaciones, E^5 es heterocicloalquilo optativamente sustituido. Ejemplos de dichos compuestos incluyen, por ejemplo:



IIIB-1

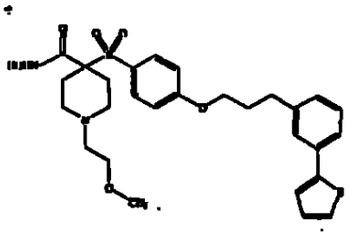


IIIB-2

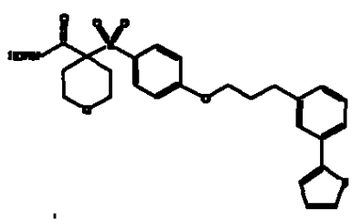


IIIB-3

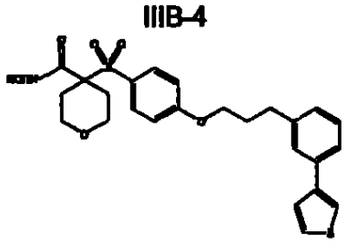
[213] En otras realizaciones preferidas, E^5 es heteroarilo de 5 miembros optativamente sustituido. Ejemplos de dichos compuestos incluyen, por ejemplo:



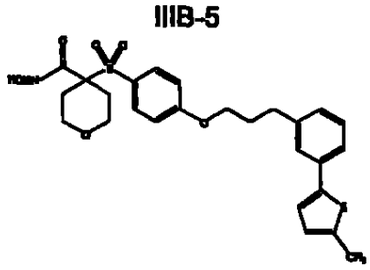
IIIB-4



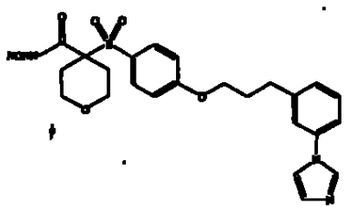
IIIB-5



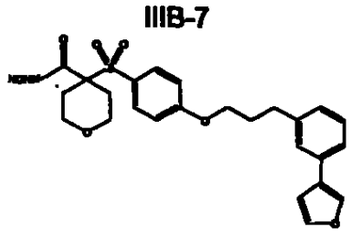
IIIB-6



IIIB-7

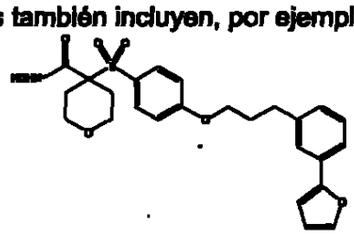


IIIB-8



IIIB-9

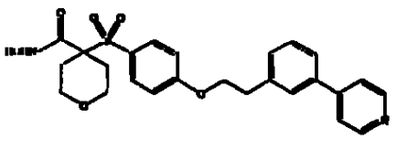
Tales compuestos también incluyen, por ejemplo:



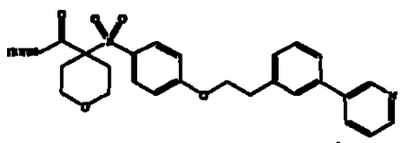
IIIB-10

[214] En otras realizaciones preferidas, E^5 es heteroarilo de 6 miembros optativamente sustituido.

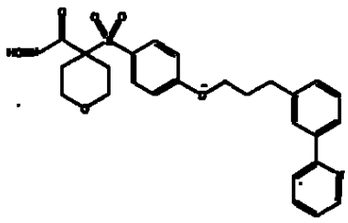
[215] En otras realizaciones preferidas, E^5 es piridinilo optativamente sustituido. Dichos compuestos incluyen, por ejemplo:



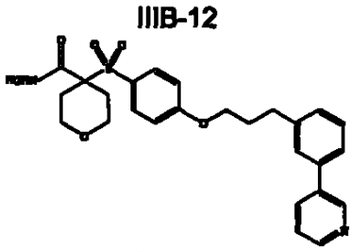
IIIB-11



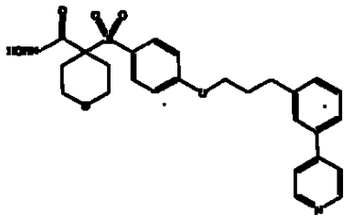
IIIB-12



IIIB-13

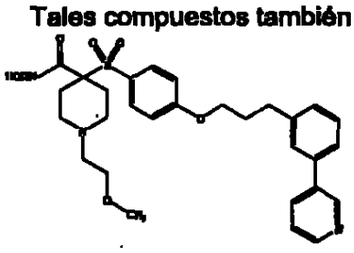


IIIB-14

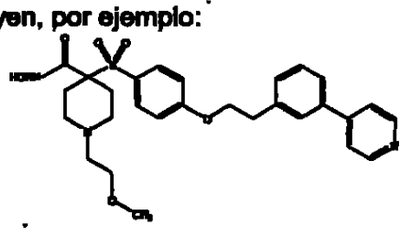


IIIB-15

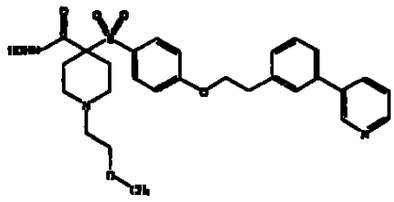
Tales compuestos también incluyen, por ejemplo:



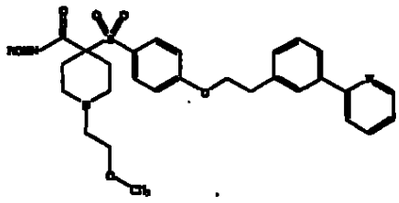
IIIB-16



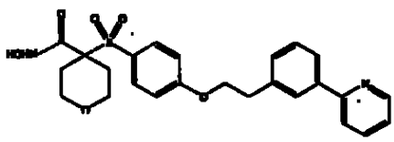
IIIB-17



IIIB-18

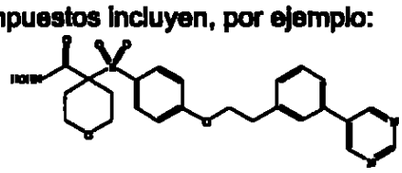


IIIB-19



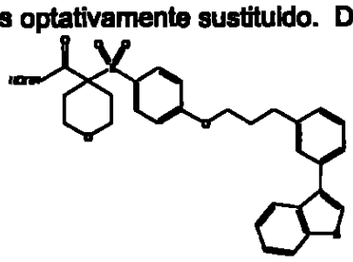
IIIB-20

[216] En otras realizaciones preferidas, E^5 es pirimidilo optativamente sustituido. Dichos compuestos incluyen, por ejemplo:

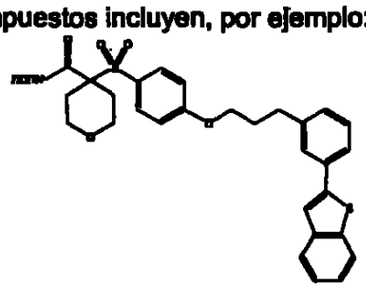


IIIB-21

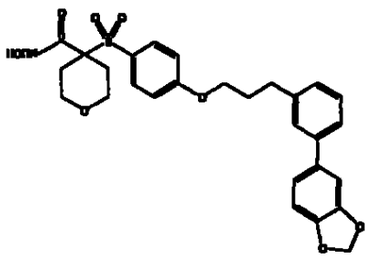
[217] En otras realizaciones preferidas, E^5 es heterocicio de múltiples anillos optativamente sustituido. Dichos compuestos incluyen, por ejemplo:



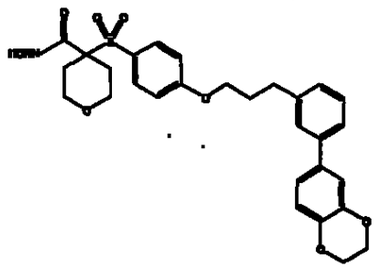
IIIB-22



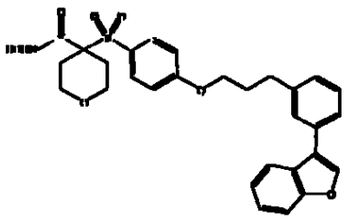
IIIB-23



IIIB-24



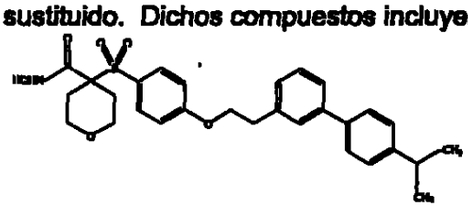
IIIB-25



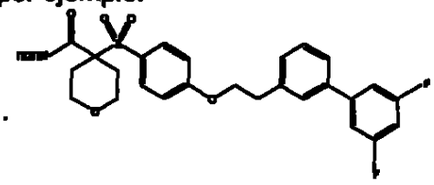
IIIB-26

[218] En algunas realizaciones preferidas, por ejemplo, E^5 es carbociclilo optativamente sustituido, generalmente preferentemente arilo optativamente sustituido,

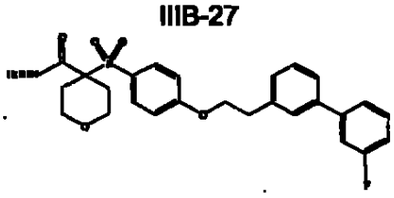
[219] En algunas realizaciones preferidas, E^5 es fenilo optativamente sustituido. Dichos compuestos incluyen, por ejemplo:



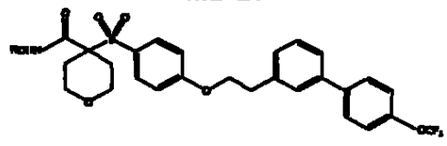
IIIB-27



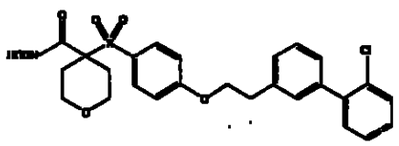
IIIB-28



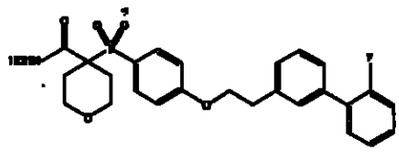
IIIB-29



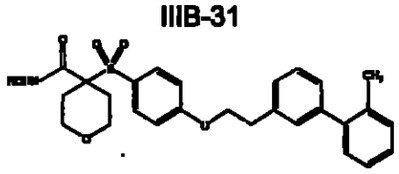
IIIB-30



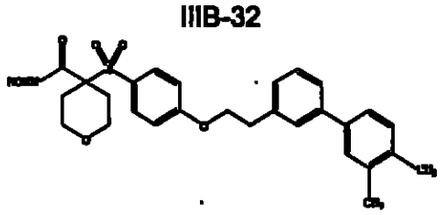
IIIB-31



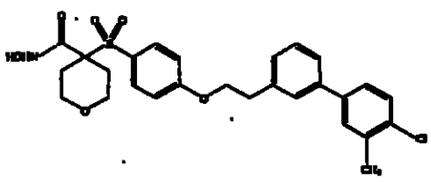
IIIB-32



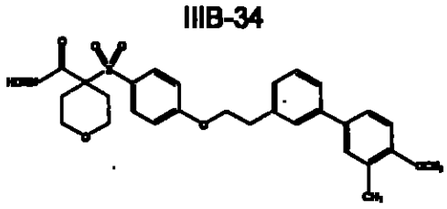
IIIB-33



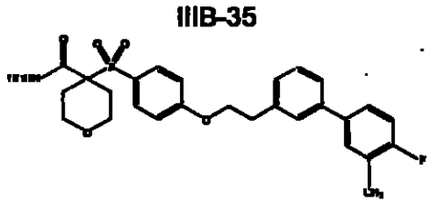
IIIB-34



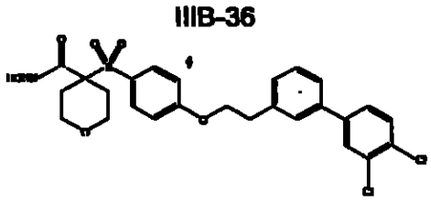
IIIB-35



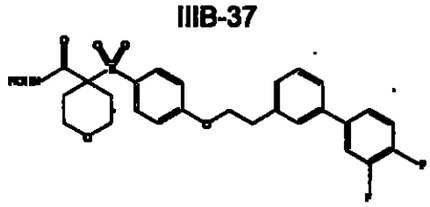
IIIB-36



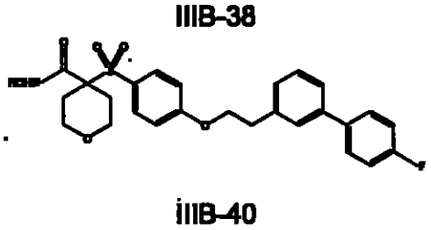
IIIB-37



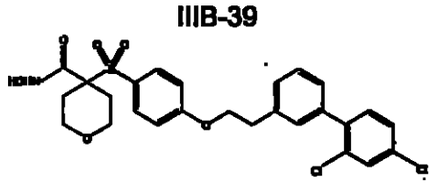
IIIB-38



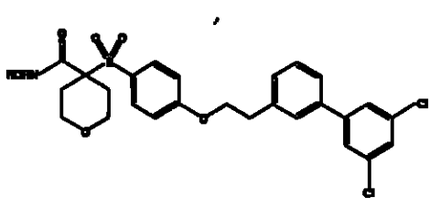
IIIB-39



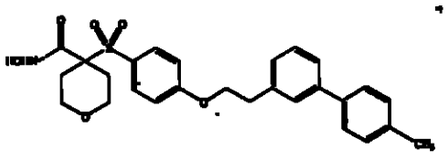
IIIB-40



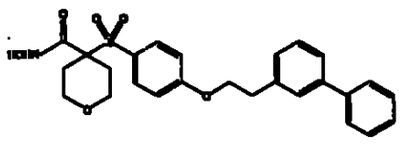
IIIB-41



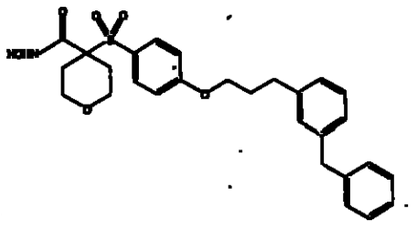
IIIB-42



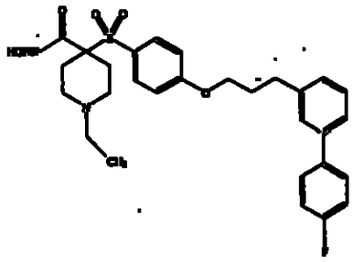
IIIB-43



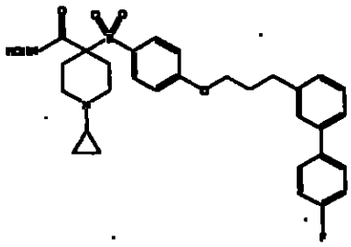
IIIB-44



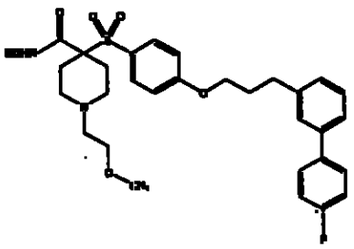
IIIB-45



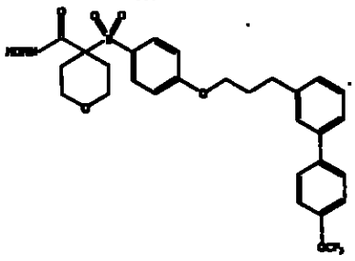
IIIB-46



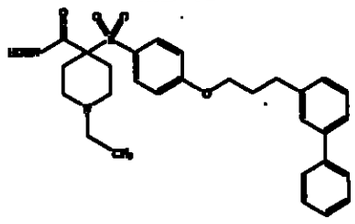
IIIB-47



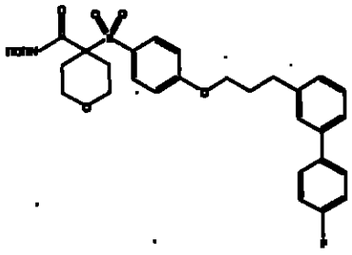
IIIB-48



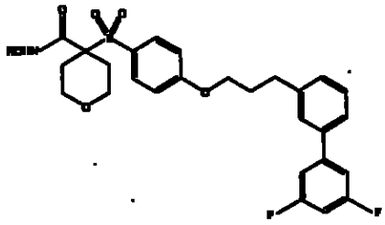
IIIB-49



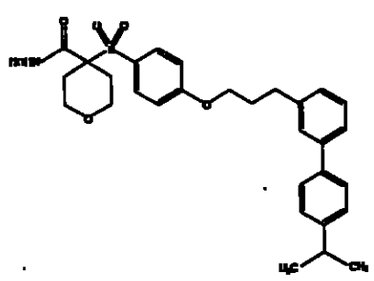
IIIB-50



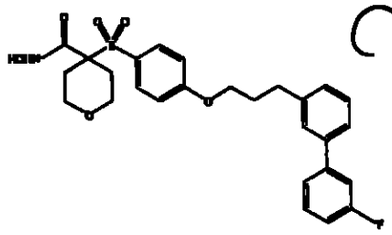
IIIB-51



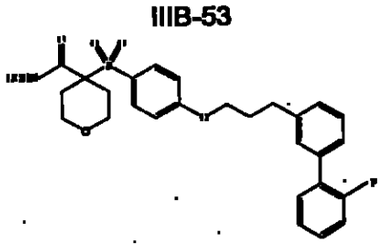
IIIB-52



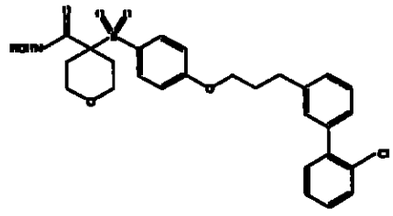
IIIB-53



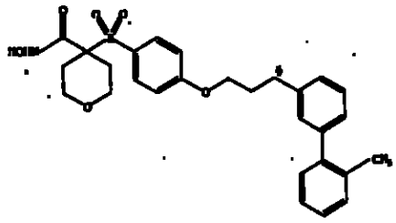
IIIB-54



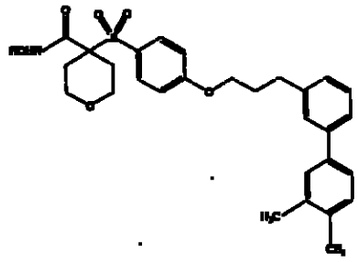
IIIB-55



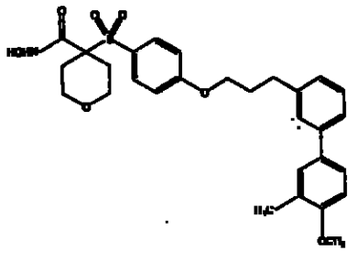
IIIB-56



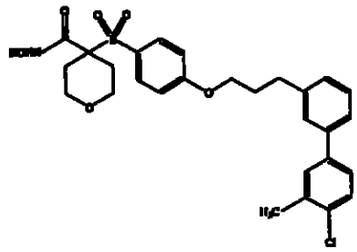
IIIB-57



IIIB-58

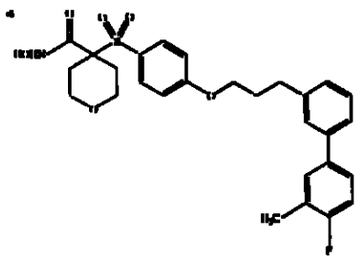


IIIB-59

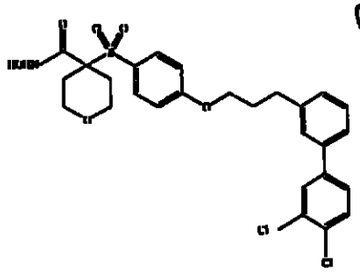


IIIB-60

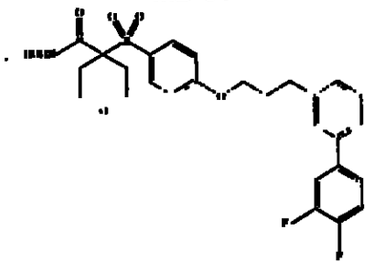
785



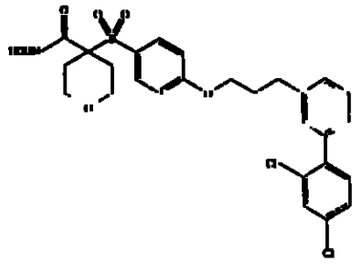
IIIB-61



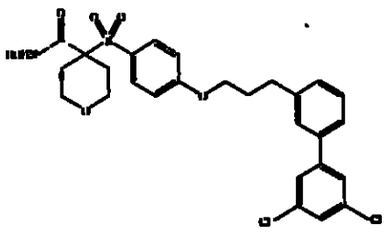
IIIB-62



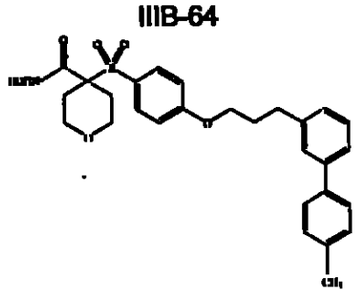
IIIB-63



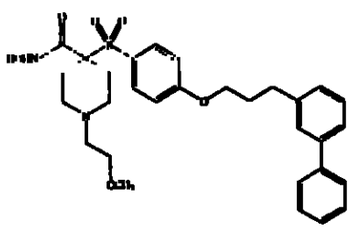
IIIB-64



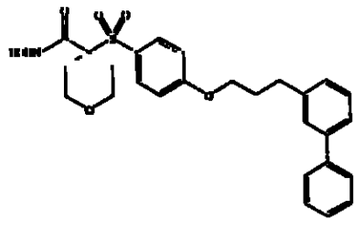
IIIB-65



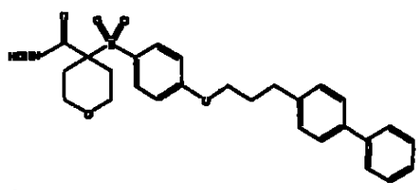
IIIB-66



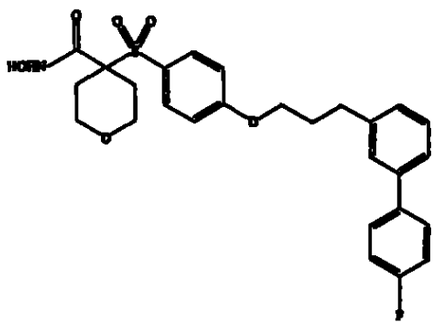
IIIB-67



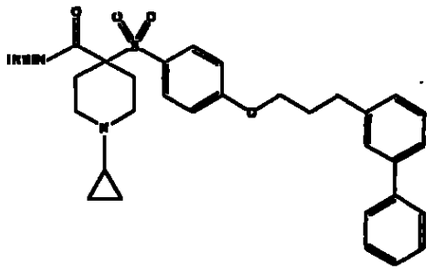
IIIB-68



IIIB-69

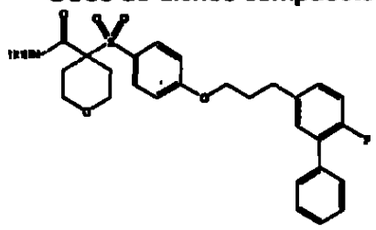


IIIB-70

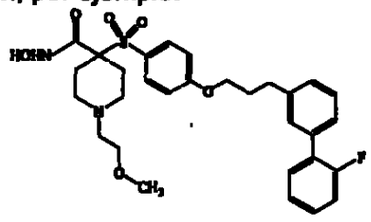


IIIB-71

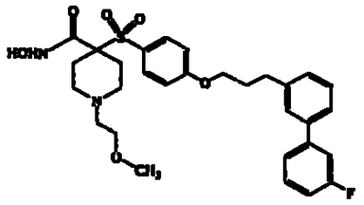
Otros de dichos compuestos incluyen, por ejemplo:



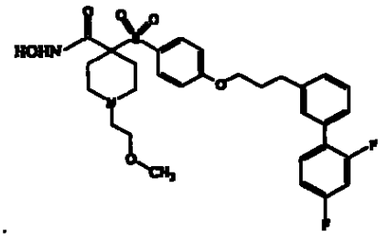
IIIB-72



IIIB-73

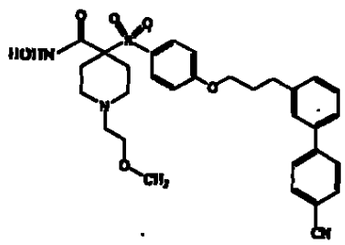


IIIB-74

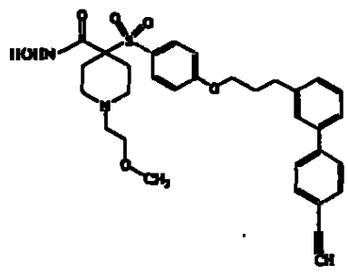


IIIB-75

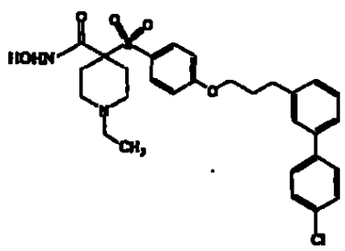
787



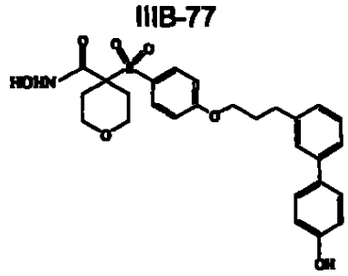
IIIB-76



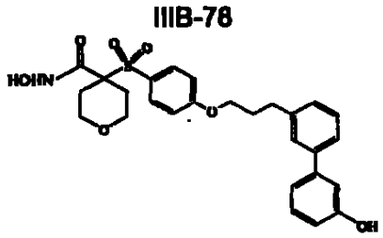
IIIB-77



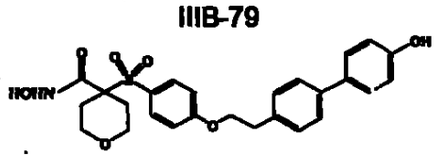
IIIB-78



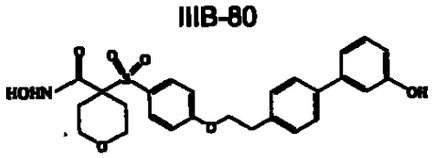
IIIB-79



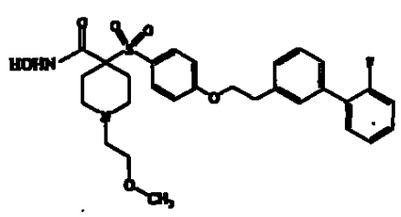
IIIB-80



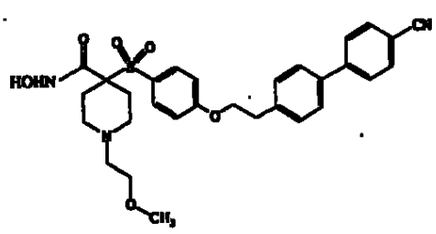
IIIB-81



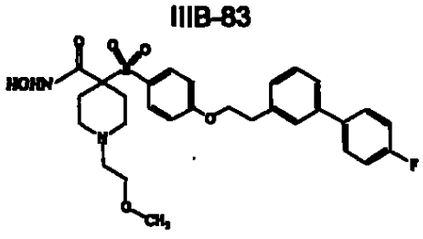
IIIB-82



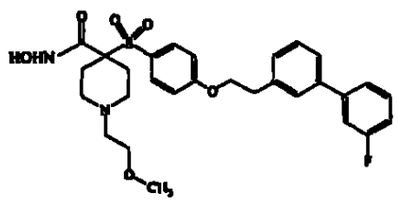
IIIB-83



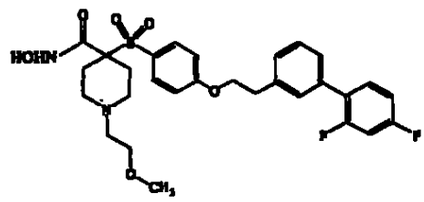
IIIB-84



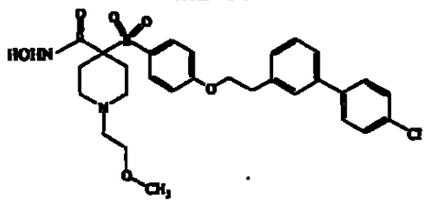
IIIB-85



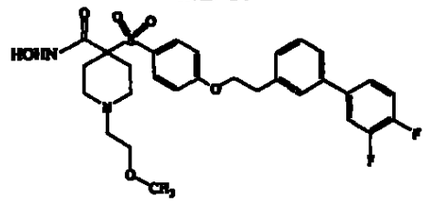
IIIB-86



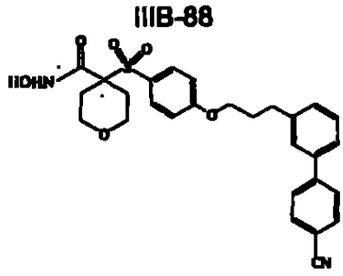
IIIB-87



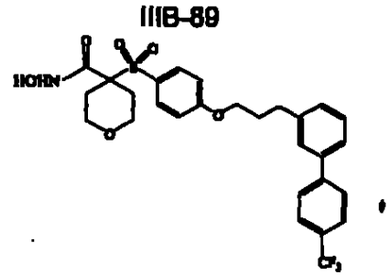
IIIB-88



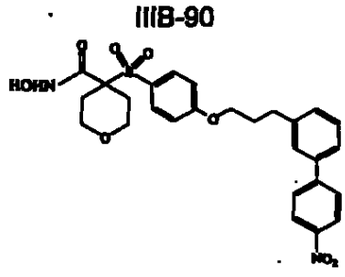
IIIB-89



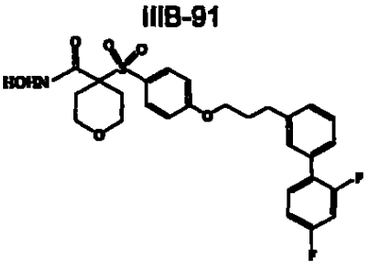
IIIB-90



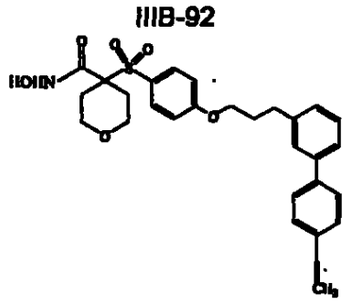
IIIB-91



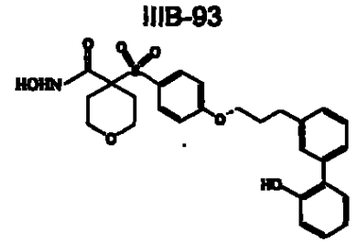
IIIB-92



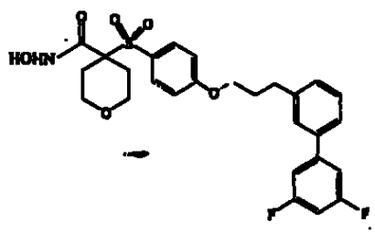
IIIB-93



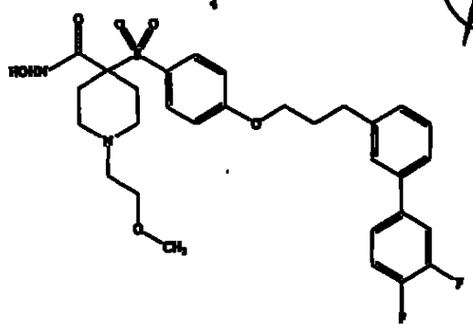
IIIB-94



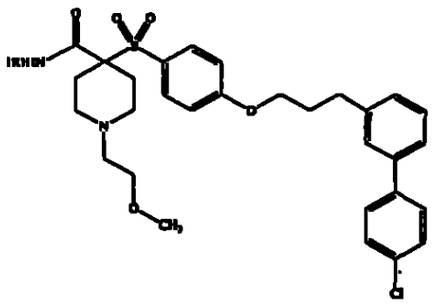
IIIB-95



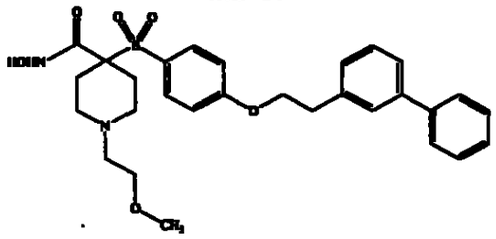
IIIB-96



IIIB-97

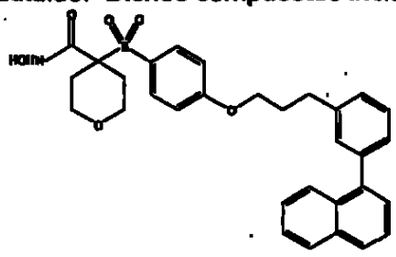


IIIB-98

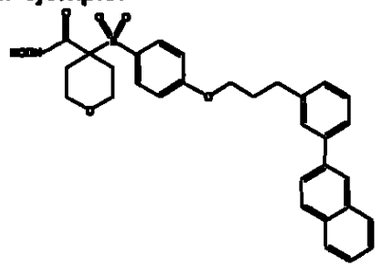


IIIB-99

[220] En otras realizaciones preferidas, E^5 es naftalenilo optativamente sustituido. Dichos compuestos incluyen, por ejemplo:



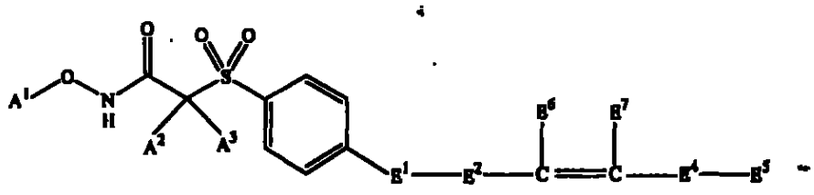
IIIB-100



IIIB-101

Realización preferida Nro. 3

[221] En algunas realizaciones de esta invención, el compuesto tiene una estructura que corresponde a la Fórmula IV:



IV

[222] A^1, A^2, y A^3 tienen los valores definidos anteriormente para la Fórmula I.

[223] E^1 es s -O-, $-S(O)_2-$, -S(O)-, $-N(R^1)-$, $-C(O)-N(R^1)-$, $-N(R^1)-C(O)-$, o $-C(R^1)(R^2)-$.

[224] E^2 es alquilo, cicloalquilo, alquilcicloalquilo, cicloalquilalquilo, o alquilcicloalquilalquilo. Cualquier miembro de este grupo es optativamente sustituido.

[225] En algunas realizaciones preferidas, E^2 es C_1-C_{20}-alquilo, cicloalquilo, C_1-C_{10}-alquilcicloalquilo, cicloalquil-C_1-C_{10}-alquilo, o C_1-C_{10}-alquilcicloalquil-C_1-C_{10}-alquilo. Cualquier miembro de este grupo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, C_1-C_6-alquilo, y halo-C_1-C_6-alquilo.

[226] En algunas realizaciones preferidas, E^2 es C_1-C_6-alquilo, cicloalquilo, C_1-C_6-alquilcicloalquilo, cicloalquil-C_1-C_6-alquilo, o C_1-C_6-alquilcicloalquil-C_1-C_6-alquilo. Cualquier miembro de este grupo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, C_1-C_2-alquilo, y halo-C_1-C_2-alquilo.

[227] En algunas realizaciones preferidas, E^2 es C_1-C_6-alquilo, cicloalquilo, C_1-C_6-alquilcicloalquilo, cicloalquil-C_1-C_6-alquilo, o C_1-C_6-

alquilcicloalquil-C_1-C_6-alquilo. Cualquier miembro de este grupo es optativamente sustituido con uno o más C_1-C_2-alquilo.

[228] E^4 es un enlace o alquilo. El alquilo es optativamente sustituido.

[229] En algunas realizaciones preferidas, E^4 es un enlace, C_1-C_{20}-alquilo, o halo-C_1-C_{20}-alquilo.

[230] En algunas realizaciones preferidas, E^4 es un enlace, C_1-C_3-alquilo, o halo-C_1-C_3-alquilo.

[231] En algunas realizaciones preferidas, E^4 es un enlace o C_1-C_3-alquilo.

[232] En algunas realizaciones preferidas, E^4 es un enlace.

[233] E^5 es alquilo, alquenilo, alquinilo, alcoxi, alcoxialquilo, carbociclilo, o heterociclilo. Cualquier miembro de este grupo es optativamente sustituido.

[234] En algunas realizaciones preferidas, E^5 es C_1-C_{20}-alquilo, C_2-C_{20}-alquenilo, C_2-C_{20}-alquinilo, C_1-C_{20}-alcoxi, C_1-C_{20}-alcoxi-C_1-C_{20}-alquilo, carbociclilo, o heterociclilo. El C_1-C_{20}-alquilo, C_2-C_{20}-alquenilo, C_2-C_{20}-alquinilo, C_1-C_{20}-alcoxi, y C_1-C_{20}-alcoxi-C_1-C_{20}-alquilo son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, y -CN. El carbociclilo y heterociclilo son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, ceto, C_1-C_8-alquilo, halo-C_1-C_8-alquilo, C_1-C_8-alcoxi, C_1-C_8-alcoxi-C_1-C_8-alquilo, halo-C_1-C_8-alcoxi, -$N(R^7)(R^8)$, -$C(O)(R^8)$, -S-R^7, -$S(O)_2$-R^7, carbociclilo, halocarbociclilo, carbociclil-C_1-C_8-alquilo, y C_1-C_8-alcoxi-C_1-C_8-alquilo sustituido con halógeno .

[235] En algunas realizaciones preferidas, E^5 es C_1-C_6-alquilo, C_2-C_6-alquenilo, C_2-C_6-alquinilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, carbociclilo, o heterociclilo. El C_1-C_6-alquilo, C_2-C_6-alquenilo, C_2-C_6-alquinilo, C_1-C_6-alcoxi, o C_1-C_6-alcoxi-C_1-C_6-alquilo son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, y -CN. El carbociclilo y heterociclilo son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, -CN, ceto, C_1-C_6-alquilo, halo-C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, -$N(R^7)(R^8)$, -$C(O)(R^8)$, -S-R^7, -$S(O)_z$-R^7, carbociclilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo, y C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno.

[236] E^6 es -H, halógeno, o alquilo. El alquilo es optativamente sustituido.

[237] En algunas realizaciones preferidas, E^6 es -H, halógeno, o C_1-C_6-alquilo. El C_1-C_6-alquilo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[238] En algunas realizaciones preferidas, E^6 es -H, halógeno, o C_1-C_6-alquilo. El C_1-C_6-alquilo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[239] E^7 es -H, alquilo, alquenilo, alquinilo, -$S(O)_z$-R^3, $-NO_2$, -$C(O)$-$N(R^3)(R^4)$, -$(C)(OR^3)$, carbociclilo, carbociclilalquilo, alcoxicarbociclilo, -CN, -C=N-OH, o -C=NH. El alquilo, alquenilo, alquinilo, carbociclilo, carbociclilalquilo, y alcoxicarbociclilo son optativamente sustituidos.

[240] En algunas realizaciones preferidas, E^7 es -H, C_1-C_6-alquilo, C_1-C_6-alquenilo, C_1-C_6-alquinilo, -$S(O)_z$-R^3, $-NO_2$, -$C(O)$-$N(R^3)(R^4)$, -$(C)(OR^3)$, carbociclilo, carbociclil-C_1-C_6-alquilo, C_1-C_6-alcoxicarbociclilo, -CN, -C=N-OH, o

793

-C=NH. El C_1-C_6-alquilo, C_1-C_6-alquenilo, C_1-C_6-alquinilo, carbociclilo, carbociclil-C_1-C_6-alquilo, o C_1-C_6-alcoxicarbociclilo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[241] En algunas realizaciones preferidas, E^7 es -H, C_1-C_6-alquilo, C_1-C_6-alquenilo, C_1-C_6-alquinilo, $-S(O)_2-R^3$, $-NO_2$, $-C(O)-N(R^3)(R^4)$, $-(C)(OR^3)$, carbociclilo, carbociclil-C_1-C_6-alquilo, C_1-C_6-alcoxicarbociclilo, -CN, -C=N-OH, o -C=NH. El C_1-C_6-alquilo, C_1-C_6-alquenilo, C_1-C_6-alquinilo, carbociclilo, carbociclil-C_1-C_6-alquilo, o C_1-C_6-alcoxicarbociclilo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[242] R^1 y R^2 se seleccionan independientemente del grupo formado por -H y alquilo. El alquilo es optativamente sustituido. Ni R^1 ni R^2 forman una estructura de anillo con E^2, E^4, E^5, E^6, o E^7.

[243] En algunas realizaciones preferidas, R^1 y R^2 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, y halo-C_1-C_6-alquilo.

[244] En algunas realizaciones preferidas, R^1 y R^2 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, y halo-C_1-C_6-alquilo.

[245] En algunas realizaciones preferidas, R^1 y R^2 se seleccionan independientemente del grupo formado por -H y C_1-C_6-alquilo.

[246] R^3 y R^4 se seleccionan independientemente del grupo formado por -H, alquilo, carbociclilo, carbociclilalquilo, heterociclilo, y heterociclilalquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo es optativamente sustituido.

794

[247] En algunas realizaciones preferidas, R^3 y R^4 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[248] En algunas realizaciones preferidas, R^3 y R^4 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[249] R^7 y R^8 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[250] En algunas realizaciones preferidas, R^7 y R^8 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[251] R^9 es -H, C_1-C_6-alquilo, -O-R^{10}, -N(R^{10})(R^{11}), carbociclil-C_1-C_6-alquilo, o heterociclil-C_1-C_6-alquilo. El C_1-C_6-alquilo, carbociclil-C_1-C_6-alquilo, o

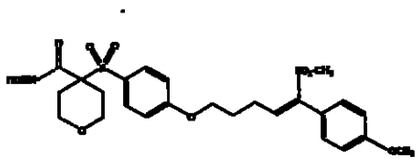
heterociclil-C_1-C_6-alquilo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[252] En algunas realizaciones preferidas, R^9 es -H, C_1-C_6-alquilo, -O-R^{10}, -N(R^{10})(R^{11}), carbociclil-C_1-C_6-alquilo, o heterociclil-C_1-C_6-alquilo. El C_1-C_6-alquilo, carbociclil-C_1-C_6-alquilo, o heterociclil-C_1-C_6-alquilo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

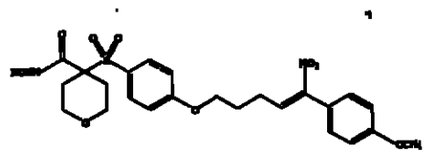
[253] R^{10} y R^{11} se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[254] En algunas realizaciones preferidas, R^{10} y R^{11} se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

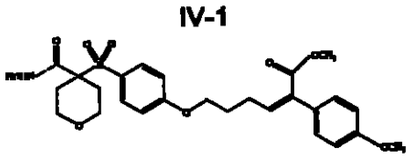
[255] En algunas realizaciones preferidas, E^5 es carbociclilo optativamente sustituido o heterociclilo optativamente sustituido. Por ejemplo, en algunas de dichas realizaciones, E^5 es carbociclilo optativamente sustituido, generalmente preferentemente arilo optativamente sustituido, y más preferentemente fenilo optativamente sustituido. Dichos compuestos incluyen, por ejemplo:



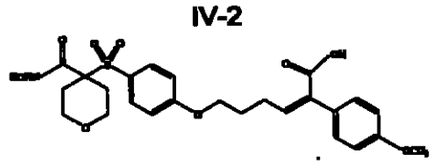
IV-1



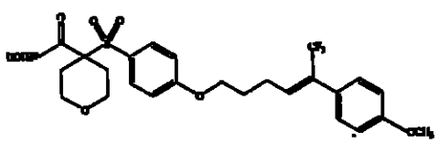
IV-2



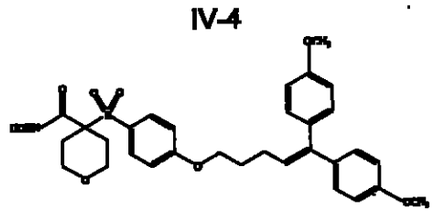
IV-3



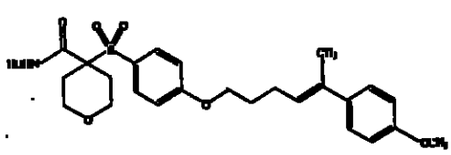
IV-4



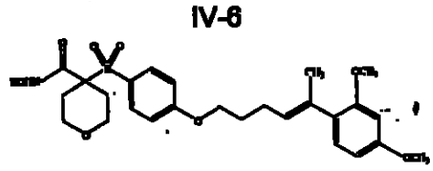
IV-5



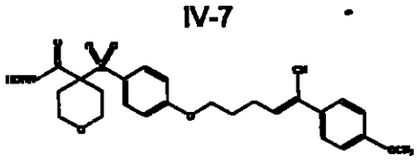
IV-6



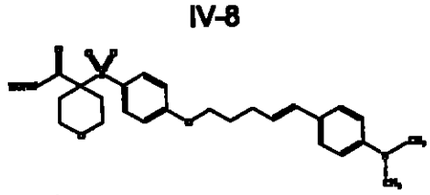
IV-7



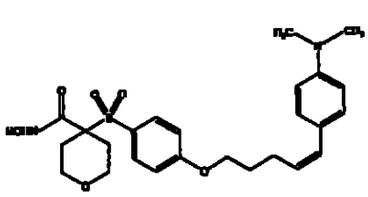
IV-8



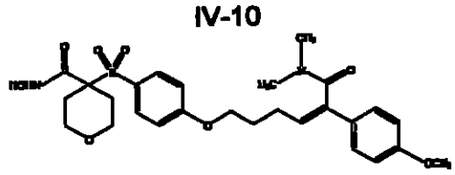
IV-9



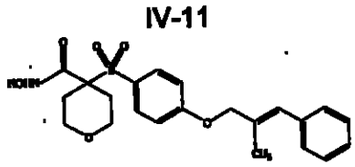
IV-10



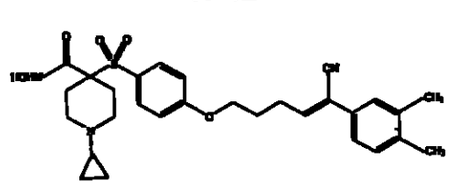
IV-11



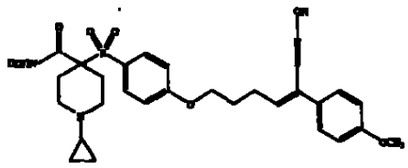
IV-12



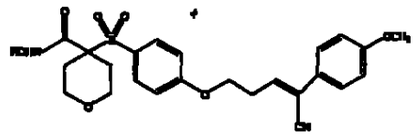
IV-13



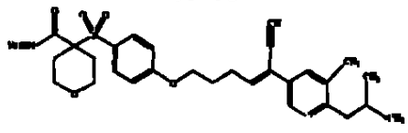
IV-14



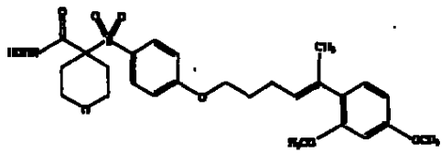
IV-15



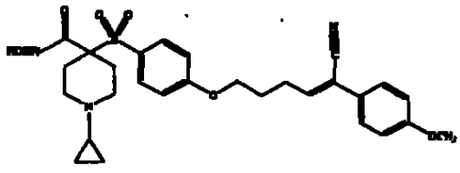
IV-16



IV-17



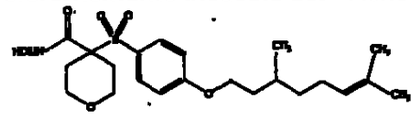
IV-18



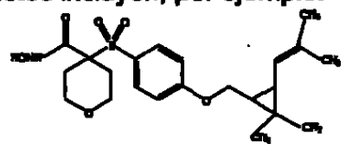
IV-19

[256] En algunas realizaciones preferidas, E^5 es C_1-C_6-alquilo, C_2-C_6-alquenilo, C_2-C_6-alquinilo, C_1-C_6-alcoxi, o C_1-C_6-alcoxi-C_1-C_6-alquilo. Cualquier miembro de este grupo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, y -CN.

[257] En algunas realizaciones preferidas, E^5 es optativamente-sustituido C_1-C_6-alquilo, siendo el C_1-C_6-alquilo generalmente más preferentemente insustituido. Dichos compuestos incluyen, por ejemplo:



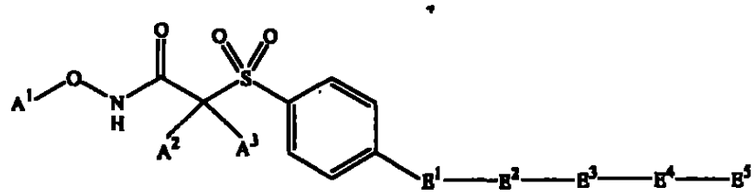
IV-20



IV-21

Realización preferida Nro. 4

[258] En algunas realizaciones de esta invención, el compuesto tiene una estructura que corresponde a la Fórmula V:



V

[259] A^1, A^2, y A^3 tienen los valores definidos anteriormente para la Fórmula I.

[260] E^1 es -O-, $-S(O)_2-$, -S(O)-, $-N(R^3)-$, $-C(O)-N(R^3)-$, $-N(R^3)-C(O)-$, o $-C(R^1)(R^2)-$.

[261] E^2 es un enlace, alquilo, cicloalquilo, alquilcicloalquilo, cicloalquilalquilo, o alquilcicloalquilalquilo. Salvo cuando el miembro es un enlace, cualquier miembro de dicho grupo es optativamente sustituido.

[262] En algunas realizaciones preferidas, E^2 es un enlace, C_1-C_{20}-alquilo, cicloalquilo, C_1-C_{10}-alquilcicloalquilo, cicloalquil-C_1-C_{10}-alquilo, o C_1-C_{10}-alquilcicloalquil-C_1-C_{10}-alquilo. Cualquier miembro de este grupo (con la excepción del enlace) es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, C_1-C_6-alquilo, y halo-C_1-C_6-alquilo.

[263] En algunas realizaciones preferidas, E^2 es un enlace, C_1-C_6-alquilo, o halo-C_1-C_6-alquilo.

[264] En algunas realizaciones preferidas E^2 es un enlace o C_1-C_6-alquilo.

[265] E^3 es carbonilpirrolidinilo. El carbonilpirrolidinilo es optativamente sustituido.

[266] En algunas realizaciones preferidas, E^3 es carbonilpirrolidinilo donde el carbonilpirrolidinilo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[267] E^4 es un enlace, alquilo, o alquenilo. El alquilo y alquenilo son optativamente sustituidos.

[268] En algunas realizaciones preferidas, E^4 es un enlace, C_1-C_{20}-alquilo, halo-C_1-C_{20}-alquilo, C_2-C_{20}-alquenilo, o halo-C_2-C_{20}-alquenilo.

[269] En algunas realizaciones preferidas, E^4 es un enlace, C_1-C_3-alquilo, halo-C_1-C_3-alquilo, C_2-C_3-alquenilo, o halo-C_2-C_3-alquenilo.

[270] En algunas realizaciones preferidas, E^4 es un enlace, C_1-C_3-alquilo, o C_2-C_3-alquenilo.

[271] En algunas realizaciones preferidas, E^4 es un enlace.

[272] E^5 es alquilo, alquenilo, alquinilo, alcoxi, alcoxialquilo, carbociclilo, o heterociclilo. Cualquier miembro de este grupo es optativamente sustituido.

[273] En algunas realizaciones preferidas, E^5 es C_1-C_{20}-alquilo, C_2-C_{20}-alquenilo, C_2-C_{20}-alquinilo, C_1-C_{20}-alcoxi, C_1-C_{20}-alcoxi-C_1-C_{20}-alquilo, carbociclilo, o heterociclilo. El C_1-C_{20}-alquilo, C_2-C_{20}-alquenilo, C_2-C_{20}-alquinilo, C_1-C_{20}-alcoxi, y C_1-C_{20}-alcoxi-C_1-C_{20}-alquilo son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, y -CN. El carbociclilo y heterociclilo son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, -CN, ceto, C_1-C_8-alquilo, halo-C_1-C_8-alquilo, C_1-C_8-alcoxi, halo-C_1-C_8-alcoxi, C_1-C_8-alcoxi-C_1-C_8-alquilo, C_1-C_8-alcoxi-C_1-C_8-alquilo sustituido con halógeno , $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbociclilo, halocarbociclilo, carbociclil-C_1-C_8-alquilo, y carbociclil-C_1-C_8-alquilo sustituido con halógeno.

[274] En algunas realizaciones preferidas, E^5 es C_1-C_8-alquilo, C_2-C_8-alquenilo, C_2-C_8-alquinilo, C_1-C_8-alcoxi, C_1-C_8-alcoxi-C_1-C_8-alquilo, carbociclilo, o heterociclilo. El C_1-C_8-alquilo, C_2-C_8-alquenilo, C_2-C_8-alquinilo, C_1-C_8-alcoxi, y C_1-C_8-alcoxi-C_1-C_8-alquilo son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, y -CN. El carbociclilo y heterociclilo son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, -CN, ceto, C_1-C_8-alquilo, halo-C_1-C_8-alquilo, C_1-C_8-alcoxi, halo-C_1-C_8-alcoxi, C_1-C_8-alcoxi-C_1-C_8-alquilo, C_1-C_8-alcoxi-C_1-C_8-alquilo sustituido con halógeno, $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbociclilo, halocarbociclilo, carbociclil-C_1-C_8-alquilo, y carbociclil-C_1-C_8-alquilo sustituido con halógeno.

[275] R^1 y R^2 se seleccionan independientemente del grupo formado por -H y alquilo. El alquilo es optativamente sustituido. Ni R^1 ni R^2 forman una estructura de anillo con E^2, E^3, E^4, o E^5.

[276] En algunas realizaciones preferidas, R^1 y R^2 se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, y halo-C_1-C_8-alquilo.

[277] En algunas realizaciones preferidas, R^1 y R^2 se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, y halo-C_1-C_8-alquilo.

[278] En algunas realizaciones preferidas, R^1 y R^2 se seleccionan independientemente del grupo formado por -H y C_1-C_8-alquilo.

[279] R^5 y R^6 se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, carbociclilo, carbociclil-C_1-C_8-alquilo, heterociclilo, y heterociclil-C_1-C_8-alquilo. Salvo cuando el miembro es -H, cualquier miembro

de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[280] En algunas realizaciones preferidas, R^5 y R^6 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[281] R^7 es -H, C_1-C_6-alquilo, -O-R^8, -N(R^8)(R^9), carbociclil-C_1-C_6-alquilo, o heterociclil-C_1-C_6-alquilo. El C_1-C_6-alquilo, carbociclil-C_1-C_6-alquilo, o heterociclil-C_1-C_6-alquilo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

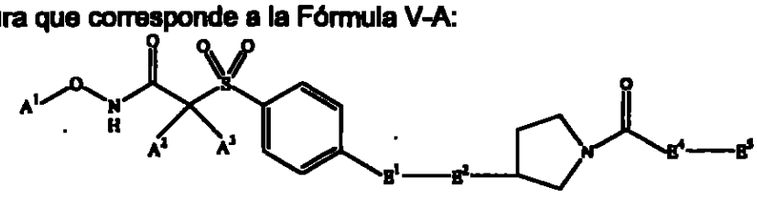
[282] En algunas realizaciones preferidas, R^7 es -H, C_1-C_6-alquilo, -O-R^8, -N(R^8)(R^9), carbociclil-C_1-C_6-alquilo, o heterociclil-C_1-C_6-alquilo. El C_1-C_6-alquilo, carbociclil-C_1-C_6-alquilo, o heterociclil-C_1-C_6-alquilo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[283] R^8 y R^9 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[284] En algunas realizaciones preferidas, R^8 y R^9 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo puede ser

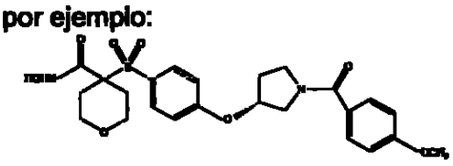
sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[285] En algunas realizaciones preferidas, el compuesto tiene una estructura que corresponde a la Fórmula V-A:

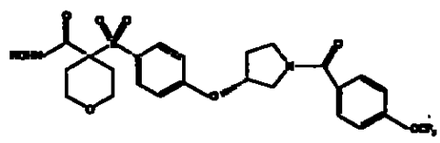


V-A

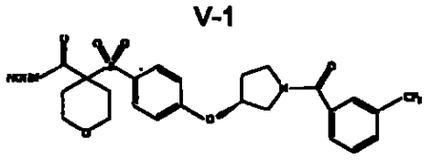
[286] En algunas realizaciones preferidas, E^5 es carbociclilo optativamente sustituido o optativamente sustituido heterociclilo. Por ejemplo, en algunas de dichas realizaciones, E^5 es carbociclilo optativamente sustituido, generalmente preferentemente arilo optativamente sustituido, y más preferentemente fenilo optativamente sustituido. Dichos compuestos incluyen, por ejemplo:



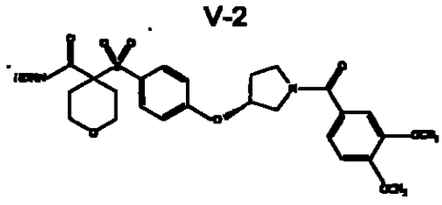
V-1



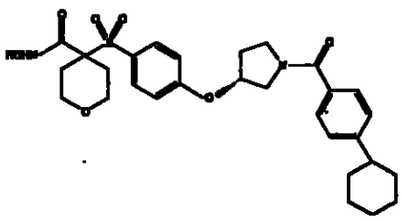
V-2



V-3



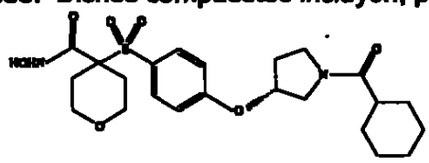
V-4



V-5

803

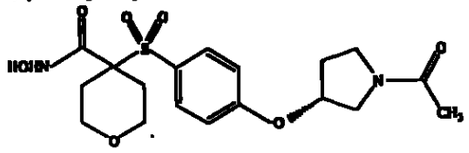
[287] En algunas realizaciones preferidas, E^5 es C_5-C_6-cicloalquilo optativamente sustituido. Dichos compuestos incluyen, por ejemplo:



V-6

[288] En algunas realizaciones preferidas, E^5 es C_1-C_8-alquilo, C_2-C_8-alquenilo, C_2-C_8-alquinilo, C_1-C_8-alcoxi, o C_1-C_8-alcoxi-C_1-C_8-alquilo. El C_1-C_8-alquilo, C_2-C_8-alquenilo, C_2-C_8-alquinilo, C_1-C_8-alcoxi, y C_1-C_8-alcoxi-C_1-C_8-alquilo son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, y -CN.

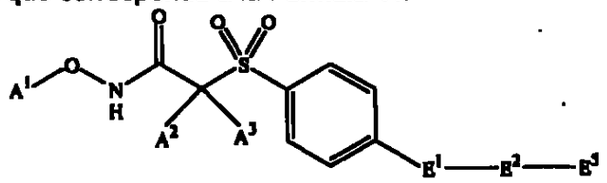
[289] En algunas realizaciones preferidas, E^5 es optativamente-sustituido C_1-C_8-alquilo, siendo C_1-C_8 generalmente el más preferido. Dichos compuestos incluyen, por ejemplo:



V-7

Realización preferida Nro. 5

[290] En algunas realizaciones de esta invención, el compuesto tiene una estructura que corresponde a la Fórmula VI:



VI

804

[291] A^1, A^2, y A^3 tienen los valores definidos anteriormente para la Fórmula I.

[292] E^1 es -O-, -$S(O)_2$-, -S(O)-, -$N(R^1)$-, -C(O)-$N(R^1)$-, -$N(R^1)$-C(O)-, o -$C(R^1)(R^2)$-.

[293] E^2 es alquilo, cicloalquilo, alquilcicloalquilo, cicloalquilalquilo, o alquilcicloalquilalquilo. Cualquier miembro de este grupo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, alquilo, y haloalquilo.

[294] En algunas realizaciones preferidas, E^2 es C_1-C_{20}-alquilo, cicloalquilo, C_1-C_{10}-alquilcicloalquilo, cicloalquil-C_1-C_{10}-alquilo, o C_1-C_{10}-alquilcicloalquil-C_1-C_{10}-alquilo. Cualquier miembro de este grupo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, C_1-C_6-alquilo, y halo-C_1-C_6-alquilo.

[295] En algunas realizaciones preferidas, E^2 es C_1-C_6-alquilo, cicloalquilo, C_1-C_6-alquilcicloalquilo, cicloalquil-C_1-C_6-alquilo, o C_1-C_6-alquilcicloalquil-C_1-C_6-alquilo. Cualquier miembro de este grupo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, C_1-C_2-alquilo, y halo-C_1-C_2-alquilo.

[296] En algunas realizaciones preferidas, E^2 es C_1-C_6-alquilo, cicloalquilo, C_1-C_6-alquilcicloalquilo, cicloalquil-C_1-C_6-alquilo, o C_1-C_6-alquilcicloalquil-C_1-C_6-alquilo. Cualquier miembro de este grupo es optativamente sustituido con uno o más C_1-C_2-alquilo.

[297] E^5 es alquilo, alquenilo, alquinilo, cicloalquilo, ciclopentenilo, ciclopentadienilo, ciclohexenilo, o ciclohexadienilo. En este caso, el

805

cicloalquilo, ciclopentenilo, ciclopentadienilo, ciclohexenilo, y ciclohexadienilo son optativamente sustituidos. El alquilo, alquenilo, y alquinilo (a) contienen al menos 4 átomos de carbono, y (b) son optativamente sustituidos con uno o más sustituyentes seleccionados del grupo formado por -OH, -NO_2, -CN, y halógeno.

[298] En algunas realizaciones preferidas, E^5 es C_4-C_{20}-alquilo, C_4-C_{20}-alquenilo, C_4-C_{20}-alquinilo, cicloalquilo, ciclopentenilo, ciclopentadienilo, ciclohexenilo, o ciclohexadienilo. El C_4-C_{20}-alquilo, C_4-C_{20}-alquenilo, y C_4-C_{20}-alquinilo son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por -OH, -NO_2, -CN, y halógeno. El cicloalquilo, ciclopentenilo, ciclopentadienilo, ciclohexenilo, y ciclohexadienilo son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, ceto, C_1-C_8-alquilo, halo-C_1-C_8-alquilo, C_1-C_8-alcoxi, halo-C_1-C_8-alcoxi, C_1-C_8-alcoxi-C_1-C_8-alquilo, C_1-C_8-alcoxi-C_1-C_8-alquilo sustituido con halógeno , -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbociclilo, halocarbociclilo, carbociclil-C_1-C_8-alquilo, y carbociclil-C_1-C_8-alquilo sustituido con halógeno.

[299] En algunas realizaciones preferidas, E^5 es C_4-C_8-alquilo, C_4-C_8-alquenilo, C_4-C_8-alquinilo, cicloalquilo, ciclopentenilo, ciclopentadienilo, ciclohexenilo, o ciclohexadienilo. El C_4-C_8-alquilo, C_4-C_8-alquenilo, y C_4-C_8-alquinilo son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por -OH, -NO_2, -CN, y halógeno. El cicloalquilo, ciclopentenilo, ciclopentadienilo, ciclohexenilo, y ciclohexadienilo son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -

NO_2, -CN, ceto, C_1-C_6-alquilo, halo-C_1-C_6-alquilo, C_1-C_6-alcoxi, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbociclilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo, y carbociclil-C_1-C_6-alquilo sustituido con halógeno.

[300] R^1 y R^2 se seleccionan independientemente del grupo formado por -H y alquilo. El alquilo es optativamente sustituido. Ni R^1 ni R^2 forman una estructura de anillo con E^5.

[301] En algunas realizaciones preferidas, R^1 y R^2 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, y halo-C_1-C_6-alquilo.

[302] En algunas realizaciones preferidas, R^1 y R^2 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, y halo-C_1-C_6-alquilo.

[303] En algunas realizaciones preferidas, R^1 y R^2 se seleccionan independientemente del grupo formado por -H y C_1-C_6-alquilo.

[304] R^5 y R^6 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[305] En algunas realizaciones preferidas, R^5 y R^6 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

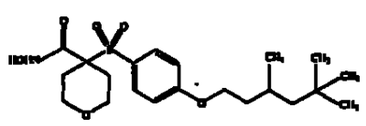
[306] R^7 es -H, C_1-C_8-alquilo, -O-R^8, -N(R^8)(R^9), carbociclil-C_1-C_8-alquilo, o heterociclil-C_1-C_8-alquilo. El C_1-C_8-alquilo, carbociclil-C_1-C_8-alquilo, o heterociclil-C_1-C_8-alquilo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[307] En algunas realizaciones preferidas, R^7 es -H, C_1-C_8-alquilo, -O-R^8, -N(R^8)(R^9), carbociclil-C_1-C_8-alquilo, o heterociclil-C_1-C_8-alquilo. El C_1-C_8-alquilo, carbociclil-C_1-C_8-alquilo, o heterociclil-C_1-C_8-alquilo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

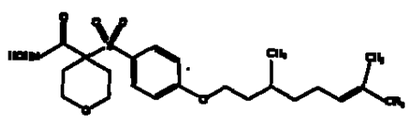
[308] R^8 y R^9 se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, carbociclilo, carbociclil-C_1-C_8-alquilo, heterociclilo, y heterociclil-C_1-C_8-alquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[309] En algunas realizaciones preferidas, R^8 y R^9 se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, carbociclilo, carbociclil-C_1-C_8-alquilo, heterociclilo, y heterociclil-C_1-C_8-alquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

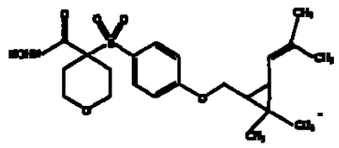
[310] En algunas realizaciones preferidas, E^5 es C_4-C_8-alquilo, C_4-C_8-alquenilo, o C_4-C_8-alquinilo. El C_4-C_8-alquilo, C_4-C_8-alquenilo, y C_4-C_8-alquinilo son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por -OH, -NO_2, -CN, y halógeno. Dichos compuestos incluyen, por ejemplo:



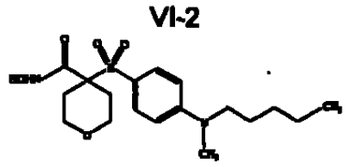
VI-1



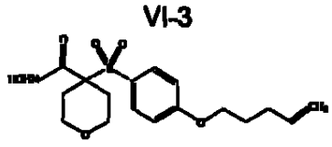
VI-2



VI-3

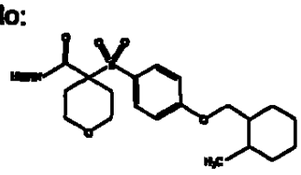


VI-4

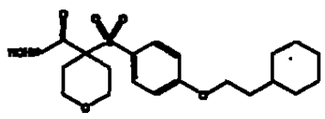


VI-5

[311] En algunas realizaciones preferidas, E^5 es carbociclilo optativamente sustituido. En algunas de dichas realizaciones, E^5 es C_5-C_6-cicloalquilo optativamente sustituido. Dichos compuestos incluyen, por ejemplo:

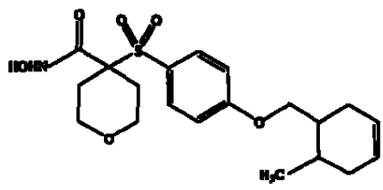


VI-6



VI-7

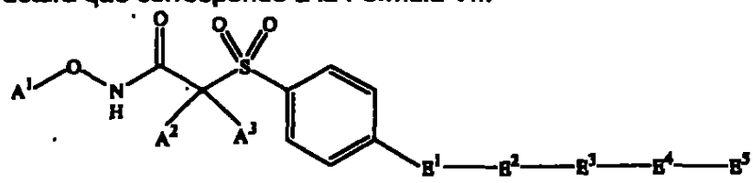
En otras tales realizaciones, E^5 es un carbociclilo parcialmente saturado optativamente sustituido seleccionado del grupo formado por ciclopentenilo, ciclopentadienilo, ciclohexenilo, y ciclohexadienilo. Dichos compuestos incluyen, por ejemplo:



VI-8

Realización preferida Nro. 6

[312] En algunas realizaciones de esta invención, el compuesto tiene una estructura que corresponde a la Fórmula VII:



VII

[313] A^1, A^2, y A^3 tienen los valores definidos anteriormente para la Fórmula I.

[314] E^1 es -O-, -$S(O)_2$-, -S(O)-, -$N(R^1)$-, -C(O)-$N(R^1)$-, -$N(R^1)$-C(O)-, o -$C(R^1)(R^2)$-.

[315] E^2 es alquilo, cicloalquilo, alquilcicloalquilo, cicloalquilalquilo, o alquilcicloalquilalquilo. Cualquier miembro de este grupo es optativamente sustituido.

[316] En algunas realizaciones preferidas, E^2 es C_1-C_{20}-alquilo, cicloalquilo, C_1-C_{10}-alquilcicloalquilo, cicloalquil-C_1-C_{10}-alquilo, o C_1-C_{10}-alquilcicloalquil-C_1-C_{10}-alquilo. Cualquier miembro de este grupo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, C_1-C_6-alquilo, y halo-C_1-C_6-alquilo.

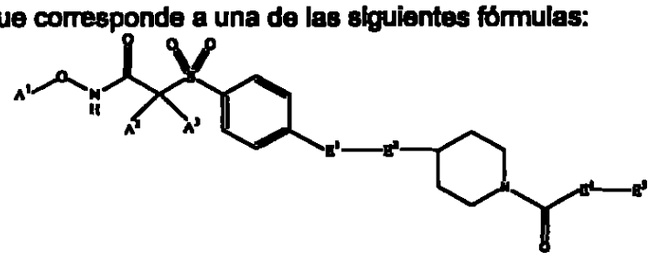
[317] En algunas realizaciones preferidas, E^2 es C_1-C_6-alquilo optativamente sustituido con uno o más halógenos.

[318] En algunas realizaciones preferidas, E^2 es C_1-C_6-alquilo.

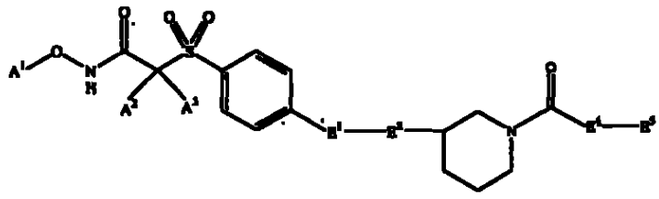
[319] E^3 es carbonilpiperidinilo. El carbonilpiperidinilo es optativamente sustituido.

[320] En algunas realizaciones preferidas, E^3 es carbonilpiperidinilo donde el carbonilpiperidinilo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[321] En algunas realizaciones preferidas, el compuesto tiene una estructura que corresponde a una de las siguientes fórmulas:



VII-A



VII-B

[322] E^4 es un enlace, alquilo, o alquenilo. El alquilo y alquenilo son optativamente sustituidos.

[323] En algunas realizaciones preferidas, E^4 es un enlace, C_1-C_{20}-alquilo, halo-C_1-C_{20}-alquilo, C_2-C_{20}-alquenilo, o halo-C_2-C_{20}-alquenilo.

[324] En algunas realizaciones preferidas, E^4 es un enlace, C_1-C_3-alquilo, halo-C_1-C_3-alquilo, C_2-C_3-alquenilo, o halo-C_2-C_3-alquenilo.

[325] En algunas realizaciones preferidas, E^4 es un enlace, C_1-C_3-alquilo, o C_2-C_3-alquenilo.

[326] En algunas realizaciones preferidas, E^4 es un enlace.

[327] E^5 es alquilo, alquenilo, alquinilo, alcoxi, alcoxialquilo, carbociclilo, o heterociclilo. Cualquier miembro de este grupo es optativamente sustituido.

[328] En algunas realizaciones preferidas, E^5 es C_1-C_{20}-alquilo, C_2-C_{20}-alquenilo, C_2-C_{20}-alquinilo, C_1-C_{20}-alcoxi, C_1-C_{20}-alcoxi-C_1-C_{20}-alquilo, carbociclilo, o heterociclilo. El C_1-C_{20}-alquilo, C_2-C_{20}-alquenilo, C_2-C_{20}-alquinilo, C_1-C_{20}-alcoxi, y C_1-C_{20}-alcoxi-C_1-C_{20}-alquilo son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, y -CN. El carbociclilo y heterociclilo son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, ceto, C_1-C_8-alquilo, halo-C_1-C_8-alquilo, C_1-C_8-alcoxi, halo-C_1-C_8-alcoxi, C_1-C_8-alcoxi-C_1-C_8-alquilo, C_1-C_8-alcoxi-C_1-C_8-alquilo sustituido con halógeno , -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbociclilo, halocarbociclilo, y carbociclil-C_1-C_8-alquilo.

[329] En algunas realizaciones preferidas, E^5 es C_1-C_8-alquilo, C_2-C_8-alquenilo, C_2-C_8-alquinilo, C_1-C_8-alcoxi, C_1-C_8-alcoxi-C_1-C_8-alquilo, carbociclilo, o heterociclilo. En este caso, el C_1-C_8-alquilo, C_2-C_8-alquenilo, C_2-C_8-alquinilo, C_1-C_8-alcoxi, y C_1-C_8-alcoxi-C_1-C_8-alquilo son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, y -CN. El carbociclilo y heterociclilo son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, ceto, C_1-C_8-alquilo, halo-C_1-C_8-alquilo, C_1-C_8-alcoxi, halo-C_1-C_8-alcoxi, C_1-C_8-alcoxi-C_1-C_8-alquilo, C_1-C_8-alcoxi-C_1-C_8-alquilo sustituido con halógeno, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbociclilo, halocarbociclilo, carbociclil-C_1-C_8-alquilo, y carbociclil-C_1-C_8-alquilo sustituido con halógeno.

[330] R^1 y R^2 se seleccionan independientemente del grupo formado por -H y alquilo. El alquilo es optativamente sustituido. Ni R^1 ni R^2 forman una estructura de anillo con E^2, E^3, E^4, o E^5.

[331] En algunas realizaciones preferidas, R^1 y R^2 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, y halo-C_1-C_6-alquilo.

[332] En algunas realizaciones preferidas, R^1 y R^2 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, y halo-C_1-C_6-alquilo.

[333] En algunas realizaciones preferidas, R^1 y R^2 se seleccionan independientemente del grupo formado por -H y C_1-C_6-alquilo.

[334] R^5 y R^6 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[335] En algunas realizaciones preferidas, R^5 y R^6 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

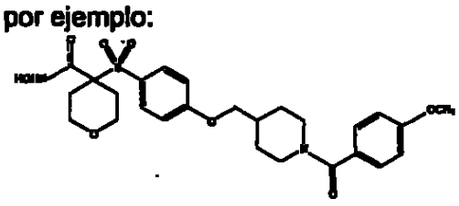
[336] R^7 es -H, C_1-C_6-alquilo, -O-R^8, -N(R^8)(R^9), carbociclil-C_1-C_6-alquilo, o heterociclil-C_1-C_6-alquilo. El C_1-C_6-alquilo, carbociclil-C_1-C_6-alquilo, o heterociclil-C_1-C_6-alquilo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[337] En algunas realizaciones preferidas, R^7 es -H, C_1-C_6-alquilo, -O-R^8, -N(R^8)(R^9), carbociclil-C_1-C_6-alquilo, o heterociclil-C_1-C_6-alquilo. El C_1-C_6-alquilo, carbociclil-C_1-C_6-alquilo, o heterociclil-C_1-C_6-alquilo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

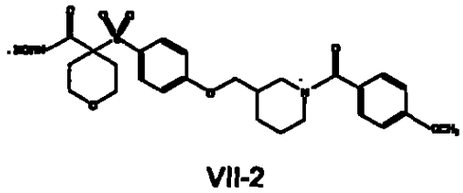
[338] R^8 y R^9 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[339] En algunas realizaciones preferidas, R^8 y R^9 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[340] En algunas realizaciones preferidas, E^5 es carbociclilo optativamente sustituido o optativamente sustituido heterociclilo. En algunas de dichas realizaciones, E^5 es arilo optativamente sustituido, generalmente preferentemente fenilo optativamente sustituido. Dichos compuestos incluyen, por ejemplo:



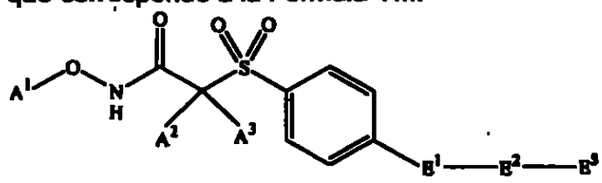
VII-1



VII-2

Realización preferida Nro. 7

[341] En algunas realizaciones de esta invención, el compuesto tiene una estructura que corresponde a la Fórmula VIII:



VIII

[342] A^1, A^2, y A^3 tienen los valores definidos anteriormente para la Fórmula I.

[343] E^1 es -O-, $-S(O)_2-$, -S(O)-, $-N(R^1)-$, $-C(O)-N(R^1)-$, $-N(R^1)-C(O)-$, o $-C(R^1)(R^2)-$.

[344] E^2 forma un enlace de al menos 3 átomos de carbono entre E^1 y E^5. E^2 es alquilo, cicloalquilo, alquilcicloalquilo, cicloalquilalquilo, o alquilcicloalquilalquilo. Cualquier miembro de este grupo es optativamente sustituido.

[345] En algunas realizaciones preferidas, E^2 es C_3-C_{20}-alquilo, cicloalquilo, C_1-C_{10}-alquil-cicloalquilo, cicloalquil-C_1-C_{10}-alquilo, o C_1-C_{10}-alquil-cicloalquil-C_1-C_{10}-alquilo. Cualquier miembro de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[346] En algunas realizaciones preferidas, E^2 es C_3-C_6-alquilo optativamente sustituido con uno o más halógenos.

[347] En algunas realizaciones preferidas, E^2 es C_3-C_6-alquilo.

[348] E^5 es heterociclilo optativamente sustituido, carbociclilo de anillos fusionados optativamente sustituido, o carbociclilo de anillo único sustituido.

[349] En algunas realizaciones preferidas, E^5 es carbociclilo de un solo anillo, carbociclilo de anillos fusionados, o heterociclilo.

[350] En este caso, el carbociclilo de anillo único es sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, -CN, ceto, C_1-C_6-alquilo, halo-C_1-C_6-alquilo, C_1-C_6-alcoxi, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxil-C_1-C_6-alquilo, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno , $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbociclilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo, carbociclil-C_1-C_6-alquilo sustituido con halógeno. El carbociclilo de anillo único también es optativamente sustituido en el mismo átomo con dos sustituyentes seleccionados independientemente del grupo formado por alquilo y haloalquilo, donde los dos sustituyentes juntos forman C_3-C_6-cicloalquilo o halo-C_3-C_6-cicloalquilo.

[351] En algunas realizaciones preferidas, el carbociclilo de anillo único es sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, -CN, ceto, C_1-C_6-alquilo, halo-C_1-C_6-alquilo, C_1-C_6-alcoxi, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbociclilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo, y carbociclil-C_1-C_6-alquilo sustituido con halógeno. El carbociclilo de anillo único también es optativamente sustituido en el mismo átomo con dos sustituyentes seleccionados independientemente del grupo formado por alquilo y haloalquilo, donde los dos sustituyentes juntos forman C_3-C_6-cicloalquilo o halo-C_3-C_6-cicloalquilo.

[352] El heterociclilo y carbociclilo de anillos fusionados son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, -CN, ceto, C_1-C_6-

816

alquilo, halo-C_1-C_6-alquilo, C_1-C_6-alcoxi, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno , -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbociclilo, halocarbociclilo, y carbociclil-C_1-C_6-alquilo. El heterociclilo y carbociclilo de anillos fusionados también son optativamente sustituidos en el mismo átomo con dos sustituyentes seleccionados independientemente del grupo formado por alquilo y haloalquilo, donde los dos sustituyentes juntos forman C_3-C_6-cicloalquilo o halo-C_3-C_6-cicloalquilo.

[353] En algunas realizaciones preferidas, el heterociclilo y carbociclilo de anillos fusionados son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, ceto, C_1-C_6-alquilo, halo-C_1-C_6-alquilo, C_1-C_6-alcoxi, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbociclilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo, y carbociclil-C_1-C_6-alquilo sustituido con halógeno. El heterociclilo y carbociclilo de anillos fusionados también son optativamente sustituidos en el mismo átomo con dos sustituyentes seleccionados independientemente del grupo formado por alquilo y haloalquilo, donde los dos sustituyentes juntos forman C_3-C_6-cicloalquilo o halo-C_3-C_6-cicloalquilo.

[354] R^1 y R^2 se seleccionan independientemente del grupo formado por -H y alquilo. El alquilo es optativamente sustituido. Ni R^1 ni R^2 forman una estructura de anillo con E^5.

[355] En algunas realizaciones preferidas, R^1 y R^2 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, y halo-C_1-C_6-alquilo.

817

[356] En algunas realizaciones preferidas, R^1 y R^2 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, y halo-C_1-C_6-alquilo.

[357] En algunas realizaciones preferidas, R^1 y R^2 se seleccionan independientemente del grupo formado por -H y C_1-C_6-alquilo.

[358] R^5 y R^6 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[359] En algunas realizaciones preferidas, R^5 y R^6 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[360] R^7 es -H, C_1-C_6-alquilo, -O-R^8, -N(R^8)(R^9), carbociclil-C_1-C_6-alquilo, o heterociclil-C_1-C_6-alquilo. El C_1-C_6-alquilo, carbociclil-C_1-C_6-alquilo, o heterociclil-C_1-C_6-alquilo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

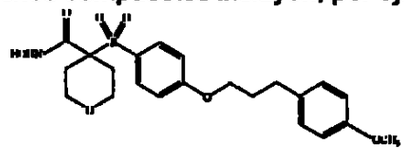
[361] En algunas realizaciones preferidas, R^7 es -H, C_1-C_6-alquilo, -O-R^8, -N(R^8)(R^9), carbociclil-C_1-C_6-alquilo, o heterociclil-C_1-C_6-alquilo. El C_1-C_6-alquilo, carbociclil-C_1-C_6-alquilo, o heterociclil-C_1-C_6-alquilo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[362] R^8 y R^9 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

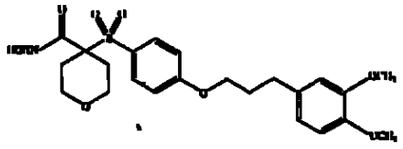
[363] En algunas realizaciones preferidas, R^8 y R^9 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[364] En algunas realizaciones preferidas, E^5 es un carbociclilo de anillo único sustituido. E^5 puede ser, por ejemplo un carbociclilo de anillo único sustituido seleccionado del grupo formado por ciclopropilo, ciclobutilo, ciclopentilo, ciclopentenilo, ciclopentadienilo, ciclohexilo, ciclohexenilo, ciclohexadienilo, y fenilo.

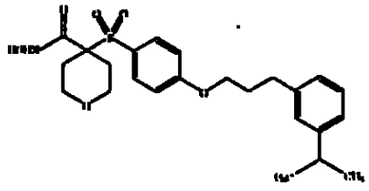
[365] En algunas realizaciones preferidas, E^5 es sustituido fenilo. Dichos compuestos incluyen, por ejemplo:



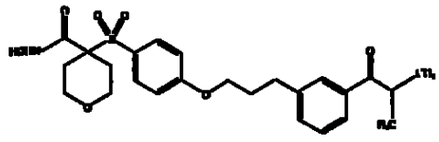
VIII-1



VIII-2

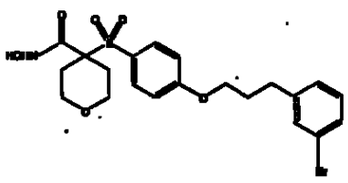


VIII-3

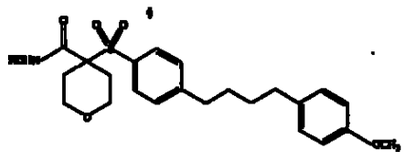


VIII-4

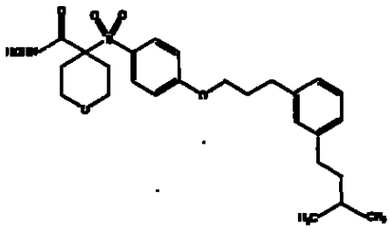
819



VIII-5

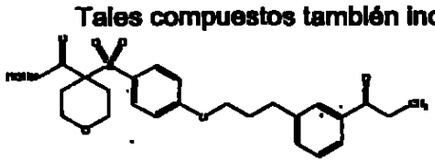


VIII-6

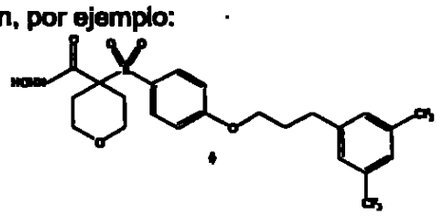


VIII-7

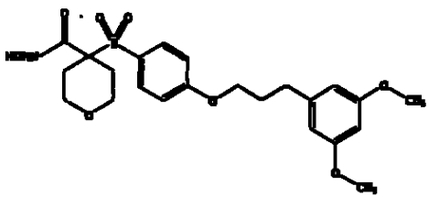
Tales compuestos también incluyen, por ejemplo:



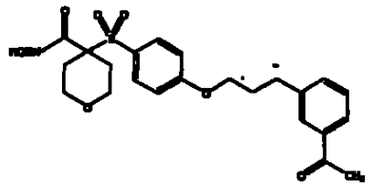
VIII-8



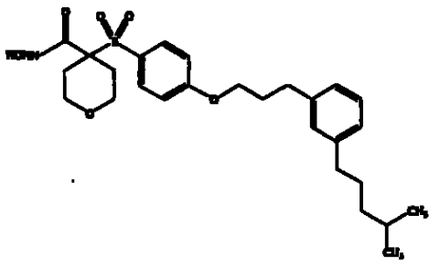
VIII-9



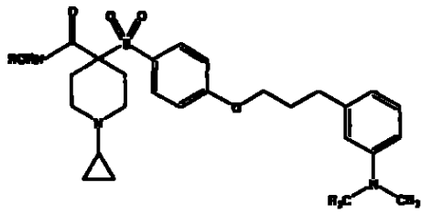
VIII-10



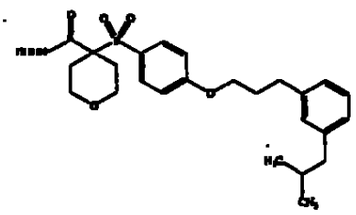
VIII-11



VIII-12



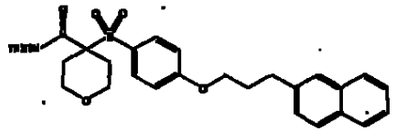
VIII-13



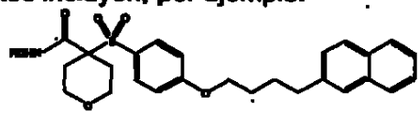
VIII-14

[366] En algunas realizaciones preferidas, E^5 es carbociclilo de anillos fusionados optativamente sustituido. E^5 puede ser, por ejemplo, carbociclilo de anillos fusionados optativamente sustituido seleccionado del grupo formado por naftalenilo, tetrahidronaftalenilo, indenilo, isoindenilo, indanilo, biciclodecanilo, antracenilo, fenantreno, benzonaftenilo, fluoreneilo, decalinilo, y norpinanilo.

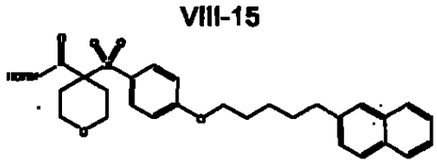
[367] En algunas realizaciones preferidas, E^5 es naftalenilo optativamente sustituido. Dichos compuestos incluyen, por ejemplo:



VIII-15



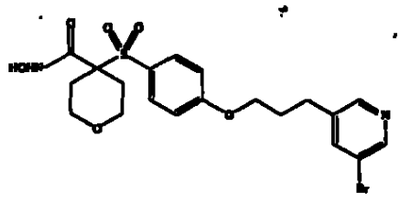
VIII-16



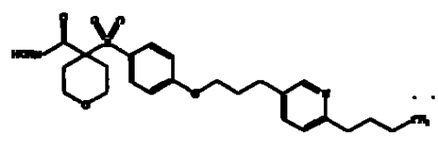
VIII-17

[368] En algunas realizaciones preferidas, E^5 es heterociclilo de un solo anillo optativamente sustituido.

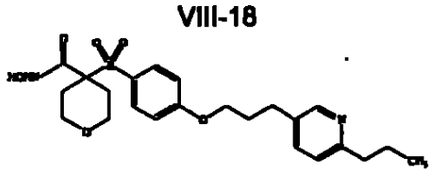
[369] En algunas realizaciones preferidas, E^5 es un piridinilo optativamente sustituido. Dichos compuestos incluyen, por ejemplo:



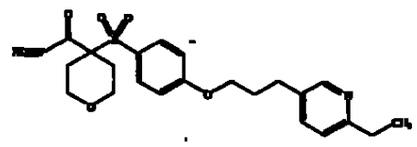
VIII-18



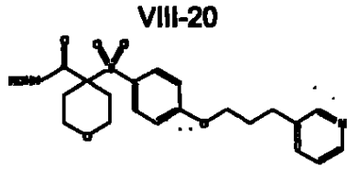
VIII-19



VIII-20

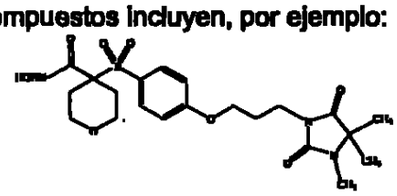


VIII-21

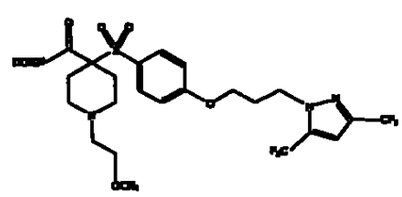


VIII-22

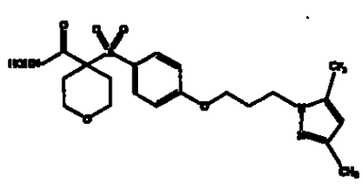
[370] En algunas realizaciones preferidas, E^5 es un heterociclo optativamente sustituido seleccionado del grupo formado por imidazolilo, imidazolinilo, imidazolidinilo, pirazolilo, pirazolinilo, y pirazolidinilo. Dichos compuestos incluyen, por ejemplo:



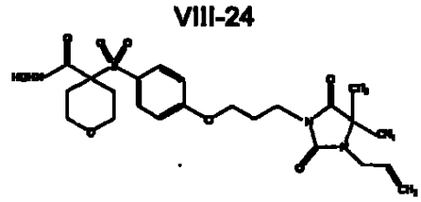
VIII-23



VIII-24



VIII-25

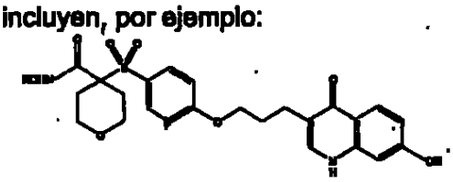


VIII-26

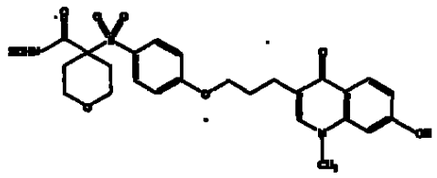
[371] En algunas realizaciones preferidas, E^5 es heterociclilo de anillos fusionados optativamente sustituido. E^5 puede ser, por ejemplo, un

822

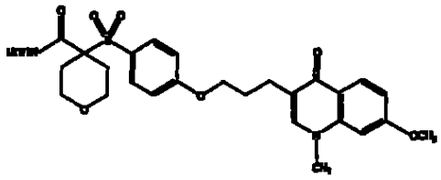
heterociclilo de anillos fusionados optativamente sustituido seleccionado del grupo formado por indolizinilo, pirindinilo, piranopirrolilo, 4H-quinolizinilo, purinilo, naftiridinilo, piridopiridinilo, pteridinilo, indolilo, isoindolilo, indoleninilo, isoindazolilo, benzazinilo, ftalazinilo, quinoxalinilo, quinazolinilo, benzodiazinilo, benzopiranilo, benzotiopiranilo, benzoxazolilo, indoxazinilo, antranililo, benzodioxolilo, benzodioxanilo, benzoxadiazolilo, benzofuranilo, isobenzofuranilo, benzotienilo, isobenzotienilo, benzotiazolilo, benzotiadiazolilo, bencimidazolilo, benzotriazolilo, benzoxazinilo, bencisoxazinilo, tetrahidroisoquinolinilo , carbazolilo, xantenilo, y acridinilo. Los compuestos donde E^5 es un heterociclilo de anillos fusionados optativamente sustituido incluyen, por ejemplo:



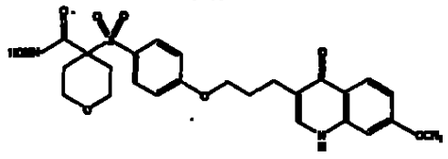
VIII-27



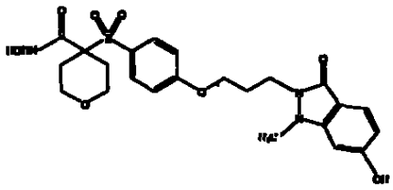
VIII-28



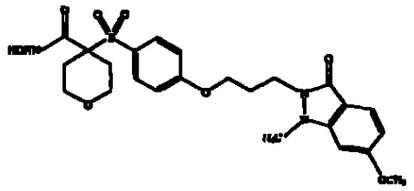
VIII-29



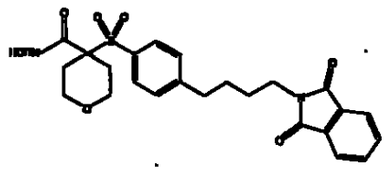
VIII-30



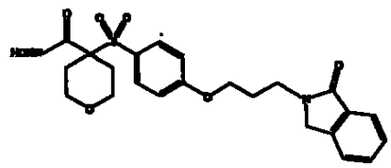
VIII-31



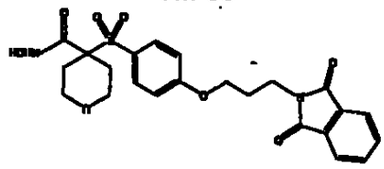
VIII-32



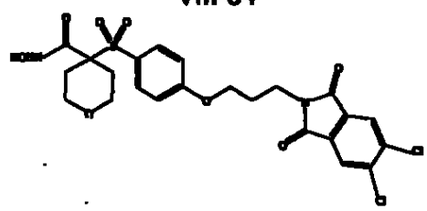
VIII-33



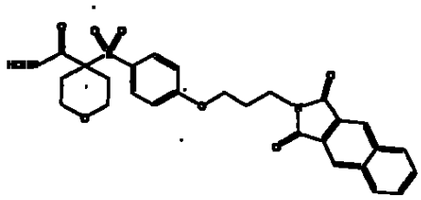
VIII-34



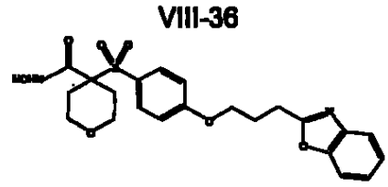
VIII-35



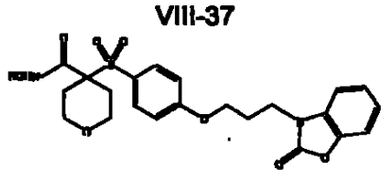
VIII-36



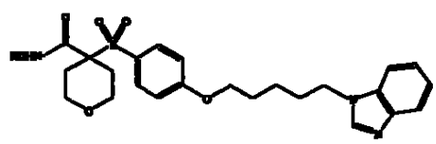
VIII-37



VIII-38

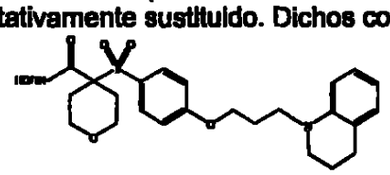


VIII-39

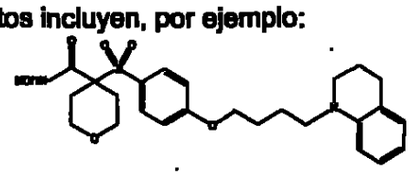


VIII-40

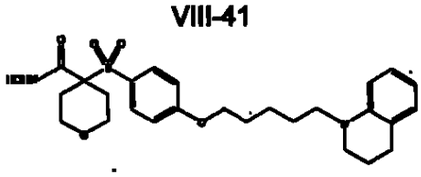
[372] En algunas realizaciones preferidas, E^5 es tetrahidroisoquinolinilo optativamente sustituido. Dichos compuestos incluyen, por ejemplo:



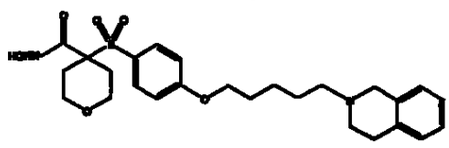
VIII-41



VIII-42

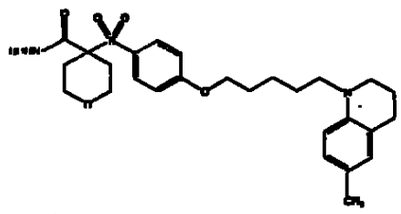


VIII-43

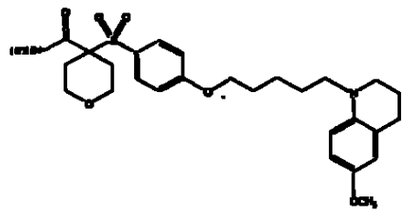


VIII-44

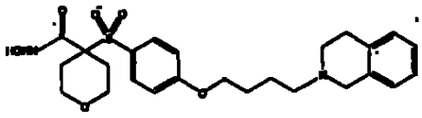
824



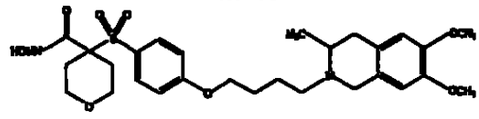
VIII-45



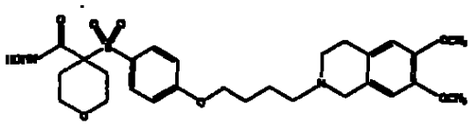
VIII-46



VIII-47



VIII-48

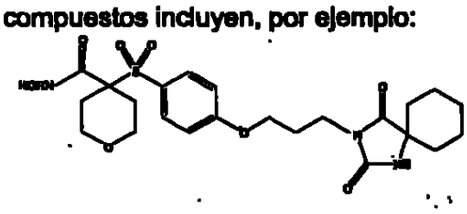


VIII-49

[373] En algunas realizaciones preferidas, E^5 es heterociclilo que es sustituido en el mismo átomo con dos sustituyentes seleccionados independientemente del grupo formado por alquilo y haloalquilo, donde los dos sustituyentes juntos forman C_5-C_8-cicloalquilo o halo-C_5-C_8-cicloalquilo. Este heterociclilo también es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, ceto, C_1-C_8-alquilo, halo-C_1-C_8-alquilo, C_1-C_8-alcoxi, halo-C_1-C_8-alcoxi, C_1-C_8-alcoxi-C_1-C_8-alquilo, C_1-C_8-alcoxi-C_1-C_8-alquilo sustituido con halógeno, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbociclilo, halocarbociclilo, carbociclil-C_1-C_8-alquilo, y carbociclil-C_1-C_8-alquilo sustituido con halógeno. El heterociclilo que es sustituido puede ser, por ejemplo, seleccionado del grupo formado por dihidrofuranilo, tetrahidrofuranilo, dihidrotiofenilo, tetrahidrotiofenilo, pirrolinilo, pirrolidinilo, imidazolinilo, imidazolidinilo,

825

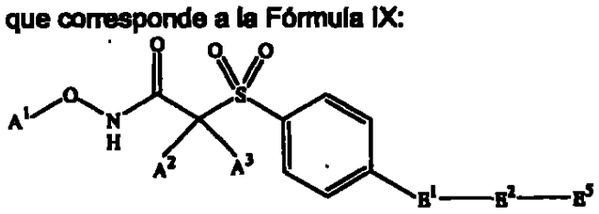
pirazolinilo, pirazolidinilo, ditiolilo, oxatiolilo, tiazolinilo, isotiazolinilo, tiazolidinilo, isotiazolidinilo, oxatiolanilo, piranilo, dihidropiranilo, piperidinilo, piperazinilo, y morfolinilo. Dichos compuestos incluyen, por ejemplo:



VIII-50

Realización preferida Nro. 8

[374] En algunas realizaciones de esta invención, el compuesto tiene una estructura que corresponde a la Fórmula IX:



IX

[375] A^1, A^2, y A^3 tienen los valores definidos anteriormente para la Fórmula I.

[376] E^1 es -O-, -$S(O)_2$-, -S(O)-, -$N(R^1)$-, -C(O)-$N(R^1)$-, -$N(R^1)$-C(O)-, o -$C(R^1)(R^2)$-.

[377] E^2 forma un enlace de al menos 4 átomos de carbono entre E^1 y E^3. E^2 es alquilo, cicloalquilo, alquilcicloalquilo, cicloalquilalquilo, o alquilcicloalquilalquilo. Cualquier miembro de este grupo es optativamente sustituido.

[378] En algunas realizaciones preferidas, E^2 es C_4-C_{20}-alquilo, cicloalquilo, C_1-C_{10}-alquil-cicloalquilo, cicloalquil-C_1-C_{10}-alquilo, o C_1-C_{10}-alquil-cicloalquil-C_1-C_{10}-alquilo. Cualquier miembro de este grupo es optativamente

826

sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, C_1-C_6-alquilo, y halo-C_1-C_6-alquilo.

[379] En algunas realizaciones preferidas, E^2 es C_4-C_6-alquilo optativamente sustituido con uno o más halógenos.

[380] En algunas realizaciones preferidas, E^2 es C_4-C_6-alquilo.

[381] E^5 es -OH o carbociclilo optativamente sustituido.

[382] En algunas realizaciones preferidas, E^5 es -OH o carbociclilo donde el carbociclilo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, ceto, C_1-C_6-alquilo, halo-C_1-C_6-alquilo, C_1-C_6-alcoxi, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno , -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbociclilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo, y carbociclil-C_1-C_6-alquilo sustituido con halógeno. El carbociclilo también es optativamente sustituido con dos grupos C_1-C_6-alquilo o halo-C_1-C_6-alquilo en el mismo átomo que forman un C_5-C_6-cicloalquilo o C_3-C_6-halocicloalquilo.

[383] En algunas realizaciones preferidas, E^5 es -OH o carbociclilo donde el carbociclilo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, ceto, C_1-C_6-alquilo, halo-C_1-C_6-alquilo, C_1-C_6-alcoxi, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbociclilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo, y carbociclil-C_1-C_6-alquilo sustituido con halógeno.

[384] R^1 y R^2 se seleccionan independientemente del grupo formado por -H y alquilo. El alquilo es optativamente sustituido. Ni R^1 ni R^2 forman una estructura de anillo con E^5.

[385] En algunas realizaciones preferidas, R^1 y R^2 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, y halo-C_1-C_6-alquilo.

[386] En algunas realizaciones preferidas, R^1 y R^2 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, y halo-C_1-C_6-alquilo.

[387] En algunas realizaciones preferidas, R^1 y R^2 se seleccionan independientemente del grupo formado por -H y C_1-C_6-alquilo.

[388] R^5 y R^6 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[389] En algunas realizaciones preferidas, R^5 y R^6 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[390] R^7 es -H, C_1-C_6-alquilo, -O-R^8, -N(R^8)(R^9), carbociclil-C_1-C_6-alquilo, o heterociclil-C_1-C_6-alquilo. El C_1-C_6-alquilo, carbociclil-C_1-C_6-alquilo, o heterociclil-C_1-C_6-alquilo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

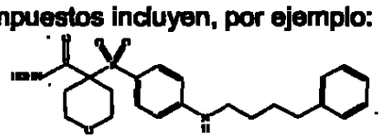
[391] En algunas realizaciones preferidas, R^7 es -H, C_1-C_6-alquilo, -O-R^8, -N(R^8)(R^9), carbociclil-C_1-C_6-alquilo, o heterociclil-C_1-C_6-alquilo. El C_1-C_6-alquilo, carbociclil-C_1-C_6-alquilo, o heterociclil-C_1-C_6-alquilo puede ser

sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

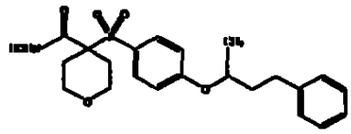
[392] R^8 y R^9 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[393] En algunas realizaciones preferidas, R^8 y R^9 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno. Dichos compuestos incluyen, por ejemplo:

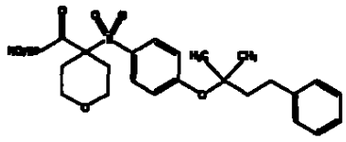
[394] En algunas realizaciones preferidas, E^5 es carbociclilo optativamente sustituido, generalmente preferentemente arilo optativamente sustituido, y más preferentemente fenilo optativamente sustituido. Dichos compuestos incluyen, por ejemplo:



IX-1

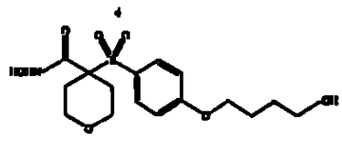


IX-2

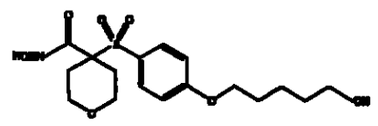


IX-3

[395] En algunas realizaciones preferidas, E^5 es -OH. Dichos compuestos incluyen, por ejemplo:



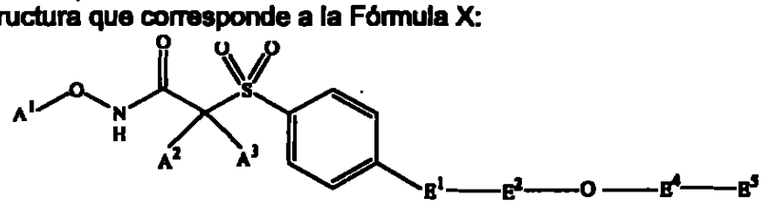
IX-4



IX-5

Realización preferida Nro. 9 .

[396] En algunas realizaciones de esta invención, el compuesto tiene una estructura que corresponde a la Fórmula X:



X

[397] A^1, A^2, y A^3 tienen los valores definidos anteriormente para la Fórmula I.

[398] E^1 es $-S(O)_2-$, $-S(O)-$, $-N(R^1)-$, $-C(O)-N(R^1)-$, $-N(R^1)-C(O)-$, o $-C(R^1)(R^2)-$.

[399] E^2 es alquilo, cicloalquilo, alquilcicloalquilo, cicloalquilalquilo, o alquilcicloalquilalquilo. Cualquier miembro de este grupo es optativamente sustituido.

[400] En algunas realizaciones preferidas, E^2 es C_1-C_{20}-alquilo, cicloalquilo, C_1-C_{10}-alquilcicloalquilo, cicloalquil-C_1-C_{10}-alquilo, o C_1-C_{10}-alquilcicloalquil-C_1-C_{10}-alquilo. Cualquier miembro de este grupo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, C_1-C_6-alquilo, C_1-C_6-halo-alquilo.

[401] En algunas realizaciones preferidas, E^2 es C_2-C_6-alquilo optativamente sustituido con uno o más halógenos.

[402] En algunas realizaciones preferidas, E^2 es C_2-C_6-alquilo.

[403] E^4 es un enlace, alquilo, o alquenilo. El alquilo y alquenilo son optativamente sustituidos.

[404] En algunas realizaciones preferidas, E^4 es un enlace, C_1-C_{20}-alquilo, halo-C_1-C_{20}-alquilo, C_2-C_{20}-alquenilo, o halo-C_2-C_{20}-alquenilo.

[405] En algunas realizaciones preferidas, E^4 es un enlace, C_1-C_3-alquilo, halo-C_1-C_3-alquilo, C_2-C_3-alquenilo, o halo-C_2-C_3-alquenilo.

[406] En algunas realizaciones preferidas, E^4 es un enlace, C_1-C_3-alquilo, o C_2-C_3-alquenilo.

[407] E^5 es alquilo, alquenilo, alquinilo, alcoxi, alcoxialquilo, carbociclilo, o heterociclilo. Cualquier miembro de este grupo es optativamente sustituido.

[408] En algunas realizaciones preferidas, E^5 es C_1-C_{20}-alquilo, C_2-C_{20}-alquenilo, C_2-C_{20}-alquinilo, C_1-C_{20}-alcoxi, C_1-C_{20}-alcoxi-C_1-C_{20}-alquilo, carbociclilo, o heterociclilo. El C_1-C_{20}-alquilo, C_2-C_{20}-alquenilo, C_2-C_{20}-alquinilo, C_1-C_{20}-alcoxi, y C_1-C_{20}-alcoxi-C_1-C_{20}-alquilo son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, y -CN. El carbociclilo y heterociclilo son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, ceto, C_1-C_8-alquilo, halo-C_1-C_8-alquilo, C_1-C_8-alcoxi, halo-C_1-C_8-alcoxi, C_1-C_8-alcoxi-C_1-C_8-alquilo, C_1-C_8-alcoxi-C_1-C_8-alquilo sustituido con halógeno , -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbociclilo, halocarbociclilo, carbociclil-C_1-C_8-alquilo, y carbociclil-C_1-C_8-alquilo sustituido con halógeno.

[409] En algunas realizaciones preferidas, E^5 es C_1-C_8-alquilo, C_2-C_8-alquenilo, C_2-C_8-alquinilo, C_1-C_8-alcoxi, C_1-C_8-alcoxi-C_1-C_8-alquilo, carbociclilo,

o heterociclilo. El C_1-C_6-alquilo, C_2-C_6-alquenilo, C_2-C_6-alquinilo, C_1-C_6-alcoxi, y C_1-C_6-alcoxi-C_1-C_6-alquilo son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, y -CN. El carbociclilo y heterociclilo son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, -CN, ceto, C_1-C_6-alquilo, halo-C_1-C_6-alquilo, C_1-C_6-alcoxi, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbociclilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo, y carbociclil-C_1-C_6-alquilo sustituido con halógeno.

[410] R^1 y R^2 se seleccionan independientemente del grupo formado por -H y alquilo. El alquilo es optativamente sustituido. Ni R^1 ni R^2 forman una estructura de anillo con E^2, E^4, o E^5.

[411] En algunas realizaciones preferidas, R^1 y R^2 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, y halo-C_1-C_6-alquilo.

[412] En algunas realizaciones preferidas, R^1 y R^2 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, y halo-C_1-C_6-alquilo.

[413] En algunas realizaciones preferidas, R^1 y R^2 se seleccionan independientemente del grupo formado por -H y C_1-C_6-alquilo.

[414] R^5 y R^6 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[415] En algunas realizaciones preferidas, R^5 y R^6 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[416] R^7 es -H, C_1-C_6-alquilo, -O-R^8, -N(R^8)(R^9), carbociclil-C_1-C_6-alquilo, o heterociclil-C_1-C_6-alquilo. El C_1-C_6-alquilo, carbociclil-C_1-C_6-alquilo, o heterociclil-C_1-C_6-alquilo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

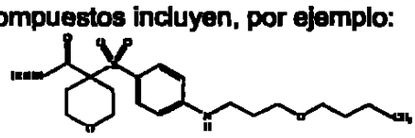
[417] En algunas realizaciones preferidas, R^7 es -H, C_1-C_6-alquilo, -O-R^8, -N(R^8)(R^9), carbociclil-C_1-C_6-alquilo, o heterociclil-C_1-C_6-alquilo. El C_1-C_6-alquilo, carbociclil-C_1-C_6-alquilo, o heterociclil-C_1-C_6-alquilo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[418] R^8 y R^9 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

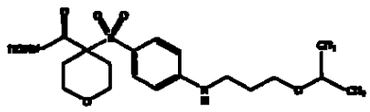
[419] En algunas realizaciones preferidas, R^8 y R^9 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[420] En algunas realizaciones preferidas, E^5 es C_1-C_8-alquilo, C_2-C_8-alquenilo, C_2-C_8-alquinilo, C_1-C_8-alcoxi, o C_1-C_8-alcoxi-C_1-C_8-alquilo. El C_1-C_8-alquilo, C_2-C_8-alquenilo, C_2-C_8-alquinilo, C_1-C_8-alcoxi, y C_1-C_8-alcoxi-C_1-C_8-alquilo son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, y -CN.

[421] En algunas realizaciones preferidas, E^5 es C_1-C_8-alquilo. Dichos compuestos incluyen, por ejemplo:



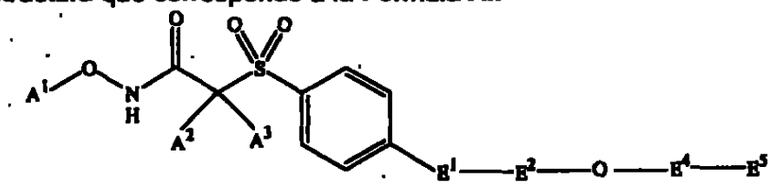
X-1



X-2

Realización preferida Nro. 10

[422] En algunas realizaciones de esta invención, el compuesto tiene una estructura que corresponde a la Fórmula XI:



XI

[423] A^1, A^2, y A^3 tienen los valores definidos anteriormente para la Fórmula I.

[424] E^2 comprende al menos 3 átomos de carbono. E^2 es alquilo, cicloalquilo, alquilcicloalquilo, cicloalquilalquilo, o alquilcicloalquilalquilo. Cualquier miembro de este grupo es optativamente sustituido.

[425] En algunas realizaciones preferidas, E^2 es C_3-C_{20}-alquilo, cicloalquilo, C_1-C_{10}-alquilcicloalquilo, cicloalquil-C_1-C_{10}-alquilo, o C_1-C_{10}-alquilcicloalquil-C_1-C_{10}-alquilo. Cualquier miembro de este grupo es

optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, C_1-C_6-alquilo, y halo-C_1-C_6-alquilo.

[426] En algunas realizaciones preferidas, E^2 es C_3-C_{10}-alquilo es optativamente sustituido con uno o más halógenos.

[427] En algunas realizaciones preferidas, E^2 es C_3-C_{10}-alquilo.

[428] En algunas realizaciones preferidas, E^2 es C_3-C_5-alquilo.

[429] E^5 es -H, alquilo, alquenilo, alquinilo, alcoxialquilo, carbociclilo, carbociclilalcoxialquilo, heterociclilo, heterociclilalquilo, o heterociclilalcoxialquilo. El alquilo, alquenilo, alquinilo, y alcoxialquilo son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, y -CN. El carbociclilo, carbociclilalcoxialquilo, heterociclilo, heterociclilalquilo, y heterociclilalcoxialquilo son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, -CN, alquilo, haloalquilo, alcoxi, haloalcoxi, alcoxialquilo, alcoxialquilo sustituido con halógeno, $-N(R^3)(R^4)$, $-C(O)(R^5)$, $-S-R^3$, $-S(O)_2-R^3$, carbociclilo, halocarbociclilo, carbociclilalquilo, y carbociclilalquilo sustituido con halógeno.

[430] En algunas realizaciones preferidas, E^5 es -H, C_1-C_{20}-alquilo, C_2-C_{20}-alquenilo, C_2-C_{20}-alquinilo, C_1-C_{20}-alcoxi-C_1-C_{20}-alquilo, carbociclilo, carbociclil-C_1-C_{10}-alcoxi-C_1-C_{10}-alquilo, heterociclilo, heterociclil-C_1-C_{10}-alquilo, o heterociclil-C_1-C_{10}-alcoxi-C_1-C_{10}-alquilo. El C_1-C_{20}-alquilo, C_2-C_{20}-alquenilo, C_2-C_{20}-alquinilo, y C_1-C_{20}-alcoxi-C_1-C_{20}-alquilo son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, y -CN. El carbociclilo, carbociclil-C_1-C_{10}-

835

alcoxi-C_1-C_{10}-alquilo, heterociclilo, heterociclil-C_1-C_{10}-alquilo, y heterociclil-C_1-C_{10}-alcoxi-C_1-C_{10}-alquilo son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, ceto, C_1-C_8-alquilo, halo-C_1-C_8-alquilo, C_1-C_8-alcoxi, halo-C_1-C_8-alcoxi, C_1-C_8-alcoxi-C_1-C_8-alquilo, C_1-C_8-alcoxi-C_1-C_8-alquilo sustituido con halógeno , -$N(R^3)(R^4)$, -$C(O)(R^5)$, -S-R^3, -$S(O)_2$-R^3, carbociclilo, halocarbociclilo, carbociclil-C_1-C_8-alquilo, y carbociclil-C_1-C_8-alquilo sustituido con halógeno.

[431] En algunas realizaciones preferidas, E^5 es -H, C_1-C_8-alquilo, C_2-C_8-alquenilo, C_2-C_8-alquinilo, C_1-C_8-alcoxi-C_1-C_8-alquilo, carbociclilo, carbociclil-C_1-C_8-alcoxi-C_1-C_8-alquilo, heterociclilo, heterociclil-C_1-C_8-alquilo, o heterociclil-C_1-C_8-alcoxi-C_1-C_8-alquilo. El C_1-C_8-alquilo, C_2-C_8-alquenilo, C_2-C_8-alquinilo, y C_1-C_8-alcoxi-C_1-C_8-alquilo son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, y -CN. El carbociclilo, carbociclil-C_1-C_8-alcoxi-C_1-C_8-alquilo, heterociclilo, heterociclil-C_1-C_8-alquilo, y heterociclil-C_1-C_8-alcoxi-C_1-C_8-alquilo son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, ceto, C_1-C_8-alquilo, halo-C_1-C_8-alquilo, C_1-C_8-alcoxi, halo-C_1-C_8-alcoxi, C_1-C_8-alcoxi-C_1-C_8-alquilo, C_1-C_8-alcoxi-C_1-C_8-alquilo sustituido con halógeno, -$N(R^3)(R^4)$, -$C(O)(R^5)$, -S-R^3, -$S(O)_2$-R^3, carbociclilo, halocarbociclilo, carbociclil-C_1-C_8-alquilo, y carbociclil-C_1-C_8-alquilo sustituido con halógeno.

[432] R^1 y R^2 se seleccionan independientemente del grupo formado por -H, alquilo, carbociclilo, carbociclilalquilo, heterociclilo, y heterociclilalquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo puede ser

sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[433] En algunas realizaciones preferidas, R^1 y R^2 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[434] En algunas realizaciones preferidas, R^1 y R^2 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[435] R^3 es -H, alquilo, -O-R^4, -N(R^4)(R^5), carbociclilalquilo, o heterociclilalquilo. El alquilo, carbociclilalquilo, o heterociclilalquilo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[436] En algunas realizaciones preferidas, R^3 es -H, C_1-C_6-alquilo, -O-R^4, -N(R^4)(R^5), carbociclil-C_1-C_6-alquilo, o heterociclil-C_1-C_6-alquilo. El C_1-C_6-alquilo, carbociclil-C_1-C_6-alquilo, o heterociclil-C_1-C_6-alquilo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[437] En algunas realizaciones preferidas, R^3 es -H, C_1-C_6-alquilo, -O-R^4, -N(R^4)(R^5), carbociclil-C_1-C_6-alquilo, o heterociclil-C_1-C_6-alquilo. El C_1-C_6-alquilo, carbociclil-C_1-C_6-alquilo, o heterociclil-C_1-C_6-alquilo puede ser

837

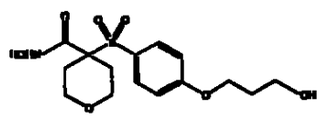
sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[438] R^4 y R^5 se seleccionan independientemente del grupo formado por -H, alquilo, carbociclilo, carbociclilalquilo, heterociclilo, y heterociclilalquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

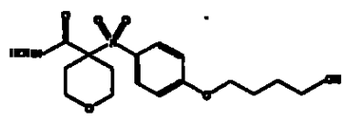
[439] En algunas realizaciones preferidas, R^4 y R^5 se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, carbociclilo, carbociclil-C_1-C_8-alquilo, heterociclilo, y heterociclil-C_1-C_8-alquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[440] En algunas realizaciones preferidas, R^4 y R^5 se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, carbociclilo, carbociclil-C_1-C_8-alquilo, heterociclilo, y heterociclil-C_1-C_8-alquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

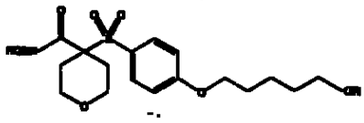
[441] En algunas realizaciones preferidas, E^5 es -H, C_1-C_8-alquilo, C_2-C_8-alquenilo, C_2-C_8-alquinilo, o C_1-C_8-alcoxi-C_1-C_8-alquilo. El C_1-C_8-alquilo, C_2-C_8-alquenilo, C_2-C_8-alquinilo, y C_1-C_8-alcoxi-C_1-C_8-alquilo son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, y -CN. Dichos compuestos incluyen, por ejemplo:



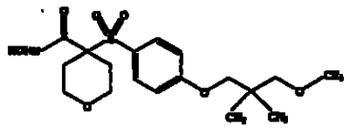
XI-1



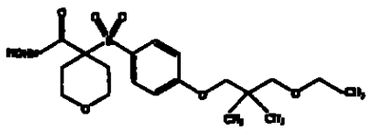
XI-2



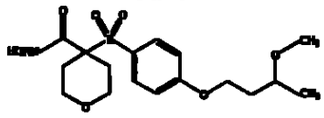
XI-3



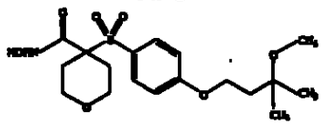
XI-4



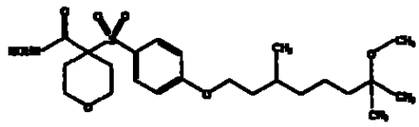
XI-5



XI-6



XI-7



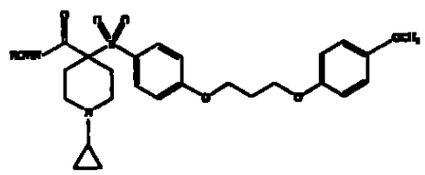
XI-8

[442] En algunas realizaciones preferidas, E^5 es carbociclilo, carbociclil-C_1-C_8-alcoxi-C_1-C_8-alquilo, heterociclilo, heterociclil-C_1-C_8-alquilo, o heterociclil-C_1-C_8-alcoxi-C_1-C_8-alquilo. el carbociclilo, carbociclil-C_1-C_8-alcoxi-C_1-C_8-alquilo, heterociclilo, heterociclil-C_1-C_8-alquilo, y heterociclil-C_1-C_8-alcoxi-C_1-C_8-alquilo son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, ceto, C_1-C_8-alquilo, halo-C_1-C_8-alquilo, C_1-C_8-alcoxi, halo-C_1-C_8-alcoxi, C_1-C_8-alcoxi-C_1-C_8-alquilo, C_1-C_8-alcoxi-C_1-C_8-alquilo sustituido con halógeno, -$N(R^3)(R^4)$, -$C(O)(R^5)$, -S-R^3, -$S(O)_2$-R^3, carbociclilo, halocarbociclilo, carbociclil-C_1-C_8-alquilo, y carbociclil-C_1-C_8-alquilo sustituido con halógeno.

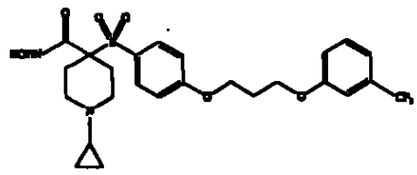
[443] En algunas realizaciones preferidas, E^5 es carbociclilo optativamente sustituido.

[444] En algunas realizaciones preferidas, E^5 es fenilo optativamente sustituido. Dichos compuestos incluyen, por ejemplo:

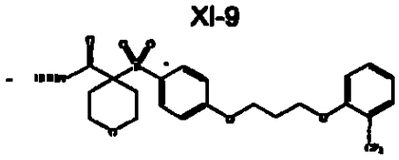
839



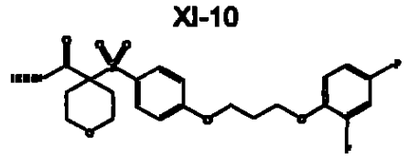
XI-9



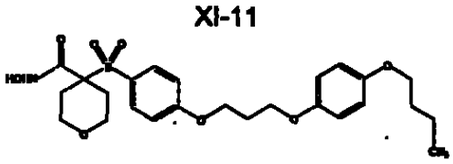
XI-10



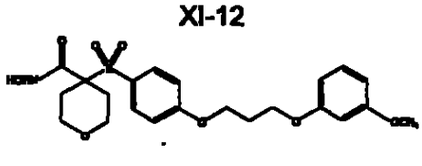
XI-11



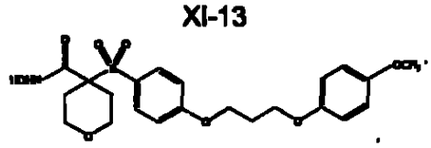
XI-12



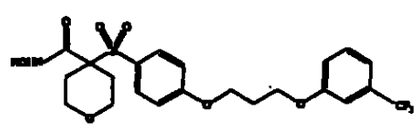
XI-13



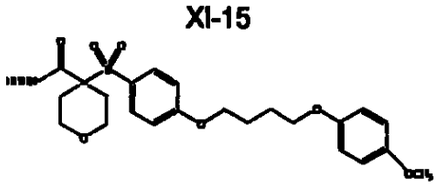
XI-14



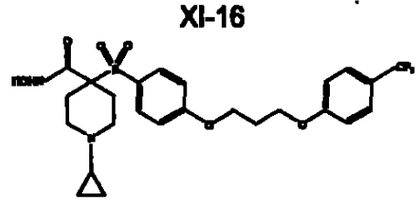
XI-15



XI-16

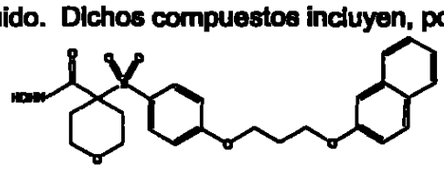


XI-17



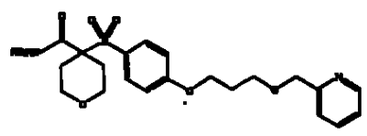
XI-18

[445] En algunas realizaciones preferidas, E^5 es naftalenilo optativamente sustituido. Dichos compuestos incluyen, por ejemplo:

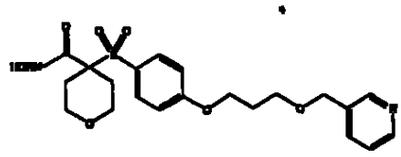


XI-19

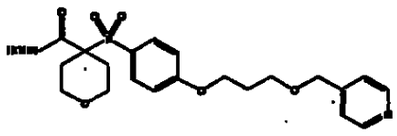
[446] En algunas realizaciones preferidas, E^5 es heterociclilo o heterociclil-C_1-C_6-alquilo. Dichos compuestos incluyen, por ejemplo:



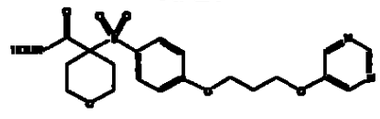
XI-20



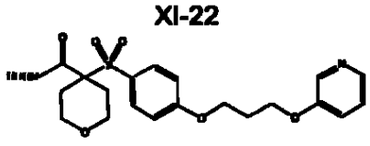
XI-21



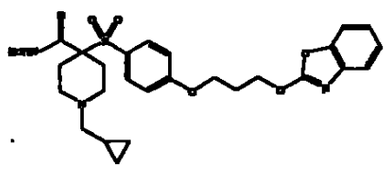
XI-22



XI-23



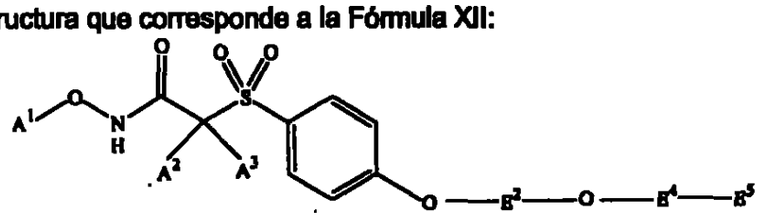
XI-24



XI-24

Realización preferida Nro. 11

[447] En algunas realizaciones de esta invención, el compuesto tiene una estructura que corresponde a la Fórmula XII:



XII

[448] A^1, A^2, y A^3 tienen los valores definidos anteriormente para la Fórmula I.

[449] E^2 es alquilo, cicloalquilo, alquilcicloalquilo, cicloalquilalquilo, o alquilcicloalquilalquilo. Cualquier miembro de este grupo es optativamente sustituido. Un átomo en E^2 optativamente está unido a un átomo en E^5 para formar un anillo.

[450] En algunas realizaciones preferidas, E^2 es C_1-C_{20}-alquilo, cicloalquilo, C_1-C_{10}-alquilcicloalquilo, cicloalquil-C_1-C_{10}-alquilo, o C_1-C_{10}-

941

alquilcicloalquil-C_1-C_{10}-alquilo. Cualquier miembro de este grupo es optativamente sustituido con uno o más sustituyentes seleccionados del grupo formado por halógeno, C_1-C_6-alquilo, halo-C_1-C_6-alquilo.

[451] En algunas realizaciones preferidas, E^2 es C_2-C_6-alquilo optativamente sustituido con uno o más halógenos.

[452] En algunas realizaciones preferidas, E^2 es C_2-C_6-alquilo.

[453] E^4 es un enlace, alquilo, o alquenilo. El alquilo y alquenilo son optativamente sustituidos.

[454] En algunas realizaciones preferidas, E^4 es un enlace, C_1-C_{20}-alquilo, halo-C_1-C_{20}-alquilo, C_2-C_{20}-alquenilo, o halo-C_2-C_{20}-alquenilo.

[455] En algunas realizaciones preferidas, E^4 es un enlace, C_1-C_3-alquilo, halo-C_1-C_3-alquilo, C_2-C_3-alquenilo, o halo-C_2-C_3-alquenilo.

[456] En algunas realizaciones preferidas, E^4 es un enlace, C_1-C_3-alquilo, o C_2-C_3-alquenilo.

[457] En algunas realizaciones preferidas, E^4 es metilo.

[458] En algunas realizaciones preferidas, E^4 es un enlace.

[459] E^5 es:

un radical optativamente sustituido seleccionado del grupo formado por alquenilo, alquinilo, alcoxi, alcoxialquilo, carbociclilo de anillos fusionados, y heterociclilo; o

carbociclilo de anillo único sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por -OH, -NO_2, -CN, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbociclilo, halocarbociclilo, carbociclilalquilo, carbociclilalquilo sustituido con halógeno, heterociclilo, haloheterociclilo, heterociclilalquilo, y heterociclilalquilo sustituido con halógeno; o

842

carbociclilo de anillo único con sustituciones múltiples.

[460] En algunas realizaciones preferidas, E^5 es C_2-C_{20}-alquenilo, C_2-C_{20}-alquinilo, C_1-C_{20}-alcoxi, C_1-C_{20}-alcoxi-C_1-C_{20}-alquilo, heterociclilo, carbociclilo de un solo anillo, o carbociclilo de anillos fusionados. El C_2-C_{20}-alquenilo, C_2-C_{20}-alquinilo, C_1-C_{20}-alcoxi, y C_1-C_{20}-alcoxi-C_1-C_{20}-alquilo son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, y -CN. El heterociclilo y carbociclilo de anillos fusionados son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, -CN, C_1-C_8-alquilo, halo-C_1-C_8-alquilo, C_1-C_8-alcoxi, halo-C_1-C_8-alcoxi, C_1-C_8-alcoxi-C_1-C_8-alquilo, C_1-C_8-alcoxi-C_1-C_8-alquilo sustituido con halógeno , $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbociclilo, halocarbociclilo, carbociclil-C_1-C_8-alquilo, carbociclil-C_1-C_8-alquilo sustituido con halógeno, heterociclilo, haloheterociclilo, heterociclil-C_1-C_8-alquilo, y heterociclil-C_1-C_8-alquilo sustituido con halógeno. El carbociclilo de anillo único es ya sea:

sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por -OH, $-NO_2$, -CN, $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbociclilo, halocarbociclilo, carbociclil-C_1-C_8-alquilo, carbociclil-C_1-C_8-alquilo sustituido con halógeno, heterociclilo, haloheterociclilo, heterociclil-C_1-C_8-alquilo, y heterociclil-C_1-C_8-alquilo sustituido con halógeno, o

sustituido con 2 ó más sustituyentes seleccionados independientemente del grupo formado por halógeno, -OH, $-NO_2$, -CN, C_1-C_8-alquilo, halo-C_1-C_8-alquilo, C_1-C_8-alcoxi, halo-C_1-C_8-alcoxi, C_1-C_8-alcoxi-C_1-C_8-alquilo, C_1-C_8-alcoxi-C_1-C_8-alquilo sustituido con halógeno

843

, -N(R^5)(R^6), -C(O)(R^7), -S-R^5, -S(O)$_2$-R^5, carbociclilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo, carbociclil-C_1-C_6-alquilo sustituido con halógeno, heterociclilo, haloheterociclilo, heterociclil-C_1-C_6-alquilo, y heterociclil-C_1-C_6-alquilo sustituido con halógeno.

[461] En algunas realizaciones preferidas, E^5 es C_2-C_6-alquenilo, C_2-C_6-alquinilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_2-C_6-alquilo, heterociclilo, carbociclilo de un solo anillo, o carbociclilo de anillos fusionados. El C_2-C_6-alquenilo, C_2-C_6-alquinilo, C_1-C_6-alcoxi, y C_1-C_6-alcoxi-C_1-C_6-alquilo son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, y -CN. El heterociclilo y carbociclilo de anillos fusionados son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_6-alquilo, halo-C_1-C_6-alquilo, C_1-C_6-alcoxi, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, -N(R^5)(R^6), -C(O)(R^7), -S-R^5, -S(O)$_2$-R^5, carbociclilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo, carbociclil-C_1-C_6-alquilo sustituido con halógeno, heterociclilo, haloheterociclilo, heterociclil-C_1-C_6-alquilo, y heterociclil-C_1-C_6-alquilo sustituido con halógeno. El carbociclilo de anillo único es ya sea:

sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por -OH, -NO_2, -CN, -N(R^5)(R^6), -C(O)(R^7), -S-R^5, -S(O)$_2$-R^5, carbociclilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo, carbociclil-C_1-C_6-alquilo sustituido con halógeno, heterociclilo, haloheterociclilo, heterociclil-C_1-C_6-alquilo, y heterociclil-C_1-C_6-alquilo sustituido con halógeno; o

sustituido con 2 ó más sustituyentes seleccionados independientemente del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_6-alquilo, halo-C_1-C_6-alquilo, C_1-C_6-alcoxi, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbociclilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo, carbociclil-C_1-C_6-alquilo sustituido con halógeno, heterociclilo, haloheterociclilo, heterociclil-C_1-C_6-alquilo, y heterociclil-C_1-C_6-alquilo sustituido con halógeno.

[462] R^1 y R^2 se seleccionan independientemente del grupo formado por -H, alquilo, carbociclilo, carbociclilalquilo, heterociclilo, y heterociclilalquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[463] En algunas realizaciones preferidas, R^1 y R^2 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[464] En algunas realizaciones preferidas, R^1 y R^2 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

845

[465] R^3 es -H, alquilo, -O-R^4, -N(R^4)(R^5), carbociclilalquilo, o heterociclilalquilo. El alquilo, carbociclilalquilo, o heterociclilalquilo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[466] En algunas realizaciones preferidas, R^3 es -H, C_1-C_6-alquilo, -O-R^4, -N(R^4)(R^5), carbociclil-C_1-C_6-alquilo, o heterociclil-C_1-C_6-alquilo. El C_1-C_6-alquilo, carbociclil-C_1-C_6-alquilo, o heterociclil-C_1-C_6-alquilo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[467] En algunas realizaciones preferidas, R^3 es -H, C_1-C_6-alquilo, -O-R^4, -N(R^4)(R^5), carbociclil-C_1-C_6-alquilo, o heterociclil-C_1-C_6-alquilo. El C_1-C_6-alquilo, carbociclil-C_1-C_6-alquilo, o heterociclil-C_1-C_6-alquilo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

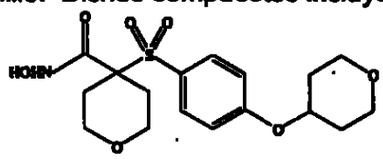
[468] R^4 y R^5 se seleccionan independientemente del grupo formado por -H, alquilo, carbociclilo, carbociclilalquilo, heterociclilo, y heterociclilalquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[469] En algunas realizaciones preferidas, R^4 y R^5 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

846

[470] En algunas realizaciones preferidas, R^4 y R^5 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

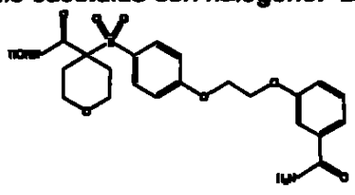
[471] En algunas realizaciones preferidas, E^2 está unido a un átomo de E^5 para formar un anillo. Dichos compuestos incluyen, por ejemplo:



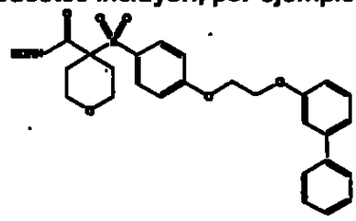
XII-1

[472] En algunas realizaciones preferidas, E^2 no está unido a un átomo de E^5 para formar un anillo.

[473] En algunas de dichas realizaciones preferidas, E^5 es un carbociclilo de anillo único (preferentemente fenilo) sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por -OH, -NO_2, -CN, -$N(R^6)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbociclilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo, carbociclil-C_1-C_6-alquilo sustituido con halógeno, heterociclilo, haloheterociclilo, heterociclil-C_1-C_6-alquilo, y heterociclil-C_1-C_6-alquilo sustituido con halógeno. Dichos compuestos incluyen, por ejemplo:



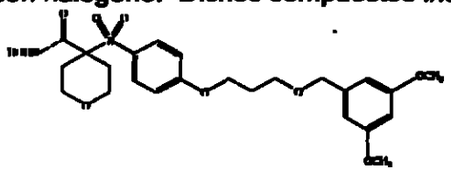
XII-2



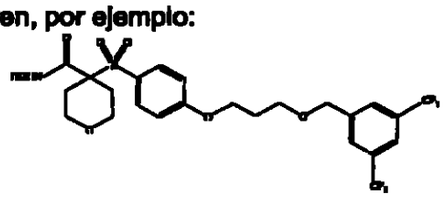
XII-3

847

[474] En algunas realizaciones preferidas, E^5 es carbociclilo de anillo único (preferentemente fenilo) sustituido con 2 ó más sustituyentes seleccionados independientemente del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_6-alquilo, halo-C_1-C_6-alquilo, C_1-C_6-alcoxi, halo-C_1-C_6-alcoxi, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbociclilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo, carbociclil-C_1-C_6-alquilo sustituido con halógeno, heterociclilo, haloheterociclilo, heterociclil-C_1-C_6-alquilo, y heterociclil-C_1-C_6-alquilo sustituido con halógeno. Dichos compuestos incluyen, por ejemplo:

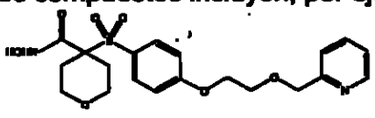


XII-4

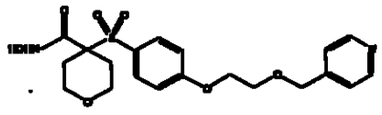


XII-5

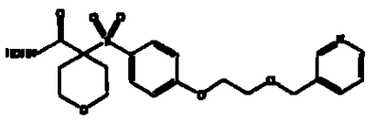
[475] En algunas realizaciones preferidas, E^5 es heterociclilo optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_6-alquilo, halo-C_1-C_6-alquilo, C_1-C_6-alcoxi, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbociclilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo, carbociclil-C_1-C_6-alquilo sustituido con halógeno, heterociclilo, haloheterociclilo, heterociclil-C_1-C_6-alquilo, y heterociclil-C_1-C_6-alquilo sustituido con halógeno. Dichos compuestos incluyen, por ejemplo:



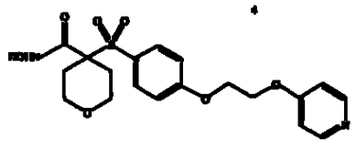
XII-6



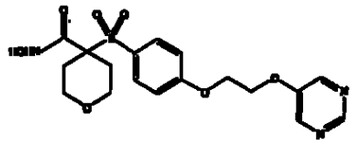
XII-7



XII-8



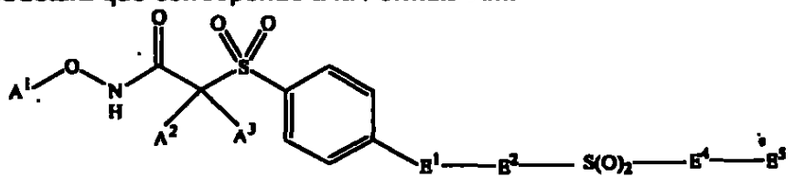
XII-9



XII-10

Realización preferida Nro. 12

[476] En algunas realizaciones de esta invención, el compuesto tiene una estructura que corresponde a la Fórmula XIII:



XIII

[477] A^1, A^2, y A^3 tienen los valores definidos anteriormente para la Fórmula I.

[478] E^1 es $-S(O)_2-$, $-S(O)-$, $-N(R^1)-$, $-C(O)-N(R^1)-$, $-N(R^1)-C(O)-$, o $-C(R^1)(R^2)-$.

[479] E^2 es alquilo, cicloalquilo, alquilcicloalquilo, cicloalquilalquilo, o alquilcicloalquilalquilo. Cualquier miembro de este grupo es optativamente sustituido.

[480] En algunas realizaciones preferidas, E^2 es C_1-C_{20}-alquilo, cicloalquilo, C_1-C_{10}-alquilcicloalquilo, cicloalquil-C_1-C_{10}-alquilo, o C_1-C_{10}-alquilcicloalquil-C_1-C_{10}-alquilo. Cualquier miembro de este grupo es optativamente sustituido con uno o más sustituyentes seleccionados del grupo formado por halógeno, C_1-C_6-alquilo, y halo-C_1-C_6-alquilo.

849

[481] En algunas realizaciones preferidas, E^2 es C_1-C_8-alquilo, cicloalquilo, C_1-C_8-alquilcicloalquilo, cicloalquil-C_1-C_8-alquilo, o C_1-C_8-alquilcicloalquil-C_1-C_8-alquilo. Cualquier miembro de este grupo es optativamente sustituido con uno o más halógenos, aunque tal sustituyente típicamente es preferentemente no sustituido con halógeno.

[482] E^4 es un enlace, alquilo, o alquenilo. El alquilo y alquenilo son optativamente sustituidos.

[483] En algunas realizaciones preferidas, E^4 es un enlace, C_1-C_{20}-alquilo, halo-C_1-C_{20}-alquilo, C_2-C_{20}-alquenilo, o halo-C_2-C_{20}-alquenilo.

[484] En algunas realizaciones preferidas, E^4 es un enlace, C_1-C_3-alquilo, halo-C_1-C_3-alquilo, C_2-C_3-alquenilo, o halo-C_2-C_3-alquenilo.

[485] En algunas realizaciones preferidas, E^4 es un enlace, C_1-C_3-alquilo, o C_2-C_3-alquenilo.

[486] E^5 es alquilo, alquenilo, alquinilo, alcoxi, alcoxialquilo, carbociclilo, o heterociclilo. Cualquier miembro de este grupo es optativamente sustituido.

[487] En algunas realizaciones preferidas, E^5 es C_1-C_{20}-alquilo, C_2-C_{20}-alquenilo, C_2-C_{20}-alquinilo, C_1-C_{20}-alcoxi, C_1-C_{20}-alcoxi-C_1-C_{20}-alquilo, carbociclilo, o heterociclilo. El C_1-C_{20}-alquilo, C_2-C_{20}-alquenilo, C_2-C_{20}-alquinilo, C_1-C_{20}-alcoxi, y C_1-C_{20}-alcoxi-C_1-C_{20}-alquilo son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, y -CN. El carbociclilo y heterociclilo son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_8-alquilo, halo-C_1-C_8-alquilo, C_1-C_8-alcoxi, halo-C_1-C_8-alcoxi, -

$N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbociclilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo, y carbociclil-C_1-C_6-alquilo sustituido con halógeno.

[488] En algunas realizaciones preferidas, E^5 es C_1-C_6-alquilo, C_2-C_6-alquenilo, C_2-C_6-alquinilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, carbociclilo, o heterociclilo. El C_1-C_6-alquilo, C_2-C_6-alquenilo, C_2-C_6-alquinilo, C_1-C_6-alcoxi, y C_1-C_6-alcoxi-C_1-C_6-alquilo son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, $-OH$, $-NO_2$, y $-CN$. El carbociclilo y heterociclilo son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, $-OH$, $-NO_2$, $-CN$, C_1-C_6-alquilo, halo-C_1-C_6-alquilo, C_1-C_6-alcoxi, halo-C_1-C_6-alcoxi, $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbociclilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo, y carbociclil-C_1-C_6-alquilo sustituido con halógeno.

[489] R^1 y R^2 se seleccionan independientemente del grupo formado por -H y alquilo. El alquilo es optativamente sustituido. Ni R^1 ni R^2 forman una estructura de anillo con E^2, E^4, o E^5.

[490] En algunas realizaciones preferidas, R^1 y R^2 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, y halo-C_1-C_6-alquilo.

[491] En algunas realizaciones preferidas, R^1 y R^2 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, y halo-C_1-C_6-alquilo.

[492] En algunas realizaciones preferidas, R^1 y R^2 se seleccionan independientemente del grupo formado por -H y C_1-C_6-alquilo.

[493] R^5 y R^6 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y

heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[494] En algunas realizaciones preferidas, R^5 y R^6 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[495] R^7 es -H, C_1-C_6-alquilo, -O-R^8, -N(R^8)(R^9), carbociclil-C_1-C_6-alquilo, o heterociclil-C_1-C_6-alquilo. El C_1-C_6-alquilo, carbociclil-C_1-C_6-alquilo, o heterociclil-C_1-C_6-alquilo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[496] En algunas realizaciones preferidas, R^7 es -H, C_1-C_6-alquilo, -O-R^8, -N(R^8)(R^9), carbociclil-C_1-C_6-alquilo, o heterociclil-C_1-C_6-alquilo. El C_1-C_6-alquilo, carbociclil-C_1-C_6-alquilo, o heterociclil-C_1-C_6-alquilo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[497] R^8 y R^9 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

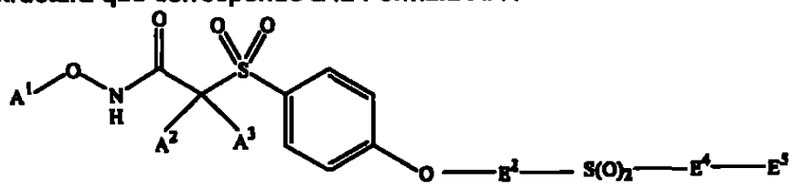
[498] En algunas realizaciones preferidas, R^8 y R^9 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo

852

cuando el miembro es -H, cualquier miembro de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

Realización preferida Nro. 13

[498] En algunas realizaciones de esta invención, el compuesto tiene una estructura que corresponde a la Fórmula XIV:



XIV

[500] A^1, A^2, y A^3 tienen los valores definidos anteriormente para la Fórmula I.

[501] E^2 es alquilo, cicloalquilo, alquilcicloalquilo, cicloalquilalquilo, o alquilcicloalquilalquilo. Cualquier miembro de este grupo es optativamente sustituido.

[502] En algunas realizaciones preferidas, E^2 es C_1-C_{20}-alquilo, cicloalquilo, C_1-C_{10}-alquilcicloalquilo, cicloalquil-C_1-C_{10}-alquilo, o C_1-C_{10}-alquilcicloalquil-C_1-C_{10}-alquilo. Cualquier miembro de este grupo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, C_1-C_6-alquilo, y halo-C_1-C_6-alquilo.

[503] En algunas realizaciones preferidas, E^2 es C_1-C_6-alquilo optativamente sustituido con uno o más halógenos.

[504] En algunas realizaciones preferidas, E^2 es C_1-C_6-alquilo.

[505] E^4 es alquilo o alquenilo. El alquilo y alquenilo son optativamente sustituidos.

953

[506] En algunas realizaciones preferidas, E^4 es C_1-C_{20}-alquilo, halo-C_1-C_{20}-alquilo, C_2-C_{20}-alquenilo, o halo-C_2-C_{20}-alquenilo.

[507] En algunas realizaciones preferidas, E^4 es C_1-C_3-alquilo, halo-C_1-C_3-alquilo, C_2-C_3-alquenilo, o halo-C_2-C_3-alquenilo.

[508] En algunas realizaciones preferidas, E^4 es C_1-C_3-alquilo o C_2-C_3-alquenilo.

[509] E^5 es -H, alquilo, alquenilo, alquinilo, alcoxi, carbociclilo, o heterociclilo. Cualquier miembro de este grupo es optativamente sustituido.

[510] En algunas realizaciones preferidas, E^5 es -H, C_1-C_{20}-alquilo, C_2-C_{20}-alquenilo, C_2-C_{20}-alquinilo, C_1-C_{20}-alcoxi, carbociclilo, o heterociclilo. El C_1-C_{20}-alquilo, C_2-C_{20}-alquenilo, C_2-C_{20}-alquinilo, y C_1-C_{20}-alcoxi son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, y -CN. El carbociclilo y heterociclilo son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, -CN, C_1-C_8-alquilo, halo-C_1-C_8-alquilo, C_1-C_8-alcoxi, halo-C_1-C_8-alcoxi, $-N(R^3)(R^4)$, $-C(O)(R^5)$, $-S-R^3$, $-S(O)_2-R^3$, carbociclilo, halocarbociclilo, carbociclil-C_1-C_8-alquilo, y carbociclil-C_1-C_8-alquilo sustituido con halógeno.

[511] En algunas realizaciones preferidas, E^5 es -H, C_1-C_8-alquilo, C_2-C_8-alquenilo, C_2-C_8-alquinilo, C_1-C_8-alcoxi, carbociclilo, o heterociclilo. El C_1-C_8-alquilo, C_2-C_8-alquenilo, C_2-C_8-alquinilo, y C_1-C_8-alcoxi son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, y -CN. El carbociclilo y heterociclilo son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -

NO_2, -CN, C_1-C_6-alquilo, halo-C_1-C_6-alquilo, C_1-C_6-alcoxi, halo-C_1-C_6-alcoxi, -$N(R^3)(R^4)$, -$C(O)(R^5)$, -S-R^3, -$S(O)_2$-R^3, carbociclilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo, y carbociclil-C_1-C_6-alquilo sustituido con halógeno.

[512] R^3 y R^4 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[513] En algunas realizaciones preferidas, R^3 y R^4 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[514] R^5 es -H, C_1-C_6-alquilo, -O-R^6, -$N(R^6)(R^7)$, carbociclil-C_1-C_6-alquilo, o heterociclil-C_1-C_6-alquilo. El C_1-C_6-alquilo, carbociclil-C_1-C_6-alquilo, o heterociclil-C_1-C_6-alquilo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

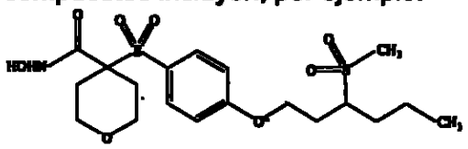
[515] En algunas realizaciones preferidas, R^5 es -H, C_1-C_6-alquilo, -O-R^6, -$N(R^6)(R^7)$, carbociclil-C_1-C_6-alquilo, o heterociclil-C_1-C_6-alquilo. El C_1-C_6-alquilo, carbociclil-C_1-C_6-alquilo, o heterociclil-C_1-C_6-alquilo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[516] R^6 y R^7 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es -H, cualquier miembro

de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[517] En algunas realizaciones preferidas, R^6 y R^7 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

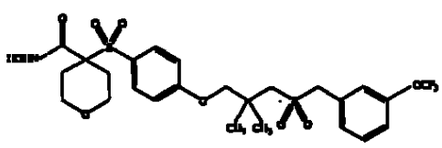
[518] En algunas realizaciones preferidas, E^5 es -H, C_1-C_6-alquilo, C_2-C_6-alquenilo, C_2-C_6-alquinilo, o C_1-C_6-alcoxi. El C_1-C_6-alquilo, C_2-C_6-alquenilo, C_2-C_6-alquinilo, y C_1-C_6-alcoxi son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, y -CN. En una de tales realizaciones, E^5 es C_1-C_6-alquilo optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, y -CN. Dichos compuestos incluyen, por ejemplo:



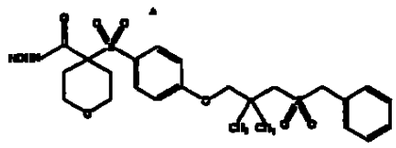
XIV-1

[519] En algunas realizaciones preferidas, E^5 es carbociclilo optativamente sustituido y heterociclilo optativamente sustituido.

[520] En algunas realizaciones preferidas, E^5 es arilo optativamente sustituido, generalmente preferentemente fenilo optativamente sustituido. Dichos compuestos incluyen, por ejemplo:



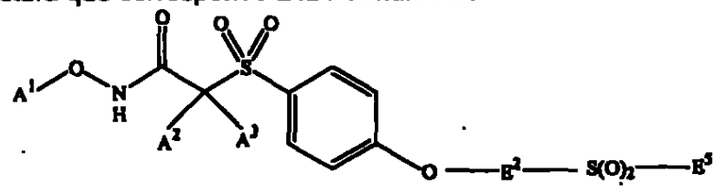
XIV-2



XIV-3

Realización preferida Nro. 14

[521] En algunas realizaciones de esta invención, el compuesto tiene una estructura que corresponde a la Fórmula XV:



XV

[522] A^1, A^2, y A^3 tienen los valores definidos anteriormente para la Fórmula I.

[523] E^2 comprende menos de 5 átomos de carbono. E^2 es alquilo, cicloalquilo, alquilcicloalquilo, cicloalquilalquilo, o alquilcicloalquilalquilo. Cualquier miembro de este grupo es optativamente sustituido, pero preferentemente no es sustituido.

[524] E^5 es alquilo, alquenilo, alquinilo, alcoxialquilo, carbociclilo, o heterociclilo. Cualquier miembro de este grupo es optativamente sustituido.

[525] En algunas realizaciones preferidas, E^5 es C_1-C_{20}-alquilo, C_2-C_{20}-alquenilo, C_2-C_{20}-alquinilo, C_1-C_{20}-alcoxi-C_1-C_{20}-alquilo, carbociclilo, o heterociclilo. El C_1-C_{20}-alquilo, C_2-C_{20}-alquenilo, C_2-C_{20}-alquinilo, y C_1-C_{20}-alcoxi-C_1-C_{20}-alquilo son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, y -CN. El carbociclilo y heterociclilo son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, ceto, C_1-C_6-alquilo, halo-C_1-

C_8-alquilo, C_1-C_8-alcoxi, halo-C_1-C_8-alcoxi, C_1-C_8-alcoxi-C_1-C_8-alquilo, C_1-C_8-alcoxi-C_1-C_8-alquilo sustituido con halógeno , -$N(R^3)(R^4)$, -$C(O)(R^5)$, -S-R^3, -$S(O)_2$-R^3, carbociclilo, halocarbociclilo, carbociclil-C_1-C_8-alquilo, carbociclil-C_1-C_8-alquilo sustituido con halógeno, C_1-C_8-alquilcarbociclíloxi, y C_1-C_8-alquilcarbociclilo sustituido con halógenoxi.

[526] En algunas realizaciones preferidas, E^3 es C_1-C_8-alquilo, C_2-C_8-alquenilo, C_2-C_8-alquinilo, C_1-C_8-alcoxi-C_1-C_8-alquilo, carbociclilo, o heterociclilo. El C_1-C_8-alquilo, C_2-C_8-alquenilo, C_2-C_8-alquinilo, y C_1-C_8-alcoxi-C_1-C_8-alquilo son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, y -CN. El carbociclilo y heterociclilo son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, ceto, C_1-C_8-alquilo, halo-C_1-C_8-alquilo, C_1-C_8-alcoxi, halo-C_1-C_8-alcoxi, C_1-C_8-alcoxi-C_1-C_8-alquilo, C_1-C_8-alcoxi-C_1-C_8-alquilo sustituido con halógeno, -$N(R^3)(R^4)$, -$C(O)(R^5)$, -S-R^3, -$S(O)_2$-R^3, carbociclilo, halocarbociclilo, carbociclil-C_1-C_8-alquilo, carbociclil-C_1-C_8-alquilo sustituido con halógeno, C_1-C_8-alquilcarbociclíloxi, y halógeno-sustituido C_1-C_8-alquilcarbociclíloxi.

[527] R^3 y R^4 se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, carbociclilo, carbociclil-C_1-C_8-alquilo, heterociclilo, y heterociclil-C_1-C_8-alquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[528] En algunas realizaciones preferidas, R^3 y R^4 se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, carbociclilo, carbociclil-C_1-C_8-alquilo, heterociclilo, y heterociclil-C_1-C_8-alquilo. Salvo

cuando el miembro es -H, cualquier miembro de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[529] R^5 es -H, C_1-C_6-alquilo, -O-R^6, -N(R^6)(R^7), carbociclil-C_1-C_6-alquilo, o heterociclil-C_1-C_6-alquilo. El C_1-C_6-alquilo, carbociclil-C_1-C_6-alquilo, o heterociclil-C_1-C_6-alquilo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[530] En algunas realizaciones preferidas, R^5 es -H, C_1-C_6-alquilo, -O-R^6, -N(R^6)(R^7), carbociclil-C_1-C_6-alquilo, o heterociclil-C_1-C_6-alquilo. El C_1-C_6-alquilo, carbociclil-C_1-C_6-alquilo, o heterociclil-C_1-C_6-alquilo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[531] R^6 y R^7 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

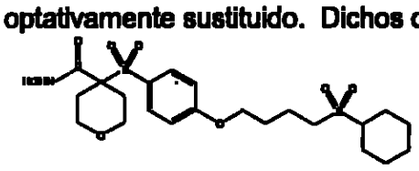
[532] En algunas realizaciones preferidas, R^6 y R^7 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[533] En algunas realizaciones preferidas, E^5 es C_1-C_6-alquilo, C_2-C_6-alquenilo, C_2-C_6-alquinilo, o C_1-C_6-alcoxi-C_1-C_6-alquilo. El C_1-C_6-alquilo, C_2-C_6-alquenilo, C_2-C_6-alquinilo, y C_1-C_6-alcoxi-C_1-C_6-alquilo son optativamente

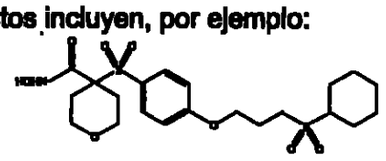
sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, y -CN.

[534] En algunas realizaciones preferidas, E^5 es carbociclilo optativamente sustituido.

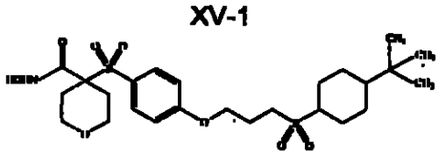
[535] En algunas realizaciones preferidas, E^5 es C_5-C_6-cicloalquilo optativamente sustituido. Dichos compuestos incluyen, por ejemplo:



XV-1

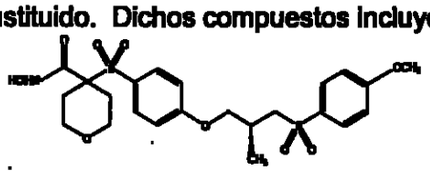


XV-2

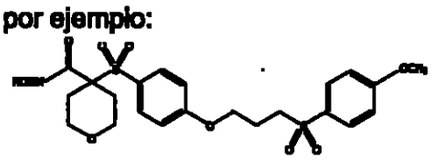


XV-3

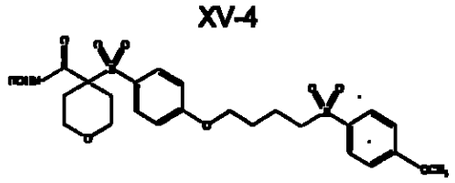
[536] En algunas realizaciones preferidas, E^5 es fenilo optativamente sustituido. Dichos compuestos incluyen, por ejemplo:



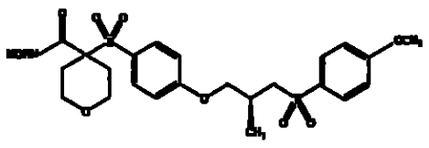
XV-4



XV-5



XV-6

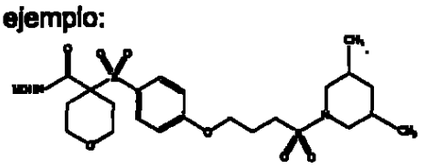


XV-7

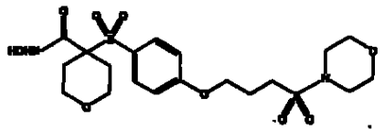
[537] En algunas realizaciones preferidas, E^5 es heterociclilo optativamente sustituido.

[538] En algunas realizaciones preferidas, E^5 es heterociclilo optativamente sustituido seleccionado del grupo formado por piperidinilo,

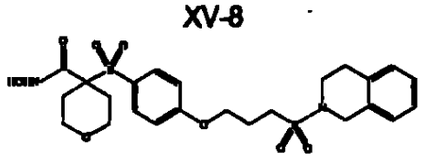
morfolinilo, y tetrahidroisoquinolinilo. Dichos compuestos incluyen, por ejemplo:



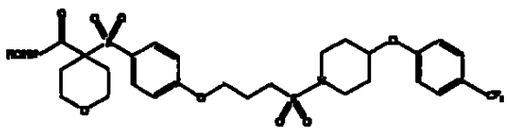
XV-8



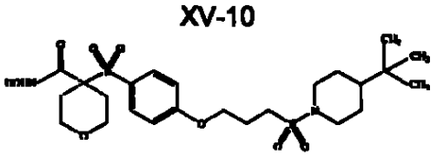
XV-9



XV-10



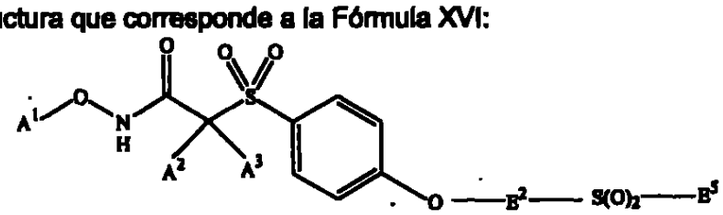
XV-11



XV-12

Realización preferida Nro. 15

[539] En algunas realizaciones de esta invención, el compuesto tiene una estructura que corresponde a la Fórmula XVI:



XVI

[540] A^1, A^2, y A^3 tienen los valores definidos anteriormente para la Fórmula I.

[541] E^2 es alquilo, cicloalquilo, alquilcicloalquilo, cicloalquilalquilo, o alquilcicloalquilalquilo. Cualquier miembro de este grupo es optativamente sustituido.

[542] En algunas realizaciones preferidas, E^2 es C_1-C_{20}-alquilo, cicloalquilo, C_1-C_{10}-alquilcicloalquilo, cicloalquil-C_1-C_{10}-alquilo, o C_1-C_{10}-

861

alquilcicloalquil-C_1-C_{10}-alquilo. Cualquier miembro de este grupo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, C_1-C_8-alquilo, halo-C_1-C_8-alquilo.

[543] En algunas realizaciones preferidas, E^2 es C_1-C_8-alquilo optativamente sustituido con uno o más halógenos.

[544] En algunas realizaciones preferidas, E^2 es C_1-C_8-alquilo.

[545] E^5 es alquilo, alquenilo, alquinilo, alcoxialquilo, carbociclilo saturado, carbociclilo parcialmente saturado, o heterociclilo. Cualquier miembro de este grupo es optativamente sustituido.

[546] En algunas realizaciones preferidas, E^5 es C_1-C_{20}-alquilo, C_2-C_{20}-alquenilo, C_2-C_{20}-alquinilo, C_1-C_{20}-alcoxi-C_1-C_{20}-alquilo, carbociclilo saturado, carbociclilo parcialmente saturado, o heterociclilo. El C_1-C_{20}-alquilo, C_2-C_{20}-alquenilo, C_2-C_{20}-alquinilo, y C_1-C_{20}-alcoxi-C_1-C_{20}-alquilo son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, y -CN. El carbociclilo saturado, carbociclilo parcialmente saturado, y heterociclilo son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, -CN, C_1-C_8-alquilo, halo-C_1-C_8-alquilo, C_1-C_8-alcoxi, halo-C_1-C_8-alcoxi, C_1-C_8-alcoxi-C_1-C_8-alquilo, C_1-C_8-alcoxi-C_1-C_8-alquilo sustituido con halógeno , $-N(R^3)(R^4)$, $-C(O)(R^5)$, $-S-R^3$, $-S(O)_2-R^3$, carbociclilo, halocarbociclilo, carbociclil-C_1-C_8-alquilo, carbociclil-C_1-C_8-alquilo sustituido con halógeno, C_1-C_8-alquilcarbocicliloxi, y C_1-C_8-alquilcarbociclilo sustituido con halógenoxi.

[547] En algunas realizaciones preferidas, E^5 es C_1-C_8-alquilo, C_2-C_8-alquenilo, C_2-C_8-alquinilo, C_1-C_8-alcoxi-C_1-C_8-alquilo, carbociclilo saturado,

862

carbociclilo parcialmente saturado, o heterociclilo. El C_1-C_6-alquilo, C_2-C_6-alquenilo, C_2-C_6-alquinilo, y C_1-C_6-alcoxi-C_1-C_6-alquilo son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, y -CN. El carbociclilo saturado, carbociclilo parcialmente saturado, y heterociclilo son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, -CN, C_1-C_6-alquilo, halo-C_1-C_6-alquilo, C_1-C_6-alcoxi, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, $-N(R^3)(R^4)$, $-C(O)(R^5)$, $-S-R^3$, $-S(O)_2-R^3$, carbociclilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo, carbociclil-C_1-C_6-alquilo sustituido con halógeno, C_1-C_6-alquilcarbocicliloxi, y halógeno-sustituido C_1-C_6-alquilcarbocicliloxi.

[548] R^3 y R^4 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[549] En algunas realizaciones preferidas, R^3 y R^4 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[550] R^5 es s -H, C_1-C_6-alquilo, $-O-R^6$, $-N(R^6)(R^7)$, carbociclil-C_1-C_6-alquilo, o heterociclil-C_1-C_6-alquilo. El C_1-C_6-alquilo, carbociclil-C_1-C_6-alquilo, o

463

heterociclil-C_1-C_6-alquilo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[551] En algunas realizaciones preferidas, R^5 es -H, C_1-C_6-alquilo, -O-R^6, -N(R^6)(R^7), carbociclil-C_1-C_6-alquilo, o heterociclil-C_1-C_6-alquilo. El C_1-C_6-alquilo, carbociclil-C_1-C_6-alquilo, o heterociclil-C_1-C_6-alquilo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

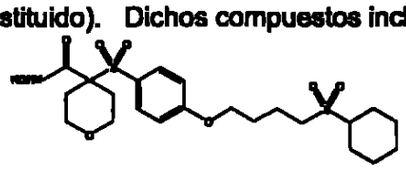
[552] R^6 y R^7 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[553] En algunas realizaciones preferidas, R^6 y R^7 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

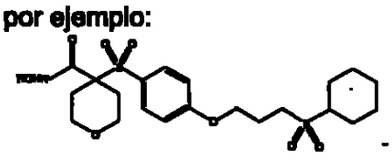
[554] En algunas realizaciones preferidas, E^5 es C_1-C_6-alquilo, C_2-C_6-alquenilo, C_2-C_6-alquinilo, o C_1-C_6-alcoxi-C_1-C_6-alquilo. El C_1-C_6-alquilo, C_2-C_6-alquenilo, C_2-C_6-alquinilo, y C_1-C_6-alcoxi-C_1-C_6-alquilo son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, y -CN.

[555] En algunas realizaciones preferidas, E^5 es carbociclilo parcialmente saturado optativamente sustituido.

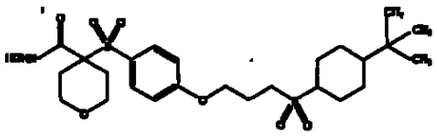
[556] En algunas realizaciones preferidas, E^5 es carbociclilo saturado optativamente sustituido (preferentemente C5-C6 cicloalquilo optativamente sustituido). Dichos compuestos incluyen, por ejemplo:



XVI-1

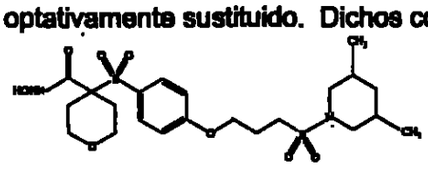


XVI-2

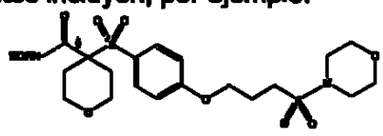


XVI-3

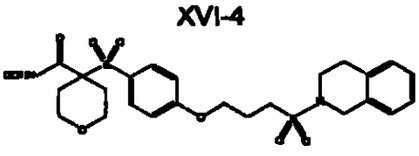
[557] En algunas realizaciones preferidas, E^5 es heterociclilo optativamente sustituido. Dichos compuestos incluyen, por ejemplo:



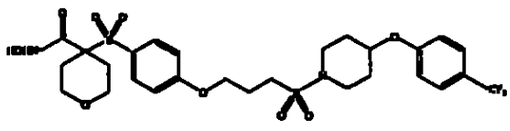
XVI-4



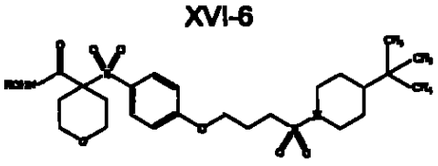
XVI-5



XVI-6



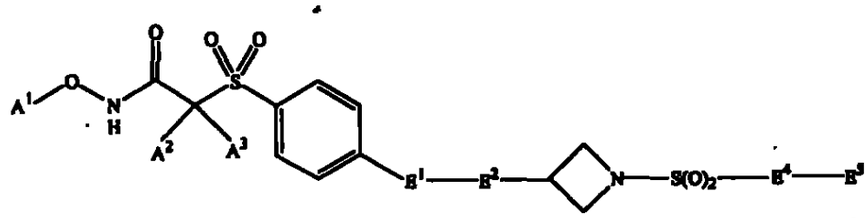
XVI-7



XVI-8

Realización preferida Nro. 16

[558] En algunas realizaciones de esta invención, el compuesto tiene una estructura que corresponde a la Fórmula XVII:



XVII

[559] A^1, A^2, y A^3 tienen los valores definidos anteriormente para la Fórmula I.

[560] E^1 es $-S(O)_2-$, $-S(O)-$, $-N(R^1)-$, $-C(O)-N(R^1)-$, $-N(R^1)-C(O)-$, o $-C(R^1)(R^2)-$.

[561] E^2 es alquilo, cicloalquilo, alquilcicloalquilo, cicloalquilalquilo, o alquilcicloalquilalquilo. Cualquier miembro de este grupo es optativamente sustituido.

[562] En algunas realizaciones preferidas, E^2 es C_1-C_{20}-alquilo, cicloalquilo, C_1-C_{10}-alquilcicloalquilo, cicloalquil-C_1-C_{10}-alquilo, o C_1-C_{10}-alquilcicloalquil-C_1-C_{10}-alquilo. Cualquier miembro de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[563] En algunas realizaciones preferidas, E^2 es C_1-C_6-alquilo optativamente sustituido con uno o más halógenos.

[564] En algunas realizaciones preferidas, E^2 es C_1-C_6-alquilo.

[565] E^4 es un enlace, alquilo, o alquenilo, El alquilo y alquenilo son optativamente sustituidos.

[566] En algunas realizaciones preferidas, E^4 es un enlace, C_1-C_{20}-alquilo, halo-C_1-C_{20}-alquilo, C_2-C_{20}-alquenilo, o halo-C_2-C_{20}-alquenilo.

[567] En algunas realizaciones preferidas, E^4 es un enlace, C_1-C_3-alquilo, halo-C_1-C_3-alquilo, C_2-C_3-alquenilo, o halo-C_2-C_3-alquenilo.

[568] En algunas realizaciones preferidas, E^4 es un enlace, C_1-C_3-alquilo, o C_2-C_3-alquenilo.

[569] E^5 es alquilo, alquenilo, alquinilo, alcoxi, alcoxialquilo, carbociclilo, o heterociclilo. Cualquier miembro de este grupo es optativamente sustituido.

[570] En algunas realizaciones preferidas, E^5 es C_1-C_{20}-alquilo, C_2-C_{20}-alquenilo, C_2-C_{20}-alquinilo, C_1-C_{20}-alcoxi, C_1-C_{20}-alcoxi-C_1-C_{20}-alquilo, carbociclilo, o heterociclilo. El C_1-C_{20}-alquilo, C_2-C_{20}-alquenilo, C_2-C_{20}-alquinilo, C_1-C_{20}-alcoxi, y C_1-C_{20}-alcoxi-C_1-C_{20}-alquilo son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, y -CN. El carbociclilo y heterociclilo son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_6-alquilo, halo-C_1-C_6-alquilo, C_1-C_6-alcoxi, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno , -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbociclilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo, y carbociclil-C_1-C_6-alquilo sustituido con halógeno.

[571] En algunas realizaciones preferidas, E^5 es C_1-C_6-alquilo, C_2-C_6-alquenilo, C_2-C_6-alquinilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, carbociclilo, o heterociclilo. El C_1-C_6-alquilo, C_2-C_6-alquenilo, C_2-C_6-alquinilo, C_1-C_6-alcoxi, y C_1-C_6-alcoxi-C_1-C_6-alquilo son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, y -CN. El carbociclilo y heterociclilo son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_6-alquilo, halo-C_1-C_6-alquilo, C_1-C_6-alcoxi, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-

alcoxi-C_1-C_6-alquilo sustituido con halógeno, -$N(R^5)(R^5)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbociclilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo, y carbociclil-C_1-C_6-alquilo sustituido con halógeno.

[572] R^1 y R^2 se seleccionan independientemente del grupo formado por -H y alquilo. El alquilo es optativamente sustituido. Ni R^1 ni R^2 forman una estructura de anillo con E^2, E^4, o E^5.

[573] En algunas realizaciones preferidas, R^1 y R^2 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, y halo-C_1-C_6-alquilo.

[574] En algunas realizaciones preferidas, R^1 y R^2 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, y halo-C_1-C_6-alquilo.

[575] En algunas realizaciones preferidas, R^1 y R^2 se seleccionan independientemente del grupo formado por -H y C_1-C_6-alquilo.

[576] R^5 y R^6 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[577] En algunas realizaciones preferidas, R^5 y R^6 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

868

[578] R^7 es -H, C_1-C_6-alquilo, -O-R^8, -N(R^8)(R^9), carbociclil-C_1-C_6-alquilo, o heterociclil-C_1-C_6-alquilo. El C_1-C_6-alquilo, carbociclil-C_1-C_6-alquilo, o heterociclil-C_1-C_6-alquilo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

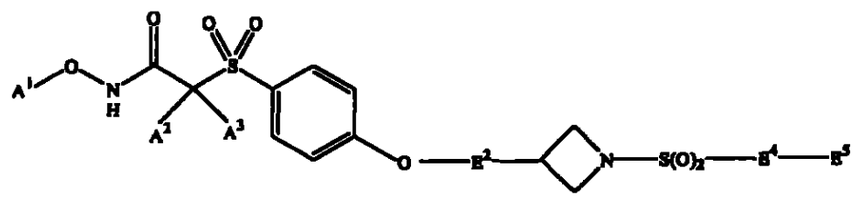
[579] En algunas realizaciones preferidas, R^7 es -H, C_1-C_6-alquilo, -O-R^8, -N(R^8)(R^9), carbociclil-C_1-C_6-alquilo, o heterociclil-C_1-C_6-alquilo. El C_1-C_6-alquilo, carbociclil-C_1-C_6-alquilo, o heterociclil-C_1-C_6-alquilo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[580] R^8 y R^9 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[581] En algunas realizaciones preferidas, R^8 y R^9 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

Realización preferida Nro. 17

[582] En algunas realizaciones de esta invención, el compuesto tiene una estructura que corresponde a la Fórmula XVII:



XVIII

[583] A^1, A^2, y A^3 tienen los valores definidos anteriormente para la Fórmula I.

[584] E^2 es un enlace, alquilo, cicloalquilo, alquilcicloalquilo, cicloalquilalquilo, o alquilcicloalquilalquilo. Cualquier miembro de este grupo es optativamente sustituido.

[585] En algunas realizaciones preferidas, E^2 es un enlace, C_1-C_{20}-alquilo, cicloalquilo, C_1-C_{10}-alquilcicloalquilo, cicloalquil-C_1-C_{10}-alquilo, o C_1-C_{10}-alquilcicloalquil-C_1-C_{10}-alquilo. Cualquier miembro de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[586] En algunas realizaciones preferidas, E^2 es un enlace, C_1-C_6-alquilo, o halo-C_1-C_6-alquilo.

[587] En algunas realizaciones preferidas, E^2 es un enlace o C_1-C_6-alquilo.

[588] En algunas realizaciones preferidas, E^2 es un enlace.

[589] E^4 es un enlace, alquilo, o alquenilo. El alquilo y alquenilo son optativamente sustituidos.

[590] En algunas realizaciones preferidas, E^4 es un enlace, C_1-C_{20}-alquilo, halo-C_1-C_{20}-alquilo, C_2-C_{20}-alquenilo, o halo-C_2-C_{20}-alquenilo.

[591] En algunas realizaciones preferidas, E^4 es un enlace, C_1-C_3-alquilo, halo-C_1-C_3-alquilo, C_2-C_3-alquenilo, o halo-C_2-C_3-alquenilo.

870

[592] En algunas realizaciones preferidas, E^4 es un enlace, C_1-C_3-alquilo, o C_2-C_3-alquenilo.

[593] En algunas realizaciones preferidas, E^4 es un enlace.

[594] E^5 es heterociclilo optativamente sustituido o sustituido carbociclilo.

[595] El heterociclilo E^5 es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, -CN, alquilo, haloalquilo, alcoxi, haloalcoxi, alcoxialquilo, alcoxialquilo sustituido con halógeno, $-N(R^3)(R^4)$, $-C(O)(R^5)$, $-S-R^3$, $-S(O)_2-R^3$, carbociclilo, halocarbociclilo, carbociclilalquilo, y carbociclilalquilo sustituido con halógeno.

[596] En algunas realizaciones preferidas, E^5 es heterociclilo optativamente sustituido con uno o más sustituyentes. independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, -CN, C_1-C_6-alquilo, halo-C_1-C_6-alquilo, C_1-C_6-alcoxi, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, halógeno-sustituido C_1-C_6-alcoxi-C_1-C_6-alquilo, $-N(R^3)(R^4)$, $-C(O)(R^5)$, $-S-R^3$, $-S(O)_2-R^3$, carbociclilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo, y carbociclil-C_1-C_6-alquilo sustituido con halógeno.

[597] En algunas realizaciones preferidas, E^5 es heterociclilo optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, -CN, C_1-C_6-alquilo, halo-C_1-C_6-alquilo, C_1-C_6-alcoxi, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, $-N(R^3)(R^4)$, $-C(O)(R^5)$, $-S-R^3$, $-S(O)_2-R^3$, carbociclilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo, y carbociclil-C_1-C_6-alquilo sustituido con halógeno.

[598] El carbociclilo E^5 es sustituido con:

2 ó más sustituyentes seleccionados independientemente del grupo formado por halógeno, -OH, $-NO_2$, -CN, alquilo, haloalquilo, alcoxi, haloalcoxi, alcoxialquilo, alcoxialquilo sustituido con halógeno, $-N(R^3)(R^4)$, $-C(O)(R^5)$, $-S-R^3$, $-S(O)_2-R^3$, carbociclilo, halocarbociclilo, carbociclilalquilo, y carbociclilalquilo sustituido con halógeno; o

un sustituyente seleccionado del grupo formado por halógeno, -OH, $-NO_2$, -CN, $-C(O)-O-R^3$, $-S-R^3$, $-S(O)_2-R^3$, carbociclilo, halocarbociclilo, carbociclilalquilo, y carbociclilalquilo sustituido con halógeno.

[599] En algunas realizaciones preferidas, E^5 es carbociclilo sustituido con:

2 ó más sustituyentes seleccionados independientemente del grupo formado por halógeno, -OH, $-NO_2$, -CN, C_1-C_6-alquilo, halo-C_1-C_6-alquilo, C_1-C_6-alcoxi, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno , $-N(R^3)(R^4)$, $-C(O)(R^5)$, $-S-R^3$, $-S(O)_2-R^3$, carbociclilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo, y carbociclil-C_1-C_6-alquilo sustituido con halógeno, o

un sustituyente seleccionado del grupo formado por halógeno, -OH, $-NO_2$, -CN, $-C(O)-O-R^3$, $-S-R^3$, $-S(O)_2-R^3$, carbociclilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo, y carbociclil-C_1-C_6-alquilo sustituido con halógeno.

[600] En algunas realizaciones preferidas, E^5 es carbociclilo sustituido con:

2 ó más sustituyentes seleccionados independientemente del grupo formado por halógeno, -OH, $-NO_2$, -CN, C_1-C_6-alquilo, halo-C_1-C_6-alquilo, C_1-C_6-alcoxi, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-

C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, -$N(R^3)(R^4)$, -$C(O)(R^5)$, -S-R^3, -$S(O)_2$-R^3, carbociclilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo, y carbociclil-C_1-C_6-alquilo sustituido con halógeno, or

un sustituyente seleccionado del grupo formado por halógeno, -OH, -NO_2, -CN, -$C(O)$-O-R^3, -S-R^3, -$S(O)_2$-R^3, carbociclilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo, y carbociclil-C_1-C_6-alquilo sustituido con halógeno.

[601] R^3 y R^4 se seleccionan independientemente del grupo formado por -H, alquilo, carbociclilo, carbociclilalquilo, heterociclilo, y heterociclilalquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[602] En algunas realizaciones preferidas, R^3 y R^4 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[603] En algunas realizaciones preferidas, R^3 y R^4 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[604] R^5 es -H, alquilo, -O-R^6, -$N(R^6)(R^7)$, carbociclilalquilo, o heterociclilalquilo. El alquilo, carbociclilalquilo, o heterociclilalquilo puede ser

sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[605] En algunas realizaciones preferidas, R^5 es -H, C_1-C_6-alquilo, -O-R^6, -N(R^6)(R^7), carbociclil-C_1-C_6-alquilo, o heterociclil-C_1-C_6-alquilo. El C_1-C_6-alquilo, carbociclil-C_1-C_6-alquilo, o heterociclil-C_1-C_6-alquilo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[606] En algunas realizaciones preferidas, R^5 es -H, C_1-C_6-alquilo, -O-R^6, -N(R^6)(R^7), carbociclil-C_1-C_6-alquilo, o heterociclil-C_1-C_6-alquilo. El C_1-C_6-alquilo, carbociclil-C_1-C_6-alquilo, o heterociclil-C_1-C_6-alquilo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[607] R^6 y R^7 se seleccionan independientemente del grupo formado por -H, alquilo, carbociclilo, carbociclilalquilo, heterociclilo, y heterociclilalquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[608] En algunas realizaciones preferidas, R^6 y R^7 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

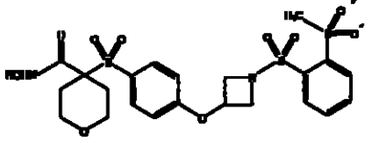
[609] En algunas realizaciones preferidas, R^6 y R^7 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo

874

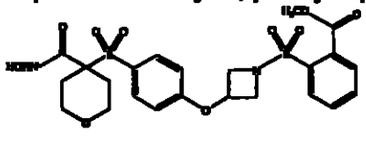
cuando el miembro es -H, cualquier miembro de este grupo puede ser sustituido con uno o más halógenos, pero más típicamente es preferentemente no sustituido con halógeno.

[610] En algunas realizaciones preferidas, E^5 es heterociclilo optativamente sustituido.

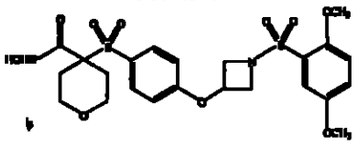
[611] En algunas realizaciones preferidas, E^5 es sustituido carbociclilo (preferentemente sustituido fenilo). Dichos compuestos incluyen, por ejemplo:



XVIII-1



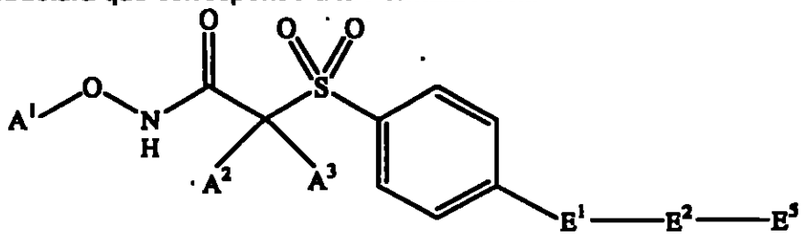
XVIII-2



XVIII-3

Realización preferida Nro. 18

[612] En algunas realizaciones de esta invención, el compuesto tiene una estructura que corresponde a la Fórmula XVIII:



XIX

[613] A^1, A^2 y A^3 tienen los valores definidos anteriormente para la Fórmula I.

[614] E^1 es -O-, $-S(O)_2-$, -S(O)-, -S-, $-N(R^1)-$, $-C(O)-N(R^1)-$, $-N(R^1)-C(O)-$, o $-C(R^1)(R^2)-$.

875

[615] E^2 es alquilo, cicloalquilo, alquilcicloalquilo, cicloalquilalquilo, o alquilcicloalquilalquilo. Cualquier miembro de este grupo es optativamente sustituido.

[616] En algunas realizaciones preferidas, E^2 es C_1-C_{20}-alquilo, cicloalquilo, C_1-C_{10}-alquil-cicloalquilo, cicloalquil-C_1-C_{10}-alquilo, o C_1-C_{10}-alquil-cicloalquil-C_1-C_{10}-alquilo. Cualquier miembro de este grupo es optativamente sustituido con uno o más halógenos.

[617] En algunas realizaciones preferidas, E^2 es C_1-C_6-alquilo. El alquilo es optativamente sustituido con uno o más halógenos.

[618] E^5 es sustituido heterociclilo.

[619] En algunas realizaciones preferidas, E^5 es heterociclilo que es:

sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, ceto, C_1-C_6-alquilo, halo-C_1-C_6-alquilo, C_1-C_6-alcoxi, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbociclilo, halocarbociclilo, y carbociclil-C_1-C_6-alquilo, y/o

sustituido en el mismo átomo con dos sustituyentes seleccionados independientemente del grupo formado por alquilo y haloalquilo, donde los dos sustituyentes juntos forman C_3-C_6-cicloalquilo o halo-C_3-C_6-cicloalquilo.

[620] En algunas realizaciones preferidas, E^5 es heterociclilo que es:

sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, ceto, C_1-C_6-alquilo, halo-C_1-C_6-alquilo, C_1-C_6-alcoxi, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno,

876

$-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_z-R^5$, carbociclilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo, y carbociclil-C_1-C_6-alquilo sustituido con halógeno, y/o

sustituido en el mismo átomo con dos sustituyentes seleccionados independientemente del grupo formado por alquilo y haloalquilo, donde los dos sustituyentes juntos forman C_3-C_6-cicloalquilo o halo-C_3-C_6-cicloalquilo.

[621] R^1 y R^2 se seleccionan independientemente del grupo formado por -H y alquilo. El alquilo es optativamente sustituido.

[622] En algunas realizaciones preferidas, R^1 y R^2 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, y halo-C_1-C_6-alquilo.

[623] R^3 y R^4 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, C_1-C_6-alcoxicarbonilo, C_1-C_6-alquilcarbonilo, carbociclil-C_1-C_6-alquilo, y carbociclil-C_1-C_6-alcoxicarbonilo.

[624] R^5 y R^6 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo es optativamente sustituido con uno o más halógenos.

[625] En algunas realizaciones preferidas, R^5 y R^6 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo es optativamente sustituido con uno o más halógenos.

877

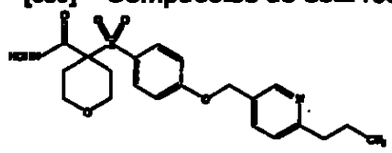
[626] R^7 es -H, C_1-C_6-alquilo, -O-R^8, -N(R^8)(R^9), carbociclil-C_1-C_6-alquilo, o heterociclil-C_1-C_6-alquilo. El alquilo, carbociclilalquilo, o heterociclilalquilo puede ser sustituido con uno o más halógenos.

[627] En algunas realizaciones preferidas, R^7 es -H, C_1-C_6-alquilo, -O-R^8, -N(R^8)(R^9), carbociclil-C_1-C_6-alquilo, o heterociclil-C_1-C_6-alquilo. El alquilo, carbociclilalquilo, y heterociclilalquilo son optativamente sustituidos con uno o más halógenos.

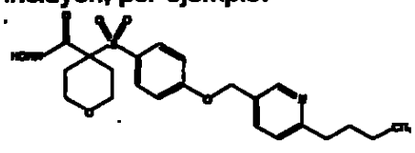
[628] R^8 y R^9 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo es optativamente sustituido con uno o más halógenos.

[629] En algunas realizaciones preferidas, R^8 y R^9 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es –H, cualquier miembro de este grupo es optativamente sustituido con uno o más halógenos.

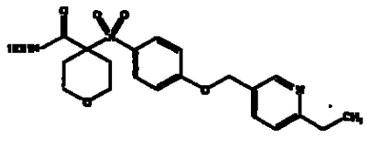
[630] Compuestos de esta realización incluyen, por ejemplo:



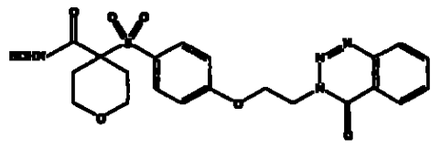
XIX-1



XIX-2



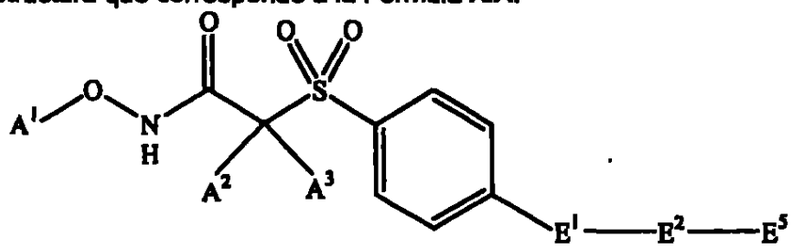
XIX -3



XIX -4

Realización preferida Nro. 19

[631] En algunas realizaciones de esta invención, el compuesto tiene una estructura que corresponde a la Fórmula XIX:



XX

[632] A^1, A^2, y A^3 tienen los valores definidos anteriormente para la Fórmula I.

[633] E^1 es -O-, $-S(O)_2-$, -S(O)-, $-N(R^1)-$, $-C(O)-N(R^1)-$, $-N(R^1)-C(O)-$, o $-C(R^1)(R^2)-$.

[634] E^2 comprende al menos dos átomos de carbono. E^2 es alquilo, cicloalquilo, alquilcicloalquilo, cicloalquilalquilo, o alquilcicloalquilalquilo. Cualquier miembro de este grupo es optativamente sustituido.

[635] En algunas realizaciones preferidas, E^2 es C_2-C_{20}-alquilo, cicloalquilo, C_1-C_{10}-alquil-cicloalquilo, cicloalquil-C_1-C_{10}-alquilo, o C_1-C_{10}-alquil-cicloalquil-C_1-C_{10}-alquilo. Cualquier miembro de este grupo es optativamente sustituido con uno o más halógenos.

[636] En algunas realizaciones preferidas, E^2 es C_2-C_8-alquilo. El alquilo puede ser optativamente sustituido con uno o más halógenos.

[637] E^5 es heterociclilo optativamente sustituido.

[638] En algunas realizaciones preferidas, E^5 es heterociclilo que es:

optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, -CN, ceto, C_1-C_8-alquilo, halo-C_1-C_8-alquilo, C_1-C_8-alcoxi,

halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno , $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbociclilo, halocarbociclilo, y carbociclil-C_1-C_6-alquilo, y/o

optativamente sustituido en el mismo átomo con dos sustituyentes seleccionados independientemente del grupo formado por alquilo y haloalquilo, donde los dos sustituyentes juntos forman C_5-C_6-cicloalquilo o halo-C_5-C_6-cicloalquilo.

[639] En algunas realizaciones preferidas, E^5 es heterociclilo que es:

optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, -CN, ceto, C_1-C_6-alquilo, halo-C_1-C_6-alquilo, C_1-C_6-alcoxi, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbociclilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo, y carbociclil-C_1-C_6-alquilo sustituido con halógeno, y

optativamente sustituido en el mismo átomo con dos sustituyentes seleccionados independientemente del grupo formado por alquilo y haloalquilo, donde los dos sustituyentes juntos forman C_5-C_6-cicloalquilo o halo-C_5-C_6-cicloalquilo.

[640] R^1 y R^2 se seleccionan independientemente del grupo formado por -H y alquilo. El alquilo es optativamente sustituido.

[641] En algunas realizaciones preferidas, R^1 y R^2 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, y halo-C_1-C_6-alquilo.

[642] En algunas realizaciones preferidas, R^1 y R^2 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, y halo-C_1-C_6-alquilo.

[643] R^3 y R^4 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, C_1-C_6-alcoxicarbonilo, C_1-C_6-alquilcarbonilo, carbociclil-C_1-C_6-alquilo, y carbociclil-C_1-C_6-alcoxicarbonilo.

[644] R^5 y R^6 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es –H, cualquier miembro de este grupo es optativamente sustituido con uno o más halógenos.

[645] En algunas realizaciones preferidas, R^5 y R^6 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es –H, cualquier miembro de este grupo es optativamente sustituido con uno o más halógenos.

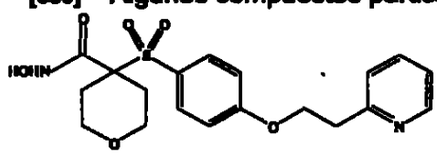
[646] R^7 es -H, C_1-C_6-alquilo, -O-R^8, -N(R^8)(R^9), carbociclil-C_1-C_6-alquilo, o heterociclil-C_1-C_6-alquilo. El alquilo, carbociclilalquilo, y heterociclilalquilo son optativamente sustituidos con uno o más halógenos.

[647] En algunas realizaciones preferidas, R^7 es -H, C_1-C_6-alquilo, -O-R^8, -N(R^8)(R^9), carbociclil-C_1-C_6-alquilo, o heterociclil-C_1-C_6-alquilo. El alquilo, carbociclilalquilo, y heterociclilalquilo son optativamente sustituidos con uno o más halógenos.

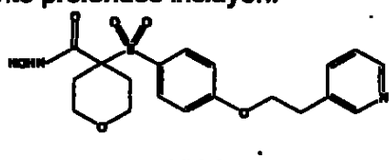
[648] R^8 y R^9 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es –H, cualquier miembro de este grupo es optativamente sustituido con uno o más halógenos.

[649] En algunas realizaciones preferidas, R^8 y R^9 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es –H, cualquier miembro de este grupo es optativamente sustituido con uno o más halógenos.

[650] Algunos compuestos particularmente preferidos incluyen:



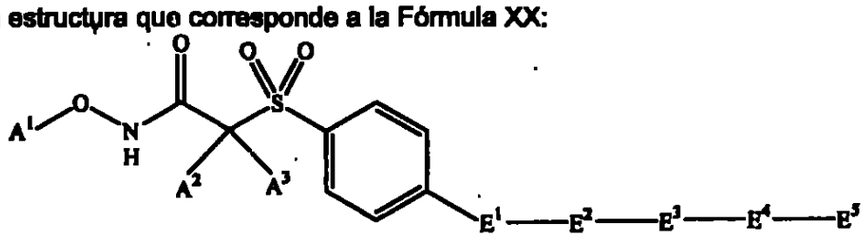
XX-1



XX-2

Realización preferida Nro. 20

[651] En algunas realizaciones de esta invención, el compuesto tiene una estructura que corresponde a la Fórmula XX:



XXI

[652] A^1, A^2, y A^3 tienen los valores definidos anteriormente para la Fórmula I.

[653] E^1 es -O-, -$S(O)_2$-, -S(O)-, -S-, -$N(R^1)$-, -C(O)-$N(R^1)$-, -$N(R^1)$-C(O)-, o -$C(R^1)(R^2)$-.

[654] E^2 es alquilo, cicloalquilo, alquilcicloalquilo, cicloalquilalquilo, o alquilcicloalquilalquilo. Cualquier miembro de este grupo es optativamente sustituido.

[655] En algunas realizaciones preferidas, E^2 es C_2-C_{20}-alquilo, cicloalquilo, C_1-C_{10}-alquilcicloalquilo, cicloalquil-C_1-C_{10}-alquilo, o C_1-C_{10}-

alquilcicloalquil-C_1-C_{10}-alquilo. Cualquier miembro de este grupo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, C_1-C_6-alquilo, y halo-C_1-C_6-alquilo.

[656] En algunas realizaciones preferidas, E^2 es C_2-C_6-alquilo. El alquilo puede ser optativamente sustituido con uno o más halógenos.

[657] E^3 es -C(O)-, -O-(CO)-, -C(O)-O-, -C(NR^3)-, -N(R^4)-, -N(R^4)-C(NR^3)-, -C(NR^3)-N(R^4)-, -C(O)-N(R^4)-, -N(R^4)-C(O)-, -N(R^4)-C(O)-N(R^5)-, -S-, -S(O)-, -N(R^4)-$S(O)_2$-, -$S(O)_2$-N(R^4)-, -C(O)-N(R^4)-N(R^5)-C(O)-, -C(R^4)(R^6)-C(O)-, o -C(R^7)(R^8)-.

[658] E^4 es un enlace, alquilo, o alquenilo. El alquilo y alquenilo son optativamente sustituidos.

[659] En algunas realizaciones preferidas, E^4 es un enlace, C_1-C_{20}-alquilo, o C_2-C_{20}-alquenilo. El alquilo y alquenilo son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, y carbociclilo. El carbociclilo, a su vez, es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno , halocarbociclilo, y carbociclil-C_1-C_6-alquilo sustituido con halógeno.

[660] En algunas realizaciones preferidas, E^4 es un enlace, C_1-C_3-alquilo, o C_2-C_3-alquenilo. El alquilo y alquenilo son optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno y carbociclilo. El carbociclilo, a su vez, es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del

883

grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_8-alquilo, C_1-C_8-alcoxi, C_1-C_8-alcoxi-C_1-C_8-alquilo, carbociclilo, carbociclil-C_1-C_8-alquilo, halo-C_1-C_8-alquilo, halo-C_1-C_8-alcoxi, C_1-C_8-alcoxi-C_1-C_8-alquilo sustituido con halógeno, halocarbociclilo, y carbociclil-C_1-C_8-alquilo sustituido con halógeno.

[661] E^5 es carbociclilo o heterociclilo. El carbociclilo y heterociclilo son:

sustituidos con un sustituyente seleccionado del grupo formado por carbociclilo optativamente sustituido, carbociclilalquilo optativamente sustituido, heterociclilo optativamente sustituido, y heterociclilalquilo optativamente sustituido, y

optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, alquilo, alcoxi, alcoxialquilo, -$N(R^{11})(R^{12})$, -$C(O)(R^{13})$, -S-R^{11}, -$S(O)_2$-R^{11}, carbociclilo, carbociclilalquilo, haloalquilo, haloalcoxi, alcoxialquilo sustituido con halógeno, halocarbociclilo, carbociclilalquilo sustituido con halógeno, hidroxicarbociclilo, y heteroarilo.

[662] En algunas realizaciones preferidas, E^5 es carbociclilo o heterociclilo. El carbociclilo y heterociclilo son:

sustituidos con un sustituyente seleccionado del grupo formado por carbociclilo optativamente sustituido, optativamente-sustituido carbociclil-C_1-C_8-alquilo, heterociclilo optativamente sustituido, y heterociclilo optativamente sustituido-C_1-C_8-alquilo, y

optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_8-alquilo, C_1-C_8-alcoxi, C_1-C_8-alcoxi-C_1-C_8-alquilo, -$N(R^{11})(R^{12})$, -$C(O)(R^{13})$, -S-R^{11}, -$S(O)_2$-R^{11}, carbociclilo, carbociclil-C_1-

884

C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno , halocarbociclilo, carbociclil-C_1-C_6-alquilo sustituido con halógeno, hidroxicarbociclilo, y heteroarilo.

[663] En algunas realizaciones preferidas, E^5 es carbociclilo o heterociclilo, donde el carbociclilo y heterociclilo son:

sustituidos con un sustituyente seleccionado del grupo formado por carbociclilo optativamente sustituido, optativamente-sustituido carbociclil-C_1-C_6-alquilo, heterociclilo optativamente sustituido, y heterociclilo optativamente sustituido-C_1-C_6-alquilo, y

optativamente sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, -$N(R^{11})(R^{12})$, -$C(O)(R^{13})$, -S-R^{11}, -$S(O)_2$-R^{11}, carbociclilo, carbociclil-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, halocarbociclilo, carbociclil-C_1-C_6-alquilo sustituidos con halógeno, hidroxicarbociclilo, y heteroarilo.

[664] R^1 y R^2 se seleccionan independientemente del grupo formado por -H y alquilo. El alquilo es optativamente sustituido.

[665] En algunas realizaciones preferidas, R^1 y R^2 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, y halo-C_1-C_6-alquilo.

[666] En algunas realizaciones preferidas, R^1 y R^2 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, y halo-C_1-C_6-alquilo.

[667] R^3 es -H o -OH.

[668] R^4 y R^5 se seleccionan independientemente del grupo formado por -H, alquilo, carbociclilo, carbociclilalquilo, heterociclilo, y heterociclilalquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo es optativamente sustituido.

[669] En algunas realizaciones preferidas, R^4 y R^5 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es –H, cualquier miembro de este grupo es optativamente sustituido con uno o más halógenos.

[670] En algunas realizaciones preferidas, R^4 y R^5 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo es optativamente sustituido con uno o más halógenos.

[671] R^6 es -CN o –OH.

[672] R^7 es -H, halógeno, -OH, alquilo, alcoxi, o alcoxialquilo. El alquilo, alcoxi, y alcoxialquilo son optativamente sustituidos.

[673] En algunas realizaciones preferidas, R^7 es -H, halógeno, -OH, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, o C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno.

[674] En algunas realizaciones preferidas, R^7 es -H, halógeno, -OH, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, o C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno.

[675] R^8 es -OH o alcoxi. El alcoxi es optativamente sustituido.

[676] En algunas realizaciones preferidas, R^8 es -OH, C_1-C_6-alcoxi, o halo-C_1-C_6-alcoxi.

[677] En algunas realizaciones preferidas, R^8 es -OH, C_1-C_6-alcoxi, o halo-C_1-C_6-alcoxi.

[678] R^9 y R^{10} se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, C_1-C_6-alcoxicarbonilo, C_1-C_6-alquilcarbonilo, carbociclil-C_1-C_6-alquilo, y carbociclil-C_1-C_6-alcoxicarbonilo.

[679] R^{11} y R^{12} se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo es optativamente sustituido con uno o más halógenos.

[680] En algunas realizaciones preferidas, R^{11} y R^{12} se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo es optativamente sustituido con uno o más halógenos.

[681] En algunas realizaciones preferidas, R^{11} y R^{12} se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo es optativamente sustituido con uno o más halógenos.

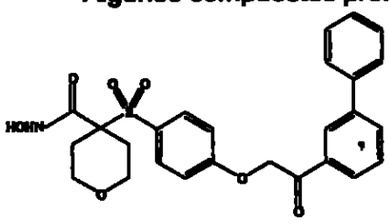
[682] R^{13} es -H, C_1-C_6-alquilo, -O-R^{14}, -N(R^{14})(R^{15}), carbociclil-C_1-C_6-alquilo, heterociclil-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, carbociclil-C_1-C_6-alquilo sustituido con halógeno, o heterociclil-C_1-C_6-alquilo sustituido con halógeno.

[683] En algunas realizaciones preferidas, R^{13} es de -H, C_1-C_6-alquilo, -O-R^{14}, -N(R^{14})(R^{15}), carbociclil-C_1-C_6-alquilo, heterociclil-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, carbociclil-C_1-C_6-alquilo sustituido con halógeno, o heterociclil-C_1-C_6-alquilo sustituido con halógeno.

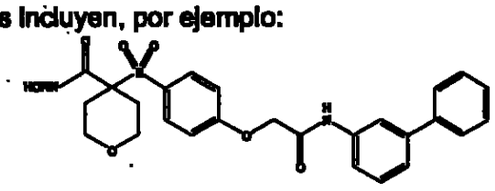
[684] R^{14} y R^{15} se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es –H, cualquier miembro de este grupo es optativamente sustituido con uno o más halógenos.

[685] En algunas realizaciones preferidas, R^{14} y R^{15} se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo. Salvo cuando el miembro es -H, cualquier miembro de este grupo es optativamente sustituido con uno o más halógenos.

Algunos compuestos preferidos incluyen, por ejemplo:



XXI-1



XXI-2

A-2. Selectividades preferidas

[686] El compuesto de hidroxamato o su sal preferentemente tiene una actividad inhibidora contra MMP-1 o MMP-14 que es substancialmente menos de su actividad inhibidora contra MMP-2, MMP-9, o MMP-13. En otras palabras, el compuesto de hidroxamato o su sal preferentemente tiene una constante inhibición contra al menos una de MMP-2, MMP-9, y MMP-13 que es no mayor de aproximadamente 0.1 veces su o sus constante(s) inhibición(es) contra al menos una de MMP-1 y MMP-14. La constante inhibición de un compuesto o sal del mismo puede determinarse usando un ensayo de inhibición in vitro, tal como el ensayo K_i que se describe en los Ejemplos 55-89.

[687] En algunas realizaciones particularmente preferidas, el compuesto de hidroxamato o su sal preferentemente tiene un K_i contra MMP-2 que es no mayor de aproximadamente 0.1 (más preferentemente no mayor de aproximadamente 0.01, aún más preferentemente no mayor de aproximadamente 0.001, todavía más preferentemente no mayor de aproximadamente 0.0001, y todavía aún más preferentemente no mayor de aproximadamente 0.00001) veces su o sus K_i contra una o ambas de MMP-1 y MMP-14.

[688] En algunas realizaciones particularmente preferidas, el compuesto de hidroxamato o su sal preferentemente tiene un K_i contra MMP-9 que es no mayor de aproximadamente 0.1 (más preferentemente no mayor de aproximadamente 0.01, aún más preferentemente no mayor de aproximadamente 0.001, todavía más preferentemente no mayor de aproximadamente 0.0001, y todavía aún más preferentemente no mayor de aproximadamente 0.00001) veces su o sus K_i contra una o ambas de MMP-1 y MMP-14.

[689] En algunas realizaciones particularmente preferidas, el compuesto de hidroxamato o su sal preferentemente tiene un K_i contra MMP-13 que es no mayor de aproximadamente 0.1 (más preferentemente no mayor de aproximadamente 0.01, aún más preferentemente no mayor de aproximadamente 0.001, todavía más preferentemente no mayor de aproximadamente 0.0001, y todavía aún más preferentemente no mayor de aproximadamente 0.00001) veces su o sus K_i contra una o ambas de MMP-1 y MMP-14. Se estima que dicho perfil de selectividad es generalmente particularmente preferido para prevenir o tratar, por ejemplo, un trastorno cardiovascular o artritis.

889

[690] En algunas realizaciones particularmente preferidas, el compuesto de hidroxamato o su sal preferentemente tiene un K_i contra ambas MMP-2 y MMP-9 que no son mayores de aproximadamente 0.1 (más preferentemente no mayor de aproximadamente 0.01, aún más preferentemente no mayor de aproximadamente 0.001, todavía más preferentemente no mayor de aproximadamente 0.0001, y todavía aún más preferentemente no mayor de aproximadamente 0.00001) veces su o sus K_i contra una o ambas de MMP-1 y MMP-14. Se estima que dicho perfil de selectividad es generalmente particularmente preferido para prevenir o tratar, por ejemplo, cáncer, un trastorno cardiovascular, o un trastorno oftalmológico.

[691] En algunas realizaciones particularmente preferidas, el compuesto de hidroxamato o su sal preferentemente tiene un K_i contra MMP-2, MMP-9, y MMP-13 que no son mayores de aproximadamente 0.1 (más preferentemente no mayor de aproximadamente 0.01, aún más preferentemente no mayor de aproximadamente 0.001, todavía más preferentemente no mayor de aproximadamente 0.0001, y todavía aún más preferentemente no mayor de aproximadamente 0.00001) veces sus K_i contra una o ambas de MMP-1 y MMP-14. Se estima que dicho perfil de selectividad es generalmente particularmente preferido para prevenir o tratar, por ejemplo, cáncer, un trastorno cardiovascular, artritis, o un trastorno oftalmológico.

[692] En algunas realizaciones particularmente preferidas, el compuesto de hidroxamato o su sal preferentemente tiene un K_i contra MMP-2 que es no mayor de aproximadamente 0.1 (más preferentemente no mayor de aproximadamente 0.01, aún más preferentemente no mayor de aproximadamente 0.001, todavía más preferentemente no mayor de

890

aproximadamente 0.0001, y todavía aún más preferentemente no mayor de aproximadamente 0.00001) veces sus K_i contra ambas MMP-1 y MMP-14.

[693] En algunas realizaciones particularmente preferidas, el compuesto de hidroxamato o su sal preferentemente tiene un K_i contra MMP-9 que es no mayor de aproximadamente 0.1 (más preferentemente no mayor de aproximadamente 0.01, aún más preferentemente no mayor de aproximadamente 0.001, todavía más preferentemente no mayor de aproximadamente 0.0001, y todavía aún más preferentemente no mayor de aproximadamente 0.00001) veces sus K_i contra ambas MMP-1 y MMP-14.

[694] En algunas realizaciones particularmente preferidas, el compuesto de hidroxamato o su sal preferentemente tiene un K_i contra MMP-13 que es no mayor de aproximadamente 0.1 (más preferentemente no mayor de aproximadamente 0.01, aún más preferentemente no mayor de aproximadamente 0.001, todavía más preferentemente no mayor de aproximadamente 0.0001, y todavía aún más preferentemente no mayor de aproximadamente 0.00001) veces sus K_i contra ambas MMP-1 y MMP-14. Se estima que dicho perfil de selectividad es generalmente particularmente preferido para prevenir o tratar, por ejemplo, un trastorno cardiovascular o artritis.

[695] En algunas realizaciones particularmente preferidas, el compuesto de hidroxamato o su sal preferentemente tiene un K_i contra ambas MMP-2 y MMP-9 que no son mayores de aproximadamente 0.1 (más preferentemente no mayor de aproximadamente 0.01, aún más preferentemente no mayor de aproximadamente 0.001, todavía más preferentemente no mayor de aproximadamente 0.0001, y todavía aún más preferentemente no mayor de aproximadamente 0.00001) veces sus K_i contra

ambas de MMP-1 y MMP-14. Se estima que dicho perfil de selectividad es generalmente particularmente preferido para prevenir o tratar, por ejemplo, cáncer, un trastorno cardiovascular, o un trastorno oftalmológico.

[696] En algunas realizaciones particularmente preferidas, el compuesto de hidroxamato o su sal preferentemente tiene un K_i contra todas las MMP-2, MMP-9, y MMP-3 que no son mayores de aproximadamente 0.1 (más preferentemente no mayor de aproximadamente 0.01, aún más preferentemente no mayor de aproximadamente 0.001, todavía más preferentemente no mayor de aproximadamente 0.0001, y todavía aún más preferentemente no mayor de aproximadamente 0.00001) veces sus K_i contra ambas de MMP-1 y MMP-14. Se estima que dicho perfil de selectividad es generalmente particularmente preferido para prevenir o tratar, por ejemplo, cáncer, un trastorno cardiovascular, artritis, o un trastorno oftalmológico.

[697] La actividad y selectividad de un compuesto de hidroxamato o su sal puede determinarse usando un ensayo de IC_{50} in vitro, tal como el ensayo de IC_{50} que se describe en los Ejemplos 55-89. En otras palabras, el compuesto de hidroxamato o su sal preferentemente tiene valor de IC_{50} contra al menos una de MMP-2, MMP-9, y MMP-13 que es no mayor de aproximadamente 0.1 veces su o sus valores IC_{50} contra al menos una de MMP-1 y MMP-14.

[698] En algunas realizaciones particularmente preferidas, el compuesto de hidroxamato o su sal preferentemente tiene valor de IC_{50} contra MMP-2 que es no mayor de aproximadamente 0.1 (más preferentemente no mayor de aproximadamente 0.01, aún más preferentemente no mayor de aproximadamente 0.001, todavía más preferentemente no mayor de aproximadamente 0.0001, y todavía aún más preferentemente no mayor de

892 274

aproximadamente 0.00001) veces su o sus valores IC_{50} contra una o ambas de MMP-1 y MMP-14.

[699] En algunas realizaciones particularmente preferidas, el compuesto de hidroxamato o su sal preferentemente tiene valor de IC_{50} contra MMP-9 que es no mayor de aproximadamente 0.1 (más preferentemente no mayor de aproximadamente 0.01, aún más preferentemente no mayor de aproximadamente 0.001, todavía más preferentemente no mayor de aproximadamente 0.0001, y todavía aún más preferentemente no mayor de aproximadamente 0.00001) veces su o sus valores IC_{50} contra una o ambas de MMP-1 y MMP-14.

[700] En algunas realizaciones particularmente preferidas, el compuesto de hidroxamato o su sal preferentemente tiene valor de IC_{50} contra MMP-13 que es no mayor de aproximadamente 0.1 (más preferentemente no mayor de aproximadamente 0.01, aún más preferentemente no mayor de aproximadamente 0.001, todavía más preferentemente no mayor de aproximadamente 0.0001, y todavía aún más preferentemente no mayor de aproximadamente 0.00001) veces su o sus valores IC_{50} contra una o ambas de MMP-1 y MMP-14. Se estima que dicho perfil de selectividad es generalmente particularmente preferido para prevenir o tratar, por ejemplo, un trastorno cardiovascular o artritis.

[701] En algunas realizaciones particularmente preferidas, el compuesto de hidroxamato o su sal preferentemente tiene valores IC_{50} contra ambas MMP-2 y MMP-9 que no son mayores de aproximadamente 0.1 (más preferentemente no mayor de aproximadamente 0.01, aún más preferentemente no mayor de aproximadamente 0.001, todavía más preferentemente no mayor de aproximadamente 0.0001, y todavía aún más

893

preferentemente no mayor de aproximadamente 0.00001) veces su o sus valores IC_{50} contra una o ambas de MMP-1 y MMP-14. Se estima que dicho perfil de selectividad es generalmente particularmente preferido para prevenir o tratar, por ejemplo, cáncer, un trastorno cardiovascular, o un trastorno oftalmológico.

[702] En algunas realizaciones particularmente preferidas, el compuesto de hidroxamato o su sal preferentemente tiene valores IC_{50} contra MMP-2, MMP-9, y MMP-13 que no son mayores de aproximadamente 0.1 (más preferentemente no mayor de aproximadamente 0.01, aún más preferentemente no mayor de aproximadamente 0.001, todavía más preferentemente no mayor de aproximadamente 0.0001, y todavía aún más preferentemente no mayor de aproximadamente 0.00001) veces su o sus valores IC_{50} contra una o ambas de MMP-1 y MMP-14. Se estima que dicho perfil de selectividad es generalmente particularmente preferido para prevenir o tratar, por ejemplo, cáncer, un trastorno cardiovascular, artritis, o un trastorno oftalmológico.

[703] En algunas realizaciones particularmente preferidas, el compuesto de hidroxamato o su sal preferentemente tiene valor de IC_{50} contra MMP-2 que es no mayor de aproximadamente 0.1 (más preferentemente no mayor de aproximadamente 0.01, aún más preferentemente no mayor de aproximadamente 0.001, todavía más preferentemente no mayor de aproximadamente 0.0001, y todavía aún más preferentemente no mayor de aproximadamente 0.00001) veces sus valores de IC_{50} contra ambas MMP-1 y MMP-14.

[704] En algunas realizaciones particularmente preferidas, el compuesto de hidroxamato o su sal preferentemente tiene valor de IC_{50} contra

894

MMP-9 que es no mayor de aproximadamente 0.1 (más preferentemente no mayor de aproximadamente 0.01, aún más preferentemente no mayor de aproximadamente 0.001, todavía más preferentemente no mayor de aproximadamente 0.0001, y todavía aún más preferentemente no mayor de aproximadamente 0.00001) veces sus valores de IC_{50} contra ambas MMP-1 y MMP-14.

[705] En algunas realizaciones particularmente preferidas, el compuesto de hidroxamato o su sal preferentemente tiene valor de IC_{50} contra MMP-13 que es no mayor de aproximadamente 0.1 (más preferentemente no mayor de aproximadamente 0.01, aún más preferentemente no mayor de aproximadamente 0.001, todavía más preferentemente no mayor de aproximadamente 0.0001, y todavía aún más preferentemente no mayor de aproximadamente 0.00001) veces sus valores de IC_{50} contra ambas MMP-1 y MMP-14. Se estima que dicho perfil de selectividad es generalmente particularmente preferido para prevenir o tratar, por ejemplo, un trastorno cardiovascular o artritis.

[706] En algunas realizaciones particularmente preferidas, el compuesto de hidroxamato o su sal preferentemente tiene valores IC_{50} contra ambas MMP-2 y MMP-9 que no son mayores de aproximadamente 0.1 (más preferentemente no mayor de aproximadamente 0.01, aún más preferentemente no mayor de aproximadamente 0.001, todavía más preferentemente no mayor de aproximadamente 0.0001, y todavía aún más preferentemente no mayor de aproximadamente 0.00001) veces sus valores de IC_{50} contra ambas de MMP-1 y MMP-14. Se estima que dicho perfil de selectividad es generalmente particularmente preferido para prevenir o tratar, por ejemplo, cáncer, un trastorno cardiovascular, o un trastorno oftalmológico.

895

[707] En algunas realizaciones particularmente preferidas, el compuesto de hidroxamato o su sal preferentemente tiene valores IC_{50} contra todas las MMP-2, MMP-9, y MMP-3 que no son mayores de aproximadamente 0.1 (más preferentemente no mayor de aproximadamente 0.01, aún más preferentemente no mayor de aproximadamente 0.001, todavía más preferentemente no mayor de aproximadamente 0.0001, y todavía aún más preferentemente no mayor de aproximadamente 0.00001) veces sus valores de IC_{50} contra ambas de MMP-1 y MMP-14. Se estima que dicho perfil de selectividad es generalmente particularmente preferido para prevenir o tratar, por ejemplo, cáncer, un trastorno cardiovascular, artritis, o un trastorno oftalmológico.

B. Sales de los compuestos de esta invención

[708] Los compuestos de esta invención se pueden usar en la forma de sales derivadas de ácidos inorgánicos u orgánicos. Según el compuesto particular, puede ser ventajosa utilizar la sal del compuesto debido a una o varias propiedades físicas de dicha sal, tal como una mayor estabilidad farmacéutica a diferentes temperaturas y grados de humedad o la solubilidad deseada en agua o aceite. En algunos casos, la sal de los compuestos también se puede usar para facilitar el aislamiento, la purificación y/o la resolución de los compuestos.

[709] Cuando el uso pretendido de la sal es la administración a un paciente (en oposición, por ejemplo, a su uso en un contexto in vitro), la sal es preferentemente aceptable para uso farmacéutico. Las sales incluyen las sales usadas comúnmente para formar sales de metales alcalinos y para formar sales de adición de ácidos libres o de bases libres. En general, estas sales se pueden preparar típicamente utilizando los medios convencionales con un

896

compuesto de esta invención haciendo reaccionar, por ejemplo, el ácido o la base apropiada con el compuesto.

[710] Las sales de adición ácida aceptables para uso farmacéutico de los compuestos de esta invención se pueden preparar a partir de un ácido inorgánico u orgánico. Los ejemplos de ácidos inorgánicos adecuados incluyen los ácidos clorhídrico, bromhídrico, iodhídrico, carbónico, sulfúrico y fosfórico. Los ácidos orgánicos adecuados incluyen generalmente, por ejemplo, las clases de ácidos orgánicos alifáticos, cicloalifáticos, aromáticos, araliféticos, heterocíclicos, carboxílicos y sulfónicos. Los ejemplos específicos de ácidos orgánicos adecuados incluyen acetato, trifluoroacetato, formiato, propionato, succinato, glicolato, gluconato, digluconato, lactato, malato, ácido tartárico, citrato, ascorbato, glucoronato, maleato, fumarato, piruvato, aspartato, glutamato, benzoato, ácido antranílico, mesilato, estearato, salicilato, p-hidroxibenzoato, fenilacetato, mandelato, embonato (pamoato), metansulfonato, etansulfonato, bencensulfonato, pantotenato, toluensulfonato, 2-hidroxietansulfonato, sulfanilato, ciclohexilaminosulfonato, ácido algínico, ácido b-hidroxibutírico, galactarato, galacturonato, adipato, alginato, bisulfato, butirato, alcanforato, alcanforsulfonato, ciclopentanpropionato, dodecilsulfato, glicoheptanoato, glicerofosfato, hemisulfato, heptanoato, hexanoato, nicotinato, 2-naftalensulfonato, oxalato, palmoato, pectinato, persulfato, 3-fenilpropionato, picrato, pivalato, tiocianato, tosilato y undecanoato.

[711] Las sales de adición básica aceptables para uso farmacéutico de los compuestos de esta invención incluyen, por ejemplo, sales de metales y sales orgánicas. Las sales de metales preferidas incluyen sales de metales alcalinos (grupo Ia), sales de metales alcalino-térreos (grupo IIa) y otras sales de metales fisiológicamente aceptables. Dichas sales se pueden elaborar con

aluminio, calcio, litio, magnesio, potasio, sodio y zinc. Las sales orgánicas preferidas se pueden elaborar a partir de sales de aminas terciarias y cuaternarias, tal como trimetilamina, dietilamina, N,N'-dibenciletilendiamina, cloroprocaína, colina, dietanolamina, etilendiamina, meglumin-(N-metilglucamina) y procaína. Los grupos básicos que contienen nitrógeno se pueden cuaternizar con agentes tales como haluros de alquilo inferior (C_1-C_6) (por ejemplo, cloruros, bromuros y ioduros de metilo, etilo, propilo y butilo), dialquilsulfatos (por ejemplo, sulfatos de dimetilo, dietilo, dibutilo y diamilo), haluro de cadena larga (por ejemplo, cloruros, bromuros y loduros de decilo, laurilo, miristilo y estearilo), haluros de aralquilo (por ejemplo, bromuros de bencilo y fenetilo) y otras.

[712] Las sales particularmente preferidas de los compuestos de esta invención incluyen sales de ácidos clorhídrico (HCl) y las sales trifluoroacetato (CF_3COOH o TFA).

C. Prevención o tratamiento de afecciones usando los compuestos y las sales de esta invención

[713] Una realización de esta invención tiene como objeto un proceso para prevenir o tratar una condición patológica asociada con la actividad MMP en un mamífero (por ejemplo, un ser humano, un animal de compañía, un animal de granja, un animal de laboratorio, un animal de zoológico o un animal salvaje) que padecen o tienen predisposición de padecer dicha condición. Dicha condición puede ser, por ejemplo, destrucción de tejidos, una enfermedad fibrótica, debilitación patológica de la matriz, reparación deficiente de heridas, una enfermedad cardiovascular, una enfermedad pulmonar, una enfermedad renal, una enfermedad hepática, una enfermedad oftalmológica o una enfermedad del sistema nervioso central. Los ejemplos específicos de

dichas afecciones incluyen osteoartritis, artritis reumatoidea, artritis séptica, invasión tumoral, metástasis tumoral, angiogénesis tumoral, una úlcera de decúbito, una úlcera gástrica, una úlcera de córnea, enfermedad periodonal, cirrosis hepática, enfermedad fibrótica pulmonar, otoesclerosis, ateroesclerosis, esclerosis múltiple, cardiomiopatía dilatada, ulceración epidérmica, epidermólisis ampollar, aneurisma aórtico, reparación de lesiones leves, una adherencia , escarificación, deficiencia cardiaca congestiva, infarto pos-miocárdico, trombosis coronaria, enfisema, proteinuria, enfermedad ósea, enfermedades de obstrucción pulmonar crónica y mal de Alzheimer.

[714] En algunas realizaciones particularmente preferidas, la condición comprende artritis.

[715] En algunas realizaciones particularmente preferidas, la condición comprende metástasis tumoral, invasión tumoral o angiogénesis tumoral.

[716] En algunas realizaciones particularmente preferidas, la condición comprende enfermedad periodontal.

[717] En algunas realizaciones particularmente preferidas, la condición comprende aterosclerosis.

[718] En algunas realizaciones particularmente preferidas, la condición comprende esclerosis múltiple.

[719] En algunas realizaciones particularmente preferidas, la condición comprende cardiomiopatía dilatada.

[720] En algunas realizaciones particularmente preferidas, la condición comprende infarto pos-miocardial.

[721] En algunas realizaciones particularmente preferidas, la condición comprende deficiencia cardiaca congestiva.

899

[722] En algunas realizaciones particularmente preferidas, la condición comprende enfermedad de obstrucción pulmonar crónica.

[723] Como alternativa (o además) la condición puede estar asociada con la actividad TNF-α convertasa. Los ejemplos de dichas afecciones incluyen inflamación (por ejemplo, artritis reumatoidea), enfermedades autoinmunes, rechazo de injertos, esclerosis múltiple, una enfermedad fibrótica, cáncer, una enfermedad infecciosa (por ejemplo, malaria, infección micobacteriana, meningitis, etc.), fiebre, psoriasis, una enfermedad cardiovascular (por ejemplo, lesiones por reperfusión post-isquémica y deficiencia cardiaca congestiva), una enfermedad pulmonar, hemorragia, coagulación, lesiones alveolares hiperóxicas, lesiones por radiación, respuestas de fase aguda como las observadas con infecciones y sepsis y durante shock (por ejemplo, shock séptico, shock hemodinámico, etc.), caquexia y anorexia.

[724] Como alternativa (o además) la condición puede estar asociada con la actividad agrecanasa. Los ejemplos de dichas afecciones incluyen enfermedades inflamatorias (por ejemplo, osteoartritis, artritis reumatoidea, lesiones articulares, artritis reactiva, artritis aguda de pirofosfato y artritis psoriática) y cáncer.

[725] En esta patente, la frase "prevenir una condición" significa reducir (o demorar) el riesgo de comenzar la condición en un mamífero que no padece dicha condición, pero que tiene predisposición de padecerla. Por el contrario, la frase "tratar una condición" significa aliviar, suprimir o erradicar una condición existente. La condición patológica puede ser (a) el resultado de una actividad MMP patológica en sí misma y/o (b) afectada por una actividad MMP (por ejemplo, las enfermedades asociadas con TNF-α).

900

[726] Se puede emplear una amplia variedad de métodos ya sea solos o combinados para administrar los hidroxamatos y las sales de los mismos que se describieron previamente. Por ejemplo, los hidroxamatos o las sales de los mismos se pueden administrar por vía oral, parenteral, con atomizador inhalante, por vía rectal o tópicamente.

[727] Típicamente, los compuestos (o una sal aceptable para uso farmacéutico de los mismos) que se describen en este documento se administran en una cantidad efectiva para inhibir una o varias MMP blanco. La o las MMP blanco comprenden típicamente MMP-2, MMP-9 y/o MMP-13, siendo la MMP-13 en general un blanco particularmente preferido. La dosis diaria total preferida de hidroxamato o de una sal del mismo (administrada como dosis únicas o divididas) comprende típicamente entre aproximadamente 0,001 y aproximadamente 100 mg/kg, más preferentemente entre aproximadamente 0,001 y aproximadamente 30 mg/kg y más preferentemente aún entre aproximadamente 0,01 y aproximadamente 10 mg/kg (es decir, mg de hidroxamato o sal del mismo por kg de peso corporal). Las composiciones de dosificación unitaria pueden contener dichas cantidades o submúltiplos de los mismos para conformar la dosis diaria. En muchos casos, la administración del compuesto o de la sal se repetirá una pluralidad de veces. Típicamente, se pueden usar múltiples dosis por día para incrementar la dosis diaria total, si así se deseara.

[728] Los factores que afectan el régimen de dosificación preferido incluyen el tipo, edad, peso, sexo, dieta y estado de salud del paciente; la severidad de la condición patológica; la ruta de administración; consideraciones farmacológicas, tal como la actividad, eficacia, perfiles farmacocinéticos y toxicológicos del hidroxamato o una sal del mismo

particular empleado; del uso de un sistema de administración de fármacos; y si el hidroxamato o la sal del mismo se administra como parte de una combinación de fármacos. Por consiguiente, el régimen de dosificación realmente empleado puede variar ampliamente y, por lo tanto, puede apartarse del régimen de dosificación preferido recién descripto.

D. Composiciones farmacéuticas que contienen los compuestos y las sales de esta invención

[729] Esta invención también tiene como objeto composiciones farmacéuticas que comprenden un hidroxamato, o una sal del mismo, descripto previamente, y métodos para elaborar dichas composiciones farmacéuticas (o medicamentos) que contienen un hidroxamato, o una sal del mismo, descripto previamente.

[730] La composición preferida depende del método de administración y comprende típicamente uno o varios transportadores, adyuvantes y/o vehículos convencionales aceptables para uso farmacéutico. La formulación de drogas se describe en general en, por ejemplo, Hoover, John E., Remington's Pharmaceutical Sciences (Mack Publishing Co., Easton, PA: 1975). Véase también, Liberman, H.A. Véase también, Lachman, L., eds., Pharmaceutical Dosage Form (Marcel Decker, Nueva York, N.Y., 1980).

[731] Las formas de dosificación sólidas para una administración por vía oral incluyen cápsulas, tabletas, píldoras, polvos y gránulos. En dichas formas de dosificación sólidas, los hidroxamatos o las sales de los mismos se combinan con uno o varios adyuvantes. Si se administran per os, los hidroxamatos o las sales de los mismos se mezclan con lactosa, sacarosa, almidón en polvo, ésteres celulósicos de ácidos alcanoicos, alquilésteres de celulosa, talco, ácido esteárico, estearato de magnesio, óxido de magnesio,

902

sales de sodio y calcio de ácidos fosfórico y sulfúrico, gelatina, goma de acacia, alginato de sodio, polivinilpirrolidona y/o alcohol polivinílico, y luego se pueden encapsular o conformar en tabletas para una administración conveniente. Dichas cápsulas o tabletas pueden contener una formulación de liberación controlada, provista en una dispersión del compuesto activo en hidroxipropilmetilcelulosa. En el caso de cápsulas, tabletas y píldoras, las formas de dosificación también pueden comprender agentes reguladores, tales como citrato de sodio, carbonato o bicarbonato de magnesio o calcio. Las tabletas y píldoras se pueden preparar además con recubrimientos entéricos.

[732] Las formas de dosificación líquidas para la administración por vía oral pueden incluir emulsiones, soluciones, suspensiones, jarabes y elixires que contengan los diluyentes inertes habitualmente conocidos en el arte (por ejemplo, agua). Dichas composiciones también pueden comprender adyuvantes, tales como agentes humectantes, agentes emulsionantes y de suspensión y agentes saborizantes (por ejemplo, edulcorantes) y de perfumes.

[733] Una "administración parenteral" incluye inyecciones subcutáneas, inyecciones intravenosas, inyecciones intramusculares, inyecciones intraesternales e infusiones. Las preparaciones inyectables (por ejemplo, suspensiones acuosas u oleaginosas inyectables) se pueden formular como es sabido en el arte usando los agentes de dispersión, humectantes y/o de suspensión adecuados. Los vehículos y solventes aceptables incluyen, por ejemplo, agua, 1,3-butandiol, solución de Ringer, solución isotónica de cloruro de sodio, aceites (por ejemplo, mono- o diglicéridos sintéticos), ácidos grasos (por ejemplo, ácido oleico), dimetilacetamida, agentes tensioactivos (por ejemplo, detergentes iónicos y no iónicos) y/o polietilenglicoles.

903

[734] Las formulaciones para la administración por vía parenteral se pueden preparar, por ejemplo, a partir de polvos o gránulos estériles que poseen uno o más de los vehículos o diluyentes mencionados para su uso en las formulaciones de administración por vía oral. Los hidroxamatos o las sales de los mismos se pueden disolver en agua, polietilenglicol, propilenglicol, etanol, aceite de maíz, aceite de semillas de algodón, aceite de maní, aceite de sésamo, alcohol bencílico, cloruro de sodio y/o diversos buffers.

[735] Los supositorios para la administración por vía rectal se pueden preparar, por ejemplo, mezclando la droga con un excipiente no irritante adecuado, tal como manteca de cacao, mono, di o triglicéridos sintéticos, ácidos grasos y polietilenglicoles, comercializados a temperaturas normales pero que son líquidos a la temperatura rectal y que por consiguiente se derriten en el recto y de esa manera liberan la droga. Los excipientes adecuados incluyen, por ejemplo, manteca de cacao; mono-, di- o triglicéridos sintéticos; ácidos grasos; y/o polietilenglicoles.

[736] La "administración tópica" incluye el uso de una administración transdérmica, tal como parches transdérmicos o dispositivos de iontoforesis.

[737] También se pueden usar otros adyuvantes y modos de administración bien conocidos en el arte farmacéutico.

E. Definiciones

[738] El término "alquilo" (ya sea solo o en combinación con otro(s) término(s)) se refiere una cadena lineal o ramificada saturada de hidrocarbilo que típicamente contiene entre 1 y 20 átomos de carbono aproximadamente, más típicamente entre 1 y 8 átomos de carbono aproximadamente y más típicamente aún entre 1 y aproximadamente 6 átomos de carbono aproximadamente. Los ejemplos de tales sustituyentes incluyen metilo, etilo, n-

propilo, isopropilo, n-butilo, isobutilo, sec-butilo, ter-butilo, pentilo, iso-amilo, hexilo, octilo y semejantes.

[739] El término "alquenilo" (ya sea solo o en combinación con otro(s) término(s)) se refiere a una cadena lineal o ramificada de hidrocarbilo que contiene uno o varios enlaces dobles y típicamente entre 2 y 20 átomos de carbono aproximadamente, más típicamente entre aproximadamente 2 y aproximadamente 8 átomos de carbono y más típicamente aún entre aproximadamente 2 y aproximadamente 6 átomos de carbono. Los ejemplos de tales sustituyentes incluyen etenilo (vinilo); 2-propenilo; 3-propenilo; 1,4-pentadienilo; 1,4-butadienilo; 1-butenilo; 2-butenilo; 3-butenilo; decenilo; y semejantes.

[740] El término "alquinilo" (ya sea solo o en combinación con otro(s) término(s)) se refiere a una cadena lineal o ramificada de hidrocarbilo que contiene uno o más enlaces triples y típicamente entre 2 y 20 átomos de carbono aproximadamente, más típicamente entre aproximadamente 2 y aproximadamente 8 átomos de carbono, y más típicamente aún entre aproximadamente 2 y aproximadamente 6 átomos de carbono. Los ejemplos de tales sustituyentes incluyen etinilo, 2-propinilo, 3-propinilo, decenilo, 1-butinilo, 2-butinilo, 3-butinilo y semejantes.

[741] El término "carbociclilo" (ya sea solo o en combinación con otro(s) término(s)) se refiere a un cíclico saturado (es decir, "cicloalquilo"), cíclico parcialmente saturado o arilhidrocarbilo que contiene entre 3 y 14 átomos de carbono en el anillo (los "átomos del anillo" son los átomos unidos entre sí para forma el o los anillos de un grupo cíclico). Un carbociclilo puede ser un solo anillo, que típicamente contiene entre 3 y 6 átomos del anillo. Los ejemplos de dichos carbociclicos de un solo anillo incluyen ciclopropanilo,

905

ciclobutanilo, ciclopentilo, ciclopentenilo, ciclopentadienilo, ciclohexilo, ciclohexenilo, ciclohexadienilo y fenilo. Como alternativa, el carbociclilo puede estar formado por 2 ó 3 anillos fusionados entre sí, tal como naftalenilo, tetrahidronaftalenilo (también conocido como "tetralinilo"), indenilo, isoindenilo, indanilo, biciclodecanilo, antracenilo, fenantreno, benzonaftenilo (también conocido "fenalenilo"), fluorenelio, decalinilo y norpinanilo.

[742] El término "cicloalquilo" (ya sea solo o en combinación con otro(s) término(s)) se refiere a un hidrocarbilo cíclico saturado que contiene entre 3 y 14 átomos de carbono en el anillo. El cicloalquilo puede ser un solo anillo de carbono, que típicamente contiene entre 3 y 6 átomos de carbono en el anillo. Los ejemplos de cicloalquilos de un solo anillo incluyen ciclopropilo (o "ciclopropanilo"), ciclobutilo (o "ciclobutanilo"), ciclopentilo (o "ciclopentanilo") y ciclohexilo (o "ciclohexanilo"). Como alternativa, el cicloalquilo puede estar formado por 2 ó 3 anillos de carbono fusionados entre sí, tal como, decalinilo o norpinanilo.

[743] El término "arilo" (ya sea solo o en combinación con otro(s) término(s)) se refiere a un carbociclilo aromático que contiene entre 6 y 14 átomos de carbono en el anillo. Los ejemplos de arilos incluyen fenilo, naftalenilo e indenilo.

[744] En algunos casos, la cantidad de átomos de carbono en un hidrocarbilo (por ejemplo, alquilo, alquenilo, alquinilo o cicloalquilo) está indicada por el prefijo "C_x-C_y-", donde x es la cantidad mínima e y es la cantidad máxima de átomos de carbono en el sustituyente. Así, por ejemplo, "C_1-C_6-alquilo" significa un alquilo que contiene entre 1 y 6 átomos de carbono. Como ilustración adicional, un C_3-C_6-cicloalquilo significa un anillo hidrocarbilo saturado que contiene entre 3 y 6 átomos de carbono en el anillo.

906

[745] El término "hidrógeno" (ya sea solo o en combinación con otro(s) término(s)) se refiere a un radical hidrógeno y se puede representar con -H.

[746] El término "hidroxi" (ya sea solo o en combinación con otro(s) término(s)) significa -OH.

[747] El término "nitro" (ya sea solo o en combinación con otro(s) término(s)) significa $-NO_2$.

[748] El término "ciano" (ya sea solo o en combinación con otro(s) término(s)) significa -CN; que también se puede representar como:



[749] El término "ceto" (ya sea solo o en combinación con otro(s) término(s)) se refiere a un radical oxo y se puede representar como =O.

[750] El término "carboxi" (ya sea solo o en combinación con otro(s) término(s)) significa -C(O)-OH, que también se puede representar como:



[751] El término "amino" (ya sea solo o en combinación con otro(s) término(s)) significa $-NH_2$. El término "amina monosustituida" (ya sea solo o en combinación con otro(s) término(s)) se refiere a una amina donde uno de los radicales hidrógeno es reemplazado por un sustituyente que no es hidrógeno. El término "amina disustituida" (ya sea solo o en combinación con otro(s) término(s)) se refiere a una amina donde los dos átomos de hidrógeno están reemplazados por sustituyentes que no son hidrógeno, que pueden ser idénticos o diferentes.

907

[752] El término "halógeno" (ya sea solo o en combinación con otro(s) término(s)) se refiere un radical flúor (que puede ser representado como -F), un radical cloro (que puede ser representado como -Cl), un radical bromo (que puede ser representado como -Br) o un radical yodo (que puede ser representado como -I). Típicamente, se prefiere un radical flúor o cloro, siendo en general particularmente preferido un radical flúor.

[753] Si un sustituyente se describe como "sustituido", significa que hay un radical que no es hidrógeno en el lugar de un radical hidrógeno sobre un carbono o nitrógeno del sustituyente. Así, por ejemplo, un sustituyente alquilo sustituido es un sustituyente alquilo en el cual al menos un radical que no es hidrógeno está en el lugar de un radical hidrógeno sobre el sustituyente alquilo. A fines ilustrativos, un monofluoroalquilo es alquilo sustituido con un radical flúor y difluoroalquilo es alquilo sustituido con dos radicales flúor. Se debe tener en cuenta que si hay más que una sustitución sobre un sustituyente, los radical que no es hidrógeno pueden ser idénticos o diferentes (a menos que se indique lo contrario).

[754] Si un sustituyente se describe como "optativamente sustituido", el sustituyente puede estar (1) sustituido o (2) no sustituido.

[755] En esta memoria descriptiva los términos "sustituyente" y "radical" se utilizan indistintamente.

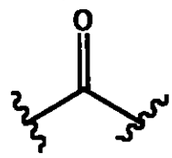
[756] El prefijo "halo" indica que el sustituyente al cual se refiere dicho prefijo está sustituido con uno o varios radicales halógeno seleccionados independientemente entre sí. Por ejemplo, un haloalquilo se refiere a un alquilo en el cual al menos un radical hidrógeno está reemplazado por un radical halógeno. Los ejemplos de haloalquilos incluyen clorometilo, 1-bromoetilo, fluorometilo, difluorometilo, trifluorometilo, 1,1,1-trifluoroetilo y semejantes. A

908

fines ilustrativos, un "haloalcoxi" se refiere a un alcoxi en el cual al menos un radical hidrógeno está reemplazado por un radical halógeno. Los ejemplos de sustituyentes haloalcoxi incluyen clorometoxi, 1-bromoetoxi, fluorometoxi, difluorometoxi, trifluorometoxi (también conocido como "perfluorometoxi"), 1,1,1,-trifluoroetoxi y semejantes. Se debe tener en cuenta que si un sustituyente está sustituido por más de un radical halógeno, dichos radicales halógeno pueden ser idénticos o diferentes (a menos que se indique lo contrario).

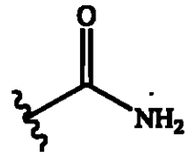
[757] El *prefijo "perhalo" indica que cada radical hidrógeno sobre el* sustituyente al cual está unido el prefijo está reemplazado por radicales halógeno seleccionados independientemente, es decir, cada radical hidrógeno sobre el sustituyente está reemplazado por un radical halógeno. Si todos los radicales halógeno son idénticos, el prefijo identificará típicamente el radical halógeno. Así, por ejemplo, el término "perfluoro" significa que cada radical hidrógeno sobre el sustituyente al cual está unido el prefijo, está sustituido con un radical flúor. A fines ilustrativos, el término "perfluoroalquilo" se refiere a un alquilo donde hay un radical flúor en lugar de cada radical hidrógeno. Los ejemplos de sustituyentes perfluoroalquilo incluyen trifluorometilo ($-CF_3$), perfluorobutilo, perfluoroisopropilo, perfluorododecilo, perfluorodecilo y semejantes. A fines ilustrativos adicionales, el término "perfluoroalcoxi" se refiere a un alcoxi donde cada radical hidrógeno está reemplazado por un radical flúor. Los ejemplos de sustituyentes perfluoroalcoxi incluyen trifluorometoxi ($-O-CF_3$), perfluorobutoxi, perfluoroisopropoxi, perfluorododecoxi, perfluorodecoxi y semejantes.

[758] El término "carbonilo" (ya sea solo o en combinación con otro(s) término(s)) significa -C(O)-, que también se puede representar como:



Este término también pretende abarcar un sustituyente carbonilo hidratado, es decir, $-C(OH)_2-$.

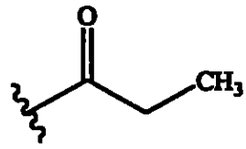
[759] El término "aminocarbonilo" (ya sea solo o en combinación con otro(s) término(s)) significa $-C(O)-NH_2$, que también se puede representar como:



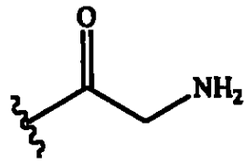
[760] El término "oxi" (ya sea solo o en combinación con otro(s) término(s)) se refiere a un sustituyente éter y se puede representar como -O-.

[761] El término "alcoxi" (ya sea solo o en combinación con otro(s) término(s)) se refiere a un alquiléter, es decir, -O-alquilo. Los ejemplos de dicho sustituyente incluyen metoxi ($-O-CH_3$), etoxi, n-propoxi, isopropoxi, n-butoxi, iso-butoxi, sec-butoxi, ter-butoxi y semejantes.

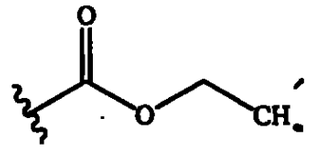
[762] El término "alquilcarbonilo" (ya sea solo o en combinación con otro(s) término(s)) significa -C(O)-alquilo. Por ejemplo, un "etilcarbonilo" se puede representar como:



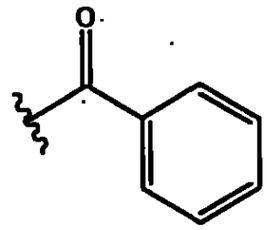
[763] El término "aminoalquilcarbonilo" (ya sea solo o en combinación con otro(s) término(s)) significa $-C(O)-alquil-NH_2$. Por ejemplo, "aminometilcarbonilo" se puede representar como:



[764] El término "alcoxicarbonilo" (ya sea solo o en combinación con otro(s) término(s)) significa -C(O)-O-alquilo. Por ejemplo, un "etoxicarbonilo" se puede representar como:

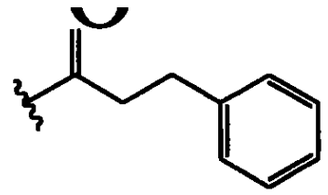


[765] El término "carbociclilcarbonilo" (ya sea solo o en combinación con otro(s) término(s)) significa -C(O)-carbociclilo. Por ejemplo, "fenilcarbonilo" se puede representar como:



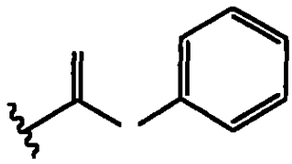
De manera similar, el término "heterociclilcarbonilo" (ya sea solo o en combinación con otro(s) término(s)) significa -C(O)-heterociclilo.

[766] El término "carbociclilalquilcarbonilo" (ya sea solo o en combinación con otro(s) término(s)) significa -C(O)-alquil-carbociclilo. Por ejemplo, "feniletilcarbonilo" se puede representar como:

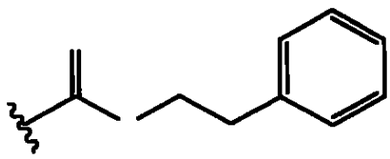


De manera similar, el término "heterociclilalquilcarbonilo" (ya sea solo o en combinación con otro(s) término(s)) significa -C(O)-alquil-heterociclilo.

[767] El término "carbociclíloxicarbonilo" (ya sea solo o en combinación con otro(s) término(s)) significa -C(O)-O-carbociclilo. Por ejemplo, "feniloxicarbonilo" se puede representar como:



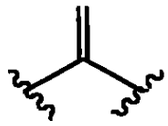
[768] El término "carbociclilalcoxicarbonilo" (ya sea solo o en combinación con otro(s) término(s)) significa -C(O)-O-alquil-carbociclilo. Por ejemplo, "feniletoxicarbonilo" se puede representar como:



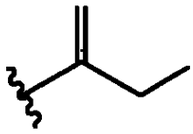
[769] El término "tio" o "tia" (ya sea solo o en combinación con otro(s) término(s)) se refiere a un tiaéter, es decir, un sustituyente éter en el cual hay un átomo de azufre divalente en lugar del átomo de oxígeno del éter. Dicho sustituyente se puede representar como -S-. Entonces, por ejemplo, "alquil-tio-alquilo" se refiere a un alquil-S-alquilo.

[770] El término "tiol" o "sulfhidrilo" (ya sea solo o en combinación con otro(s) término(s)) se refiere a sulfhidrilo y se puede representar como -SH.

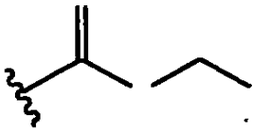
[771] El término "(tiocarbonilo)" (ya sea solo o en combinación con otro(s) término(s)) se refiere a un carbonilo en el cual el átomo de oxígeno ha sido reemplazado por un azufre. Dicho sustituyente se puede representar como -C(S)- y también se puede representar como:



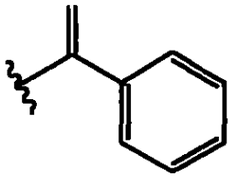
[772] El término "alquil(tiocarbonilo)" (ya sea solo o en combinación con otro(s) término(s)) significa -C(S)-alquilo. Por ejemplo, "etil(tiocarbonilo)" se puede representar como:



[773] El término "alcoxi(tiocarbonilo)" (ya sea solo o en combinación con otro(s) término(s)) significa -C(S)-O-alquilo. Por ejemplo, "etoxi(tiocarbonilo)" se puede representar como:



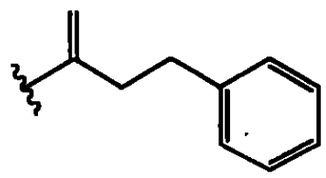
[774] El término "carbociclil(tiocarbonilo)" (ya sea solo o en combinación con otro(s) término(s)) significa -C(S)-carbociclilo. Por ejemplo, "fenil(tiocarbonilo)" se puede representar como:



De manera similar, el término "heterociclil(tiocarbonilo)" (ya sea solo o en combinación con otro(s) término(s)) significa -C(S)-heterociclilo.

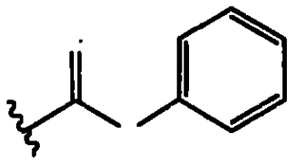
913

[775] El término "carbociclilalquil(tiocarbonilo)" (ya sea solo o en combinación con otro(s) término(s)) significa -C(S)-alquil-carbociclilo. Por ejemplo, "feniletil(tiocarbonilo)" se puede representar como:

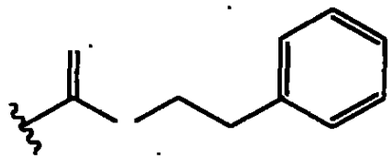


De manera similar, el término "heterociclilalquil(tiocarbonilo)" (ya sea solo o en combinación con otro(s) término(s)) significa -C(S)-alquil-heterociclilo.

[776] El término "carbociclíloxi(tiocarbonilo)" (ya sea solo o en combinación con otro(s) término(s)) significa -C(S)-O-carbociclilo. Por ejemplo, "feniloxi(tiocarbonilo)" se puede representar como:



[777] El término "carbociclilalcoxi(tiocarbonilo)" (ya sea solo o en combinación con otro(s) término(s)) significa -C(S)-O-alquil-carbociclilo. Por ejemplo, "feniletoxi(tiocarbonilo)" se puede representar como:



[778] El término "sulfonilo" (ya sea solo o en combinación con otro(s) término(s)) significa $-S(O)_2-$, que también se puede representar como:



914

Así, por ejemplo, "alquil-sulfonil-alquilo" se refiere a alquil-$S(O)_2$-alquilo.

[779] El término "aminosulfonilo" (ya sea solo o en combinación con otro(s) término(s)) significa -$S(O)_2$-NH_2, que también se puede representar como:



[780] El término "sulfóxido" (ya sea solo o en combinación con otro(s) término(s)) significa -S(O)-, que también se puede representar como:



Así, por ejemplo, "alquil-sulfóxido-alquilo" se refiere alquil-S(O)-alquilo.

[781] El término "heterociclilo" (ya sea solo o en combinación con otro(s) término(s)) se refiere a una estructura en anillo saturada (es decir, "heterocicloalquilo"), parcialmente saturada o arilo (es decir, "heteroarilo") que contiene un total de 3 a 14 átomos del anillo. Al menos uno de los átomos del anillo es un heteroátomo (es decir, oxígeno, nitrógeno o azufre), donde los restantes átomos del anillo se seleccionan independientemente del grupo formado por carbono, oxígeno, nitrógeno y azufre.

[782] Un heterociclilo puede ser un solo anillo, que típicamente contiene entre 3 y 7 átomos de anillo, más típicamente entre 3 y 6 átomos de anillo y más típicamente aún entre 5 y 6 átomos de anillo. Los ejemplos de heterociclilos de un solo anillo incluyen furanilo, dihidrofuranilo, tetrahidrofuranilo, tiofenilo (también conocido como "tiofuranilo"), dihidrotiofenilo, tetrahidrotiofenilo, pirrolilo, isopirrolilo, pirrolinilo, pirrolidinilo, imidazolilo, isoimidazolilo, imidazolinilo, imidazolidinilo, pirazolilo, pirazolinilo,

915

pirazolidinilo, triazolilo, tetrazolilo, ditiolilo, oxatiolilo, oxazolilo, isoxazolilo, tiazolilo, isotiazolilo, tiazolinilo, isotiazolinilo, tiazolidinilo, isotiazolidinilo, tiodiazolilo, oxatiazolilo, oxadiazolilo (incluyendo 1,2,3-oxadiazolilo, 1,2,4-oxadiazolilo (también conocido como "azoximilo"), 1,2,5-oxadiazolilo (también conocido como "furazanilo") o 1,3,4-oxadiazolilo), oxatriazolilo (incluyendo 1,2,3,4-oxatriazolilo o 1,2,3,5-oxatriazolilo), dioxazolilo (incluyendo 1,2,3-dioxazolilo, 1,2,4-dioxazolilo, 1,3,2-dioxazolilo o 1,3,4-dioxazolilo), oxatiazolilo, oxatiolilo, oxatiolanilo, piranilo (incluyendo 1,2-piranilo o 1,4-piranilo), dihidropiranilo, piridinilo (también conocido como "azinilo"), piperidinilo, diazinilo (incluyendo piridazinilo (también conocido como "1,2-diazinilo"), pirimidinilo (también conocido como "1,3-diazinilo") o pirazinilo (también conocido como "1,4-diazinilo")), piperazinilo, triazinilo (incluyendo s-triazinilo (también conocido como "1,3,5-triazinilo"), as-triazinilo (también conocido como 1,2,4-triazinilo) y v-triazinilo (también conocido como "1,2,3-triazinilo")), oxazinilo (incluyendo 1,2,3-oxazinilo, 1,3,2-oxazinilo, 1,3,6-oxazinilo (también conocido como "pentoxazolilo"), 1,2,6-oxazinilo o 1,4-oxazinilo), isoxazinilo (incluyendo o-isoxazinilo o p-isoxazinilo), oxazolidinilo, isoxazolidinilo, oxatiazinilo (incluyendo 1,2,5-oxatiazinilo o 1,2,6-oxatiazinilo), oxadiazinilo (incluyendo 1,4,2-oxadiazinilo o 1,3,5,2-oxadiazinilo), morfolinilo, azepinilo, oxepinilo, tiepinilo y diazepinilo.

[783] Como alternativa, el heterociclilo puede estar formado por 2 ó 3 anillos fusionados entre sí, tal como, por ejemplo, indolizinilo, pirindinilo, piranopirrolilo, 4H-quinolizinilo, purinilo, naftiridinilo, piridopiridinilo (incluyendo pirido[3,4-b]-piridinilo, pirido[3,2-b]-piridinilo o pirido[4,3-b]-piridinilo) y pteridinilo. Otros ejemplos de heterociclilos de anillos fusionados incluyen heterociclilos benzo-fusionados, tal como indolilo, isoindolilo (también conocido

como "isobenzazolilo" o "pseudoisoindolilo"), indoleninilo (también conocido como "pseudoindolilo"), isoindazolilo (también conocido como "benzpirazolilo"), benzazinilo (incluyendo quinolinilo (también conocido como "1-benzazinilo") o isoquinolinilo (también conocido como "2-benzazinilo")), ftalazinilo, quinoxalinilo, quinazolinilo, benzodiazinilo (incluyendo cinolinilo (también conocido como "1,2-benzodiazinilo") o quinazolinilo (también conocido como "1,3-benzodiazinilo")), benzopiranilo (incluyendo "cromanilo" o "isocromanilo"), benzotiopiranilo (también conocido como "tiocromanilo"), benzoxazolilo, indoxazinilo (también conocido como "benzisoxazolilo"), antranililo, benzodioxolilo, benzodioxanilo, benzoxadiazolilo, benzofuranilo (también conocido como "cumaronilo"), isobenzofuranilo, benzotienilo (también conocido como "benzotiofenilo", "tionaftenilo" o "benzotiofuranilo"), isobenzotienilo (también conocido como "isobenzotiofenilo", "isotionaftenilo" o "isobenzotiofuranilo"), benzotiazolilo, benzotiadiazolilo, bencimidazolilo, benzotriazolilo, benzoxazinilo (incluyendo 1,3,2-benzoxazinilo, 1,4,2-benzoxazinilo, 2,3,1-benzoxazinilo o 3,1,4-benzoxazinilo), benzisoxazinilo (incluyendo 1,2-benzisoxazinilo o 1,4-benzisoxazinilo), tetrahidroisoquinolinilo, carbazolilo, xantenilo y acridinilo.

[784] El término heterociclilo de "2 anillo fusionados" (ya sea solo o en combinación con otro(s) término(s)) se refiere a un heterociclilo saturado, parcialmente saturado o arilo que contiene 2 anillos fusionados. Los ejemplos de heterociclilos de 2 anillos fusionados incluyen indolizinilo, pirindinilo, piranopirrolilo, 4H-quinolizinilo, purinilo, naftiridinilo, piridopiridinilo, pteridinilo, indolilo, isoindolilo, indoleninilo, isoindazolilo, benzazinilo, ftalazinilo, quinoxalinilo, quinazolinilo, benzodiazinilo, benzopiranilo, benzotiopiranilo, benzoxazolilo, indoxazinilo, antranililo, benzodioxolilo, benzodioxanilo,

benzoxadiazolilo, benzofuranilo, isobenzofuranilo, benzotienilo, isobenzotienilo, benzotiazolilo, benzotiadiazolilo, bencimidazolilo, benzotriazolilo, benzoxazinilo, benz-isoxasinilo y tetrahidroisoquinolinilo.

[785] El término "heteroarilo" (ya sea solo o en combinación con otro(s) término(s)) se refiere a un heterociclilo aromático que contiene entre 5 y 14 átomos de anillo. Un heteroarilo puede ser un solo anillo o 2 ó 3 anillos fusionados. Los ejemplos de sustituyentes heteroarilo incluyen sustituyentes de un anillo de 6 miembros, tal como piridilo, pirazilo, pirimidinilo y piridazinilo; sustituyentes de un anillo de 5 miembros tal como 1,3,5-, 1,2,4- o 1,2,3-tiazinilo, imidazilo, furanilo, tiofenilo, pirazolilo, oxazolilo, isoxazolilo, tiazolilo, 1,2,3-, 1,2,4-, 1,2,5- o 1,3,4-oxadiazolilo y isotiazolilo; sustituyentes de anillos fusionados de 6/5 miembros, tal como benzotiofuranilo, isobenzotiofuranilo, bencisoxazolilo, benzoxazolilo, purinilo y antranililo; y sustituyentes de anillos fusionados de 6/6 miembros, tal como 1,2-, 1,4-, 2,3- y 2, 1-benzopironilo, quinolinilo, isoquinolinilo, cinnolinilo, quinazolinilo y 1,4-benzoxazinilo.

[786] El carbociclilo o heterociclilo puede estar optativamente sustituido con, por ejemplo, uno o más sustituyentes seleccionados independientemente del grupo formado por halógeno, hidroxi, carboxi, ceto, alquilo, alcoxi, alcoxialquilo, alquilcarbonilo (también conocido como "alcanoílo"), arilo, arilalquilo, arilalcoxi, arilalcoxialquilo, arilalcoxicarbonilo, cicloalquilo, cicloalquilalquilo, cicloalquilalcoxi, cicloalquilalcoxialquilo y cicloalquilalcoxicarbonilo. Más típicamente, un carbociclilo o heterociclilo puede estar optativamente sustituido con, por ejemplo, uno o más sustituyentes seleccionados independientemente del grupo formado por halógeno, -OH, -C(O)-OH, ceto, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alquilcarbonilo, arilo, aril-C_1-C_6-alquilo, aril-C_1-C_6-alcoxi, aril-C_1-C_6-alcoxi-C_1-

C_6-alquilo, aril-C_1-C_6-alcoxicarbonilo, cicloalquilo, cicloalquil-C_1-C_6-alquilo, cicloalquil-C_1-C_6-alcoxi, cicloalquil-C_1-C_6-alcoxi-C_1-C_6-alquilo y cicloalquil-C_1-C_6-alcoxicarbonilo. El o los sustituyentes alquilo, alcoxi, alcoxialquilo, alquilcarbonilo, arilo, arilalquilo, arilalcoxi, arilalcoxialquilo o arilalcoxicarbonilo pueden estar sustituido además con, por ejemplo, uno o más halógenos. Los arilos o cicloalquilos son típicamente sustituyentes de un solo anillo que contiene entre 3 y 6 átomos de anillo y más típicamente entre 5 y 6 átomos de anillo.

[787] El arilo o heteroarilo puede estar sustituido optativamente con, por ejemplo, uno o más sustituyentes seleccionados independientemente del grupo formado por halógeno, -OH, -CN, -NO_2, -SH, -C(O)-OH, amino, aminocarbonilo, aminalquilo, alquilo, alquiltio, carboxialquiltio, alquilcarbonilo, alquilcarboniloxi, alcoxi, alcoxialquilo, alcoxicarbonilo, alcoxicarbonilalcoxi, alcoxialquiltio, alcoxicarbonilalquiltio, carboxialcoxi, alcoxicarbonilalcoxi, carbociclilo, carbociclilalquilo, carbocicliloxi, carbociclitio, carbociclilalquiltio, carbociclilamino, carbociclilalquilamino, carbociclilcarbonilamino, carbociclilcarbonilo, carbociclilalquilo, carbonilo, carbociclilcarboniloxi, carbociclioxicarbonilo, carbociclilalcoxicarbonilo, carbociclioxialcoxicarbociclilo, carbociclitioalquiltiocarbociclilo, carbociclitioalcoxicarbociclilo, carbociclioxialquiltiocarbociclilo, heterociclilo, heterociclilalquilo, heterociclioxi, heterociclitio, heterociclilalquiltio, heterociclilamino, heterociclilalquilamino, heterociclilcarbonilamino, heterociclilcarbonilo, heterociclilalquilcarbonilo, heterocicliloxicarbonilo, heterociclilcarboniloxi, heterociclilalcoxicarbonilo, heterocicliloxialcoxiheterociclilo, heterociclitioalquiltioheterociclilo, heterociclitioalcoxiheterociclilo y heterocicliloxialquiltioheterociclilo. Más

919

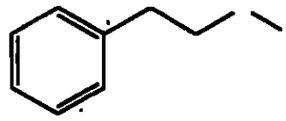
típicamente, el arilo o heteroarilo puede estar sustituido optativamente, por ejemplo, con uno o más sustituyentes seleccionados independientemente del grupo formado por halógeno, -OH, -CN, $-NO_2$, -SH, -C(O)-OH, amino, aminocarbonilo, amino-C_1-C_6-alquilo, C_1-C_6-alquilo, C_1-C_6-alquiltio, carboxi-C_1-C_6-alquiltio, C_1-C_6-alquilcarbonilo, C_1-C_6-alquilcarboniloxi, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alcoxicarbonilo, C_1-C_6-alcoxicarbonil-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquiltio, C_1-C_6-alcoxicarbonil-C_1-C_6-alquiltio, carboxi-C_1-C_6-alcoxi, C_1-C_6-alcoxicarbonil-C_1-C_6-alcoxi, arilo, aril-C_1-C_6-alquilo, ariloxi, ariltio, aril-C_1-C_6-alquiltio, arilamino, aril-C_1-C_6-alquilamino, arilcarbonilamino, arilcarbonilo, aril-C_1-C_6-alquilcarbonilo, arilcarboniloxi, ariloxicarbonilo, aril-C_1-C_6-alcoxicarbonilo, ariloxi-C_1-C_6-alcoxiarilo, ariltio-C_1-C_6-alquiltioarilo, ariltio-C_1-C_6-alcoxiarilo, ariloxi-C_1-C_6-alquiltioarilo, cicloalquilo, cicloalquil-C_1-C_6-alquilo, cicloalquiloxi, cicloalquiltio, cicloalquil-C_1-C_6-alquiltio, cicloalquilamino, cicloalquil-C_1-C_6-alquilamino, cicloalquilcarbonilamino, cicloalquilcarbonilo, cicloalquil-C_1-C_6-alquilcarbonilo, cicloalquilcarboniloxi, cicloalquiloxicarbonilo, cicloalquil-C_1-C_6-alcoxicarbonilo, heteroarilo, heteroaril-C_1-C_6-alquilo, heteroariloxi, heteroariltio, heteroaril-C_1-C_6-alquiltio, heteroarilamino, heteroaril-C_1-C_6-alquilamino, heteroarilcarbonilamino, heteroarilcarbonilo, heteroaril-C_1-C_6-alquilcarbonilo, heteroariloxicarbonilo, heteroarilcarboniloxi y heteroaril-C_1-C_6-alcoxicarbonilo. En este caso, uno o más de los hidrógenos unidos a un carbono en cualquiera de estos sustituyentes puede ser reemplazado optativamente por, por ejemplo, un halógeno. Además, el cicloalquilo, arilo y heteroarilo son típicamente sustituyentes de un solo anillo que contiene entre 3 y 6 átomos de anillo y más típicamente 5 ó 6 átomos de anillo.

[788] El prefijo unido a un sustituyente de múltiples componentes solamente se aplica al primer componente. A fines ilustrativos, el término

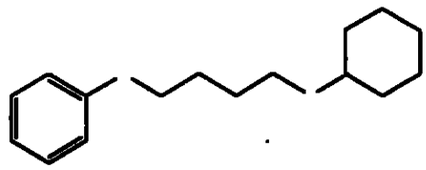
"alquilcicloalquilo" contiene dos componentes: alquilo y cicloalquilo. Por consiguiente, el prefijo C_1-C_6- sobre el C_1-C_6-alquilcicloalquilo significa que el componente alquilo del alquilcicloalquilo contiene entre 1 y 6 átomos de carbono; el prefijo C_1-C_6- no describe el componente cicloalquilo. A fines ilustrativos adicionales, el prefijo "halo" en el término haloalcoxialquilo indica que solamente el componente alcoxi del sustituyente alcoxialquilo está sustituido con uno o más radicales halógeno. Si la sustitución con halógeno puede tener lugar como alternativa o adicionalmente sobre el componente alquilo, el sustituyente se describiría como "alcoxialquilo sustituido con halógeno" en lugar de "haloalcoxialquilo. Y finalmente, si la sustitución con halógeno solamente se puede producir sobre el componente alquilo, el sustituyente se describiría como "alcoxihaloalquilo.

[789] Si los sustituyentes se describen como "seleccionados independientemente" de un grupo, cada sustituyente se selecciona de una forma independiente del otro. Cada sustituyente puede entonces ser idéntico o diferente del o de los otros sustituyentes.

[790] Cuando se utilizan términos para describir un sustituyente, el componente ubicado más hacia la derecha del sustituyente es el componente que tiene la valencia libre. A fines ilustrativos, un benceno sustituido con metoxietilo tiene la siguiente estructura:

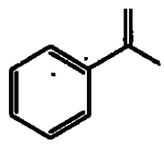


Como se puede observar, el etilo está unido al benceno y el metoxi es el componente del sustituyente que está más alejado del benceno. A modo ilustrativo adicional, un benceno sustituido con ciclohexaniltiobutoxi tiene la siguiente estructura:

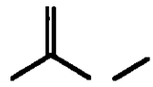


[791] Cuando se utilizan términos para describir un elemento ligador entre otros dos elementos de una estructura química representada, el componente ubicado más hacia la derecha del sustituyente es el componente que está unido al elemento de la izquierda en la estructura representada. A fines ilustrativos, si la estructura química es X-L-Y y L se describe como metilciclohexaniletilo, entonces la sustancia sería X-etil-ciclohexanil-metil-Y.

[792] Cuando una fórmula química se usa para describir un sustituyente, el guión sobre la izquierda de la fórmula indica la porción del sustituyente que tiene la valencia libre. A fines ilustrativos, un benceno sustituido con -C(O)-OH tiene la siguiente estructura:



[793] Cuando se usa una fórmula química para describir un elemento ligador entre otros dos elementos de la estructura química representada, el guión de la izquierda del sustituyente indica la porción del sustituyente que está unido al elemento de la izquierda en la estructura representada. El guión de la derecha, por otra parte, indica la porción del sustituyente que está unida al elemento de la derecha en la estructura representada. A fines ilustrativos, si la estructura química representada es X-L-Y y L se describe como -C(O)-N(H)-, entonces la sustancia química sería:



[794] El término "aceptable para uso farmacéutico" se usa en este documento como un adjetivo para indicar que el sustantivo modificado es apropiado para su uso como un producto farmacéutico o como parte de un producto farmacéutico.

[795] Con referencia al uso de los términos "comprenden" o "comprende" o "que comprende" en este documento (incluyendo las reivindicaciones), los solicitantes indican que a menos que el contexto indique lo contrario, dichos términos se usan sobre la base y para una clara comprensión que se deben interpretar de una forma inclusiva, antes que exclusiva, y que los Solicitantes pretenden que cada uno de dichos términos se interpreten en tal sentido con referencia a esta patente, incluyendo más adelante las reivindicaciones.

F. Preparación de Compuestos

[796] Los siguientes ejemplos detallados ilustran la preparación de compuestos y sales de esta invención. Otros compuestos y sales de esta invención se pueden preparar usando los métodos ilustrados en estos ejemplos (solo o en combinación con técnicas generalmente conocidas en el arte). Dichas técnicas conocidas incluyen, por ejemplo, las descritas en la Publ. Int. Nro WO 99/25687 (Solicitud de Patente del PCT Nro. PCT/US98/23242 publicada el 27 de mayo de 1999) (que se incorpora a la presente como referencia). Dichas técnicas conocidas también incluyen, por ejemplo, las reveladas en la Publ. Int. Nro WO 00/50396 (Solicitud de Patente del PCT Nro. PCT/US00/02518 publicada el 31 de agosto de 2000) (que se incorpora a la presente como referencia). Tales técnicas conocidas además

923

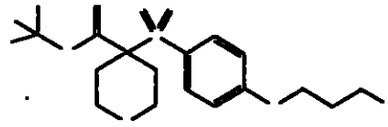
incluyen, por ejemplo, las reveladas en la Publ. Int. Nro WO 00/69821 (Solicitud de Patente del PCT Nro. PCT/US00/06719 publicada el 23 de noviembre de 2000) (que se incorpora a la presente como referencia).

$$$$

EJEMPLOS

[797] Los siguientes ejemplos son meramente ilustrativos, y no limitan de manera alguna el contenido de las otras partes de esta documentación.

[798] **Ejemplo 1. Preparación de ácido 4-[[4-(3-aminopropoxi)-fenil]sulfonil]tetrahidro-2H-piran-4-carboxílico 1,1–dimetiletiléster, monoclorhidrato.**



[799] **Parte A.** A una solución de t-butilcloroacetato (67 g, 0.44 mol) y 4-fluorotiofenol (50 g, 0.40 mol) en N,N-dimetilformamida (1 L) se agregó carbonato de potasio (62 g, 0.45 mol), seguido por dimetilaminopiridina (2 g, 0.02 mol). La mezcla se agitó a temperatura ambiente durante la noche bajo nitrógeno. Una vez que la HPLC indicó que la reacción había finalizado, la mezcla se volcó en HCl acuoso al 10% en agitación (1 L) y se extrajo con acetato de etilo (4x). Las capas orgánicas combinadas se lavaron con agua (2x), se secaron sobre sulfato de magnesio, se filtró, y se concentró al vacío para dar 112 g (100+% de rendimiento crudo) de un aceite color marrón. La ^{1}H RMN confirmó el sulfuro deseado sin formación de disulfuros. Este material se usó sin purificación adicional.

[800] **Parte B.** A una solución del producto de la **Parte A** (aproximadamente 108g, 0.45 mol) en tetrahidrofurano (400 ml) se agregó agua (700 ml), seguido por Oxone™ (600 g, 0.98 mol). La mezcla de reacción

se agitó durante la noche. Una vez que la HPLC indicó la finalización, la mezcla de reacción se filtró para eliminar el exceso de Oxone™, y el licor madre luego se extrajo con acetato de etilo (3x). Las capas orgánicas combinadas se lavaron con agua (2x), se secaron sobre sulfato de magnesio, se filtró, y se concentró al vacío para dar 78.3 g (64% de rendimiento crudo) de un aceite amarillo. Tanto los valores de ^{19}F como de ^{1}H RMN confirmaron la sulfona deseada sin remanentes del material inicial. Este material se usó sin purificación adicional.

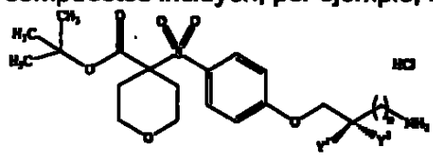
[801] **Parte C.** A una solución del producto de la **Parte B** (78 g, 0.28 mol) en N,N-dimetilacetamida (300 ml) se agregó carbonato de potasio (86 g, 0.62 mol). Después de agitar durante 5 min, se agregó2,2'- (dibromoetil) éter (79 g, 0.34 mol) , seguido por 4-dimetilaminopiridina (1.7 g, 0.014 mol) y bromuro de tetrabutilamonio (4.5 g, 0.14 mol). La mezcla de reacción se agitó durante la noche por medio de un agitador mecánico. Una vez que la HPLC indicó la finalización, la mezcla de reacción se volcó lentamente en HCl acuoso al 10% en agitación (1 L). El sólido amarillo resultante se recolectó y se lavó con hexanos para dar 84 g (86%) de un sólido color amarillo. La ^{1}H RMN confirmó el producto deseado.

[802] **Parte D.** A una solución del producto de la **Parte C** (19.8 g, 57.5 mmol) y t-butil-N-(3-hidroxipropil) carbamato (11.1 g, 63.3 mmol) en N,N-dimetilformamida anhidra (300 mL) a 0°C se agregó hidruro de sodio (2.8 g, 69.0 mmol; dispersión al 60% en aceite mineral). Después de 18 hrs., la reacción se fraguó con agua y se concentró al vacío. El residuo oleoso se particionó entre acetato de etilo y solución saturada de bicarbonato de sodio. Las capas se separaron, y la capa orgánica se lavó con solución salina (3X), se secó sobre sulfato de sodio, se filtró, y se concentró al vacío. El residuo

oleoso se recogió en acetonitrilo y nuevamente se concentró al vacío. El sólido resultante se trituró con dietiléter, y 15.3 g (53%) del producto puro deseado se recolectó como un polvo blanco. ESMS m/z = 522 $[M+Na]^+$. El filtrado contenía 11.6 g de material que según se indicó por HPLC era un 55% de producto. Este material se pudo purificar por cromatografía instantánea para obtener más material si se deseaba.

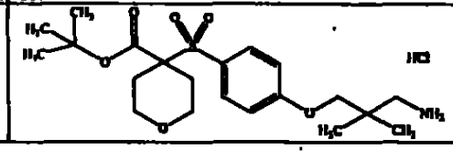
[803] **Parte E.** El producto de la **Parte D** (15.3 g, 30.6 mmol) se recogió en HCl 4N en dioxano (17 mL). Después de 1 hrs., la HPLC indicó una reacción incompleta, de modo que se agregó más HCl 4N en dioxano (2 mL). Después de 20 min, la mezcla de reacción se agregó lentamente a dietiléter en agitación rápida (400 mL). El sólido oleoso resultante se enjuagó con más dietiléter luego se disolvió en acetonitrilo y se concentró al vacío. Se obtuvieron 12.3 g (92%) del clorhidrato deseado como un sólido blanco. ESMS m/z = 400 $[M+H]^+$.

[804] Usando métodos similares un especialista puede preparar otros compuestos. Entre los ejemplos de dichos compuestos se incluyen los que tienen una estructura que corresponde a la Fórmula genérica EX-A. Dichos compuestos incluyen, por ejemplo, los que se resumen en la Tabla 1.

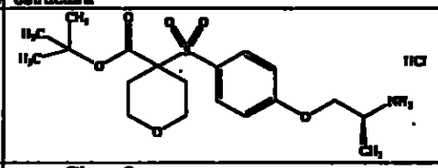
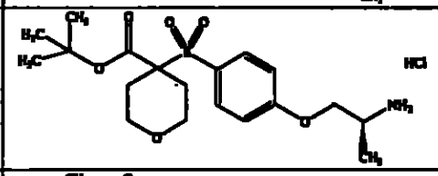
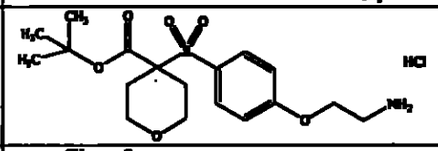
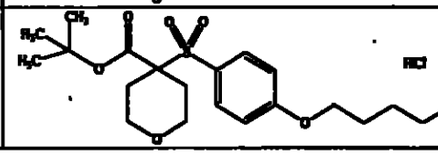


EX-A

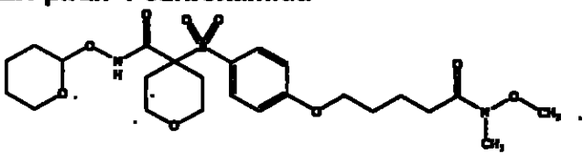
Tabla 1

Ej.Nro	estructura	n	Y^1	Y^2	ESMS m/z
2		1	CH_2	CH_2	428 $(M+H)^+$

926

Ej.Nro	estructura	n	Y^1	Y^2	ESMS m/z
3		0	CH_3	H	422 $[M+Na]^+$
4		0	H	CH_3	422 $[M+Na]^+$
5		0	H	H	408 $[M+Na]^+$
6		2	H	H	414 $[M+H]^+$

[805] **Ejemplo 7. Preparación de tetrahidro-4-[[4-[[5-(metoxi-metilamino)-5-oxopentil]oxi] fenil]sulfonil]-N-(tetrahidro-2H-piran-2-il)oxi]-2H-piran-4-carboxamida**



[806] **Parte A.** A una solución de 5-benciloxi-1-pentanol (32.6 g, 168 mmol) en N,N-dimetilformamida anhidra (150 mL) a 0°C se agregó hidruro de sodio (7.7 g, 192 mmol, dispersión al 60% en aceite mineral). Después de 15 min, la mezcla de reacción se dejó calentar a 20°C, y luego se reenfrió a 0°C. Se agregó una solución de ácido4-[(4-fluorofenil)sulfonil]tetrahidro-2H-piran-4-carboxílico, 1,1-dimetiletiléster (55.1 g, 160 mmol, según se prepara en el Ejemplo 1, Parte C) en N,N-dimetilformamida anhidra (100 mL) , y se retiró el baño frío. Después de 4 hrs., la reacción se concentró al vacío. El residuo oleoso se particionó entre acetato de etilo y solución saturada de bicarbonato

de sodio. Las capas se separaron, y la capa acuosa se volvió a extraer con acetato de etilo (2X). Los extractos combinados se lavaron con sulfato ácido de potasio al 5%, agua, y solución salina (3X); se secó sobre sulfato de magnesio, se filtró; y se concentró al vacío. El aceite opaco resultante solidificó en reposo, y a continuación se purificó por cromatografía de columna usando 10-20% acetato de etilo/ hexanos para dar 67.6 g (81%) del producto deseado como un sólido blanco. ESMS *m/z* = 541 $[M+Na]^+$.

[807] **Parte B.** El producto de la **Parte A** (20.0 g, 38.6 mmol) se disolvió en tetrahidrofurano (80 mL) en un Fisher/Porter pequeño. Después de purgar con una corriente de nitrógeno por 5 min, la reacción se cargó con catalizador de paladio sobre carbón al 5% (4.0 g, Degussa E101 NO/W, 50% agua) y se presurizó hasta aproximadamente ~80 psi con hidrógeno. Después de 1.5 hrs., la captación de hidrógeno había cesado y el análisis por HPLC indicó que la reacción había finalizado. La reacción se filtró a través de un lecho de celite y el filtrado se concentró para dar 17.2 g (100%) del alcohol deseado como un aceite viscoso. Este material se usó sin purificación adicional.

[808] **Parte C.** El producto de la **Parte B** (16.5 g, 38.6 mmol) se disolvió en acetonitrilo (80 mL). La mezcla de reacción se trató con tetracloruro de carbono (80 mL), agua (120 mL), luego periodato de sodio (24.7 g, 115.7 mmol), y finalmente tricloruro de rutenio (180 mg, 0.9 mmol). Después de 1 hrs., el análisis por HPLC indicó que la reacción había finalizado. La mezcla de reacción se diluyó con cloruro de metileno (300 mL), y los sólidos se eliminaron por filtrado por gravedad. Las capas se separaron, y la capa acuosa se extrajo con cloruro de metileno (3X). Los extractos orgánicos combinados se secaron sobre sulfato de magnesio, se filtró, y se concentró al vacío para dar un sólido

928

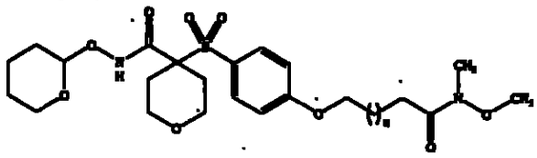
color azul. Este se redisolvió en tetrahidrofurano, se suspendió con carbón activado, se filtró, y se concentró al vacío para dar 17.1 g (100%) de un sólido blancuzco. La ^{1}HRMN confirmó el producto deseado. Este material se usó sin purificación adicional.

[809] **Parte D.** A una solución del producto de la **Parte C** (17.1 g, 38.6 mmol) en N,N-dimetilformamida (160 ml) se agregó 1-hidroxibenzotriazol (7.8g, 57.9 mmol), y luego clorhidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (10.3 g, 54.0 mmol). Después de 1.5 hrs., se agregaron clorhidrato de N,O-dimetilhidroxilamina (11.3 g, 115.7 mmol) y trietilamina (32.2 ml, 231.4 mmol) . La mezcla de reacción se dejó en agitación a temperatura ambiente durante la noche. La mezcla se concentró, y el residuo se particionó entre acetato de etilo y solución saturada de bicarbonato de sodio. La capa acuosa se volvió a extraer con acetato de etilo (2X), y las capas orgánicas combinadas se lavaron con solución de sulfato ácido de potasio al 5%, agua, y solución salina (3X), luego se secaron sobre sulfato de magnesio, se filtró, y se concentró al vacío. El sólido crudo se purificó por cromatografía de columna usando acetato de etilo/hexanos al 50%, y 14.7 g (79%) de la amina de weinreb deseada se obtuvieron como un sólido blancuzco. ESMS m/z = 508 $[M+Na]^+$.

[810] **Parte E.** El producto de la **Parte D** (6.24 g, 12.85 mmol) se recogió en ácido trifluoroacético glacial puro (50 mL). Después de 1.5 hrs., el ácido trifluoroacético glacial se eliminó al vacío a 50°C para dar el ácido libre como un aceite tipo jarabe. ESMS m/z = 430 $[M+H]^+$. A una solución de este material en N,N-dimetilformamida anhidra (25 mL) se agregó 1-hidroxibenzotriazol (2.14 g, 15.88 mmol), tetrahidropiranhidroxilamina (4.64 g, 39.72 mmol), y trietilamina (5.5 mL, 39.72 mmol), seguido por clorhidrato de 1-

(3-dimetilaminopropil)-3-etilcarbodiimida (3.35 g, 15.83 mmol). La mezcla de reacción se calentó a 40°C por 3.5 hrs., y luego se enfrió a temperatura ambiente y se agitó durante la noche. La mezcla de reacción se concentró al vacío a 60°C. El residuo se recogió en acetato de etilo, se lavó con solución saturada de bicarbonato de sodio (2X) y solución salina (3X), se secó sobre sulfato de sodio, se filtró, y se concentró al vacío para dar 8 g de un jarabe. El material crudo se purificó por cromatografía instantánea usando 50-100% acetato de etilo/hexanos para dar el compuesto del título como un sólido blanco. ESMS m/z = 529 $[M+H]^+$. HRMS calculado para $C_{24}H_{36}N_2O_9S$: 529.2220 $[M+H]^+$, hallado: 529.2210 .

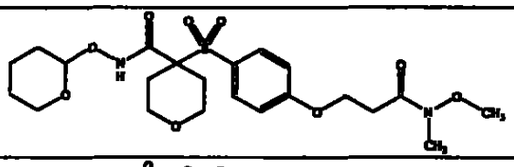
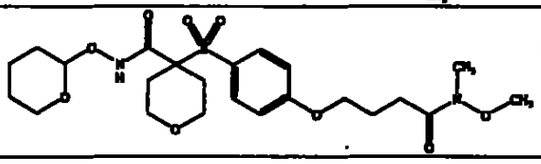
[811] Usando métodos similares un especialista puede preparar otros compuestos. Entre los ejemplos de dichos compuestos se incluyen los que tienen una estructura que corresponde a la Fórmula genérica EX-B. Dichos compuestos incluyen, por ejemplo, los compuestos que se resumen en la Tabla 2.



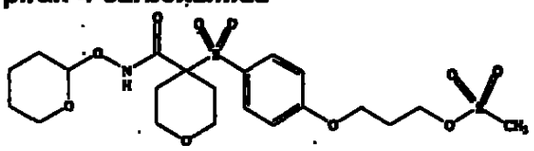
EX-B

930

Tabla 2

Ej.Nro	estructura	n	Masa calc.	Masa observada
8		0	518.2172	518.2178
9		1	532.2329	532.2307

[812] Ejemplo 10: Preparación de tetrahidro-4-[[4-[3-[(metil-sulfonil)oxi]propoxi]fenil)sulfonil]-N-[(tetrahidro-2H piran-2-il)oxi]-2H-piran-4-carboxamida



[813] Parte A. A una solución de ácido4-[(4-fluorofenil)sulfonil]-tetrahidro-2H-piran-4-carboxílico , 1,1-dimetiletiléster (5.0 g, 14.5 mmol, según se prepara en el **Ejemplo 1, Parte C**) y 3-benciloxi-l-propanol (2.3 mL, 14.5 mmol) en N,N-dimetilformamida (50 mL) a 0°C se agregó NaH (696 mg, 17.4 mmol, dispersión al 60% en aceite mineral). La solución se agitó a temperatura ambiente por 5 hrs.. La reacción se fraguó con agua, y luego se particionó entre acetato de etilo y agua. La capa orgánica se lavó con agua y solución salina, se secó sobre sulfato de sodio, se filtró, y se concentró al vacío para dar 7.89 g (rendimiento cuantitativo) del éter bencílico como un aceite amarillo. (ESMS m/z = 435 $[M- tBu]^+$.

[814] Parte B. El éter bencílico de la **Parte A** (4.39 g, 8.94 mmol) se hidrolizó en 1:1 ácido trifluoroacético glacial :cloruro de metileno (50 mL). La

931

solución se concentró al vacío para dar 3.69 g (950) del ácido libre como un sólido blanco crudo. ESMS m/z = 452 $[M+NH4]^+$. Este material se usó sin purificación.

[815] **Parte C.** A una solución del ácido crudo de la **Parte B** (3.60 g, 8.29 mmol) en N,N-dimetilformamida (40 mL) se agregó 1-hidroxibenzotriazol (1.34 g, 9.95 mmol), trietilamina (3.5 mL, 24.9 mmol), y tetrahidropiranhidroxilamina (2.91 g, 24.9 mmol). Después de 30 min, se agregó1-[3-(dimetilamino)propil]-3-etilcarbodiimida clorhidrato de (2.23 g, 11.6 mmol) . La solución se agitó por 18 hrs. a temperatura ambiente. La solución se particionó entre acetato de etilo y solución saturada de bicarbonato de sodio. La capa orgánica se lavó con solución saturada de bicarbonato de sodio y solución salina, y luego se secó sobre sulfato de sodio. La purificación por cromatografía instantánea usando acetato de etilo/hexanos dio 3.71 g (84 0) del hidroxamato protegido como un aceite crudo. ESMS m/z = 551 $(M+NH4)^+$. HRMS calculado para $C_{27}H_{35}NO_8S$ NH_4: 551.2427 $(M+NH4)^+$. Hallado: 551.2418.

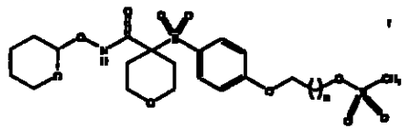
[816] **Parte D.** El éter bencílico de la **Parte C** (3.52 g, 6.6 mmol) se hidrogenó paladio sobre carbón al 10% (3.31g) en metanol con formato de amonio (2.5 g, 39.6 mmol) como fuente de hidrógeno agregada en 3 porciones y se calentó a reflujo. La solución se filtró a través de celite y se concentró al vacío para dar 2.89 g (98 %) del alcohol como un aceite incoloro. ESMS m/z = 442 $[M-H]^+$. Este material se usó sin purificación.

[817] **Parte E.** A una solución del hidroxamato protegido de la **Parte D** (2.57 g, 5.8 mmol) en cloruro de metileno (25 mL) se agregó trietilamina (2.5 mL, 18.8 mmol). La solución se enfrió a 0°C, y se agregó cloruro de metilsulfonilo (1.25 mL, 16.0 mmol) . Después de 18 hrs., la reacción se lavó

952

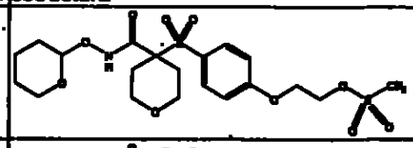
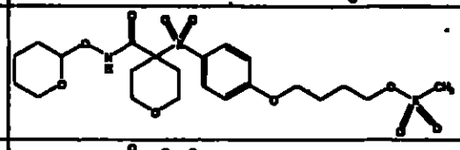
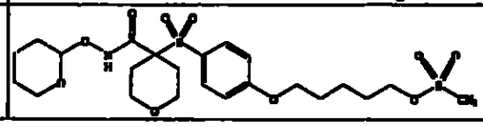
con agua, ácido cítrico al 10%, solución de bicarbonato de sodio al 5%, y solución salina, y luego se secó sobre sulfato de magnesio. La cromatografía (sobre sílice, acetato de etilo/hexanos) dio el compuesto del título como un aceite incoloro (1.48 g, 49 0). ESMS m/z = 544 $(M+Na)^+$. HRMS calculado para $C_{21}H_{31}NO_{10}S_2$ NH_4: 539. 1733 $(M+NH_4)^+$. Hallado: 539.1709.

[818] Usando métodos similares un especialista puede preparar otros compuestos. Entre los ejemplos de dichos compuestos se incluyen los que tienen una estructura que corresponde a la Fórmula genérica EX-C. Dichos compuestos incluyen, por ejemplo, los compuestos que se resumen en la Tabla 3.



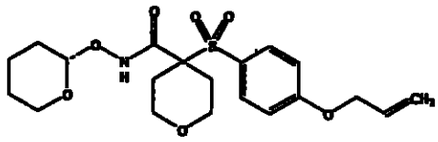
EX-C

Tabla 3

Ej.Nro	estructura	n	Masa Calc.	Masa Obs
11		1	525.1517	525.1561
12		3	558.1444	558.1429
13		4	572.16	572.1583

933

[819] **Ejemplo 14. Preparación de (tetrahidro-4-[[4-(2-propeniloxi)fenil]sulfonil]-N-[(tetrahidro-2H-piran-2-il)oxi]-2H-piran-4-carboxamida**



[820] **Parte A.** A una solución de sodio (8.97 g, 390 mmol) en metanol (1 L) a 0°C se agregaron 4-fluorotiofenol (50 g, 390 mmol) y cloroacetato de metilo (34.2 mL, 390 mmol). Después de agitar a temperatura ambiente por 4 hrs., la solución se filtró para eliminar sales, y el filtrado se concentró al vacío para dar 75.85 g (97%) para el sulfuro deseado como un aceite incoloro.

[821] **Parte B.** A una solución del producto de la **Parte A** (75.85 g, 380 mmol) en metanol (1 L) y agua (100 mL) se agregó Oxone™ (720 g, 1.17 mmol). Después de 2 hrs., la mezcla de reacción se filtró para eliminar el exceso de sales, y el filtrado se concentró al vacío. El residuo resultante se disolvió en acetato de etilo y se lavó con agua, solución saturada de bicarbonato de sodio, y solución salina, y luego se secó sobre sulfato de magnesio. Concentrando al vacío se obtuvieron 82.74 g (94%) de la sulfona deseada como un sólido blanco.

[822] **Parte C.** A una solución del producto de la **Parte B** (28.5 g, 123 mmol) en N,N-dimetilacetamida (200 mL) se agregaron carbonato de potasio (37.3 g, 270 mmol), bis-(2-bromoetiléter (19.3 mL, 147 mmol), 4-dimetilaminopiridina (750 mg, 6 mmol), y bromuro de tetrabutilamonio (1.98 g, 6 mmol). La solución resultante se agitó a temperatura ambiente por 72 hrs., y luego se volcó en HCl 1 N (300 mL). El precipitado resultante se recolectó por filtrado al vacío. La recristalización usando acetato de etilo/hexanos dio 28.74 g (77%) del producto de tetrahidrofurano como un sólido beige.

934

[823] **Parte D.** A una solución del producto de la **Parte C** (8.0 g, 26.5 mmol) en tetrahidrofurano (250 mL) se agregó trimetilsilonato de potasio (10.2 g, 79.5 mmol). Después de 1.5 hrs., la mezcla de reacción se fraguó con agua, se acidificó a pH 2.5, y se extrajo con acetato de etilo. La capa orgánica se lavó con solución salina, se secó sobre sulfato de sodio, se filtró, y se concentró al vacío para dar 5.78 g (76%) de la sal ácida deseada como un sólido blanco.

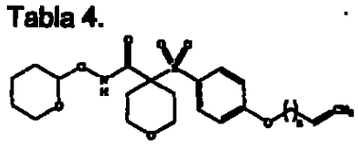
[824] **Parte E.** A una solución del producto de la **Parte D** (5.4 g, 18.7 mmol) en N,N-dimetilformamida (35 mL) se agregaron 1-hidroxibenzotriazol (3.04 g, 22.5 mmol), N-metilmorfolina (6.2 mL, 56.2 mmol), tetrahidropiranhidroxilamina (6.8 g, 58.1 mmol) y clorhidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (5.0 g, 26.2 mmol). Después de agitar durante 3 hrs. a temperatura ambiente, la solución se concentró al vacío, y el residuo se particionó entre acetato de etilo y agua. La capa orgánica se lavó con sulfato ácido de potasio acuoso al 5%, agua, solución saturada de bicarbonato de sodio, y solución salina; se secó sobre sulfato de sodio, se filtró; y se concentró al vacío para dar 6.34 g (87%) del hidroxamato protegido con THP como un sólido blanco.

[825] **Parte F.** A una solución del producto de la **Parte E** (1.0 g, 2.58 mmol) en dimetilsulfóxido (5 mL) se agregó carbonato de potasio (0.89 g, 6.45 mmol) y alcohol alílico (0.35 mL, 12.9 mmol). La mezcla se calentó a 110°C por 72 hrs.. Se agregaron más alcohol alílico (0.88 mL, 13 mmol) y carbonato de cesio (2.1 g, 6.45 mmol) , y la mezcla se calentó a 120°C por 6 hrs.. Después de enfriar a temperatura ambiente, la mezcla se diluyó con agua (50 mL), y el pH se ajustó a 8-9 con HCl 1 N. La capa acuosa se extrajo con acetato de etilo. La capa orgánica se lavó solución salina, se secó sobre sulfato de

935

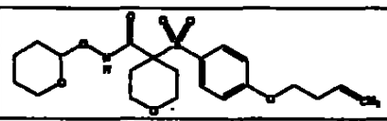
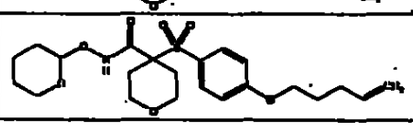
magnesio, se filtró, y se concentró al vacío. La purificación por medio de cromatografía de columna instantánea con acetato de etilo/hexanos al 12% dio 0.67 g del compuesto del título puro como un sólido blanco. ESMS m/z = 426 $[M+H]^+$.

[826] Usando métodos similares un especialista puede preparar otros compuestos. Entre los ejemplos de dichos compuestos se incluyen los que tienen una estructura que corresponde a la Fórmula genérica EX-D. Dichos compuestos incluyen, por ejemplo, los compuestos que se resumen en la Tabla 4.

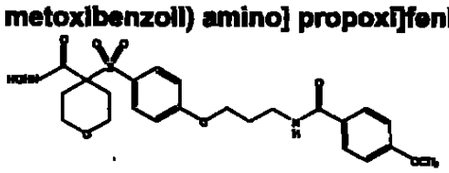


EX-D

Tabla 4

Ej. Nro	Estructura	n	ESMS m/z
15		2	440 $[M+H]^+$
16		3	454 $[M+H]^+$

[827] **Ejemplo 17. Preparación de tetrahidro-N-hidroxi-4-[[4-[3-[(4-metoxibenzoil) amino] propoxi]fenil] sulfonil]-2H-piran-4-carboxamida**



[828] **Parte A.** A una solución de ácido 4-[[4-(3-aminopropoxi)-fenil] sulfonil] tetrahidro-2H-piran-4-carboxílico 1,1-dimetiletiléster, monoclorhidrato

936

(507 mg, 1.27 mmol, preparado como en el **Ejemplo 1**) en N,N-dimetilformamida anhidra (5 mL) a temperatura ambiente se agregó trietilamina (215 uL, 1.54 mmol), y luego inmediatamente cloruro de panisoilo (260 mg, 1.52 mmol). Después de 1 hrs., la mezcla de reacción se fraguó con agua (~2 mL) y se concentró al vacío a 60°C. El residuo crudo se particionó entre acetato de etilo y agua. Las capas se separaron, y la capa orgánica se lavó con solución salina (3X), se secó sobre sulfato de sodio, se filtró, y se concentró al vacío para dar un aceite amarillo pálido. El producto crudo se purificó parcialmente por cromatografía instantánea usando acetato de etilo/hexano/s al 80% para dar 225 mg (33%) del producto acetilado deseado como un aceite translúcido e incoloro. ESMS m/z = 556 $[M+Na]^+$. Este material se usó sin purificación adicional.

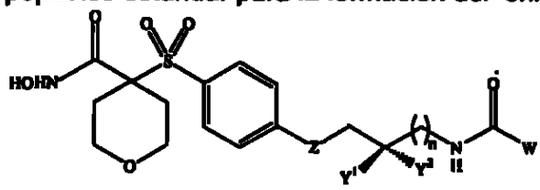
[829] **Parte B.** El producto de la **Parte A** (225 mg, 82% de pureza por HPLC) se recogió en ácido trifluoroacético glacial puro (1 mL). Después de 3 hrs., el ácido trifluoroacético glacial se eliminó al vacío a 50°C para dar el ácido libre como un aceite incoloro. ESMS m/z = 478 $[M+H]^+$. A una solución de este material en N,N-dimetilformamida anhidra (2 mL) se agregó 1-hidroxibenzotriazol (72 mg, 0.53 mmol), N-metilmorfolina (100 uL, 0.91 mmol) y tetrahidropiranhidroxilamina (78 mg, 0.67 mmol), seguido por clorhidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (119 mg, 0.62 mmol). La mezcla de reacción se agitó a temperatura ambiente por 72 hrs., y luego se concentró al vacío a 60°C. El residuo se particionó entre acetato de etilo y agua. Las capas se separaron, y la capa orgánica se lavó con solución saturada de bicarbonato de sodio y solución salina (2X), se secó sobre sulfato de sodio, se filtró, y se concentró al vacío para dar 255 mg del hidroxamato protegido con THP

937

deseado como un aceite incoloro. ESMS m/z = 599 $[M+Na]^+$. HRMS calculado para $C_{28}H_{36}N_2O_6S$: 577.2220 $[M+H]^+$, hallado: 577.2215.

[830] **Parte C.** El producto de la **Parte B** (255 mg, 88% de pureza por HPLC) se disolvió en HCl 4N en dioxano (3 mL) y metanol (300 uL). Después de 1 hr. a temperatura ambiente, la mezcla de reacción se volcó en dietiléter en agitación rápida (50 mL). Se recolectó un sólido blanco y se secó sobre P_2O_5 bajo vacío. El compuesto del título se obtuvo como un sólido color rosa débil. ESMS m/z = 493 $[M+H]^+$. HRMS calculado para $C_{23}H_{28}N_2O_6S$: 493.1645 $[M+H]^+$, hallado: 493.1636.

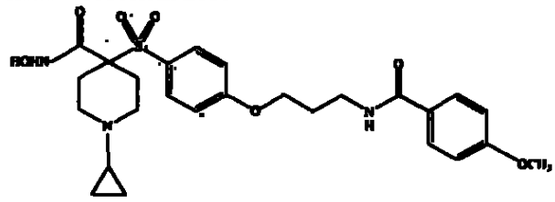
[831] Otros compuestos (tal como los que tienen una estructura que corresponde a la Fórmula genérica EX-E) pueden ser preparados por un especialista usando métodos similares con ya sea el t-butiléster o el ácido libre de ácido 4-[[4-(3-aminopropoxi)-fenil]sulfonil]-tetrahidro-2H-piran-4-carboxílico 1,1-dimetiletiléster, monoclorhidrato o materiales iniciales preparados en forma similar. Además, se pueden usar ácidos carboxílicos como agentes de acoplamiento en lugar de cloruros ácidos usando condiciones de acoplamiento peptídico estándar para la formación del enlace amida.



EX-E

938

[832] **Ejemplo 18. Preparación de 1-ciclopropil-N-hidroxi-4-[[4-[3-[(4-metoxibenzoil)amino]propoxi]fenil]sulfonil]-4-piperidincarboxamida, monoclorhidrato.**



[833] **Parte A.** A una solución de isonipecotato de etilo (15.7 g, 0.1 mol) en tetrahidrofurano (100 mL) se agregó una solución de dicarbonato de di-ter-butilo (21.8 g, 0.1 mol) en tetrahidrofurano (5 mL) por goteo durante 20 min. La solución se agitó durante la noche a temperatura ambiente y se concentró al vacío para dar un aceite liviano. El aceite se filtró a través de gel de sílice usando acetato de etilo/hexanos, luego se concentró al vacío para dar 26.2 g (100%) de la BOC-piperidina deseada como un aceite translúcido e incoloro.

[834] **Parte B.** Una solución de 4-fluorotiofenol (50.29 g, 390 mmol) en dimetilsulfóxido (500 mL) se calentó a 65°C por 6 hrs.. La reacción se fraguó por vertido sobre hielo húmedo. El sólido resultante se recolectó por filtrado al vacío para dar 34.4 g (68.9%) del disulfuro deseado como un sólido blanco.

[835] **Parte C.** A una solución del producto de la **Parte A** (16 g, 62 mmol) en tetrahidrofurano (300 mL) enfriada a -50°C se agregó diisopropilamida de litio (41.33 mL, 74 mmol). Después de permanecer a 0°C por 1.5 hrs., se agregó el producto de la **Parte B** (15.77 g, 62 mmol) . La mezcla de reacción se agitó a temperatura ambiente por 20 hrs., y luego se fraguó por el agregado de agua. La solución se concentró al vacío, y el residuo resultante se particionó entre acetato de etilo y agua. La capa orgánica se lavó con 0.5 N KOH, agua, y solución salina. La purificación por cromatografía de

columna usando acetato de etilo/hexanos dio 18.0 g (75%) del sulfuro deseado como un aceite.

[836] **Parte D.** A una solución del producto de la **Parte C** (16.5 g, 43 mmol) en cloruro de metileno (500 mL) enfriada a 0°C se agregó ácido 3-cloroperbenzoico (18.0 g, 86 mmoL). Después de agitar durante 20 hrs., la mezcla de reacción se diluyó con agua y se extrajo con cloruro de metileno. La capa orgánica se lavó con sulfito de sodio acuoso al 10%, agua, y solución salina, se secó sobre sulfato de magnesio, se filtró, y se concentró al vacío. El producto crudo se purificó por cromatografía de columna usando acetato de etilo/hexanos para dar 10.7 g (60%) de la sulfona deseada como un sólido.

[837] **Parte E.** En una solución del producto de la **Parte D** (10 g, 24.0 mmol) en acetato de etilo (250 mL) se burbujeó Gas de HCl por 10 min, seguido por agitación a temperatura ambiente por 4 hrs.. La concentración al vacío dio 7.27 g (86%) del clorhidrato de amina como un sólido blanco.

[838] **Parte F.** A una solución del producto de la **Parte E** (10.0 g, 28.4 mmol) en metanol (100 mL) se agregó ácido acético glacial (16.2 mL, 284 mmol), filtros moleculares en polvo 4A (9.1 g), y [(1-etoxiciclopropil)oxilo trimetilsilano (17.1 mL, 85.2 mmol). Luego se agregó lentamente cianoborohidruro de sodio (4,82 g, 76.7 mmol) . La reacción se calentó a reflujo con agitación vigorosa por 4.5 hrs.. La mezcla de reacción se enfrió a temperatura ambiente, se filtró a través de celite, y se concentró al vacío. El residuo se particionó entre acetato de etilo y solución saturada de bicarbonato de sodio. La capa orgánica se lavó con solución saturada de bicarbonato de sodio (3X) y solución salina, se secó sobre sulfato de magnesio, se filtró, y se concentró al vacío. El material crudo cristalizó en reposo para dar 10.9 g

940

(100%) del compuesto de amina alquilada como un cristal aceitoso amarillo pálido. ESMS m/z = 356 $(M+H)^+$. Este material se usó sin purificación.

[839] **Parte G.** El producto de la **Parte F** (28.4 mmol) se hidrolizó en tetrahidrofurano (65 mL) con LiOH (3.58 g, 85.2 mmol) en 35 mL de agua a 60°C durante 3 días. La solución se concentró al vacío, se diluyó con agua, y se lavó con dietiléter. La capa acuosa se acidificó con HCl 1N a un pH de ~4.5, causando la formación de un precipitado blanco. El sólido se recolectó por filtración se lavó con agua, y se lavó con acetato de etilo. Después de secar sobre sílice en alto vacío, se obtuvieron 8.06 g (78.2 %) del ácido como un sólido blanco crudo. ESMS m/z = 328 (M+H)+. HRMS calculado para $C_{15}H_{18}NO_4SF$: 328.1019 $(M+H)^+$, hallado: 328.1014. Este material se usó sin purificación.

[840] **Parte H.** A una solución del ácido crudo de la **Parte G** (7.92 g, 21.8 mmol) en N,N-dimetilformamida (48 mL) se agregó N-metilmorfolina (12.0 mL, 109 mmol) y PyBOP (12.5 g, 24.0 mmol). Después de agitar 15 min, se agregó tetrahidropiranhidroxilamina (3.07 g, 26.2 mmol) . La solución se agitó por 22 hrs. a temperatura ambiente. La solución se diluyó con agua (240 mL) y se extrajo con acetato de etilo (3X). Los orgánicos combinados se lavaron con solución saturada acuosa de bicarbonato de sodio (2X) y solución salina, se secó sobre sulfato de sodio, se filtró, y se concentró al vacío para obtener un aceite espumoso. El material crudo se filtró a través de un tapón de sílice usando 1% Et_3N en acetato de etilo/hexanos para dar 7.12 g (76.6%) del hidroxamato protegido como un aceite espumoso. ESMS m/z = 427 $(M+H)^+$. HRMS calculado para $C_{20}H_{27}N_2O_5SF$: 427.1703 $(M+H)^+$. Hallado: 427.1693.

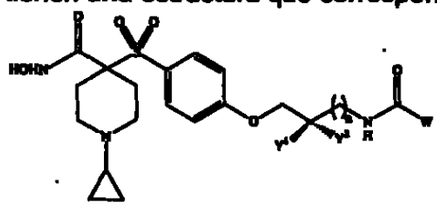
[841] **Parte I.** A una solución de 3-(dibencilamino)-1-propanol (4.3 g, 16.88 mmol) en N,N-dimetilformamida anhidra (35 mL) se agregó hidruro de

941

g, 1.59 mmol). Después de 10 min, el análisis por HPLC indicó que la reacción había finalizado. La mezcla de reacción se concentró al vacío, y el residuo se particionó entre acetato de etilo y solución saturada de bicarbonato de sodio. Las capas se separaron, y la capa acuosa se extrajo con acetato de etilo (3X). Los extractos orgánicos se combinaron y se lavó con solución salina (3X), se secó sobre sulfato de sodio, se filtró, y se concentró al vacío para dar una espuma tostada . El producto crudo se purificó por cromatografía instantánea usando 60-100% [5% (amoníaco 2M en metanol) acetato de etilo]/hexanos para dar 0.2 g (34%) del producto deseado como una espuma blanca seca. ESMS m/z = 616 $[M+H]^+$.

[844] **Parte L.** El producto de la **Parte K** (0 . 2 g, 0 . 34 mmol) se suspendió en HCl 4N en dioxano (2 mL). Después de 5 min, se agregó metanol (0.2 mL) . Después de agitar durante 10 min a temperatura ambiente, la mezcla de reacción se volcó en dietiléter en agitación rápida (50 mL). Un sólido blanco se recolectó y se secó bajo vacío. El compuesto del título (como sal de HCl) se obtuvo como un sólido blancuzco. ESMS m/z = 532 $[M+H]^+$. HRMS calculado para $C_{28}H_{33}N_3O_7S$: 532.2117 $[M+H]^+$, hallado: 532 .2098 .

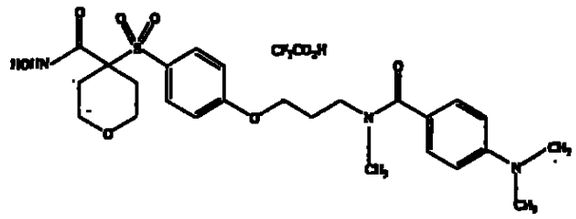
[845] Usando métodos similares un especialista puede preparar otros compuestos. Entre los ejemplos de dichos compuestos se incluyen los que tienen una estructura que corresponde a la Fórmula genérica EX-F.



EX-F

942

[846] **Ejemplo 19. Preparación de 4-[[4-[3-[[4-(dimetilamino)benzoil] metilamino] propoxi] fenil] sulfonil] tetrahidro-N-hidroxi-2H-piran-4-carboxamida.**



[847] **Parte A.** A una solución de ácido 4-[[4-[3-[[4(dimetilamino)-benzoil]amino]propoxi]fenil]· sulfonil] tetrahidro-2H-piran-4-carboxílico , 1,1-dimetiletiléster (preparado como en el **Ejemplo 17**) en N,N-dimetilformamida anhidra (3 mL) se agregó yodometano (61 uL, 0.98 mmol), seguido por hidruro de sodio (24 mg, 0.59 mmol; dispersión al 60% en aceite mineral). Después de 1 hrs. la mezcla de reacción se fraguó con agua, se lavó con solución salina (3X), se secó sobre sulfato de sodio, se filtró, y se concentró al vacío para dar el producto N-metilado deseado como un sólido pegajoso. ESMS m/z = 561 $[M+H]^+$. HRMS calculado para $C_{29}H_{40}N_3O_7S$: 561.2634 $[M+H]^+$, hallado: 561.2628.

[848] **Parte B.** El producto de la **Parte A** (400 mg, 0.71 mmol) se recogió en ácido trifluoroacético glacial puro (1 mL). Después de 1 hrs., el ácido trifluoroacético glacial se eliminó al vacío a 60°C para dar el ácido libre como un sólido pegajoso. ESMS m/z = 505 $[M+H]^+$. A una solución de este material en N,N-dimetilformamida anhidra (5 mL) se agregó 1-hidroxibenzotriazol (113 mg, 0.83 mmol), tetrahidropiranhidroxilamina (246 mg, 2.10 mmol), y trietilamina (390 uL, 2.8 mmol), seguido por clorhidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (188 mg, 0.98 mmol). La mezcla de reacción se calentó a 40°C por 4 hrs., y luego se enfrió a temperatura ambiente. La mezcla de reacción se diluyó con acetato de etilo, se lavó con

943

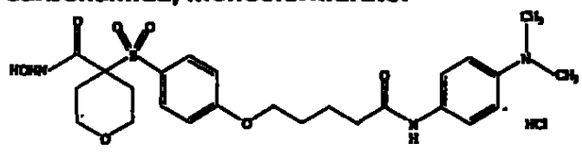
solución saturada de bicarbonato de sodio (2X) y solución salina (4X), se secó sobre sulfato de sodio, se filtró, y se concentró al vacío. El producto crudo se desprotegió y se purificó simultáneamente por HPLC en fase reversa para dar 59 mg del compuesto del título como un sólido blancuzco. ESMS m/z = 520 $[M+H]^+$. HRMS calculado para $C_{25}H_{33}N_3O_7S$: 520.2117 $[M+H]^+$, hallado: 520.2120.

[849] Usando métodos similares un especialista puede preparar otros compuestos. Entre los ejemplos de dichos compuestos se incluyen los que tienen una estructura que corresponde a la Fórmula genérica EX-G.



EX-G

[850] **Ejemplo 20. Preparación de 4-[[4-[[5-[[4-(dimetilamino)-fenil]amino]-5-oxopentil] oxi]fenil]sulfonil]tetrahidro-N-hidroxi-2H-piran-4-carboxamida, monoclorhidrato.**



[851] **Parte A.** A una solución de 4-[[4-(4-carboxibutoxi)fenil-]sulfonil]tetrahidro-2H-piran-4-carboxílico ácido, 1,1-dimetiletiléster (446 mg, 0.91 mmol, preparado como en el **Ejemplo 7**) en N,N-dimetilformamida anhidra (6 mL) se agregó 1-hidroxibenzotriazol (150 mg, 1.11 mmol), trietilamina (400 uL, 2.87 mmol), N,N-dimetil-l,4-fenilendiamina (188 mg, 1.38 mmol), y finalmente clorhidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (300 mg, 1.56 mmol). La mezcla de reacción se agitó a temperatura ambiente por 18 hrs., y luego se concentró al vacío a 60°C. El residuo se particionó entre

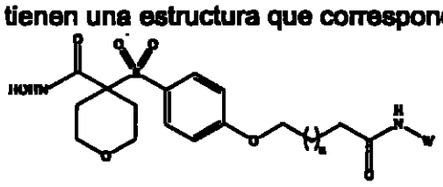
944

acetato de etilo y solución saturada de bicarbonato de sodio. La capa orgánica se lavó con solución salina (2X), se secó sobre sulfato de sodio, se filtró, y se concentró al vacío para dar la amida deseada. ESMS m/z = 561 $[M+H]^+$. Este material se recogió en ácido trifluoroacético glacial puro (5 mL). Después de 3 hrs. el ácido trifluoroacético glacial se eliminó al vacío a 60°C para dar el ácido libre. ESMS m/z = 505 $[M+H]^+$. A una solución de este material en N,N-dimetilformamida anhidra (5 mL) se agregó 1-hidroxibenzotriazol (148 mg, 1.10 mmol), trietilamina (400 uL, 2.87 mmol), y tetrahidropiranhidroxilamina (320 mg, 2.73 mmol), seguido por clorhidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (262 mg, 1.37 mmol). La mezcla de reacción se agitó a temperatura ambiente durante la noche, y luego se particionó entre acetato de etilo y solución saturada de bicarbonato de sodio. La capa orgánica se lavó con solución salina (3X), se secó sobre sulfato de sodio, se filtró, y se concentró al vacío. El material crudo se purificó por cromatografía instantánea usando acetato de etilo/hexano/s al 80% como eluyente para dar el THP hidroxamato deseado. ESMS m/z = 604 $[M+H]^+$. HRMS calculado para $C_{30}H_{41}N_3O_8S$: 604.2693 $[M+H]^+$, hallado: 604.2709.

[852] **Parte B.** El producto de la **Parte A** se disolvió en HCl 4N en dioxano (5 mL) y metanol (500 uL). Después de 3 hrs. a temperatura ambiente la mezcla de reacción se volcó en dietiléter en agitación rápida (50 mL). Se recolectó un sólido color rosa-bordó y a continuación se purificó por HPLC en fase reversa. El compuesto del título se obtuvo como un sólido color rosa débil 131 mg (28% a partir del ácido inicial parcialmente A). ESMS m/z = 520 $[M+H]^+$. HRMS calculado para $C_{25}H_{33}N_3O_7SHCl$: 520.2117 $[M+H]^+$, hallado: 520.2127.

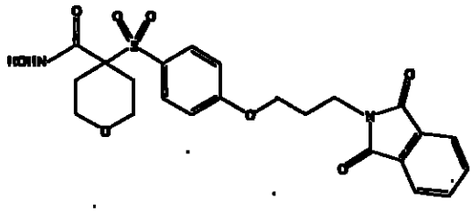
945

[853] Usando métodos similares un especialista puede preparar otros compuestos. Entre los ejemplos de dichos compuestos se incluyen los que tienen una estructura que corresponde a la Fórmula genérica EX-H.



EX-H

[854] **Ejemplo 21. Preparación de 4-[[4-[3-(1,3-dihidro-1,3-dioxo-2H-isoindol-2-il)propoxi] fenil]sulfonil]tetrahidro-N-hidroxi-2H-piran-4-carboxamida**



[855] **Parte A.** A una solución de ácido4-[(4-fluorofenil)-sulfonil]tetrahidro-2H-piran-4-carboxílico , 1,1-dimetiletiléster (6.7 g, 19 mmol, según se prepara en el **Ejemplo 1, Parte C**) en N,N-dimetilformamida anhidra (40 ml) a temperatura ambiente se agregó N-(3-hidroxipropil)ftalimida (4 g, 19 mmol), y luego inmediatamente NaH (700 mg, 20 mmol, dispersión al 60% en aceite mineral). Después de 1.5 hrs., la HPLC indicó menos de 1% del electrófilo inicial. La mezcla de reacción se fraguó con agua (60 ml). La mezcla turbia se extrajo con acetato de etilo (2x100 ml). Las capas orgánicas se combinaron, se lavó con solución salina (1x200 ml), se secó sobre sulfato de sodio, se filtró, y se concentró al vacío para dar un aceite viscoso color tostado que se cristalizó de metanol (3.2 g, 52%). ESMS m/z = 489 $[M+H]^+$. Este material se usó sin purificación adicional.

946

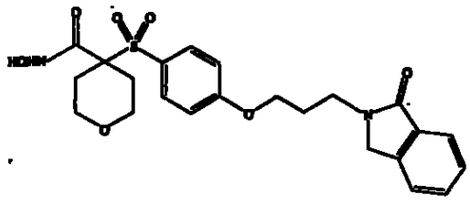
[856] **Parte B.** El producto de la **Parte A** (3 g, 6 mmol) se disolvió en cloruro de metileno (304 ml) y ácido trifluoroacético glacial (6 ml). Después de 12 hrs., la mezcla se concentró al vacío, y el residuo se trituró con dietiléter para formar un sólido que se recolectó y se secó para dar el ácido carboxílico como un sólido beige (3 g, 90%). ESMS m/z = 474 [M+H]+. Este material se usó sin purificación adicional.

[857] **Parte C.** A una solución del producto de la **Parte B** (3 g, 6.2 mmol) en N,N-dimetilformamida anhidra (25 ml) se agregó trietilamina (2 ml, 18 mmol), seguido por tetrahidropiranhidroxilamina (1 g, 8 mmol), 1-hidroxibenzotriazol (0.5 g, 3 mmol), y clorhidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (2 g, 8 mmol). La mezcla de reacción se calentó a 40°C por 0.5 hrs.. La reacción se controló por RPHPLC. Después de 2 hrs., la mezcla se concentró al vacío, al residuo se le agregó con agua, y el producto se separó como un sólido. El sólido se filtró, y tenía la suficiente pureza como para utilizarse en el siguiente paso. Los datos del espectro de masas y de RMN confirmaron el producto deseado.

[858] **Parte D.** El sólido de la parte C (3 g) se suspendió en metanol (1 mL) y dietiléter (30 ml). Se agregó HCl 4N en dioxano (10 ml) y se agitó por 2 hrs.. La RPHPLC indicó que la reacción había concluido. La mezcla de reacción se concentró a la mitad, se agregó dietiléter (100mL), se filtró el sólido blanco (1.5 g, 70% de rendimiento) y se secó bajo vacío. ^{1}H RMN confirmó el producto deseado ESMS m/z $C_{23}H_{24}N_2O_6S$ = 489 $[M+H]^+$. HRMS calculado para $C_{23}H_{24}N_2O_6S$: 489.1332 $[M+H]^+$, hallado: 489.1298.

947

[859] **Ejemplo 22. Preparación de 4-[[4-[3-(1,3-dihidro-1-oxo-2H-isoindol-2-il)propoxi]fenil]sulfonil]tetrahidro-N-hidroxi-2H-piran-4-carboxamida**



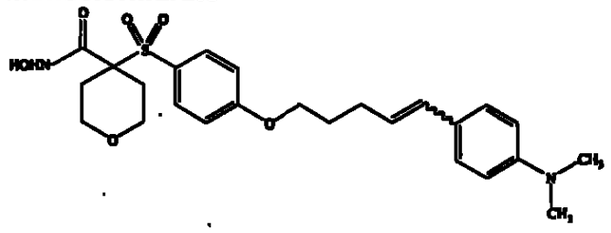
[860] **Parte A.** A una solución de ácido 4-[(4-fluorofenil)-sulfonil]tetrahidro-2H-piran-4-carboxílico, 1,1-dimetiletiléster (5.2 g, 15 mmol, según se prepara en el **Ejemplo 1, Parte C**) en dimetilsulfóxido (40 ml) a temperatura ambiente se agregó N-(3-hidroxipropil)ftalida (3 g, 15 mmol, preparada según J.Med.Chem., 146-157 (1996)), seguida por carbonato de cesio (12 g, 45 mmol). Después de 15 hrs. a 80°C, la HPLC indicó que la reacción había concluido. La mezcla de reacción se fraguó con agua (60 ml). La mezcla turbia se extrajo con acetato de etilo (2x100 ml). Las capas orgánicas se combinaron, se lavó con solución salina (1x200 ml), se secó sobre sulfato de sodio, se filtró, y se concentró al vacío para dar un aceite viscoso color tostado que se cristalizó de metanol (7 g, 720). ESMS m/z = 516 $[M+H]^+$; RMN confirmó el producto deseado. Este material se usó sin purificación adicional.

[861] **Parte B.** El producto de la **Parte A** (3 g, 6 mmol) se disolvió en cloruro de metileno (300 ml) y ácido trifluoroacético glacial (6 ml). Después de 12 hrs. de agitación, la mezcla se concentró al vacío y el residuo se trituró con dietiléter para formar un sólido que se recolectó y se secó para dar el ácido carboxílico como un sólido beige (3 g, 91%). ESMS m/z = 474 $[M+H]^+$. Este material se usó sin purificación adicional.

[862] **Parte C.** A una solución del producto de la **Parte B** (3 g, 6.2 mmol) en N,N-dimetilformamida (25 ml) se agregó trietilamina (2 ml, 18 mmol), seguida por tetrahidropiranhidroxilamina (1.2 g, 8 mmol), 1-hidroxibenzotriazol (0.5 g, 3 mmol), y clorhidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (1.5 g, 8 mmol). La mezcla de reacción se calentó a 40°C por 0.5 hrs.. La reacción se controló por RPHPLC. Una vez concluida la reacción la mezcla se concentró y al residuo se agregó agua. El sólido resultante se filtró, y tenía la suficiente pureza como para utilizarse en el siguiente paso. Datos del espectro de masas y RMN confirmaron el producto deseado.

[863] **Parte D.** El sólido de la parte C (3 g) se suspendió en metanol (1 mL) y dietiléter (30 ml). Se agregó HCl 4N en dioxano (10 ml) y se agitó por 2 hrs.. La RPHPLC indicó que la reacción había concluido. La mezcla de reacción se concentró a la mitad, se agregó dietiléter (100 mL), se filtró el sólido blanco (2.5 g, 90% de rendimiento) y se secó bajo vacío. ^{1}H RMN confirmó el producto deseado. HRMS calculado para $C_{23}H_{28}N_2O_7S$: 475.1525 $[M+H]^+$, hallado: 475.1510.

[864] **Ejemplo 23. Preparación de 4-[[4-[[4E)-5-[-4-(dimetilamino)fenil]-4-pentenil]oxi]fenil]sulfonil]tetrahidro-N-hidroxi-2H-piran-4-carboxamida y 4-[[4-[[4Z)-5-[-4-(dimetil-amino)fenil]-4-pentenil]oxi]fenil]sulfonil]tetrahidro-N-hidroxi-2H-piran-4-carboxamida, monoclorhidrato**



[865] **Parte A.** A una solución de ácido 4-[(4-fluorofenil)-sulfonil]tetrahidro-2H-piran-4-carboxílico, 1,1-dimetiletiléster (10.0 g, 29.0 mmol, según se prepara en el **Ejemplo 1, Parte C**) en N,N-dimetilformamida (60 ml) a temperatura ambiente se agregó 4-penten-1-ol (3.1 ml, 30.0 mmol), y luego inmediatamente NaH (1.4 g, 34.8 mmol, dispersión al 60% en aceite mineral). Después de 1.5 hrs., la HPLC indicó menos de 1% del material inicial. La mezcla de reacción se fraguó con agua (60 ml). La mezcla turbia se extrajo con acetato de etilo (3x-300 ml). Las capas orgánicas se combinaron; se lavaron con sulfato ácido de potasio al 5% (1x200 ml), solución saturada de bicarbonato de sodio (1x-200 ml), agua (1x-200 ml), y solución salina (1x-200 ml); se secó sobre sulfato de sodio, se filtró; y se concentró al vacío para dar un aceite de color tostado. El producto crudo se purificó parcialmente por cromatografía instantánea usando 15% acetato de etilo/hexanos para dar 11.7 g (98%) del éter deseado como un aceite translúcido e incoloro. ESMS m/z = 433 $[M+Na]^+$. Este material se usó sin purificación adicional.

[866] **Parte B.** A una solución del producto de la **Parte A** (2.0 g, 4.9 mmol) en N,N-dimetilformamida (3 ml) se agregó 4-bromo-N,N-dimetilanilina (1.2g, 5.8 mmol), seguido por trietilamina (1.4 ml, 9.8 mmol), tri-orto-tolilfosfina (34 mg, 0.10 mmol), y acetato de paladio (II) (12 mg, 0.05 mmol). La reacción se calentó a 100°C por 12 hrs.. La mezcla de reacción se enfrió y se diluyó con agua (5 ml). La fase acuosa se extrajo con acetato de etilo (3x15 ml). Los extractos orgánicos se secaron sobre sulfato de sodio, se filtró, y se concentró al vacío para dar un aceite de color negro (3.2 g). El producto crudo negro se purificó parcialmente por cromatografía instantánea usando 5% acetato de etilo/hexanos para dar 1.2 g del producto olefínico como un aceite de color

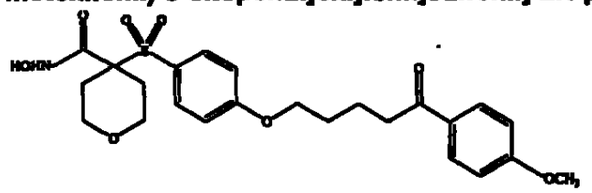
tostado (45% de rendimiento, trans:cis, 3:1). ESMS m/z = 552 $[M+Na]^+$. Este material se usó sin purificación adicional.

[867] **Parte C.** El producto de la **Parte B** (1.2 g, 2.3 mmol) se disolvió en cloruro de metileno (4 ml) y ácido trifluoroacético glacial (4 ml). Después de 1 hrs. de agitación, la mezcla se concentró y el residuo se trituró con dietiléter para formar un sólido que se recolectó y se secó para dar el ácido carboxílico-sal de TFA como un sólido beige (0.73 g, 510). ESMS m/z = 474 $[M+H]^+$. Este material se usó sin purificación adicional.

[868] **Parte D.** A una solución del producto de la **Parte C** (0.73 g, 1.2 mmol) en N,N-dimetilformamida (4 ml) se agregó trietilamina (0.9 ml, 6.2 mmol), seguido por tetrahidropiranhidroxilamina (0.28 g, 2.4 mmol), 1-hidroxibenzotriazol (0.19 g, 1.4 mmol), y clorhidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (0.32 g, 1.8 mmol). La mezcla de reacción se calentó a 40°C por 24 hrs.. La mezcla se concentró y el residuo se purificó por medio de cromatografía en fase reversa (C_{18}, acetonitrilo/agua/TFA). Se recogieron fracciones (10 ml) para separar los isómeros. Durante el análisis, las mezclas acuosas de TFA desprotegieron del producto dando los ácidos hidroxámicos como productos finales. 4-[[4-[[4E)-5-[-4-(dimetilamino) fenil]-4-pentenil] oxi]fenil]sulfonil]-tetrahidro-N-hidroxi-2H-piran-4-carboxamida, (98% isómero trans por HPLC, 0.12 g, 17% de rendimiento). HRMS calculado para $C_{23}H_{28}N_2O_6S$: 489.2059 $[M+H]^+$, hallado: 489.2067. La ^1H RMN confirmó isomerización trans (Job = 15.9 Hz). 4-[[4-[[4Z)-5-[-4-(dimetil-amino)fenil]-4-pentenil]oxi]fenil]sulfonil]tetrahidro-N-hidroxi-2H-piran-4-carboxamida, monoclorhidrato, (79% cis/17% trans por HPLC, 15 mg de sólido de color tostado, 2% de rendimiento). HRMS calculado para $C_{25}H_{32}N_2O_6S$: 489.2059 $[M+H]^+$, hallado: 489.2067.

951

[869] **Ejemplo 24. Preparación de tetrahidro-N-hidroxi-4-[[4-[[5(4-metoxifenil)-5-oxopentil]oxi]fenil]sulfonil]-2H-piran-4-carboxamida**



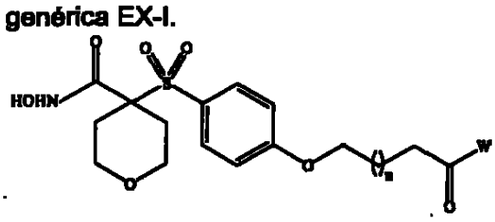
[870] **Parte A.** A una mezcla de limaduras de magnesio (344 mg, 14.18 mmol) tratada con iodo en tetrahidrofurano anhidro (4 mL) a reflujo se agregó 4-bromoanisol (1.2 mL, 9.45 mmol) por goteo durante 10 min. La mezcla de reacción se calentó a reflujo por 45 min, y luego se enfrió a temperatura ambiente. El reactivo de grignard preparado se agregó a una mezcla de tetrahidro-4-[[4-[[5-(metoximetilamino)-5-oxopentil]oxi]fenil]sulfonil]-N-[(tetrahidro-2H-piran-2-il)oxi]-2H-piran-4-carboxamida (1.0 g, 1,9 mmol, según se prepara en el Ejemplo 7) en tetrahidrofurano anhidro (10 mL) a 0°C. La mezcla de reacción se calentó a temperatura ambiente y se dejó agitando durante la noche. La reacción se fraguó con cloruro de amonio saturado, y luego se particionó entre acetato de etilo y agua. Las capas se separaron, y la capa orgánica se lavó con solución salina, se secó sobre sulfato de sodio, se filtró, y se concentró al vacío. El material crudo se purificó por cromatografía instantánea usando 50-100% acetato de etilo/hexanos para dar 320 mg (29%) de la cetona deseada como un polvo blanco. ESMS m/z = 593 $[M+NH_4]^+$. HRMS calculado para $C_{29}H_{37}NO_9S$: 593.2533 $[M+NH_4]^+$, hallado: 593.2555.

[871] **Parte B.** El producto de la **Parte A** (300 mg, 0.52 mmol) se disolvió en HCl 4N en dioxano (3 mL) y metanol (300 uL). Después de 10 min a temperatura ambiente, la mezcla de reacción se volcó en hexanos (75 mL), y el producto precipitó como un aceite. se decantó el solvente y se agregaron más hexanos. El sólido resultante se trituró con dietiléter, y el compuesto del

952

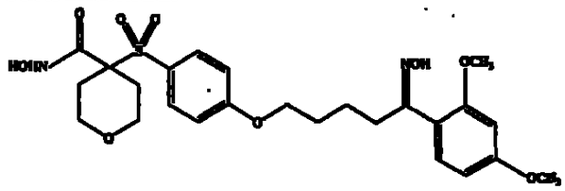
título se obtuvo como un sólido blancuzco. ESMS m/z = 492 $[M+H]^+$. HRMS calculado para $C_{24}H_{29}NO_8S$: 492.1692 $[M+H]^+$, hallado: 492.1713.

[872] Usando métodos similares un especialista puede preparar otros compuestos con el t-butiléster, hidroxamato protegido con THP, o hidroxamato unido a resina de la amida weinreb. Entre los ejemplos de dichos compuestos se incluyen los que tienen una estructura que corresponde a la Fórmula genérica EX-I.



EX-I

[873]. **Ejemplo 25. Preparación de tetrahidro-N-hidroxi-4-[[4-[[5-(hidroxiimino)-5-(4-metoxifenil)pentil]oxi]fenil]-sulfonil]-2H-piran-4-carboxamida.**



[874] **Parte A.** A una mezcla de limaduras de magnesio (1.2 g, 49.4 mmol) tratadas con iodo en tetrahidrofurano anhidro (4 mL) a reflujo se agregó 1-bromo-2,4-dimetoxibenceno (6.0 mL, 41.7 mmol) por goteo durante 10 min. La mezcla de reacción se calentó a reflujo por 30 min, y luego se enfrió a temperatura ambiente. El reactivo de grignard preparado se agregó a una mezcla de ácido tetrahidro-4-[[4-[3-(metoxímetil-amino)-3-oxopropoxi]fenil]sulfonil]-2H-piran-4-carboxílico, 1,1-dimetiletiléster (1.0 g, 1.9 mmol, preparado como en el Ejemplo 7) en THF anhidro (10 mL) a 0°C. La mezcla de reacción se calentó a temperatura ambiente, y, después de 2 hrs.,

953

se fraguó con cloruro de amonio saturado, y luego se particionó entre acetato de etilo y agua. Las capas se separaron, y la capa orgánica se lavó con solución salina, se secó sobre sulfato de sodio, se filtró, y se concentró al vacío. El material crudo se cubrió con dietiléter. El sólido verde resultante se trituró con dietiléter. El sólido final se recolectó para dar 2.2 g (94%) de la cetona deseada como un polvo color verde pálido. ESMS m/z = 585 $[M+Na]^+$. HRMS calculado para $C_{29}H_{38}NO_9S$: 563 .2315 $[M+H]^+$, hallado: 563.2319.

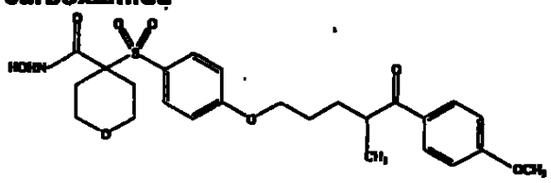
[875] **Parte B.** El producto de la **Parte A** (2.2 g, 3.91 mmol) se recogió en ácido trifluoroacético glacial puro (6 mL). Después de 2 hrs., el ácido trifluoroacético glacial se eliminó al vacío a 50°C para dar el ácido libre como un aceite de color púrpura. ESMS m/z = 507 $[M+H]^+$. A una solución de este material en N,N-dimetilformamida anhidra (20 mL) se agregó 1-hidroxibenzotriazol (670 mg, 4.96 mmol), trietilamina (1.8 mL, 12.91 mmol), tetrahidropiranhidroxilamina (1.48 g, 12.63 mmol), y clorhidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (1.13 g, 5.89 mmol). Después de 16 hrs., la mezcla de reacción se concentró al vacío a 60°C. El material crudo se particionó entre acetato de etilo y solución saturada de bicarbonato de sodio. La capa orgánica se lavó con solución salina (2X), se secó sobre sulfato de sodio, se filtró, y se concentró al vacío para dar un aceite amarillo. La purificación por cromatografía instantánea usando acetato de etilo/hexano/s al 80% dio una mezcla de hidroxamato de THP/oxima de THP (78%) y hidroxamato de THP cetona (12%). ESMS m/z = 621 $[M+H]^+$ y ESMS m/z = 628 $[M+H]^+$ respectivamente. Estos productos no se separaron, y en cambio se utilizaron en el paso siguiente como una mezcla.

[876] **Parte C.** El producto de la **Parte B** (540 mg, 0.77 mmol) se disolvió en HCl 4N en dioxano (5 mL) y metanol (500 uL). Después de 2 hrs. a

954

temperatura ambiente la mezcla de reacción se volcó en dietiléter con agitación rápida. Se recolectó un sólido rosáceo/púrpura y se purificó por HPLC en fase reversa. El compuesto del título se obtuvo como un sólido blanco. ESMS m/z = 537 $[M+H]^+$. HRMS calculado para $C_{25}H_{32}N_2O_9S$: 537.1907 $[M+H]^+$, hallado: 537.1921.

[877] Ejemplo 26. Preparación de tetrahidro-N-hidroxi-4-[[4-[[5-(4-metiloxifenil)-4-metil-5-oxopentil]oxi]fenil]sulfonil]-2H-piran-4-carboxamida



[878] Parte A. A una solución de ácido tetrahidro-4-[[4-[[5-(4-metoxifenil)-5-oxopentil]oxi]fenil]sulfonil]-2H-piran-4-carboxílico, 1,1-dimetiletiléster (532 mg, 1.0 mmol, preparado como en el **Ejemplo 24**) y iodometano (623 mg, 4.4 mmol) en 5 ml de N,N-dimetilformamida se agregó hidruro de sodio (125 mg, 3.1 mmol, dispersión al 60% en aceite mineral). La mezcla de reacción se agitó 40 min luego se fraguó con HCl_{aq} 1N. La mezcla de reacción se particionó entre acetato de etilo y sulfato ácido de potasio acuoso al 5%. La fase orgánica se secó sobre sulfato de sodio, se filtró, y se concentró al vacío para dar un aceite crudo. La purificación por cromatografía instantánea usando 40% acetato de etilo/hexanos dio 370 mg (68% de rendimiento) del monometilcetoéster. ESMS m/z = 547 $[M+H]^+$.

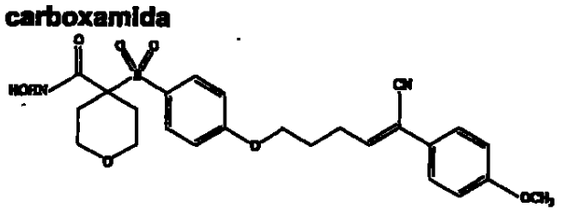
[879] Parte B. El producto de la **Parte A** (370 mg, 0.68 mmol) se recogió en ácido trifluoroacético glacial. Después de 45 min, el análisis por HPLC indicó que la reacción había finalizado. El ácido trifluoroacético glacial se eliminó al vacío, y el residuo se lavó con acetonitrilo (2x10 ml), y luego se

955

secó al vacío para dar 335 mg del ácido libre. ESMS m/z = 491 $[M+H]^+$. A una solución de este material en N,N-dimetilformamida anhidra (4 mL) se agregó 1-hidroxibenzotriazol (138 mg, 0.68 mmol) y clorhidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (150 mg, 0.78 mmol), seguido por trietilamina (190 uL, 1.36 mmol) y tetrahidropiranhidroxilamina (160 mg, 1.37 mmol). Después de 16 hrs., la mezcla de reacción se particionó entre acetato de etilo y sulfato ácido de potasio acuoso al 5%. Los extractos orgánicos combinados se lavaron con solución salina, se secó sobre sulfato de sodio, se filtró, y se concentró al vacío para dar un aceite crudo. La purificación por cromatografía instantánea usando 60% acetato de etilo/hexanos como eluyente dio 270 mg (67%) del hidroxamato protegido con THP deseado. ESMS m/z = 590 $[M+H]^+$.

[880] **Parte C.** El producto de la **Parte B** (270 mg, 0.46 mmol) se disolvió en HCl 4N en dioxano (2 mL) y metanol (500 uL). Después de 15 min a temperatura ambiente, la mezcla de reacción se particionó entre acetato de etilo y agua. La capa orgánica se secó sobre sulfato de sodio, se filtró, y se concentró al vacío para dar 200 mg (86%) del compuesto del título. ESMS m/z = 406 $[M+H]^+$. HRMS calculado para $C_{25}H_{31}NO_6S$ 506.1849 $[M+H]^+$, hallado: 506.1828.

[881] **Ejemplo 27. Preparación de 4-[[4-[[(4Z)-5-ciano-5-(4-metoxifenil)-4-pentenil]oxi]fenil]sulfonil]tetrahidro-N-hidroxi-2H-piran-4-carboxamida**



956

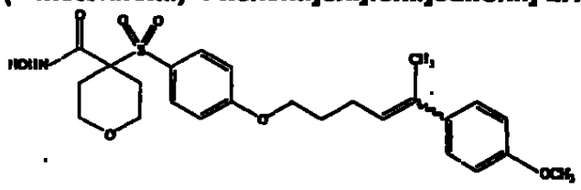
Parte A. A una solución de ácido tetrahidro-4-[[4-[[5-(4-metoxifenil)-5-oxopentil]oxi]fenil]sulfonil]-2H-piran-4-carboxílico, 1,1-dimetiletiléster (1.0 g, 1.9 mmol, preparado como en el **Ejemplo 24**) en 15 ml cloruro de metileno se agregó cianuro de trimetilsililo (300 µL, 2.2 mmol) y ioduro de zinc (660 mg, 2.1 mmol). La mezcla de reacción se agitó a temperatura ambiente por 3 hrs., y luego se concentró al vacío. El residuo se particionó entre acetato de etilo y HCl_{aq} 1N. La capa orgánica se secó sobre sulfato de sodio, se filtró, y se concentró al vacío. El producto crudo se purificó por cromatografía instantánea usando 25% acetato de etilo/hexanos para dar 950 mg (81%) de la cianohidrina sililada. Este material se recogió en ácido trifluoroacético glacial (15 mL). La solución roja oscura presentó varios picos en el análisis por HPLC durante los primeros 40 min. Después de 1 hrs., el análisis por HPLC indicó un nuevo pico a 93%. La mezcla de reacción se concentró al vacío y se lavó con acetonitrilo (2x10 ml). El sólido crudo se disolvió en metanol y se agregó a 40 ml de dietiléter. El sólido blanco resultante se filtró y se secó para dar 630 mg del ácido libre/ciano olefina. ESMS m/z = 486 $[M+H]^+$.

[882] **Parte B.** A una solución del producto de la **Parte A** (630 mg, 1.3 mmol) en N,N-dimetilformamida anhidra (15 mL) se agregó 1-hidroxibenzotriazol (285 mg, 2.1 mmol) y 1-(3-dimetilaminopropil)-3-etilcarbodiimida clorhidrato de (285 mg, 1.5 mmol), seguido por N-metilmorfolina (545 uL, 5.0 mmol) y tetrahidropiranhidroxilamina (456 mg, 3.9 mmol). Después de 20 hrs., la mezcla de reacción se concentró al vacío, y luego se particionó entre acetato de etilo y 5% sulfato ácido de potasio acuoso. Los extractos orgánicos combinados se lavaron con solución salina, se secó sobre sulfato de sodio, se filtró, y se concentró al vacío. La purificación por

cromatografía instantánea usando acetato de etilo/hexano/s al 80% para dar 530 mg (70%) del hidroxamato protegido por THP. ESMS m/z = 585 $[M+H]^+$.

[883] **Parte C.** El producto de la **Parte B** (530 mg, 0.91 mmol) se disolvió en HCl 4N en dioxano (5 mL) y metanol (1 mL). Después de 15 min a temperatura ambiente, la mezcla de reacción se particionó entre acetato de etilo y agua. La capa orgánica se secó sobre sulfato de sodio, se filtró, y se concentró al vacío para dar 360 mg de el hidroxamato deseado. La purificación por HPLC en fase reversa dio 270 mg (59%) del compuesto del título. ESMS m/z = 504 $[M+H]^+$. HRMS calculado para $C_{25}H_{29}N_2O_7S$: 501 . 1695 $[M+H]^+$, hallado: 501. 1689.

[884] **Ejemplo 28. Preparación de tetrahidro-N-hidroxi-4-[[4[[(4E)-5-(4-metoxifenil)-4-hexenil]oxi]fenil]sulfonil]-2H-piran-4-carboxamida**



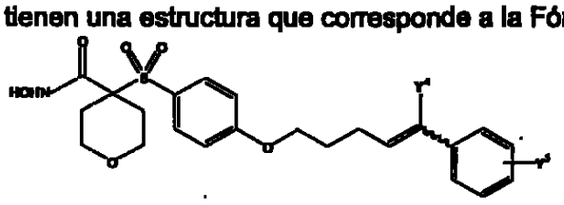
[885] **Parte A.** A una solución enfriada (0°C) de 4-[(4-[[5-(4-metoxifenil)-5-oxopentil]oxi}fenilsulfonil]-N-(tetrahidro-2H-piran-2-iloxi)tetrahidro-2H-piran-4-carboxamida (0.2 g, 0.4 mmol, según se prepara en el **Ejemplo 24**) en tetrahidrofurano (2 ml) se agregó una solución 3.0 M de bromuro de metilmagnesio (1.2 ml, 3.6 mmol). El baño de hielo se eliminó, y la mezcla de reacción se agitó por 2 hrs. a temperatura ambiente. La HPLC indicó menos de 1% de la cetona inicial. La mezcla de reacción se diluyó con acetato de etilo y se lavó con solución de cloruro de amonio saturado, agua, y solución salina. Después de secar sobre sulfato de sodio y filtrar, la capa orgánica se concentró al vacío para dar 0.25 g (100%) de un aceite de color

958

tostado. ESMS m/z = 614 $[M+Na]^+$. Este material se usó sin purificación adicional.

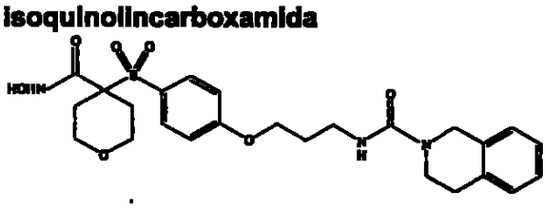
[886] **Parte B.** Al producto de la **Parte A** (0.24 g, 0.4 mmol) se agregó metanol (0.5 ml) y HCl 4N en dioxano (4.0 ml). Después de agitar 2 hrs., la HPLC indicó que se había consumido todo el material inicial. Se agregó dietiléter para formar un sólido pero se obtuvo un residuo gomoso. La mezcla se concentró y el residuo oleoso se purificó por medio de HPLC en fase reversa (C_{18}, acetonitrilo/agua/TFA) para dar 0.11 g (55%) del producto deseado como un aceite de color tostado. ^1H RMN (N.O.E) confirmó que la isomería del producto era 70% trans:30% cis. HRMS calculado para $C_{25}H_{31}NO_7S$: 490.1899 [M+H], hallado: 490.1898.

[887] Usando métodos similares un especialista puede preparar otros compuestos. Entre los ejemplos de dichos compuestos se incluyen los que tienen una estructura que corresponde a la Fórmula genérica EX-J.



EX-J

[888] **Ejemplo 29 Preparación de 3,4-dihidro-N-[3-[4-[[tetrahidro-4-[(hidroxiamino)carbonil]-2H-piran-4-il]sulfonil]-fenoxi]propil]-2-(1H)-isoquinolincarboxamida**



[889] **Parte A.** A una solución de ácido 4-[[4-(3-aminopropoxi)-fenil]sulfonil]tetrahidro-2H-piran-4-carboxílico, 1,1-dimetiletiléster,

959

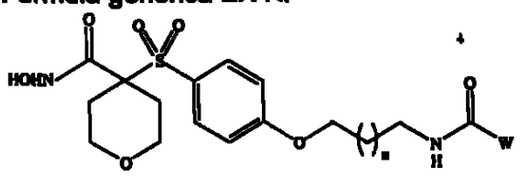
monoclorhidrato (467 mg, 1.07 mmol, preparado en el **Ejemplo 1**) en cloroformo anhidro (3 mL) a temperatura ambiente se agregó trietilamina (170 uL, 1.22 mmol) y 1,1'-carbonildiimidazol (180 mg, 1.11 mmol). Después de 1 hrs. a 50°C, se agregó 1,2,3,4-tetrahidroisoquinolina pura (162 mg, 1.22 mmol). Después de otras 2 hrs. a 50°C, la HPLC indicó que la reacción había concluido. La mezcla de reacción se particionó entre acetato de etilo y sulfato ácido de potasio acuoso al 5%. La capa orgánica se lavó con solución saturada de bicarbonato de sodio y solución salina, se secó sobre sulfato de sodio, se filtró, y se concentró al vacío para dar un aceite amarillo. ESMS m/z = 559 $[M+H]^+$. Este material se usó sin purificación adicional.

[890] **Parte B.** El producto de la **Parte A** se recogió en ácido trifluoroacético glacial puro (3 mL). Después de 13 hrs., el ácido trifluoroacético glacial se eliminó al vacío a 50°C para dar el ácido libre. ESMS m/z = 503 $[M+H]^+$. A una solución de este material en N,N-dimetilformamida anhidra (5 mL) se agregó 1-hidroxibenzotriazol (176 mg, 1.30 mmol), trietilamina (500 uL, 3.59 mmol), y tetrahidropiranhidroxilamina (254 mg, 2.17 mmol), seguido por clorhidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (310 mg, 1.62 mmol). La mezcla de reacción se calentó a 40°C por 4 hrs., y luego se agitó a temperatura ambiente durante la noche. La mezcla de reacción se concentró al vacío a 60°C. El residuo se particionó entre acetato de etilo y solución saturada de bicarbonato de sodio. Las capas se separaron, y la capa orgánica se lavó con solución salina (3X), se secó sobre sulfato de sodio, se filtró, y se concentró al vacío. El producto crudo se purificó por cromatografía instantánea para dar 260 mg (40% a partir de la amina inicial) del hidroxamato protegido con THP deseado como un sólido blanco. ESMS m/z = 624 $[M+Na]^+$. HRMS calculado para $C_{30}H_{39}N_3O_6S$: 602 .2536 $[M+H]^+$, hallado: 602 .2546 .

960

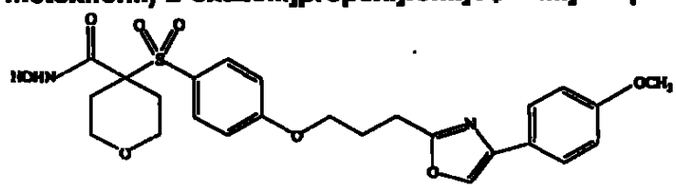
[891] **Parte C.** El producto de la **Parte B** (252 mg, 0.42 mmol) se disolvió en HCl 4N en dioxano (5 mL) y metanol (500 uL). Después de 1 hrs. a temperatura ambiente, la mezcla de reacción se volcó en dietiléter con agitación rápida. Se recolectó un sólido blanco y se secó sobre P_2O_5 bajo vacío. El compuesto del título se obtuvo como un sólido blanco. ESMS m/z = 518 $[M+H]^+$. HRMS calculado para $C_{25}H_{31}N_3O_7S$: 518. 1961 $[M+H]^+$, hallado: 518.1961.

[892] Usando métodos similares un especialista puede preparar otros compuestos (también puede ser llevada a cabo la formación de urea por copulación de la amina inicial con un isocianato). Entre los ejemplos de dichos compuestos se incluyen los que tienen una estructura que corresponde a la Fórmula genérica EX-K.



EX-K

[893] **Ejemplo 30. Preparación de tetrahidro-N-hidroxi-4-[[4-[3-[4-(4-metoxifenil)-2-oxazolil]propoxi]fenil]sulfonil]-2H-piran-4-carboxamida**



[894] **Parte A.** A una solución de ácido 4-[[4-(3-carboxipropoxi)fenil]sulfonil] tetrahidro-2H-piran-4-carboxílico, 1,1-dimetiletiléster (3.2 g, 7.5 mmol, preparado como en el **Ejemplo 7**) en acetona (15 mL) se agregó 2-bromo-4-metoxiacetofenona (1.72 g, 7.5 mmol) y carbonato de potasio (1.04 g, 7.5 mmol). La mezcla de reacción se agitó a

temperatura ambiente por 3 hrs.. La mezcla de reacción se filtró, y la torta se lavó con acetona. La solución en acetona se concentró al vacío. La purificación por cromatografía de columna instantánea usando acetato de etilo/hexanos dio 3.68 g (85%) del éster sustituido como un sólido blanco. ESMS m/z = 599 $[M+Na]^+$.

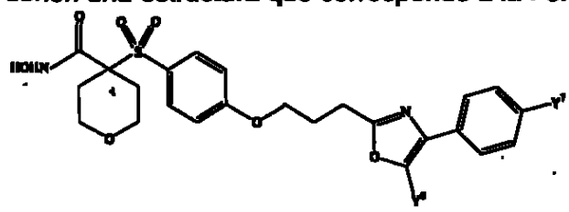
[895] **Parte B.** El producto de la **Parte A** (3.6 g, 6.25 mmol) se refluió en ácido acético glacial (12 mL) con acetato de amonio (2.41 g, 31.25 mmol) por 24 hrs.. La reacción se diluyó con acetato de etilo (50 mL) y se lavó 2 veces con agua (25 mL) y se filtró. El filtrado en acetato de etilo se extrajo con una solución de NaOH acuosa al 10% (50 mL). La solución básica luego se acidificó a un pH de 1, y luego se extrajo con acetato de etilo (25 mL). La solución orgánica luego se lavó con agua (25 mL), se secó sobre sulfato de sodio, se filtró, y se concentró al vacío para dar 1.5 g (48%) del ácido carboxílico del oxazol como un sólido marrón. ESMS m/z = 502 $[M+H]^+$.

[896] **Parte C.** En un equipo en seco bajo nitrógeno, el ácido carboxílico de la parte B (1.3 g, 2.59 mmol) se disolvió en N,N-dimetilformamida seca (5 mL), y los reactivos restantes se agregaron a la solución en el orden siguiente: 1-hidroxibenzotriazol (490 mg, 3.63 mmol), trietilamina (0.43 mL, 3.11 mmol), tetrahidropiranhidroxilamina (364 mg, 3.11 mmol), y clorhidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (746 mg, 3.89 mmol). Después de 12 hrs. a 40°C, la reacción se concentró al vacío. El residuo se recogió en acetato de etilo, se lavó con agua, solución saturada de bicarbonato de sodio, y solución salina, se secó sobre sulfato de sodio, se filtró, y se concentró al vacío. La purificación por cromatografía de columna instantánea usando acetato de etilo/hexanos dio 0.70 g (45%) del hidroxamato de THP como una espuma blanca. ESMS m/z = 601 $[M+H]^+$.

962

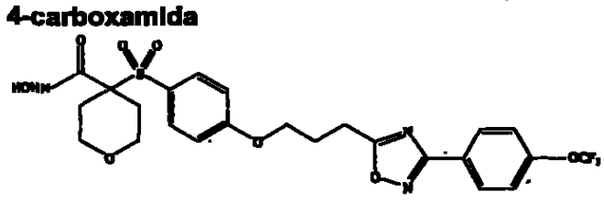
[897] **Parte D.** A una solución del producto de la **Parte C** (0.6 g, 1.0 mmol) en 1,4-dioxano (1.0 mL) se agregó HCl 4N en dioxano (1.25 mL, 5 mmol) y metanol (0.13 mL). Después de 1 hrs. a temperatura ambiente, la reacción se diluyó con acetato de etilo y se lavó con agua, se secó sobre sulfato de sodio, se filtró, y se concentró al vacío. Se agregó cloruro de metileno (20 mL), y la solución se despojó para dar 0.29 g (56%) del compuesto del título como un sólido color rosado claro. HRMS calculado para $C_{25}H_{28}N_2O_8S$: 517.1645 $[M+H]^+$, hallado: 517.1651.

[898] Usando métodos similares un especialista puede preparar otros compuestos. Entre los ejemplos de dichos compuestos se incluyen los que tienen una estructura que corresponde a la Fórmula EX-L.



EX-L

[899] **Ejemplo 31. Preparación de tetrahidro-N-hidroxi-4-[[4-[3-[3[4-(trifluorometoxi)fenil]-1,2,4-oxadiazol-5-il]propoxi]fenil]sulfonil]-2H-piran-4-carboxamida**



[900] **Parte A.** En un equipo en seco bajo nitrógeno, se disolvió ácido 4-[[4-(3-carboxipropoxi)fenil]sulfonil]tetrahidro-2H-piran-4-carboxílico, 1,1-dimetiléster (2.57 g, 6.0 mmol, preparado como en el **Ejemplo 7**) en N,N-dimetilformamida seca (12 mL), y los reactivos restantes se agregaron a la solución en el orden siguiente: hidrato de 1-hidroxibenzotriazol (1.13 g, 8.4

963

mmol), trietilamina (1.0 mL, 7.2 mmol), 4-(trifluorometoxi)benzamidoxima (1.58 g, 7.2 mmol), y clorhidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (1.73 g, 9.0 mmol). Después de 2 hrs. a 35°C, la reacción se concentró al vacío. El residuo se recogió en acetato de etilo, se lavó con agua, solución saturada de bicarbonato de sodio, y solución salina, se secó sobre sulfato de sodio, se filtró, y se concentró al vacío. La purificación por cromatografía de columna instantánea usando acetato de etilo/hexanos dio 3.05 g (81%) del producto deseado como un vidrio transparente. ESMS m/z = 631 $[M+Na]^+$.

[901] **Parte B.** El producto de la **Parte A** (2.9 g, 4.60 mmol) se calentó a 90°C en tolueno (15 mL) por 30 hrs.. La reacción se concentró al vacío. La purificación por cromatografía de columna usando acetato de etilo/hexanos dio 2.06 g (73%) del oxadiazol como un sólido blanco. ESMS m/z = 635 $[M+Na]^+$.

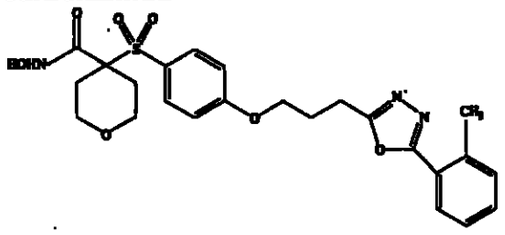
[902] **Parte C.** El producto de la **Parte B** (2.0 g, 3.27 mmol) se disolvió en ácido trifluoroacético glacial (8 mL) y se agitó a temperatura ambiente por 2 hrs.. La reacción se diluyó con cloruro de metileno (10 mL) y se concentró al vacío. Se agregó cloruro de metileno (10 mL) al residuo y se concentró al vacío nuevamente para dar 1.8 g (99%) del ácido libre como un sólido blancuzco. ESMS m/z = 557 $[M+H]^+$.

[903] **Parte D.** en un equipo en seco bajo nitrógeno, el producto de la **Parte C** (1.7 g, 3.06 mmol) se disolvió en N,N-dimetilformamida seca (6 mL), y los reactivos restantes se agregaron a la solución en el orden siguiente: hidrato de 1-hidroxibenzotriazol (578 mg, 4.28 mmol), trietilamina (0.51 mL, 3.67 mmol), tetrahidropiranhidroxilamina (429 mg, 3.67 mmol), y clorhidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (879 mg, 4.59 mmol). Después de 90 min a 40°C, la reacción se concentró al vacío. El residuo se recogió en acetato de etilo, se lavó con agua, solución saturada de bicarbonato de sodio, y

solución salina, se secó sobre sulfato de sodio, se filtró, y se concentró al vacío. La purificación por cromatografía de columna instantánea usando acetato de etilo/hexanos dio 1.9 g (95%) del hidroxamato de THP como una espuma blanca. ESMS m/z = 678 $[M+Na]^+$.

[904] **Parte E.** A una solución del producto de la **Parte D** (1.8 g, 2.75 mmol) en 1,4-dioxano (1.0 mL) se agregó HCl 4N en dioxano (3.5 mL, 13.7 mmol) y metanol (0.35 mL). Después de 2 hrs. a temperatura ambiente, la reacción se diluyó con acetato de etilo y se lavó con agua, se secó sobre sulfato de sodio, se filtró, y se concentró al vacío. La cromatografía en fase reversa dio 1.12 g (71%) del compuesto del título como un sólido blanco. HRMS calculado para $C_{24}H_{24}N_3O_8S_1F_3$: 572.1314 $[M+H]^+$, hallado: 572.1290.

[905] **Ejemplo 32. Preparación de tetrahidro-N-hidroxi-4-[[4-[3-[5-(2-metilfenil)-1,3,4-oxadiazol-2-il]propoxi]fenil]sulfonil]-2H-piran-4-carboxamida**



[906] **Parte A.** En un equipo en seco bajo nitrógeno, ácido 4-[[4-(3-carboxipropoxi)fenil] sulfonil]tetrahidro-2H-piran-4-carboxílico, 1,1-dimetiletiléster (2.14 g, 5.0 mmol, preparado como en el **Ejemplo 7**) se disolvió en N,N-dimetilformamida seca (10 mL), y los reactivos restantes se agregaron a la solución en el orden siguiente: hidrato de 1-hidroxibenzotriazol (945 mg, 7.0 mmol), trietilamina (0.84 mL, 6.0 mmol), hidrazida o-tolulca (901 mg, 6.0 mmol), y clorhidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (1.44 g, 7.5 mmol). Después de 2 hrs. a 35°C, la reacción se concentró al vacío. El residuo

965

se recogió en acetato de etilo; se lavó con agua, solución saturada de bicarbonato de sodio, y solución salina; se secó sobre sulfato de sodio, se filtró; y se concentró al vacío. La purificación por cromatografía de columna instantánea usando acetato de etilo/hexanos dio 2.32 g (83%) del producto deseado como una espuma blanca. ESMS m/z = 583 $[M+Na]^+$.

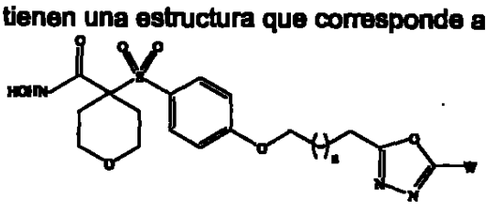
[907] **Parte B.** El producto de la **Parte A** (2.1 g, 3.75 mmol) se calentó a reflujo en tolueno (25 mL) con ácido p-toluensulfónico (100 mg) por 4 hrs.. La reacción se concentró al vacío. La recristalización de metanol caliente dio 1.6 g (88%) del ácido libre del oxadiazol como un sólido blanco. ESMS m/z = 487 $[M+Na]^+$.

[908] **Parte C.** en un equipo en seco bajo nitrógeno, el producto de la **Parte B** (1.5 g, 3.09 mmol) se disolvió en N,N-dimetilformamida seca (6 mL), y los reactivos restantes se agregaron a la solución en el orden siguiente: hidrato de 1-hidroxibenzotriazol (578 mg, 4.28 mmol), trietilamina (0.51 mL, 3.67 mmol), tetrahidropiranhidroxilamina (429 mg, 3.67 mmol), y clorhidrato de 1-(3 dimetilaminopropil)-3-etilcarbodiimida (879 mg, 4.59 mmol). Después de 6 hrs. a 40°C, la reacción se concentró al vacío. El residuo se recogió en acetato de etilo; se lavó con agua, solución saturada de bicarbonato de sodio, y solución salina; se secó sobre sulfato de sodio, se filtró; y se concentró al vacío. La purificación por cromatografía de columna instantánea usando acetato de etilo/hexanos dio 1.53 g (85%) del hidroxamato de THP como una espuma blanca. ESMS m/z = 608 $[M+Na]^+$.

[909] **Parte D.** A una solución del producto de la **Parte C** (1.4 g, 2.39 mmol) en 1,4-dioxano (1.0 mL) se agregó HCl 4N en dioxano (6 mL, 23.9 mmol) y metanol (0.6 mL). Después de 2 hrs. a temperatura ambiente, la reacción se diluyó con acetato de etilo y se lavó con agua, se secó sobre

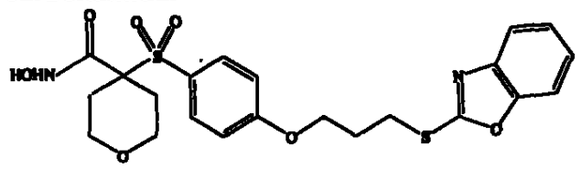
sulfato de sodio, se filtró, y se concentró al vacío. La cromatografía en fase reversa dio 1.02 g (85%) del compuesto del título como un sólido blanco. HRMS calculado para $C_{24}H_{27}N_3O_7S_1$: 502.1648 $[M+H]^+$, hallado: 502.1652.

[910] Usando métodos similares un especialista puede preparar otros compuestos. Entre los ejemplos de dichos compuestos se incluyen los que tienen una estructura que corresponde a la Fórmula genérica EX-M.



EX-M

[911] **Ejemplo 33. Preparación de 4-[[4-[3-(2-benzoxazoliltio)propoxi]fenil] sulfonil]tetrahidro-N-N-hidroxi-2H-piran-4-carboxamida.**

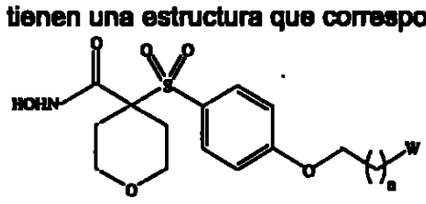


[912] **Parte A.** A una solución de 2-mercaptobenzoxazol (290 mg, 1.92 mmol) en N,N-dimetilformamida (5 mL) a 0°C se agregó NaH (128 mg, 1.92 mmol, dispersión al 60% en aceite mineral). Después de 30 min, se agregó tetrahidro-4-[[4-[3-[(metilsulfonil)oxi]propoxi]fenil]sulfonil]-N-[(tetrahidro-2H-piran-2-il)oxi]-2H-piran-4-carboxamida (1.0 g, 1.92 mmol, preparado como en el Ejemplo 29), y la solución se agitó por 2 hrs. a 65°C. La solución se particionó entre acetato de etilo y agua. La capa orgánica se lavó con agua y solución salina, se secó sobre sulfato de sodio, se filtró, y se concentró al vacío para dar 510 mg (46%) del tiobenzoxazol como un aceite oscuro crudo. ESMS m/z = 577 $[M+H]^+$.

967

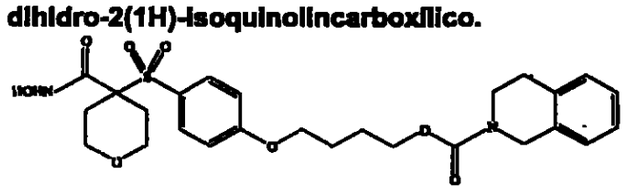
[913] **Parte B.** A una solución del tiobenzoxazol crudo de la **Parte A** (505 mg, 0.88 mmol) en 1,4-dioxano (5 mL) se agregó HCl 4N en dioxano (5 mL), y se agitó por 2 hrs.. La purificación por HPLC en fase reversa (C_{18}, acetonitrilo/agua) dio 257 mg (60%) del compuesto del título como un sólido blanco. ESMS m/z = 493 $[M+H]^+$. HRMS calculado para $C_{22}H_{24}N_2O_7S_2$: 493.1103, hallado 493.1122. Cálculo analítico para $C_{22}H_{24}N_2O_7S_2 \cdot 0.3H_2O$: C, 53.06; H, 4.98; N, 5.63; S, 12.88. Hallado: C, 53.08; H, 5.03; N, 5.62; S 12.69.

[914] Usando métodos similares un especialista puede preparar otros compuestos. Entre los ejemplos de dichos compuestos se incluyen los que tienen una estructura que corresponde a la Fórmula genérica EX-N.



EX-N

[915] **Ejemplo 34. Preparación de ácido 4-[[4-[[tetrahidro-4-[(hidroxiamino)carbonil]-2H-piran-4-il]sulfonil]ciclohexil]oxi]butiléster 3,4-dihidro-2(1H)-isoquinolincarboxílico.**

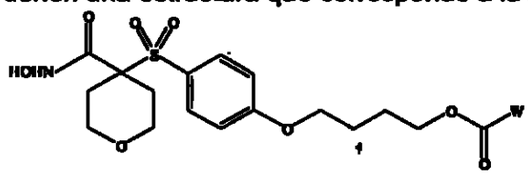


[916] **Parte A.** A una solución de tetrahidro-4-[[4-[4-[(metil-sulfonil)oxi]butoxi]fenil] sulfonil]-N-[(tetrahidro-2H-piran-2-il)oxi]-2H-piran-4-carboxamida (200 mg, 0.37 mmol, sintetizada de manera similar a la del **Ejemplo 29**) en N,N-dimetilformamida anhidra (2 mL) se agregó 1,2,3,4-tetrahidroisoquinolina (0.24 mL, 1.9 mmol) y carbonato de cesio (0.62 g, 1.9 mmol). La mezcla de reacción se agitó a temperatura ambiente durante la

968

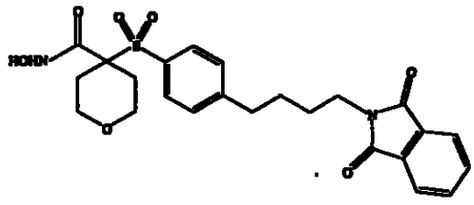
noche. La mezcla de reacción cruda se volcó sobre un tubo ChemElut (celite) de 20 mL pre-humedecido con 15 mL de agua, y se eluyó con acetato de etilo:cloruro de metileno 1:1. La purificación por HPLC en fase reversa (C18, acetonitrilo/agua), seguida por tratamiento con 2 mL de HCl 4N en dioxano, dio 12.2 mg (6.2 %) del producto deseado como un sólido amorfo después de la liofilización. ESMS m/z = 531 $[M+H]^+$. HRMS calculado para $C_{26}H_{33}N_2O_8S$: 533.1958 $[M+H]^+$, hallado: 533.1943.

[917] Usando métodos similares un especialista puede preparar otros compuestos. Entre los ejemplos de dichos compuestos se incluyen los que tienen una estructura que corresponde a la Fórmula genérica EX-O.



EX-O

[918] **Ejemplo 35. Preparación de 4-[[4-[4-(1,3-dihidro-1,3-dioxo-2H-isoindol-2-il)butil]fenil]sulfonil]tetrahidro-N-hidroxi-2H-piran-4-carboxamida**



[919] **Parte A.** Una solución de 4-bromobencentiol (28.5 g, 151 mmol) en N,N-dimetilformamida (250 mL) se purgó con nitrógeno por 10 min y luego se agregó carbonato de potasio (22.9 g, 166 mmol). Después de purgar por otros 10 min con nitrógeno, se agregó bromoacetato de t-butilo (24.5 g, 166 mmol), y la mezcla de reacción se agitó a temperatura ambiente por 1 hrs.. La reacción se enfrió a 0°C y se diluyó con agua (250 mL). La lechada se extrajo

969

con acetato de etilo. La capa orgánica se lavó con agua, solución saturada de bicarbonato de sodio, y solución salina; se secó sobre sulfato de sodio, se filtró; y se concentró al vacío para dar 49.8g (100%) del sulfuro como un aceite color amarillo claro. ESMS m/z = 3 2 0 $[M+NH4]^+$.

[920] **Parte B.** A una solución del producto de la **Parte A** (45.67 g, 151 mmol) en tetrahidrofurano (300 mL) se agregó agua (75 mL) y Oxone™ (278.5 g, 453 mmol) a 20°C. Se observó un aumento de la temperatura hasta 43°C. Después de 3 hrs., la reacción se filtró, y la torta se lavó bien con tetrahidrofurano. El filtrado se concentró al vacío a un tercio del volumen. El residuo se recogió en acetato de etilo, se lavó con solución salina, se secó sobre sulfato de magnesio, se filtró, y se concentró al vacío para dar 51.0 g (100%) de la sulfona como un sólido cristalino. ESMS m/z = 335 $[M+H]^+$.

[921] **Parte C.** A una solución del producto de la **Parte B** (23.45 g, 16 mmol) en N,N-dimetilformamida (140 mL) se agregó carbonato de potasio (19.3 g, 140 mmol), bis-(2-bromoetil)éter (9.1 mL, 70 mmol), y 18-Crown-6 (1 g). La lechada se agitó a 60°C. Después de 16 hrs., la reacción se filtró, y el filtrado se concentró al vacío. El residuo se recogió en acetato de etilo, se lavó con agua (3X) y solución salina, se secó sobre sulfato de sodio, se filtró, y se concentró al vacío. El producto se recristalizó de metanol para dar 19.79 g (70%) del compuesto deseado como un sólido blanco. (ESMS m/z = 405 $[M+H]^+$.

[922] **Parte D.** A una solución de N-(3-buten-1-il)ftalimida (1.2 g, 5.97 mmol) en tetrahidrofurano anhidro (3 mL) a 0°C se agregó 9-borobiciclononano 0.5 M en tetrahidrofurano (11.9 mL, 5.97 mmol) por goteo. La solución resultante se agitó con enfriamiento por 10 min, y luego el baño de hielo se eliminó . Después de 18 hrs., se agregaron el producto de la **Parte C** (1 g, 2.98

mmol), tetrakis(trifenil-fosfina)paladio(0) (172 mg, 0.15 mmol) y carbonato de sodio 2M (3 mL, 6 mmol), y la mezcla de reacción se calentó a 65°C por 2 hrs.. Después de enfriar a temperatura ambiente, la solución se concentró al vacío. El residuo se particionó entre acetato de etilo (50 mL) y agua (50 mL). Las capas se separaron, y la capa orgánica se lavó con agua (50 mL) y solución salina (50 mL), se secó sobre sulfato de magnesio, se filtró, y se concentró al vacío. La purificación por cromatografía de columna instantánea usando 25-50% acetato de etilo/hexanos dio 1.21 g del compuesto deseado como un sólido blancuzco. HRMS calculado para $C_{28}H_{37}N_2O_7S$: 545.2321 $[M+H]^+$, hallado: 545.2311.

[923] **Parte E.** A una solución del producto de la Parte D (1.16 g, 2.2 mmol) en cloruro de metileno anhidro (20 mL) a temperatura ambiente se agregó ácido trifluoroacético glacial (20 mL). La solución se agitó por 2 hrs., y luego se concentró al vacío. El residuo resultante se disolvió en metanol (50 mL) y se concentró al vacío, y a continuación se disolvió en cloruro de metileno (50 mL) y se concentró al vacío. La trituración con hexanos dio 0.98 g del ácido carboxílico como un sólido blancuzco. HRMS calculado para $C_{28}H_{37}N_2O_7S$: 489.1695 $[M+NH_4]$, hallado: 489.1702.

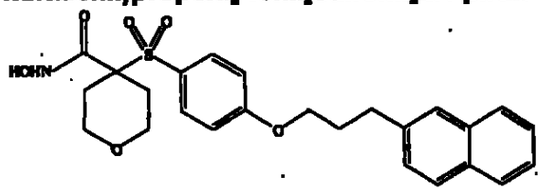
[924] **Parte F.** A una solución del producto de la Parte E (0.95 g, 2.01 mmol) en una mezcla de cloruro de metileno (4 mL) y N,N-dimetilformamida (4 mL) se agregó trietilamina (0.28 mL, 2.01 mmol), 1-hidroxibenzotriazol (0.407 g, 3.015 mmol), y clorhidrato de 1-[3-(dimetilamino)propil]-3-etilcarbodiimida (0.538 g, 2.814 mmol). Después de 10 min, se agregaron más trietilamina (0.56 mL, 4.02 mmol) y tetrahidropiranhidroxilamina (0.706 g, 6.03 mmol). La solución se calentó a 38°C y se agitó por 20 hrs.. La mezcla se particionó entre acetato de etilo (50 mL) y agua (50 mL). La capa orgánica se lavó con HCl 1M

971

(50 mL), agua y solución salina. Después de secar sobre sulfato de magnesio, la capa orgánica se concentró para dar 1.31 g de un sólido blancuzco. La purificación por cromatografía de columna instantánea usando 25-50% acetato de etilo/hexanos dio 1.05 g del producto puro como un sólido blanco. HRMS calculado para $C_{29}H_{34}N_2O_8SNa$: 593.1934 [M+Na], hallado: 593.1967.

[925] **Parte G.** A una solución del producto de la **Parte F** recién descrita (0.255 g, 0.446 mmol) en una mezcla de metanol (3 mL) y dioxano (3 mL) se agregó HCl 4N en dioxano (3 mL). La mezcla se agitó a temperatura ambiente por 10 min, y luego se concentró al vacío. La trituración con dietiléter/hexanos dio 224 mg del compuesto del título como un sólido blanco. HRMS calculado para $C_{24}H_{27}N_2O_7S$: 487.1539 [M+H], hallado: 487.1559.

[926] **Ejemplo 36. Preparación de tetrahidro-N-hidroxi-4[[4-[3-(2-naftalenil)propoxi]-fenil]sulfonil]2H-piran-4-carboxamida,**

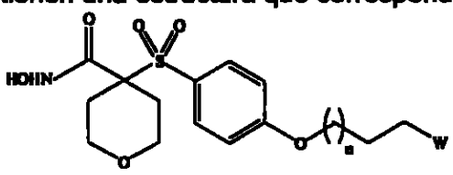


[927] A una solución de (tetrahidro-4-[[4-(2propeniloxi)fenil]sulfonil]-N-[(tetrahidro-2H-piran-2-il)oxi]-2H-piran-4-carboxamida (200 mg, 0.47 mmol, preparado como en el **Ejemplo 35**) en tetrahidrofurano (1 mL) se agregó 0.5 M 9-borobiciclononano (0.94 mL, 0.47 mmol). La solución se agitó a temperatura ambiente por 16 hrs.. A esta solución se agregó carbonato de sodio 2M (0.5 mL, 1 mmol), 2-bromonaftalenileno (108 mg, 0.52 mmol), y tetrakis(trifenilfosfina)paladio(0) (54 mg, 0.047 mmol). La mezcla se calentó a 65°C por 4 hrs., y luego se enfrió a temperatura ambiente. Se agregó una solución de cloruro de amonio saturado (3 mL) a la mezcla de reacción. La mezcla resultante se filtró a través de una pequeña columna de celite. La

972

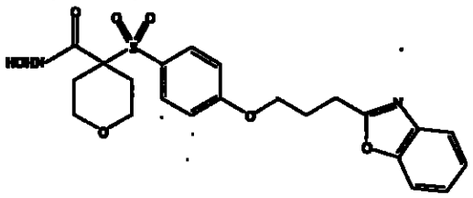
columna se lavó con acetato de etilo (35 mL). El eluyente se concentró al vacío, y el residuo se disolvió en metanol (3 mL), dioxano (3 mL), y HCl 4N en dioxano. Después de 10 min, la solución se concentró al vacío, y el residuo se purificó por HPLC preparativa en fase reversa (10-90% acetonitrilo/0.05% TFA en agua) dando 20 mg del compuesto del título como un sólido blanco. HRMS calculado para $C_{25}H_{28}NO_6S$: 470.1670 [M+H], hallado: 470.1614.

[928] Usando métodos similares un especialista puede preparar otros compuestos. Entre los ejemplos de dichos compuestos se incluyen los que tienen una estructura que corresponde a la Fórmula genérica EX-P.



EX-P.

[929] **Ejemplo 37. Preparación de 4-[[4-[3-(2-benzoxazolil)propoxi]fenil] sulfonil]tetrahidro-N-hidroxi-2H-piran-4-carboxamida**



[930] **Parte A.** A una solución de ácido 4-[[4-(3-carboxipropoxi)fenil]sulfonil] tetrahidro-2H-piran-4-carboxílico, 1,1-dimetiletiléster (3.0 g, 7.0 mmol) en N,N-dimetilformamida (14 mL) se agregó clorhidrato de 1-(3-dimetilamino-propil)-3-etilcarbodiimida (1.88 g, 9.8 mmol) y 1-hidroxibenzotriazol (1.32 g, 9.8 mmol). La suspensión resultante se tornó una solución transparente color ámbar después de agitar a 50°C por 1.5 hrs.. La reacción luego se trató con 2-aminofenol (0.76 g, 7.0 mmol), seguido por N-

metilmorfolina (2.3 mL, 21.0 mmol). La mezcla de reacción se agitó a 50°C durante la noche. Después de 21 hrs., la reacción se particionó entre acetato de etilo (50 mL) y agua (50 mL). La capa acuosa se extrajo con acetato de etilo. Las capas orgánicas se combinaron y se lavó con solución saturada de bicarbonato de sodio, agua, solución 1:1 de agua:solución salina, y solución salina; se secó sobre sulfato de sodio, se filtró; y se concentró al vacío. El aceite resultante se purificó sobre gel de sílice usando acetato de etilo/hexanos para dar 2.98 g (82%) de la amida como un aceite color ámbar. ESMS m/z = 542 $[M+Na]^+$.

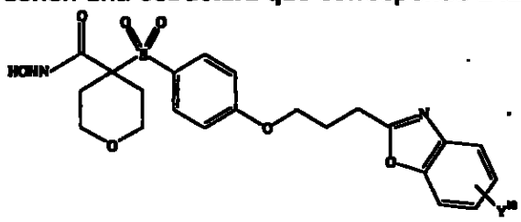
[931] **Parte B.** A una suspensión del producto de la **Parte A** (1.59 g, 3.1 mmol) en tolueno (50.0 mL) se agregó ácido p-toluensulfónico (0.12 g, 0.6 mmol), y la mezcla resultante se calentó a reflujo bajo condiciones Dean-Stark. Después de 39 hrs., la reacción se concentró al vacío, y el residuo resultante se particionó entre acetato de etilo y ácido clorhídrico acuoso 1M. La capa orgánica se lavó con ácido clorhídrico acuoso 1M, agua, y solución salina; se secó sobre sulfato de sodio, se filtró; y se concentró al vacío para dar 1.25 g (92%) de el benzoxazol de ácido carboxílico crudo como un sólido blanco tostado. ESMS m/z = 446 $[M+H]^+$.

[932] **Parte C.** A una solución del producto de la **Parte B** (0.98 g, 2.2 mmol) en N,N-dimetilformamida (10.0 mL) se agregó clorhidrato de 1-(3-dimetilamino-propil)-3-etilcarbodiimida (0.59 g, 3.1 mmol) y 1-hidroxibenzotriazol (0.42 g, 3.1 mmol). La suspensión resultante se tornó una solución transparente color ámbar después de agitar a 50°C por 0.5 hrs.. La reacción luego se trató con tetrahidropiranhidroxilamina (0.36 g, 3.1 mmol), seguida por N-metilmorfolina (0.73 mL, 6.6 mmol). La mezcla de reacción se agitó a 50°C durante la noche. Después de 12 hrs., la reacción se particionó

entre acetato de etilo y agua. La capa acuosa se extrajo con acetato de etilo. Las capas orgánicas se combinaron y se lavó con solución saturada de bicarbonato de sodio, agua, solución 1:1 de agua:solución salina, y solución salina; se secó sobre sulfato de sodio, se filtró; y se concentró al vacío. El aceite resultante se purificó sobre gel de sílice usando acetato de etilo/hexanos como eluyente para dar 1.2 g (98%) del hidroxamato de THP benzoxazol como un aceite color ámbar. ESMS m/z = 545 $[M+H]^+$.

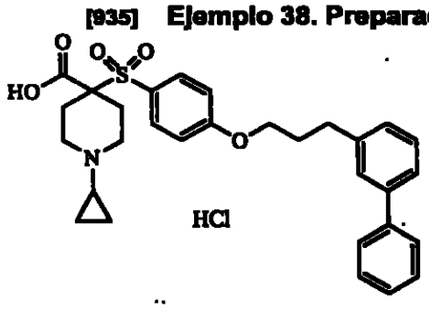
[933] **Parte D.** A una solución del producto de la **Parte C** (0.104 g, 0.19 mmol) en una mezcla de metanol (0.3 mL) y dioxano (2 mL) se agregó HCl 4N en dioxano (0.5 mL). La mezcla se agitó a temperatura ambiente por 30 min, se concentró a la mitad al vacío, y se diluyó con dietiléter. La filtración dio 17 mg (20%) del compuesto del título como un sólido de color tostado. HRMS calculado para $C_{22}H_{24}N_2O_7S$: 461.1382 $[M+H]^+$, hallado: 461.1374.

[934] Usando métodos similares un especialista puede preparar otros compuestos. Entre los ejemplos de dichos compuestos se incluyen los que tienen una estructura que corresponde a la Fórmula genérica EX-Q.

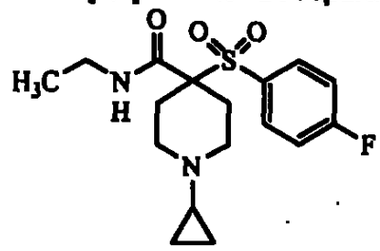


EX-Q.

[935] **Ejemplo 38. Preparación de:**

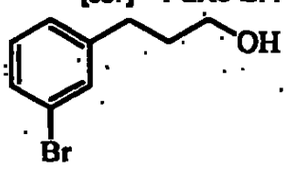


[938] **Parte A. Preparación de:**



A una solución de clorhidrato de 4-[(4-fluorofenil)sulfonil]piperidin-4-carboxilato de etilo (60.0 g, 170 mmol) en metanol (600 mL), se agregaron ácido acético glacial (97 mL, 1.7 mol), [(1-etoxiciclopropil)oxi]trimetilsilano . [(1- (102 mL, 510 mmol) y tamiz molecular de 4A (55 g) seguido por cianoborohidruro de sodio (28.8 g, 459 mmol). La solución se agitó a temperatura ambiente durante la noche, luego se refluió por 6 hrs.. La mezcla de reacción se filtró a través de celite y se concentró dando una mezcla sólido/aceite. Se agregaron acetato de etilo y bicarbonato de sodio saturado muy cuidadosamente. Cuando la capa acuosa permaneció básica, las capas se separaron y la capa orgánica se lavó 3 veces con bicarbonato de sodio saturado, luego con solución salina y luego se secó sobre sulfato de sodio. La concentración al vacío y la cristalización de acetato de etilo/hexano dio el compuesto n-ciclopropilo como un sólido blancuzco (53.8 g, 88.8%). ESMS $_{m/z}$ = 356 (M+H).

[937] **Parte B. Preparación de:**

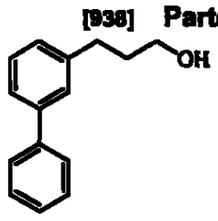


A una solución de ácido 3-(3-bromofenil)propiónico (10.0 g, 43.7 mmol) en THF anhidro (150 mL) se agregó BH_3·1.0M en THF (150 mL, 150 mmol) por medio de un embudo. Después de haber agregado BH_3·THF, la reacción se refluió por 18 hrs. La reacción se fraguó con agua (100 mL) y HCl 1N (300 mL). La

976

solución se saturó con cloruro de sodio y se extrajo con acetato de etilo. El extracto orgánico se lavó con solución salina y se secó sobre sulfato de magnesio. El material orgánico se purificó por cromatografía sobre gel de sílice eluyendo con acetato de etilo en hexano para dar 9.39 g (100 %) del alcohol deseado como un aceite incoloro. RMN ($CDCl_3$) δ 1.82-1.89 (m, 2H), 2.67 (t, 2H) , 3.64 (t, 2H), 7.11 7.15 (m, 1H), 7.29-7.31 (m, 1H), 7.34 (s, 1H).

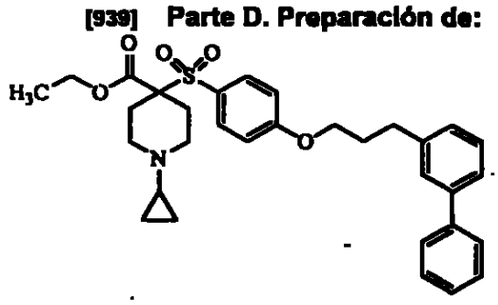
[938] **Parte C. Preparación de:**



En un recipiente se combinaron el alcohol de la parte B (3.43 g, 16.0 mmol), ácido fenilborónico (2.93 g, 24.0 mmol), tetrakis(trifenilfosfina)paladio (0.92 g, 0.8 mmol), carbonato de cesio 2M (24 mL, 48 mmol) y dimetoxietiléter (48 mL). La mezcla se agitó vigorosamente bajo nitrógeno a reflujo. Después de 1.5 hrs. la reacción se enfrió a temperatura ambiente, se diluyó con agua y se extrajo con éter 3 veces. Los extractos orgánicos combinados se lavaron con solución salina y se secaron sobre sulfato de magnesio. Por cromatografía (sobre sílice, acetato de etilo/hexano) se obtuvo 2.74 g (81% de rendimiento) del producto purificado como un sólido cristalino. RMN ($CDCl_3$) δ 1.91-1.98 (m, 2H) , 2.77 (t, 2H), 3.71 (t, 2H), 7.19 (d, 1H), 7.31-7.38 (m, 2H), 7.41-7.45 (m, 4H), 7.58 (d, 2H).

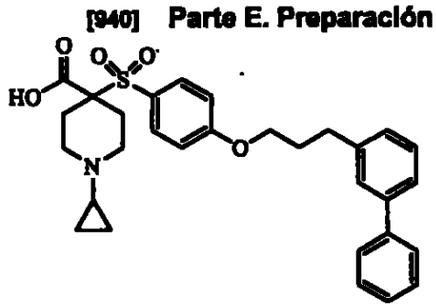
977

[939] **Parte D. Preparación de:**



A una solución del alcohol de la parte C (2.7 g, 12.7 mmol) en dimetilformamida anhidra (12 mL) a 0°C se agregó hidruro de sodio al 60 % (0.58 g, 14.5 mmol) en porciones. Después la mezcla de reacción se agitó a 0°C por 15 min y luego a temperatura ambiente por 15 min. La mezcla de reacción se enfrió a 0°C y se agregó lentamente el compuesto ciclopropilo de la parte A (4.3 g, 12.4 mmol) en dimetilformamida anhidra (10 mL). Una vez completada la reacción, se eliminó el baño de hielo y la mezcla de reacción se agitó a temperatura ambiente por 1 hrs., luego se diluyó con agua y se extrajo con acetato de etilo 3 veces. Los extractos orgánicos combinados se lavaron con $NaHCO_3$ saturado y solución salina y se secó sobre sulfato de sodio. Después de concentrar se obtuvo 4.63 g de material. Este material se usó sin purificación.

[940] **Parte E. Preparación de:**

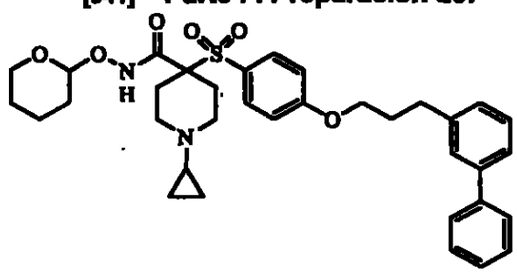


El éster de la Parte D (4.61 g, 8.4 mmol) se hidrolizó en una mezcla 1:1:0.56 de etanol:1,4-dioxano:NaOH 6N (25.6 mL) a 60°C. La solución se concentró al

978

vacío, se diluyó con agua y se extrajo con éter para eliminar color. La acidificación con HCl 1N causó la precipitación del ácido, que se recolectó por filtración, se lavó con agua y hexano y se secó bajo alto vacío dando el ácido como un sólido blancuzco (3.45 g, 79 % de rendimiento). ESMS $_{m/z}$ = 520 $(M+H)^+$. Este material se usó sin purificación.

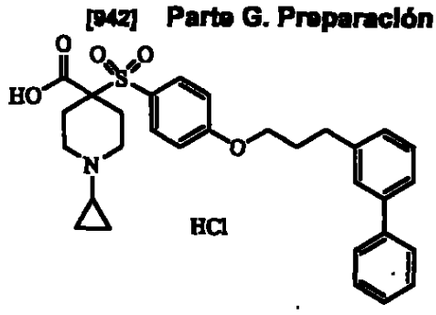
[941] **Parte F. Preparación de:**



A una suspensión del ácido crudo de la Parte E (3.44 g, 6.62 mmol) en DMF (27 mL) se agregaron HOBt (1.52 g, 9.93 mmol), N-metilmorfolina (2.2 mL, 19.9 mmol) y EDC (1.77 g, 9.27 mmol). Después de calentar a 40°C, el ácido lentamente se disolvió. Cuando la mezcla de reacción estuvo transparente, se enfrió a temperatura ambiente y se agregó THP-hidroxilamina (1.16 g, 9.93 mmol). La solución se agitó por 18 hrs. a temperatura ambiente. La solución se particionó entre acetato de etilo y agua. La capa orgánica se lavó con agua y solución salina y se secó sobre sulfato de magnesio. La cromatografía (sobre sílice, acetato de etilo/hexanos) dio el hidroxamato protegido como un sólido cristalino (3.20 g, 74 %). RMN δ 0.36 (d, 4H), 1.50-1.92 (m, 8H), 2.05-2.21 (m, 3H), 2.32 (s, 2H), 2.86 (t, 2H), 2.98 (s, 2H), 3.69 (d, 1H), 3.96-4.07 (m, 3H), 5.00 (s, 1H), 6.95 (d, 2H), 7.17 (d, 1H), 7.30-7-43 (m, 6H), 7.54 (d, 2H), 7.73 (d, 2H), 9.41 (s, 1H).

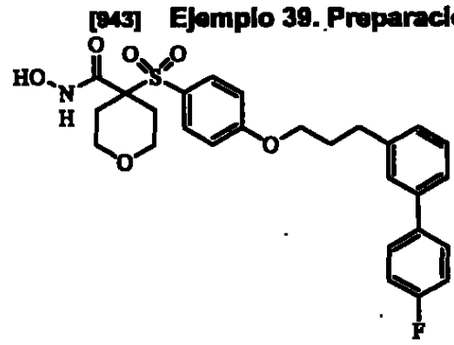
979

[942] **Parte G. Preparación de:**

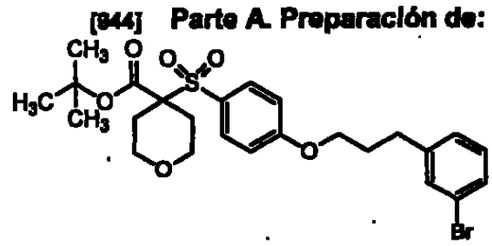


Al producto semi puro de la parte F (3.03 g, 4.89 mmol) en metanol (10 mL) y 1,4-dioxano (10 mL) se agregó ácido clorhídrico 4M en 1,4-dioxano (10 mL) y después de agitar 20-30 min el producto empezó a cristalizar. La cromatografía en fase reversa (en C_{18}, acetonitrilo/agua) para eliminar color seguida por conversión a sal de HCl con metanol y HCl 4N/dioxano, y luego recristalización de metanol/isopropanol dio 1.95 g (70 %) del compuesto del título como una sal de ácido clorhídrico incolora. ESMS $_{m/z}$ = 535 $(M+H)^+$. HRMS calculado para $C_{30}H_{35}N_{20}O_5S$ H: 535.2261 $(M+H)^+$. Hallado: 535.2270.

[943] **Ejemplo 39. Preparación de:**



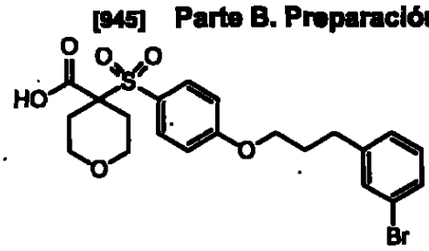
[944] **Parte A. Preparación de:**



980

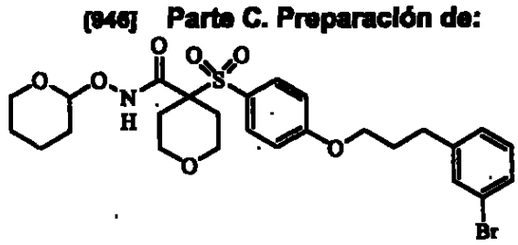
Una solución del alcohol de la parte B, Ejemplo 38 (4.4 g, 20.4 mmol), 4-[(4-fluorofenil)sulfonil]tetrahidro-2H-piran-4-carboxilato de ter-butilo (5.0 g, 14.6 mmol) y Cs_2CO_3 (9.5 g, 29.2 mmol) en dimetilformamida anhidra (30 mL) se agitó a 80°C por 30 hrs.. La reacción se diluyó con agua (300 mL) y se extrajo con acetato de etilo (3 veces). Los extractos orgánicos combinados se lavaron con solución salina y se secaron sobre sulfato de magnesio. La cristalización de cloruro de metileno/hexano dio 6.95 g (88%) del producto como un sólido incoloro. ESMS $_{m/z}$ = 556 $(M+NH_4)^+$. HRMS calcd. para $C_{23}H_{25}BrNO_6S$ H: 556.1368 $(M+NH_4)^+$. Hallado: 556.1318.

[945] **Parte B. Preparación de:**



El éster de la Parte A (6.81 g, 12.6 mmol) se hidrolizó en TFA:cloruro de metileno 1:1 (50 mL) a temperatura ambiente por 1.5 hrs.. La solución se concentró al vacío, se recogió en tolueno, se concentró para dar un sólido incoloro y se secó bajo alto vacío dando el ácido con un sólido blanco impuro (6.28 g, 100 % de rendimiento). ESMS $_{m/z}$ = 500 $(M+NH_4)^+$. HRMS calculado para $C_{21}H_{23}BrO_6SNH_4$: 500.0742 $(M+NH_4)^+$. Hallado: 500.0761.

[946] **Parte C. Preparación de:**

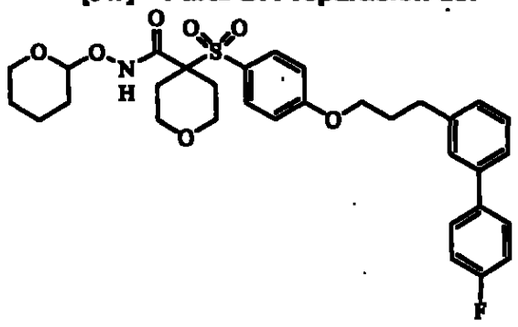


A una suspensión del ácido impuro de la Parte B (teóricamente 12.5 mmol) en DMF anhidra (25 mL) se agregaron HOBt (2.0 g, 15 mmol), trietilamina (5.2

981

mL, 37.5 mmol) y EDC (3.4 g, 17.5 mmol). Después de calentar a 40°C por 1 hrs., se agregó THP hidroxilamina (4.4 g, 37.5 mmol). La solución se agitó por 18 hrs. a temperatura ambiente, luego a 40°C por 3 hrs.. La reacción se diluyó con agua (150 mL) y se extrajo con acetato de etilo (3 veces). Los extractos orgánicos combinados se lavaron con solución salina y se secaron sobre sulfato de magnesio. La cromatografía (sobre silice, acetato de etilo/hexanos) dio el hidroxamato protegido como un aceite viscoso (4.32 g, 60 %). ESMS $_{m/z}$ = 601 $(M+NH_4)^+$. HRMS calcd. para $C_{28}H_{32}BrNO_7SNH_4$: 601.1410 $(M+NH_4)^+$. Hallado: 601.1448.

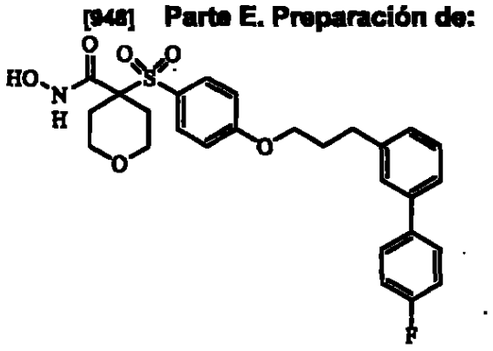
[947] **Parte D. Preparación de:**



En un recipiente se combinaron el bromuro de arilo de la parte C (0.20 g, 0.34 mmol) en 1 mL de dimetoxietiléter, ácido 4-fluorobencenborónico (74 mg, 0.53 mmol), tetrakis(trifenilfosfina)paladio (23 mg, 0.02 mmol) en 0.5 mL de dimetoxietiléter y carbonato de cesio 2M (0.51 mL, 1.02 mmol). La mezcla se agitó vigorosamente a 65°C por 18 hrs.. La mezcla de reacción se volcó sobre un tubo Chem-Elut de 5 mL pre-humedecido con 3 mL de agua y se eluyó con 10% acetato de etilo/cloruro de metileno. La concentración bajo nitrógeno dio 254 mg de producto crudo que se utilizó en el paso siguiente sin modificaciones.

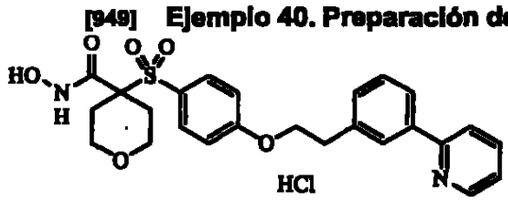
982

[948] **Parte E. Preparación de:**

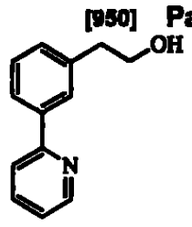


El producto crudo de la parte D (254 mg) se recogió en ácido clorhídrico 4M en 1,4-dioxano (2 mL) y metanol (1-2 mL) y se agitó por 2 hrs., luego se concentró. El material se purificó por cromatografía en fase reversa (en C_{18}, acetonitrilo/agua). El producto cristalizó luego de concentrarse dando 108.5 mg (62%) del compuesto del título como un sólido incoloro. ESMS $_{m/z}$ = 514 $(M+H)^+$. HRMS calc. para $C_{27}H_{29}FNOS$: 514.1700 $(M+H)^+$. Hallado: 514.1694 .

[949] **Ejemplo 40. Preparación de:**



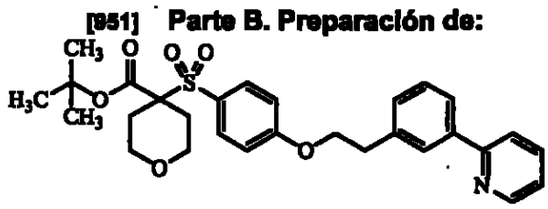
[950] **Parte A. Preparación de:**



Se combinaron 3-bromofenetilalcohol (5.0 g, 24.9 mmol) y 2-(tributilestanil)piridina (13.6 g, 37.4 mmol) en un balón con $PdCl_2(PPh_3)_2$ (0.84 g, 1.2 mmol), CuI (0.23 g, 1.2 mmol) y THF anhidro (100 mL) y se calentó a reflujo. Después de reflujar durante la noche, se agregaron más $PdCl_2(PPh_3)_2$ (0.84 g, 1.2 mmol) y CuI (0.23 g, 1.2 mmol) y la reacción se reflujó durante la

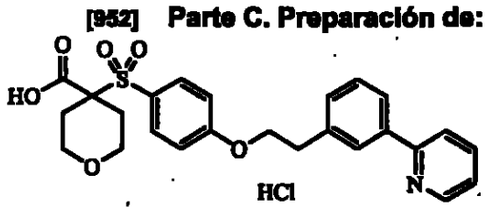
noche. La reacción se enfrió a temperatura ambiente, se agregó carbón Norit A, la mezcla se agitó y luego se filtró a través de un lecho de celite. La cromatografía (sobre sílice, acetato de etilo/hexanos) dio el alcohol como un aceite anaranjado (2.76 g, 55.8%). ESMS $_{m/z}$ = 200 $(M+H)^+$.

[951] **Parte B. Preparación de:**



A una solución del alcohol de la parte **A** (2.75 g, 13.8 mmol) en dimetilformamida anhidra (13 mL) a 0°C se agregó hidruro de sodio al 60 % (0.58 g, 14.4 mmol) en porciones. Una vez concluida la reacción, la mezcla de reacción se agitó a 0°C por 30 min. Se agregó 4-[(4-fluorofenil)sulfonil]tetrahidro-2H-piran-4-carboxilato de ter-butilo (4.51 g, 13.1 mmol) en dimetilformamida anhidra (10 mL) durante 15 min. Una vez completada la reacción, el baño de hielo se eliminó y la mezcla de reacción se agitó a temperatura ambiente. Después de 1.5 hrs. la reacción se diluyó con agua y se extrajo con acetato de etilo 3 veces. Los orgánicos combinados se lavaron con NaCl saturado y se secaron sobre sulfato de magnesio. La cromatografía (sobre sílice, acetato de etilo/hexanos) dio el producto como un sólido blancuzco (5.44 g, 79 %). ESMS $_{m/z}$ = 524 $(M+H)^+$.

[952] **Parte C. Preparación de:**

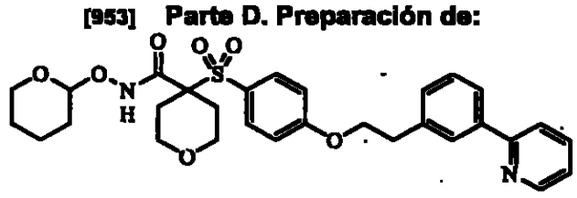


El éster de la **Parte B** (5.45 g, 10.4 mmol) se hidrolizó en una mezcla 1:1 de TFA:cloruro de metileno (30 mL) a temperatura ambiente por 8 hrs.. La

984

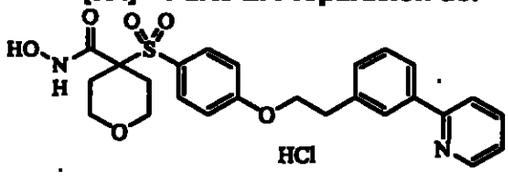
solución se concentró al vacío, se recogió en metanol y HCl 4N en dioxano y se concentró. Esto se repitió para dar un aceite viscoso (6.25 g, > 100 % de rendimiento). Este material se usó sin purificación adicional.

[953] **Parte D. Preparación de:**



A una suspensión del ácido crudo de la **Parte C** (asumido: 10.4 mmol) en NMP (40 mL) se agregaron HOBt (2.39 g, 15.6 mmol), N-metilmorfolina (3.4 mL, 31.2 mmol) y EDC (2.79 g, 14.6 mmol). Después de calentar a 40°C durante la noche, la HPLC aún indicaba la presencia de ácido por lo que se agregaron más HOBt (2.39 g, 15.6 mmol), N-metilmorfolina (3.4 mL, 31.2 mmol) y EDC (2.79 g, 14.6 mmol). Después de 1 hrs. a 40°C, se agregó THP hidroxilamina (3.66 g, 31.2 mmol). Después de 1 hrs., la solución se diluyó con agua y se extrajo con acetato de etilo 3 veces. Las capas orgánicas combinadas se lavaron con solución salina y se secaron sobre sulfato de magnesio. La cromatografía (sobre sílice, acetato de etilo/hexanos) dio el hidroxamato protegido como una espuma incolora (5.05 g, 85.7). ESMS $_{m/z}$ = 567 $(M+H)^+$.

[954] **Parte E. Preparación de:**

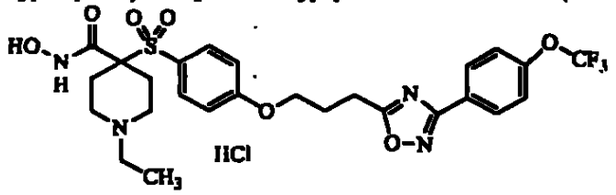


Al producto de la **Parte D** (5.05 g, 8.91 mmol) en metanol (15 mL) y 1,4-dioxano (15 mL) se agregó ácido clorhídrico 4M en 1,4-dioxano (15 mL) y después de agitar 1 hrs. la reacción concluyó. La concentración seguida por la cristalización de metanol/iso-propanol dio 3.88 g (84 %) del compuesto del

985

título como una sal de ácido clorhídrico incolora. ESMS $_{m/z}$ = 483 $(M+H)^+$. HRMS calculado para $C_{25}H_{27}N_2O_6S$ H: 483.1584 $(M+H)^+$. Hallado: 483.1585.

[955] **Ejemplo 41. Preparación de clorhidrato de 1-etil-N-hidroxi 4-{[4-(3-{3-[4-(trifluorometoxi)fenil]-1,2,4-oxadiazol-5-il}propoxi)fenil]sulfonil}piperidin-4-carboxamida.**



[956] **Parte A.** A una suspensión de 4-[(4-fluorofenil)sulfonil]-4-piperidincarboxilato de etilo, monoclorhidrato (14.06 g, 40 mmol) en dimetilacetamida (80 mL) se agregaron carbonato de potasio (13.82 g, 100 mmol) y iodoetano (3.36 mL, 42 mmol). La lechada se agitó a temperatura ambiente. Después de 3 hrs. la reacción se concentró al vacío. El residuo se recogió en acetato de etilo, se lavó con agua tres veces, con solución saturada de cloruro de sodio, se secó sobre Na_2SO_4, se filtró, y se concentró al vacío. La cromatografía (sobre sílice, cloruro de metileno/hexanos) dio la N-etilpiperidina como un sólido blanco (13.05 g, 95%).

[957] **Parte B.** En un equipo en seco bajo nitrógeno, se disolvió trimetilsilanolato de potasio (10.52 g, 73.8 mmol) en dimetilsulfóxido (40 mL) y se agregó gamma-butirolactona (4.26 mL, 55.4 mmol) durante 5 min mientras la temperatura de la mezcla de reacción se elevó a 49 C. Después de agitar a temperatura ambiente por 90 min, hidruro de sodio (2.2 g de una dispersión en aceite al 60%, 55.4 mmol) se agregó en porciones durante 20 min y la temperatura de la reacción se elevó a 38°C. También se observó evolución de gas. Después de agitar a temperatura ambiente por 40 min, se agregó una solución de la N-etilpiperidina de la parte A (12.66 g, 36.9 mmol) en

dimetilsulfóxido (10 mL) durante 10 min mientras la temperatura de la reacción se elevó hasta 8°C. La mezcla de reacción se agitó a temperatura ambiente por 30 min. La lechada se volcó lentamente en agua de hielo (400 mL) y luego se extrajo con hexanos (100 mL) dos veces seguido por una extracción con dietiléter (100 mL). La capa acuosa se enfrió a 5°C y el pH se ajustó a 7 con ácido clorhídrico concentrado. La solución acuosa se extrajo con cloruro de metileno (150 mL) hasta que no hubiera actividad UV en el extracto. Los extractos de cloruro de metileno combinados se lavaron con solución saturada de cloruro de sodio, se secó sobre Na_2SO_4, se filtró, y se concentró al vacío. El sólido se recristalizó de isopropanol (65 mL) para dar el ácido butírico como un sólido blanco (8.2 g, 52%). LCMS $_{m/z}$ = 428 $[M+H]^+$.

[958] **Parte C.** En un equipo en seco bajo nitrógeno, se disolvió el ácido butírico de la parte B (5.12 g, 12.0 mmol) en dimetilacetamida seca (20 mL) y los reactivos restantes se agregaron a la solución en el orden siguiente: hidrato de N-hidroxibenzotriazol (2.43 g, 18.0 mmol), trietilamina (3.34 mL, 24.0 mmol), 4-(trifluorometoxi)benzamidoxima (3.96 g, 18.0 mmol), y clorhidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (4.6 g, 24:0 mmol). Después de 24 hrs. a 70°C, la reacción se concentró al vacío. El residuo se recogió en acetato de etilo, se lavó con agua, con $NaHCO_3$ saturado, solución saturada de cloruro de sodio, se secó sobre Na_2SO_4, se filtró, y se concentró al vacío. La cromatografía (sobre sílice, acetato de etilo/metanol/hexanos) dio el oxadiazol como un sólido color amarillo claro (5.05 g, 69%). LCMS $_{m/z}$ = 612 $[M+H]^+$.

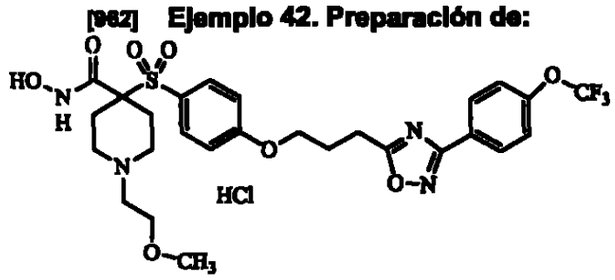
[959] **Parte D.** Una suspensión del oxadiazol de la parte C (4.9 g, 8.02 mmol), hidróxido de sodio 2.5N (9.6 mL, 24.06 mmol) e hidróxido de sodio (1.28 g, 32.08 mmol) en isopropanol (40 ml) se agitó a 70°C por 7 hrs.. Se suspendió el calentamiento y la reacción se diluyó con agua (100 ml) y se

enfrió a 5°C. Se ajustó el pH en 7 con ácido clorhídrico concentrado. Los sólidos se filtraron, se lavaron con hexanos, y se secaron al vacío para dar el ácido carboxílico como un sólido blanco (4.54 g, 97%). LCMS $_{m/z}$ = 584 $[M+H]^+$.

[960] Parte E. En un equipo en seco bajo nitrógeno, se disolvió el ácido carboxílico de la parte D (4.5 g, 7.72 mmol) en dimetilacetamida seca (15 ml) y los reactivos restantes se agregaron a la solución en el orden siguiente: hidrato de N-hidroxibenzotriazol (1.56 g, 11.6 mmol), trietilamina (3.22 mL, 23.2 mmol), O-(tetrahidro-2H-piran-2-il)hidroxilamina (1.35 g, 11.6 mmol), y clorhidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (2.96 g, 15.4 mmol). Después de 29 hrs. a 50°C, la reacción se concentró al vacío. El residuo se recogió en acetato de etilo, se lavó con agua, $NaHCO_3$ saturado, solución saturada de cloruro de sodio, se secó sobre Na_2SO_4, se filtró, y se concentró al vacío. La cromatografía (sobre sílice, acetato de etilo/metanol/hexanos) dio el hidroxamato de THP como un sólido color amarillo claro (2.4 g, 46%). LCMS $_{m/z}$ = 683 $[M+H]^+$.

[961] Parte F. Al hidroxamato de THP de la parte E (2.3 g, 3.37 mmol) se agregó Solución de HCl 4N en dioxano (8.4 mL, 33.7 mmol) y metanol (0.84 mL). La lechada se tornó muy espesa. Se agregó dietiléter (50 ml) y después de 1 hrs. a temperatura ambiente la reacción se filtró bajo nitrógeno. Los sólidos se lavaron con dietiléter (150 ml) bajo nitrógeno y se secó al vacío sobre pentóxido de fósforo para dar el compuesto del título como un sólido blanco (1.92 g, 91%). HRMS (ES+) $M+H^+$ calculado para $C_{28}H_{29}N_4O_7S_1F_3$: 599.1787, hallado 599.1766.

[962] **Ejemplo 42. Preparación de:**



[963] **Parte A.** en un equipo en seco bajo nitrógeno, se disolvió trimetilsilanolato de potasio (42.76 g, 0.3 mol) en dimetilsulfóxido (170 mL) y se agregó gamma-butirolactona (17.31 mL, 0.225 mol) durante 5 min mientras la temperatura de la mezcla de reacción se elevó a 49 C. Después de agitar a temperatura ambiente por 90 min, se agregó hidruro de sodio (9.0 g de una dispersión en aceite al 60%, 0.225 mol) en porciones durante 20 min y la temperatura de la reacción se elevó a 38°C. También se observó evolución de gas. Después de agitar a temperatura ambiente por 40 min, se agregó una solución de 4-[(4-fluorofenil)sulfonil]-1-(2-metoxietil)piperidin-4-carboxilato de etilo (56 g, 0.15 mol) en dimetilsulfóxido (20 mL) durante 10 mins mientras la temperatura de la reacción se elevó hasta 38°C. La mezcla de reacción se agitó a temperatura ambiente por 30 min. La lechada se volcó lentamente en agua de hielo (1.1 L) y luego se extrajo con hexanos (300 mL) dos veces seguido por una extracción con dietiléter (200 mL). La capa acuosa se enfrió a 5°C y el pH se ajustó a 7 con ácido clorhídrico concentrado. La solución acuosa se extrajo con cloruro de metileno (150 mL) hasta que no hubiera actividad UV en el extracto. Los extractos de cloruro de metileno combinados se lavaron con solución saturada de cloruro de sodio, se secó sobre Na_2SO_4, se filtró, y se concentró al vacío. El sólido se recristalizó de metanol (200 mL) para dar el ácido butírico como un sólido blanco (34.8 g, 51%). LCMS $_{m/z}$ = 458 $[M+H]^+$.

989

[964] **Parte B.** En un equipo en seco bajo nitrógeno, el ácido butírico de la parte A (19.19 g, 42.0 mmol) se disolvió en dimetilformamida seca (100 mL) y los reactivos restantes se agregaron a la solución en el orden siguiente: hidrato de N-hidroxibenzotriazol (8.5 g, 63.0 mmol), trietilamina (11.7 mL, 84.0 mmol), 4-(trifluorometoxi)benzamidoxima (13.9 g, 63.0 mmo1), y clorhidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (16.1 g, 84.0 mmol). Después de 24 hrs. a 70°C, la reacción se concentró al vacío. El residuo se recogió en acetato de etilo, se lavó con agua, $NaHCO_3$ saturado, solución saturada de cloruro de sodio, se secó sobre Na_2SO_4, se filtró, y se concentró al vacío. El sólido se recristalizó de metanol (35 mL) para dar el oxadiazol como un sólido blancuzco (17.86 g, 66%). LCMS $_{m/z}$ = 642 $[M+H]^+$.

[965] **Parte C.** Una suspensión del oxadiazol de la parte B (16.9 g, 26.4 mmol), hidróxido de sodio 2.5N (31.6 mL, 79.1 mmol) e hidróxido de sodio (4.22 g, 105.5 mmol) en isopropanol (30 mL) se agitó a 70°C por 7 hrs.. Se suspendió el calentamiento y la reacción se diluyó con agua (150 mL) y se enfrió a 5°C. Se ajustó el pH en 7 con ácido clorhídrico concentrado. Los sólidos se filtraron, se lavaron con hexanos, y se secó al vacío para dar el ácido carboxílico como un sólido blanco (15.78 g, 98%). LCMS $_{m/z}$ = 614 $[M+H]^+$.

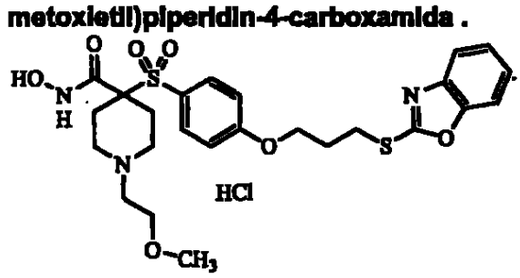
[966] **Parte D.** En un equipo en seco bajo nitrógeno, el ácido carboxílico de la parte C (15.7 g, 25.6 mmol) se disolvió en dimetilformamida seca (70 mL) y los reactivos restantes se agregaron a la solución en el orden siguiente: hidrato de N-hidroxibenzotriazol (5.19 g, 38.4 mmol), trietilamina (10.7 mL, 76.8 mmol), O-(tetrahidro-2H-piran-2-il)hidroxilamina (5.99, 51.2 mmol), y clorhidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (10.8 g, 56.3 mmol). Después de 12 hrs. a 40°C, la reacción se concentró al vacío. El

990

residuo se recogió en acetato de etilo, se lavó con agua, $NaHCO_3$ saturado, solución saturada de cloruro de sodio, se secó sobre Na_2SO_4, se filtró, y se concentró al vacío. La cromatografía (sobre sílice, acetato de etilo/hexanos) dio el hidroxamato de THP como una espuma blanca (14.94 g, 82%). LCMS $_{m/z}$ = 713 $[M+H]^+$.

[967] **Parte E.** Al hidroxamato de THP de la **Parte D** (14.88 g, 20.9mmol) se agregó solución de HCl 4N en dioxano (52 mL, 209.0 mmol) y metanol (5.2 mL). La lechada se tornó muy espesa. Se agregaron dioxanos (50 mL) y dietiléter (100 mL) para facilitar la agitación. Después de 1 hrs. a temperatura ambiente la reacción se filtró bajo nitrógeno. Los sólidos se lavaron con acetonitrilo (100 mL) bajo nitrógeno y se secaron al vacío sobre pentóxido de fósforo para dar el compuesto del título como un sólido blanco (13.25 g, 95%). HRMS (ES+) M+ H^+ calculado para $C_{27}H_{31}N_4O_6S_1F_3$: 629.1893, hallado 629.1913.

[968] **Ejemplo 43. Preparación de clorhidrato de 4-([4-[3-(1,3-benzoxazol-2-iltio)propoxi]fenil]sulfonil)-N-hidroxi-1-(2-metoxietil)piperidin-4-carboxamida .**



[969] **Parte A.** Una solución de 1-bencil-4-tert-butil-4-[(4-fluorofenil)sulfonil]piperidin-1,4-dicarboxilato (16.0 g, 33.5 mmol) en metanol/tetrahidropirano se hidrogenó por 1 hrs. a 5 psi en presencia de Pd/C 5%. La solución se filtró para eliminar el catalizador y se concentró al vacío. Se obtuvo 11.0 g (95% de rendimiento) de la amina como un sólido blanco.

991

[970] **Parte B.** La solución de la amina de la **Parte A** (11.0 g, 32.1 mmol) en N,N-dimetilformamida (100 mL) se enfrió a 0°C en un baño de hielo. Se agregaron carbonato de potasio (13.3 g, 96.4 mmol) y 2-bromoetilmetiléter (7.54 mL, 80.2 mmol) a la solución fría. La solución se agitó por 72 hrs. a temperatura ambiente y se particionó entre acetato de etilo y agua. La capa orgánica se lavó con agua y cloruro de sodio saturado y se secó sobre sulfato de sodio. Se obtuvo por concentración al vacío 14.5 g de la amina alquilada deseada como un aceite anaranjado.

[971] **Parte C.** A una solución de propanodiol (10.44 mL, 144 mmol) en 1-metil-2-pirrolidinona (40 mL) enfriada a 0°C se agregó hidruro de sodio (suspensión en aceite mineral al 60%, 3.85 g, 96.3 mmol). La amina alquilada de la parte B (14.5 g, 32.1 mmol) se disolvió en 1-metil-2-pirrolidinona (50 mL) y se agregó por goteo a la solución enfriada.. La solución se agitó a temperatura ambiente por 1 hrs.. La reacción se fraguó por el agregado de agua y se particionó entre acetato de etilo y agua. La capa orgánica se lavó con agua y cloruro de sodio saturado y se secó sobre sulfato de sodio. El alcohol deseado se obtuvo como un aceite anaranjado por concentración al vacío. MS(Cl) MH^+ calculado para $C_{22}H_{35}NO_7S$: 457, hallado 457.

[972] **Parte D.** A una solución del alcohol de la **Parte C** (32.1 mmol) en cloruro de metileno (100 mL) se agregó trietilamina (4.92 mL, 35.3 mmol). La solución se enfrió a 0°C y se agregó cloruro de metansulfonilo (2.56 mL, 33.0 mmol) por goteo. Después de 1 hrs. la reacción se concentró al vacío. El residuo se disolvió en acetato de etilo y se lavó con agua, bicarbonato de sodio saturado y cloruro de sodio saturado y se secó sobre sulfato de sodio. La solución se concentró al vacío para dar 17.5 g del mesilato deseado. MS(Cl) MH^+ calculado para $C_{23}H_{37}NO_9S_2$: 536, hallado 536.

992

[973] **Parte E.** A una solución de 2-mercaptobenzoxazol (4.86 g, 32.1 mmol) en N,N-dimetilformamida (30 mL) enfriada a 0°C se agregó hidruro de sodio (suspensión en aceite mineral al 60%, 1.54 g, 38.5 mmol). Después de 30 min se agregó el mesilato de la **Parte D** (17.5 g, 32.1 mmol) en N,N-dimetilformamida (30 mL) por goteo. La solución se calentó a 60°C por 4 hrs. y a 45°C por 18 hrs.. La solución se regresó a temperatura ambiente y se particionó entre acetato de etilo y agua. La capa orgánica se lavó con agua y cloruro de sodio saturado y se secó sobre sulfato de sodio. La cromatografía (acetato de etilo, sobre sílice) dio el mercaptobenzoxazol como un aceite incoloro (7.3 g, 39% de rendimiento luego de cuatro pasos). MS(Cl) MH^+ calculado para $C_{29}H_{38}N_2O_7S_2$: 591, hallado 591.

[974] **Parte F.** A una solución de el mercaptobenzoxazol de la **Parte E** (7.3 g, 12.4 mmol) se agregó ácido trifluoroacético glacial (20 mL) y la solución se agitó por 3 hrs.. La solución se concentró al vacío y se realizó un azeótropo con tolueno para dar el ácido como un aceite. El material se utilizó en el paso siguiente sin más purificación. MS(Cl) MH^+ calculado para $C_{28}H_{30}N_2O_7S_2$: 535, hallado 535.

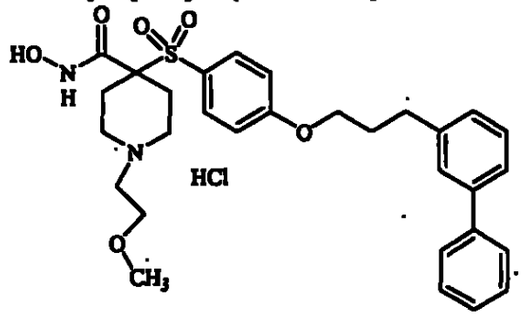
[975] **Parte G.** A una solución del ácido de la **Parte F** (12.4 mmol) en N,N-dimetilformamida (50 mL) se agregaron 1-hidroxibenztriazol (2.01 g, 14.9 mmol), 4-metilmorfolina (6.82 mL, 62 mmol) y tetrahidropiranilamina (2.18 g, 18.6 mmol). Luego de min se agregó clorhidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (3.33 g, 17.4 mmol). La solución se calentó a 65°C por 2 hrs.. La solución se particionó entre acetato de etilo y agua. La capa orgánica se lavó con agua y cloruro de sodio saturado y se secó sobre sulfato de sodio. La cromatografía (acetato de etilo/metanol, sobre sílice) dio el hidroxamato

993

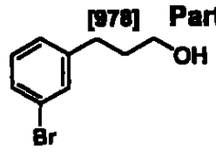
protegido como un aceite incoloro (3.9 g, 50 % de rendimiento). MS(Cl) MH^+ calculado para $C_{30}H_{39}N_3O_8S_2$: 634, hallado 634.

[976] **Parte H.** A una solución del hidroxamato protegido de la **Parte G** (3.9 g, 6.2 mmol) en 1,4-dioxano (10 mL) se agregó ácido clorhídrico 4M en 1,4-dioxano (10 mL). La reacción finalizó después de 1 hrs.. La solución se concentró al vacío. El residuo se purificó por medio de cromatografía en fase reversa (acetonitrilo/agua, sobre sílice) para dar el compuesto del título como un sólido blanco (1.49 g, 41% de rendimiento). MS(Cl) MH^+ calculado para $C_{25}H_{31}N_3O_7S_2$: 550, hallado 550. HRMS calculado para $C_{25}H_{31}N_3O_7S_2$: 550.1682, hallado 550.1668. Cálculo analítico para $C_{25}H_{31}N_3O_7S_2.HCl.H_2O$: C, 49.70; H, 5.67; N, 6.96; S, 10.62; Cl, 5.87. Hallado: C, 49.91; H, 6.03; N, 6.74; S, 10.75; Cl, 6.35.

[977] **Ejemplo 44. Preparación de:**



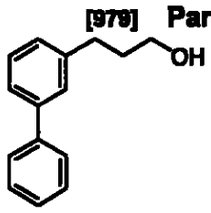
[978] **Parte A. Preparación de:**



A una solución de ácido 3-(3-bromofenil)propiónico (15.0 g, 65.5 mmol) en THF anhidro (200 mL) a 5°C se agregó, por medio de un embudo, 1.0 M BH_3·THF (200 mL, 200 mmol). La temperatura de la mezcla de reacción se mantuvo debajo de 14°C durante el agregado del BH_3·THF. Después de haber agregado todo el BH_3·THF, la reacción se refluió por 22 hrs. y luego se fraguó

con agua (100 mL) y HCl 1N (300 mL). La solución se saturó con cloruro de sodio y se extrajo con acetato de etilo (3x300 mL). El extracto orgánico se lavó con solución salina, se secó sobre sulfato de magnesio, y se concentró para dar 14.4 g (100%) de alcohol crudo como un aceite incoloro. RMN($CDCl_3$) δ 1.82-1.89 (m, 2H), 2.67 (t, 2H), 3.64 (t, 2H), 7.11-7.15 (m, 1H), 7.29-7.31 (m, 1H), 7.34 (s, 1H).

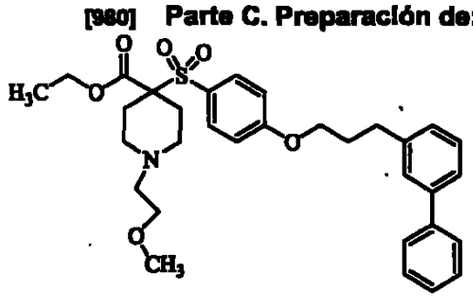
[979] **Parte B. Preparación de:**



En un recipiente se combinaron el alcohol de la parte A (65.5 mmol), ácido fenilborónico (12.0 g, 98.2 mmol), tetrakis(trifenilfosfina)paladio (3.8 g, 3.3 mmol), carbonato de cesio 2M (98 mL, 196 mmol) y dimetoxietiléter (100 mL). La mezcla se agitó vigorosamente bajo nitrógeno a reflujo durante la noche. La reacción se enfrió a temperatura ambiente, se volcó en agua (300 mL) y se extrajo 3 veces con acetato de etilo. Los extractos orgánicos combinados se lavaron con solución salina y se secaron sobre sulfato de magnesio. La cromatografía (sobre sílice, acetato de etilo / hexano) dio el producto acoplado como una aceite dorado (11.95 g, 86.0 %). RMN($CDCl_3$) δ 1.91-1.98 (m, 2H), 2.77 (t, 2H), 3.71 (t, 2H), 7.19 (d, 1H), 7.31-7.38 (m, 2H), 7.41-7.45 (m, 4H), 7.58 (d, 2H).

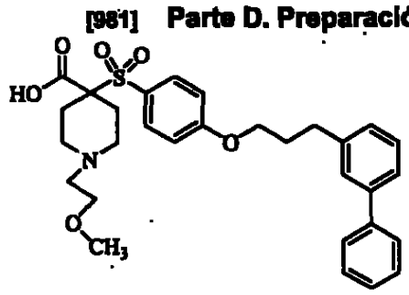
995

[980] **Parte C. Preparación de:**



A una solución del alcohol de la parte B (11.9 g, 56.1 mmol) en dimetilformamida anhidra (56 mL) a 0°C se agregó hidruro de sodio al 60% (2.55 g, 63.8 mmol) en porciones. Una vez concluida la reacción, la mezcla de reacción se agitó a 0°C por 15 min, luego a temperatura ambiente por 15 min. La reacción se enfrió a 0°C y se agregó 4-[(4-fluorofenil)sulfonil]-1-(2-metoxietil)piperidin-4-carboxilato de etilo (19.0 g, 51 mmol) en dimetilformamida anhidra (60 mL) lentamente. Una vez completada la reacción, el baño de hielo se eliminó y la mezcla de reacción se agitó a temperatura ambiente durante la noche. La mezcla de reacción se volcó en agua (1 L) y se extrajo con acetato de etilo (800 mL). Los orgánicos combinados se lavaron con agua (2x500 mL) y solución salina y se secaron sobre sulfato de magnesio. La concentración dio 34.4 g de material crudo. Este material se usó sin purificación.

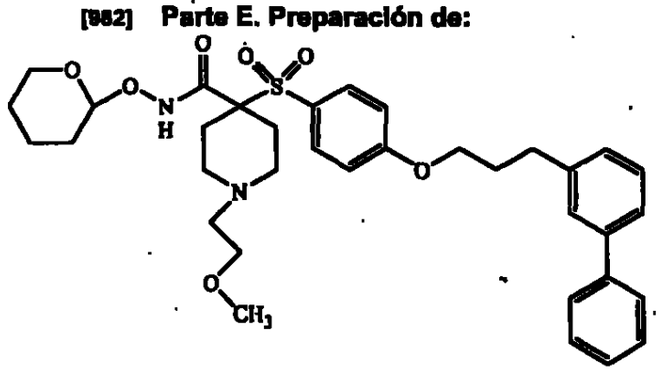
[981] **Parte D. Preparación de:**



El éster impuro de la Parte C (34.4 g, 51 mmol teóricos) se hidrolizó en 41 mL de etanol, 41 mL de 1,4-dioxano y 26.5 mL de NaOH 6N a 60°C. La solución

se volcó en agua y se extrajo con éter para eliminar color. La acidificación con HCl 1N causó la precipitación del ácido que se recolectó por filtración y se lavó con agua, acetato de etilo y hexano, y luego se secó bajo alto vacío dando el ácido como un sólido blancuzco (18.8 g, 68.6% de rendimiento). RMN (CD_3OD w/ K_2CO_3) δ 1.98 (t, 2H), 2.07-2.19 (m, 4H), 2.32 (d, 2H), 2.48 (t, 2H), 2.85-2.95 (m, 4H), 3.25 (s, 3H), 4.06 (t, 2H), 7.04 (d, 2H), 7.20 (d, 1H), 7.27-7.48 (m, 5H), 7.54 (d, 2H), 7.78 (d, 2H). ESMS m/z = 538 $(M+H)^+$.

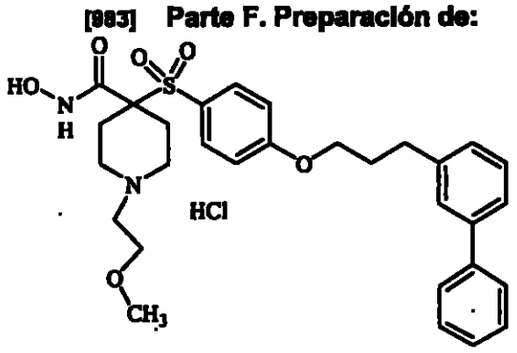
[982] **Parte E. Preparación de:**



Al ácido de la **Parte D** (12.7 g, 23.6 mmol), HOBt (5.42 g, 35.4 mmol) y EDC (6.30 g, 3.30 mmol) en un recipiente bajo N_2 se agregó 70 mL DMF anhidra. La mezcla se calentó a 60°C y se agregó trietilamina (9.85 mL, 70.8 mmol). Después de calentar a 60°C por 1 hrs., THP-hidroxilamina (4.14 g, 35.4 mmol) se agregó. La solución se agitó por 16.5 hrs. a 60°C. La solución se particionó entre acetato de etilo (300 mL) y agua (500 mL). La capa orgánica se lavó con solución salina y se secó sobre sulfato de magnesio. La concentración dio el hidroxamato protegido como un aceite (14.86 g, 98.7 %). RMN($CDCl_3$) δ 1.55-1.90 (m, 6H), 2.09-2.27 (m, 8H), 2.50 (t, 2H), 2.87 (t, 2H), 2.90-2.98 (m, 2H), 3.32 (s, 3H), 3.42 (t, 2H), 3.7.1 (d, 1H), 3.98 (d, 1H), 4.03 (t, 2H), 4.99 (s, 1H), 6.97 (d, 2H), 7.19 (d, 1H), 7.30-7.46 (m, 6H), 7.57 (d, 2H), 7.77 (d, 2H), 9.42 (s, 1H). ESMS m/z = 637 $(M+H)^+$.

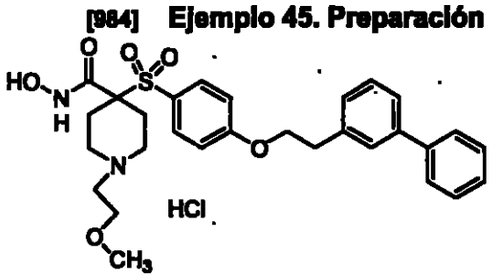
997

[983] **Parte F. Preparación de:**

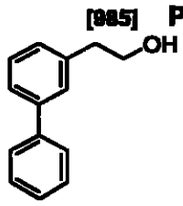


Al producto de la **Parte E** (14.7 g, 23.1 mmol) en metanol (23 mL) y 1,4-dioxano (23 mL) se agregó ácido clorhídrico 4M en 1,4-dioxano (23 mL) y después de agitar 1 hrs., el material se volcó en IPA en agitación, se dejó estacionar durante la noche. La recolección del sólido bajo N_2 seguida por el lavado con IPA y hexano, y luego el secado bajo alto vacío sobre P_2O_5 dio 12.5 g (91.8 %) del compuesto del título como una sal de ácido clorhídrico incolora. RMN(DMSO) δ 2.05-2.25 (m, 4H), 2.74, (t, 2H), 2.81 (t, 2H), 3.18-3.26 (m, 4H), 3.39 (s, 3H), 3.51-3.61 (m, 4H), 4.09 (t, 2H), 7.15 (d, 2H), 7.22 (d, 1H), 7.29-7.49 (m, 6H), 7.58 (d, 2H), 7.45 (d, 2H). ESMS m/z = 553 $(M+H)^+$. HRMS calcd. para $C_{30}H_{35}N_2O_5S$ H: 553.2369 $(M+H)^+$. Hallado: 553.2372.

[984] **Ejemplo 45. Preparación de:**

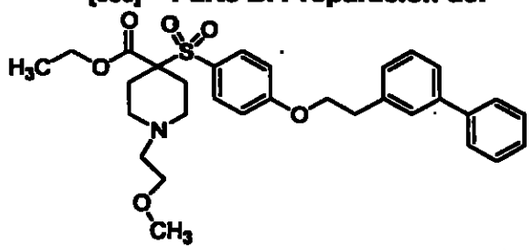


[985] **Parte A. Preparación de:**



En un recipiente se combinaron el 3-bromofenetil alcohol (17.5 g, 87.1 mmol), ácido fenilborónico (12.7 g, 104.5 mmol), tetrakis(trifenilfosfina)paladio (2.0 g, 1.74 mmol), carbonato de cesio 2M (105 mL, 210 mmol) y dimetoxietiléter (105 mL). La mezcla se agitó vigorosamente bajo nitrógeno a reflujo durante la noche. Después de enfriar a temperatura ambiente, se volcó la mezcla sobre agua (400 mL) y se extrajo con acetato de etilo (2x400 mL). Los extractos orgánicos combinados se lavaron con solución salina y se secaron sobre sulfato de magnesio. La cromatografía en gel de sílice (acetato de etilo/hexano) dio el producto acoplado como un sólido cristalino (15.04 g, 87.3 %). RMN($CDCl_3$) δ 295 (t, 2H), 3.93 (q, 2H), 7.19-18 (m, 2H), 7.31-7.51 (m, 5H), 7.58 (d, 2H). GCMS EI+ 198 (M+).

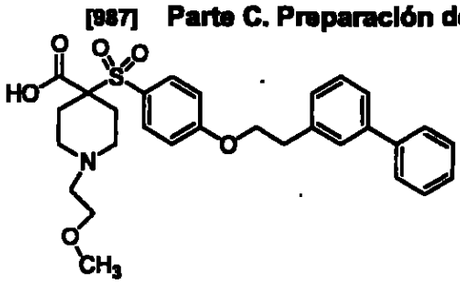
[986] Parte B. Preparación de:



A una solución del alcohol de la parte A (14.9 g, 75.2 mmol) en dimetilformamida anhidra (70 mL) a 0°C se agregó hidruro de sodio al 60 % (3.0 g, 75.2 mmol) en porciones. Una vez concluida la reacción, la mezcla de reacción se agitó a 0°C por 30 min. Se agregó 4-[(4-fluorofenil)sulfonil]-1-(2-metoxietil)piperidin-4-carboxilato de etilo (33.6 g, 90.2 mmol) en dimetilformamida anhidra (50 mL) a 5°C lentamente. Una vez completada la reacción se dejó calentar lentamente la mezcla de reacción durante la noche. La mezcla de reacción se volcó en agua (700 mL) y se extrajo con acetato de etilo (3x500 mL). Los orgánicos combinados se lavaron con solución salina y

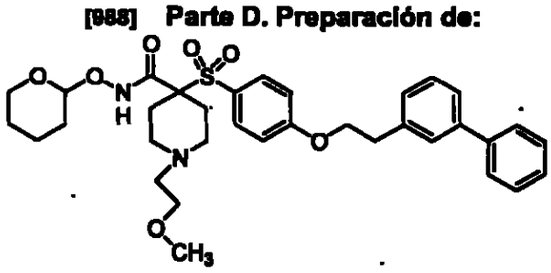
se secó sobre sulfato de sodio. La concentración dio 50.6 g de material crudo. Este material se usó sin purificación. ESMS m/z = 552 $(M+H)^+$.

[987] **Parte C. Preparación de:**



El éster impuro de la **Parte B** (75.2 mmol teóricos) se hidrolizó en 75 mL de etanol, 75 mL de 1,4-dioxano y 50 mL de NaOH 6N a 60 C por 2.5 hrs.. La solución se volcó en agua y se extrajo con éter para eliminar color. La acidificación con HCl 1N causó la precipitación del ácido que se recolectó por filtración y se lavó con agua, acetato de etilo y dietiléter, y luego se secó bajo alto vacío dando el ácido como un sólido blanco (31.7 g, 80.6% de rendimiento). ESMS m/z = 524 $(M+H)^+$. HRMS calculado para $C_{29}H_{34}NO_5S$: 524.2101 $(M+H)^+$. Hallado: 524.2075.

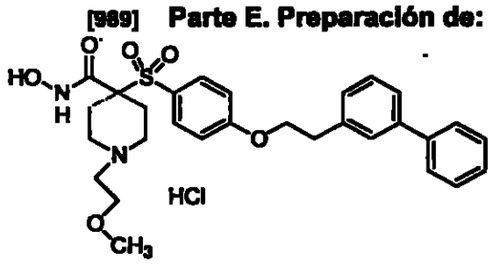
[988] **Parte D. Preparación de:**



Se agitaron el ácido de la **Parte C** (31.6 g, 60.4 mmol), HOBt (13.9 g, 90.6 mmol), EDC (16.2 g, 84.6 mmol), trietilamina (25.2 mL, 181 mmol) y THP-hidroxilamina (10.6 g, 90.6 mmol) en dimetilformamida anhidra (200 mL) bajo N_2 a 60°C durante la noche. Después de enfriar a temperatura ambiente solución se volcó en 1.6 L de agua de hielo y se extrajo con acetato de etilo (2x1 L). La capa orgánica se lavó con solución salina y se secó sobre sulfato

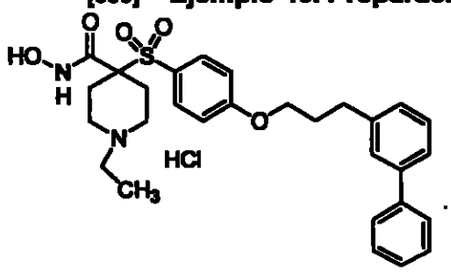
de sodio. La cromatografía en gel de sílice (2.0M NH_3 en MeOH/acetato de etilo/hexano) dio el producto deseado como una espuma incolora (30.89 g, 82%). ESMS m/z = 623 $(M+H)^+$. HRMS calculado para $C_{34}H_{43}N_2O_7S$: 623.2786 $(M+H)^+$. Hallado: 623.2793.

[989] **Parte E. Preparación de:**



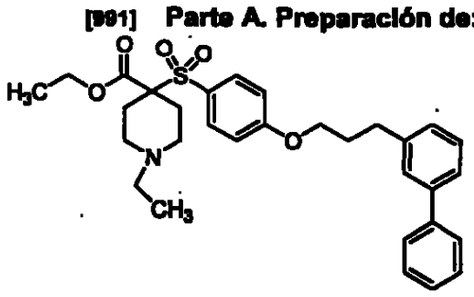
Al producto de la **Parte D** (30.7 g, 49.3 mmol) en metanol (49 mL) y 1,4-dioxano (49 mL) se agregó HCl 4N en dioxano (50 mL). El material se concentró después de 1 hrs. y se cristalizó de metanol para dar el producto deseado como un sólido cristalino incoloro (25.6 g, 90.2%). ESMS m/z = 539 $(M+H)^+$. HRMS calculado para $C_{29}H_{35}N_2O_6S$: 539.2210 $(M+H)^+$. Hallado: 539.2187.

[990] **Ejemplo 46. Preparación de:**



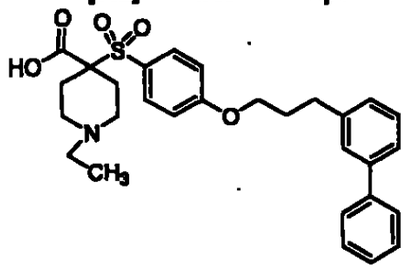
1001

[991] **Parte A. Preparación de:**



A una solución del alcohol del **Ejemplo 38, Parte B** (12.0 g, 56.1 mmol) en dimetilformamida anhidra (50 mL) a 0°C se agregó hidruro de sodio al 60 % (2.58 g, 64.5 mmol) en porciones. Una vez concluida la reacción, la mezcla de reacción se agitó a 0°C por 15 min, luego a temperatura ambiente por 15 min. La reacción se enfrió a 0°C y se agregó 1-etil-4-[(4-fluorofenil)sulfonil]piperidin-4-carboxilato de etilo (17.7 g, 51.6 mmol) en dimetilformamida anhidra (60 mL) lentamente. Una vez completada la reacción, se eliminó el baño de hielo y la mezcla de reacción se agitó a temperatura ambiente durante la noche. La mezcla de reacción se volcó en agua y se extrajo con acetato de etilo 2 veces. Los orgánicos combinados se lavaron con agua 2 veces y solución salina y se secó sobre sulfato de sodio. La concentración dio 34.4 g de material crudo. Este material se usó sin purificación. ESMS m/z = 536 $(M+H)^+$.

[992] **Parte B. Preparación de:**

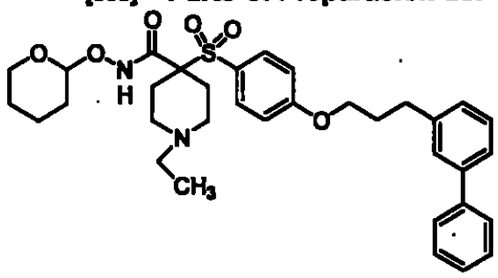


El éster impuro de la **Parte A** (51.6 mmol teóricos) se hidrolizó en 50 mL de etanol, 50 mL de 1,4-dioxano y 34.4 mL de NaOH 6N a 60°C. Después de enfriar a temperatura ambiente, la solución se volcó en agua (500 mL) y se

1002

extrajo con éter (2x250 mL) para eliminar color. La acidificación con HCl 1N causó la precipitación del ácido que se recolectó por filtración y se lavó con agua, acetato de etilo y hexano, luego se secó bajo alto vacío dando el ácido como un sólido blancuzco (18.4 g, 70% de rendimiento). ESMS m/z = 508 $(M+H)^+$. HRMS calculado para $C_{29}H_{34}NO_5S$ H: 508.2152 $(M+H)^+$. Hallado: 508.2176.

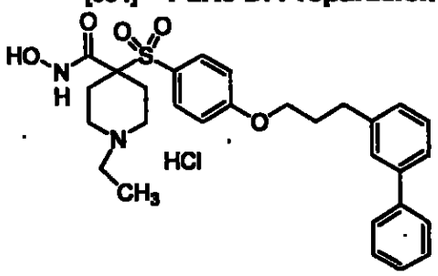
[993] **Parte C. Preparación de:**



El ácido de la **Parte B** (18.0g, 35.4 mmol), HOBt (8.12 g, 53.1 mmol), EDC (9.47 g, 49.6 mmol), trietilamina (14.8 mL, 106.2 mmol) y THP-hidroxilamina (6.21g, 53.1 mmol) se agitaron en dimetilformamida anhidra (110 mL) bajo N_2 a 60°C durante la noche. Después de enfriar a temperatura ambiente, la solución se volcó en agua (600 mL) y se extrajo con acetato de etilo. La capa orgánica se lavó con agua y solución salina y se secó sobre sulfato de sodio. La cromatografía en gel de sílice (2.0M NH_3 en MeOH/acetato de etilo/hexano) dio el producto deseado como una espuma incolora (11.0 g, 51%). ESMS m/z = 607 $(M+H)^+$. HRMS calculado para $C_{34}H_{43}N_2O_6S$: 607.2836 $(M+H)^+$. Hallado: 607.2829

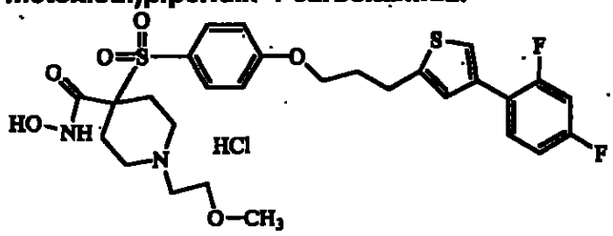
1003

[994] **Parte D. Preparación de:**



Al producto de la Parte C (10.8 g, 17.8 mmol) en metanol (18 mL) y 1,4-dioxano (18 mL) se agregó ácido clorhídrico 4M en 1,4-dioxano (18 mL) y después de agitar 1 hr, el material se concentró. Se co-cristalizó con otro lote a partir de MeOH/HCl 4N/dioxano. La recolección del sólido, seguida por el lavado con metanol, y luego el secado en alto vacío dio 11.51 g (88 %) del compuesto del título como una sal de ácido clorhídrico incolora. ESMS m/z = 523 $(M+H)^+$. HRMS calculado para $C_{28}H_{35}N_2O_6S$ H: 523.2261 $(M+H)^+$. Hallado: 523.2224.

[995] **Ejemplo 47. Preparación de clorhidrato de 4-[(4-[3-[4-(2,4-difluorofenil)tien-2-il]propoxi]fenil) sulfonil]-N-hidroxi-1-(2-metoxietil)piperidin-4-carboxamida.**



[996] **Parte A.** Un balón se cargó con 4-bromo-2-tiofencarboxaldehído (Aldrich, 55.8 g, 292 mmol), ácido 2,4-difluorofenilborónico (Aldrich, 60.0 g, 380 mmol), tetrakis(trifenilfosfina)paladio (Aldrich, 16.9 g, 14.6 mmol), $Na_2CO_{3\,aq}$ 2 M (190 ml, 380 mmol), y etilenglicol-dimetiléter (Aldrich, 500 ml). La reacción se calentó a 80°C y se agitó por 5 hr. La suspensión luego se volcó en una

mezcla de cloruro de metileno (500 ml) y agua de hielo (500ml). La capa orgánica se separó y se lavó con agua (2x-200 ml) y solución salina (1x-300 ml) luego se secó sobre Na_2SO_4 y se concentró para dar el producto tiofeno fenilo como un aceite color marrón. La purificación por gel de sílice (hexanos/acetato de etilo) dio un sólido blanco (34.2 g, 52 % de rendimiento). La ^1H RMN indicó el compuesto esperado.

[997] **Parte B.** Una solución de fosfonoacetato de trietilo (Aldrich, 24.2 g, 108 mmol) en tetrahidrofurano (100 ml) se enfrió a –78°C. Una solución 1.6 M de n-butillitio en hexanos (68 ml, 108 mmol) se volcó lentamente y luego la mezcla de reacción se agitó por 30 min a –78°C. Una solución del producto tiofenfenilcarboxaldehido de la **Parte A** en tetrahidrofurano (100 ml) se agregó lentamente. Se eliminó el baño de hielo seco y la mezcla de reacción se agitó mientras alcanzaba la temperatura ambiente durante la noche. La mezcla se diluyó con agua (200 ml) para fraguar. La capa orgánica se separó y se lavó con agua (2x-200 ml) y solución salina (1x- 300 ml), luego se secó sobre Na_2SO_4 y se concentró para dar un sólido de color tostado. Éste sólido se recristalizó a partir de metanol tibio para dar un sólido de color amarillo claro (16.1 g, 56 % de rendimiento). La ^1H RMN indicó el compuesto esperado.

[998] **Parte C.** Una solución de la etilésterolefina de la **Parte B** (16 g, 54.4 mmol) en cloruro de metileno se enfrió a 0°C. Una solución 1.0 M de hidruro de aluminio y litio se goteó lentamente, luego se continuó agitando la reacción por 45 min a 0°C. Una solución saturada de NH_4Cl_{aq} se goteó para fraguar, seguido por una solución de tartrato de sodio y potasio $_{aq}$ (10 ml). Después de agitar durante 30 min, se agregó Na_2SO_4 (40 g). La mezcla se filtró y se concentró para dar un aceite amarillo (16.8 g, 100$^+$ % de rendimiento). La ^1H RMN indicó el compuesto esperado junto con impurezas.

1005

[999] **Parte D.** A un recipiente para hidrogenación se cargó con el residuo de hidroxiolefina crudo de la parte C (~54.4 mmol), se disolvió en tetrahidrofurano (125 ml) y metanol (20 ml). Se burbujeó nitrógeno gaseoso por 15 min, luego se agregó catalizador Pd/C 10% (Aldrich, 50% agua, 2.7 g). Se conectó un cabezal para hidrogenación y el recipiente se purgó con nitrógeno (3x), seguido por hidrógeno (3x). Se sometió el recipiente a 50 psi de hidrógeno. Después de 1 hr de agitación, la reacción había finalizado según lo indicado por LCMS. La mezcla se filtró a través de un lecho de Celite y se concentró para dar un aceite de color negro que se purificó sobre gel de sílice (hexanos/acetato de etilo). La recolección de las fracciones dio el producto como un aceite transparente (8.6 g, 62% de rendimiento).). La ^{1}H RMN indicó el compuesto esperado.

[1000] **Parte E.** El alcohol saturado de la parte D (7.6 g, 30.0 mmol) se disolvió en dimetilsulfóxido (60 ml). Se agregó hidruro de sodio (Aldrich, en dispersión en aceite al 60%, 1.3 g, 32.6 mmol) en porciones durante 30 min. Después de agitar durante 1 hr, se agregó el aril-fluoruro, SC 84087, y la mezcla de reacción se agitó durante la noche a temperatura ambiente. La reacción se fraguó con NH_4Cl_{aq} saturado (100 ml), luego se extrajo con acetato de etilo (3x-125 ml). Los orgánicos combinados se lavaron con agua (2x-200 ml) y solución salina (1x-200 ml), luego se secó sobre Na_2SO_4 se filtró y se concentró para dar un aceite color marrón. El residuo se purificó sobre gel de sílice (hexanos/acetato de etilo) para dar el producto como un sólido de color tostado (14.0 g, 81% de rendimiento). La ^{1}H RMN indicó el compuesto esperado a 90% de pureza.

[1001] **Parte F.** El t-butiléster de la parte E (9.5 g, 15.0 mmol) se disolvió en cloruro de metileno (30 ml) después de lo cual se agregó ácido

1006

trifluoroacético glacial (Aldrich, 30 ml). La mezcla de reacción se agitó por 4 hr luego se concentró a un tercio del volumen por medio de a una corriente de nitrógeno. El residuo levemente viscoso luego se goteó sobre dietiléter en agitación para formar un sólido que se filtró y se secó para dar el producto como un sólido de color tostado (6.9 g, 66 % de rendimiento).). La ^{1}H RMN indicó el compuesto esperado.

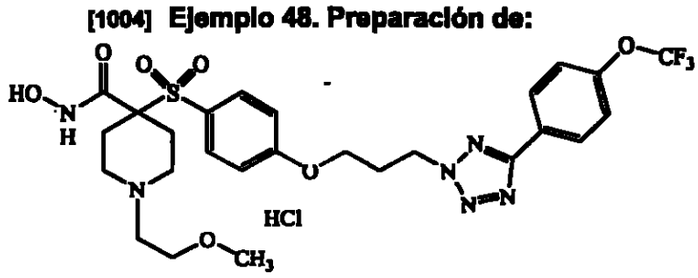
[1002] **Parte G.** A una solución del ácido carboxílico de la **Parte F** (6.9 g, 9.9 mmol) en N,N-dimetilformamida (20 ml) se agregó trietilamina (Aldrich, 4.2 ml, 30.0 mmol) seguida por hidrato de N-hidroxibenzotriazol (Aldrich, 2.7 g, 20.0 mmol), O-(tetrahidro-2H-piran-2-il)hidroxilamina (2.34 g, 20.0 mmol), y, finalmente, clorhidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (Sigma, 4.18 g, 21.8 mmol). La mezcla de reacción se agitó a temperatura ambiente por 18 hr. La mezcla se diluyó con agua (30ml) luego se extrajo con acetato de etilo (3x- 100 ml). Los extractos orgánicos se combinaron y se lavó con $NaHCO_{3\ aq}$ saturado (3x-100 ml), agua (2x- 100ml), y solución salina (1x- 150 ml). Después de secar sobre Na_2SO_4, la mezcla se filtró y se concentró para dar un aceite de color tostado. El aceite se trató con etanol (3x) y metanol (3x) para dar un aceite de color tostado (8.1 g, 100$^+$ % de rendimiento). La ^{1}H RMN indicó el compuesto esperado con trazas de impurezas.

[1003] **Parte H.** El ácido hidroxámico protegido crudo de la **Parte G** (~ 9.9 mmol) se suspendió en metanol (4 ml) y se agitó con HCl 4N en dioxano (20 ml) por 1 hr. Se redujo el volumen de solvente a la mitad, luego se agregó dietiléter, para dar un sólido gomoso que se purificó por LC en fase reversa (C_{18}, acetonitrilo/agua). La sal de TFA parcial resultante se disolvió en HCl 4N en dioxano (20 ml) y se agitó por 1 hr. El volumen de solvente se redujo nuevamente a la mitad, luego se agregó dietiléter, para dar un sólido blanco. El

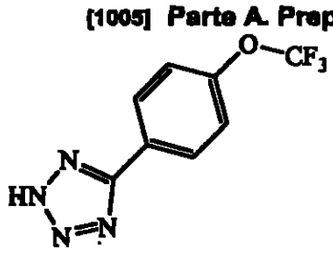
1007

sólido se recolectó y se secó para dar la sal de clorhidrato deseada como un polvo blanco (3.35g, 54% de rendimiento). La ^{1}H RMN indicó el compuesto esperado.

[1004] **Ejemplo 48. Preparación de:**



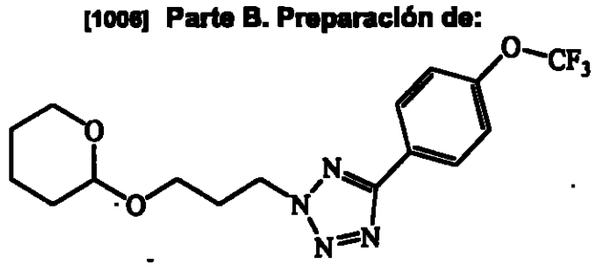
[1005] **Parte A. Preparación de:**



Se reflujó una mezcla de cloruro de litio (1.71 g, 40.3 mmol), trifluorometoxibenzonitrilo (5.00 g, 26.7 mmol), y azida sódica (1.75 g, 26.7 mmol) en 2-metoxietanol (26 mL) bajo una atmósfera de nitrógeno por 4 hr. La mezcla a temperatura ambiente se volcó en una mezcla de hielo (84 g) y Hcl concentrado (8.4 mL) y se agitó hasta que se derritió el hielo. El sólido blanco se recolectó por filtración, se lavó con agua, y se secó por 2 hr a 40°C en un horno de vacío para producir el tetrazol en la forma de un sólido blancuzco (4.86 g, 79% de rendimiento). MS MH^+ calculado para $C_8H_5N_4OF_3$ 231, hallado 231.

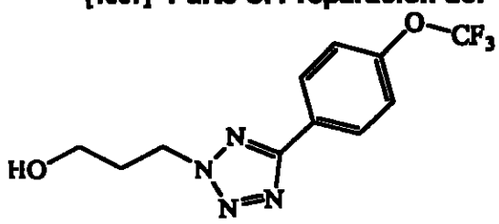
1006

[1006] **Parte B. Preparación de:**



Una solución del tetrazol de la **Parte A** (2.00 g, 8.69 mmol) en NMP (12 mL) se agregó por goteo a una mezcla a temperatura ambiente de hidruro de sodio al 95% (0.438 g, 18.2 mmol) en NMP (12 mL) bajo una atmósfera de N_2. Después de 1 hr de agitación, se agregó 2-(3-cloropropoxi)tetrahidro-2H-pirano (1.58 mL, 9.56 mmol) por goteo. La mezcla se agitó a temperatura ambiente por 18 hr y luego a 70°C por 2 hr. La mezcla se diluyó con una solución de agua (200 mL) y $NaHCO_3$ saturado (100 mL), y se extrajo con acetato de etilo (3x100 mL). La capa orgánica se lavó con agua (2x100 mL) y solución salina(100 mL), se secó sobre $MgSO_4$, y se concentró al vacío para dar un líquido color amarillo. La purificación por cromatografía instantánea (acetato de etilo hexano/gel de sílice) dio el pirano en la forma de un sólido blanco (1.46 g, 45% de rendimiento). Cálculo analítico para $C_{16}H_{19}N_4O_3F_3$: C, 56.34; H, 5.98; N, 7.73; S, 4.42. Hallado C, 56.13; H, 6.08; N, 7.65; S, 4.75.

[1007] **Parte C. Preparación de:**

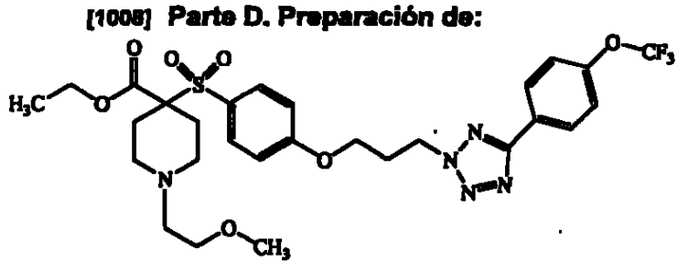


A una solución a temperatura ambiente del pirano de la **Parte B** (1.40 g, 3.76 mmol) en MeOH (13.5 mL) se agregó una solución de cloruro de acetilo (0.896 mL, 13.1 mmol) en MeOH (13.5 mL). Después de 15 min la solución se

1009

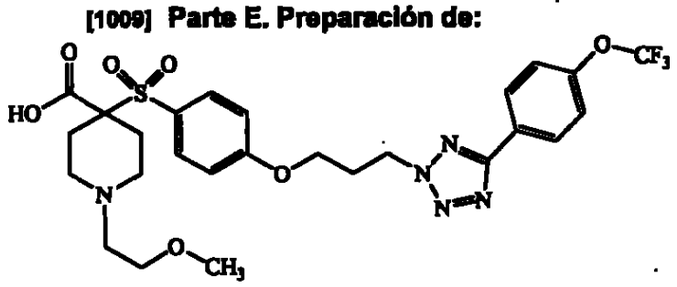
concentró al vacío para dar el alcohol como un sólido (1.02 g, 94% de rendimiento). MS MH^+ calculado para $C_{11}H_{11}N_4O_2F_3$ 289, hallado 289.

[1008] Parte D. Preparación de:



A una mezcla a temperatura ambiente de 95% hidruro de sodio (0.110 g, 3.58 mmol) en NMP (2.5 mL) bajo una atmósfera de N_2 se agregó por goteo una solución del alcohol de la Parte C (1.00 g, 3.47 mmol) en NMP (3.2 mL), y luego la mezcla se calentó a 55°C por 30 min. Se agregó una solución de 4-[(4-fluorofenil)sulfonil]-1-(2-metoxietil)piperidin-4-carboxilato de etilo (1.22 g, 3.27 mmol) en NMP (3.2 mL) por goteo a la mezcla de reacción a 55°C. Después de 1 hr a 55°C, la mezcla a temperatura ambiente se diluyó con una solución de agua (600 mL) y $NaHCO_3$ (100 mL), y se extrajo con acetato de etilo (3x200 mL). La capa orgánica se lavó con agua (2x150 mL) y solución salina(150 mL), se secó sobre $MgSO_4$, y se concentró al vacío para formar un aceite amarillo (1.96 g). La purificación por cromatografía instantánea (MeOH EA/gel de sílice) dio la sulfona en forma de aceite amarillo (1.48 g, 70% de rendimiento). MS MH^+ calculado para $C_{28}H_{35}N_5O_7SF_3$ 642, hallado 642.

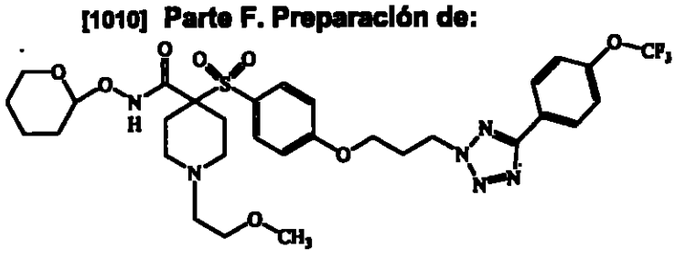
[1009] Parte E. Preparación de:



1010

Una mezcla de la sulfona de la **Parte D** (1.44 g, 2.24 mmol) y NaOH acuoso 50% (1.08 g, 22.4 mmol) en una solución de THF (23 mL) y EtOH (i 1 mL) se agitó a temperatura ambiente por 3 hr y luego a 60°C por 15 min. La mezcla se concentró al vacío, se diluyó con una solución de acetonitrilo y agua, se acidificó a alrededor de pH 2 con HCl concentrado, y se concentró al vacío para dar el ácido (que contenía NaCl) como una espuma color tostado cruda (2.77 g). MS MH^+ calculado para $C_{28}H_{31}N_6O_7SF_3$ 614, hallado 614.

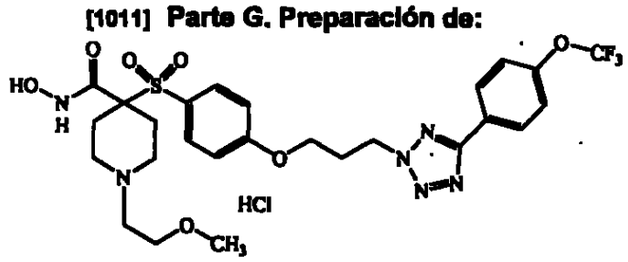
[1010] Parte F. Preparación de:



Una mezcla del ácido crudo de la **Parte E** (2.24 mmol), hidrato de 1-hidrobenzotriazol (0,534 g, 3.95 mmol), trietilamina (3.62mL, 25.9 mmol), O-(tetrahidro-2H-piran-2-il)hidroxilamina (0.542 g, 4.63 mmol), y clorhidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (0.888 g, 4.63 mmol) en DMF (23 mL) bajo una atmósfera de N_2 se agitó a temperatura ambiente por 40 hr. La mezcla se diluyó con agua (400 mL) y se extrajo con acetato de etilo (3x100 mL). La capa orgánica se lavó con agua (2x100 mL) y solución salina (100 mL), se secó sobre $MgSO_4$, y se concentró al vacío para formar una espuma blanca(1.37 g). La purificación por cromatografía (MeOH EA/gel de sílice) produjo el hidroxamato O-protegido en forma de una espuma blanca (1.04 g, 65% basado en el éster de la **Parte D**). MS MH^+ calculado para $C_{31}H_{40}N_6O_8F_3S$ 713, hallado 713. Cálculo analítico para $C_{31}H_{39}N_6O_8F_3S$: C, 52.24; H, 5.52; N, 11.79. Hallado C, 52.47; H, 5.73; N, 11.64.

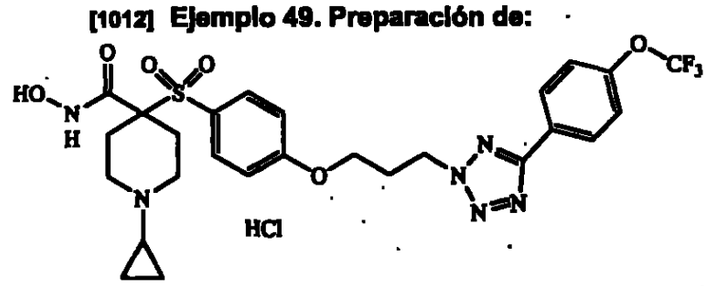
1011

[1011] **Parte G. Preparación de:**

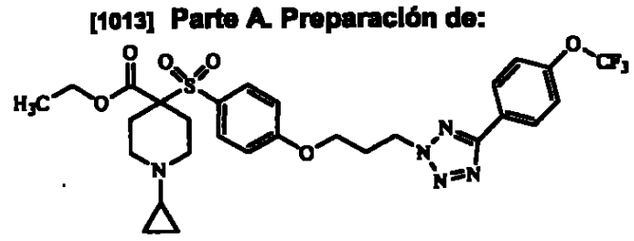


Una solución del hidroxamato O-protegido de la **Parte F** (0.960 g, 1.35 mmol) y cloruro de acetilo (0.493 g, 6.53 mmol) en metanol (15 mL) se agitó a temperatura ambiente por 1 hr. La solución se concentró al vacío para dar un sólido blanco. El sólido se trituró con éter y se concentró al vacío para dar el compuesto del título en la forma de un sólido blanco (0.66 g, 74% de rendimiento). Cálculo analítico para $C_{28}H_{31}N_6O_7F_3S$ HCl: C, 46.95; H, 4.85; N, 12.64; Cl, 5.33; S, 4.82. Hallado C, 46.59; H, 5.07; N, 12.64; Cl, 5.36; S, 5.20. MS MH^+ calculado para $C_{28}H_{32}N_6O_7F_3S$ 629, hallado 629.

[1012] **Ejemplo 49. Preparación de:**



[1013] **Parte A. Preparación de:**

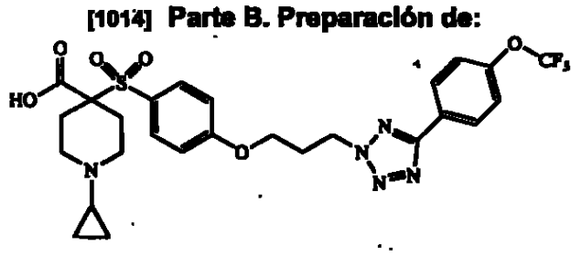


A una mezcla a temperatura ambiente de hidruro de sodio 95% (0.397g, 16.5 mmol) en NMP (7 mL) bajo una atmósfera de N_2 se agregó por goteo una solución del alcohol del **Ejemplo 48, Parte C** (3.44 g, 11.9 mmol) en NMP(7

1012

mL), y luego la mezcla se agitó a temperatura ambiente por 45 min. Se agregó 1-ciclopropil-4-[(4-fluorofenil)sulfonil]piridina-4-carboxilato de etilo (4.00 g, 11.3 mmol) en una sola porción y la mezcla se calentó a 60°C. Después de calentar por 24 hr a 60°C y agregar dos porciones más de hidruro de sodio 95 % (0.10 g, 4.0 mmol y 0.08 g, 3.0 mmol), la mezcla se diluyó con agua (300 mL) y se extrajo con acetato de etilo (3x100 mL). La capa orgánica se lavó con agua (2x100 mL) y solución salina (100 mL), se secó sobre $MgSO_4$, y se concentró al vacío para formar un aceite amarillo (5.81 g). La purificación por cromatografía instantánea (Hexano EA/gel de sílice) produjo la sulfona como un aceite amarillo (3.10 g, 44% de rendimiento). El espectro de RMN protónica ($CDC1_3$) confirmó el producto sulfona deseado.

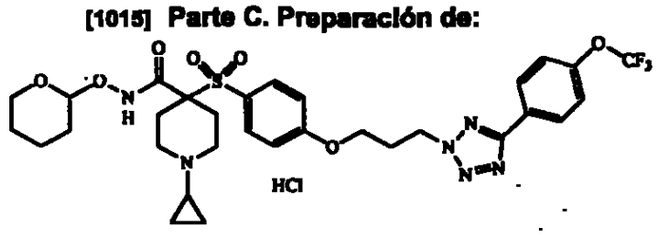
[1014] Parte B. Preparación de:



Una mezcla de la sulfona de la **Parte A** (3.00 g, 4.81 mmol) y NaOH acuoso 50% (3.85 g, 48.1 mmol) en una solución de THF (50 mL) y EtOH (24 mL) se agitó por 2.5 hr a 60°C. La mezcla se concentró al vacío, se diluyó con una solución de acetonitrilo y agua, se acidificó a alrededor de pH 2 con HCl concentrado, y se concentró al vacío. El ácido crudo se purificó por HPLC en fase reversa (H_2O-CH_3CN) para producir el ácido como un sólido blanco (1.86 g, 55% de rendimiento): MS MH^+ calculado para $C_{28}H_{29}N_5O_6F_3S$ 596, hallado 596.

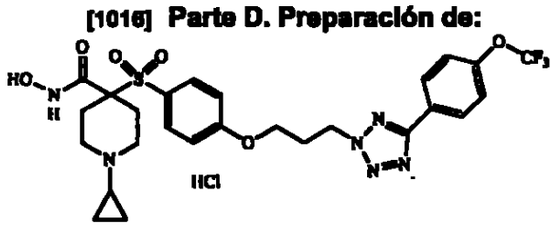
1013

[1015] **Parte C. Preparación de:**



Una mezcla del ácido de la **Parte B** (1.80 g, 2.85 mmol), hidrato de 1-hidrobenzotriazol (0.679 g, 5.02 mmol), trietilamina (4.61mL, 33.1 mmol), O-(tetrahidro-2H-piran-2-il)hidroxilamina (0.692 g, 5.91 mmol), y clorhidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (1.13 g, 5.91 mmol) en DMF (29 mL) bajo una atmósfera de N_2 se agitó a temperatura ambiente por 24 hr y 57°C por 6.5 hr. La mezcla se concentró al vacío, se diluyó con agua (300 mL) y se extrajo con acetato de etilo (3x100 mL). La capa orgánica se lavó con H_2O (2x100 mL) y solución salina (100 mL), se secó sobre $MgSO_4$, y se concentró al vacío para formar un aceite amarillo (1.80 g). La purificación por cromatografía instantánea (MeOH-CH_2Cl_2/gel de sílice) produjo el hidroxamato O-protegido en la forma de una espuma blanca (0.89 g, 45% de rendimiento): MS MH^+ calculado para $C_{31}H_{38}N_6O_7F_3S$ 695, hallado 695. Cálculo analítico para $C_{31}H_{37}N_6O_7F_3S$: C, 53.59; H, 5.37; N, 12.10; S, 4.62. Hallado C, 53.30; H, 5.43; N, 12.05; S, 4.73.

[1016] **Parte D. Preparación de:**

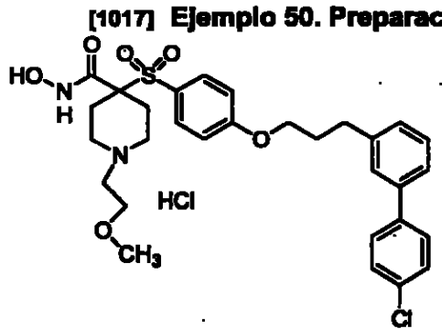


Una solución del hidroxamato O-protegido de la **Parte C** (0.870 g, 1.25 mmol) y cloruro de acetilo (0.456 g, 6.04 mmol) en metanol (14 mL) se agitó a temperatura ambiente por 30 min. La mezcla se volcó en dietiléter(250 mL). El

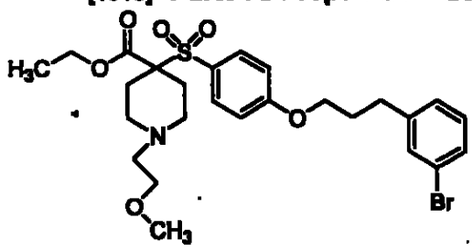
1014

sólido blanco se aisló por filtración y se secó a 40°C en un horno de vacío para producir el compuesto del título en forma de un sólido blanco (0.56 g, 69% de rendimiento): MS MH^+ calculado para $C_{28}H_{30}N_6O_6F_3S$ 611, hallado 611.

[1017] **Ejemplo 50. Preparación de:**



[1018] **Parte A. Preparación de:**

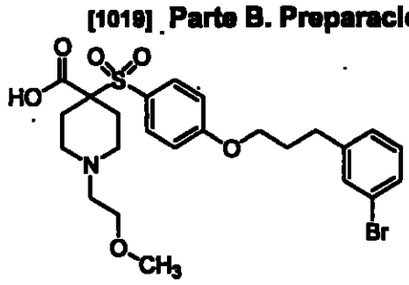


A una solución del alcohol de la parte B del Ejemplo 38 (3.65 g, 17.0 mmol) en dimetilformamida anhidra (17 mL) a 5°C se agregó hidruro de sodio al 60% (0.77 g, 19.3 mmol) en porciones. Una vez concluida la reacción, la mezcla de reacción se agitó a 5°C por 15 min y luego a temperatura ambiente por 15 min. La reacción se enfrió a 5°C y se agregó 4-[(4-fluorofenil)sulfonil]-1-(2-metoxietil)piperidin-4-carboxilato de etilo (6.0 g, 16.1 mmol) en dimetilformamida anhidra (15 mL) lentamente. La mezcla de reacción se agitó a temperatura ambiente por 2 hr, luego se diluyó con agua (250 mL) y se extrajo con acetato de etilo (3x150 mL). Los orgánicos combinados se lavaron con solución salina y se secaron sobre sulfato de magnesio. La cromatografía en gel de sílice (acetato de etilo/hexano) dio el producto como un aceite incoloro (8.06 g, 88%). RMN($CDCl_3$) δ 1.20-1.26 (m, 3H), 1.88-2.02 (m, 2H),

1015

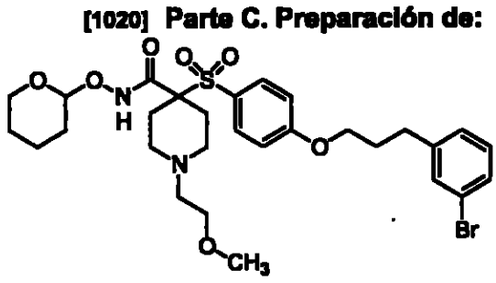
2.06-2.27 (m, 4H), 2.43 (d, 2H), 2,53 (bs, 2H), 2.78 (t, 2H), 2.97-3.08 (m, 2H), 3.32 (s, 3H), 3.47 (bs, 2H), 4.00 (t, 2H), 4.18 (q, 2H), 6.95 (d, 2H), 709-7.18 (m, 2H), 7.34 (d, 2H), 7.68 (d, 2H).

[1019] **Parte B. Preparación de:**



El éster impuro de la **Parte A** (8.06 g, 14.2 mmol teóricos) se hidrolizó en 15 mL de etanol, 15 mL de 1,4-dioxano y 9.5 mL de NaOH 6N a 60°C. La solución se volcó en agua y se extrajo con éter para eliminar color. La acidificación con HCl 1N causó la precipitación del ácido que se recolectó por filtración y se lavó con agua y hexano, luego se secó bajo alto vacío dando el ácido como un sólido blancuzco (5.90 g, 76.8 % de rendimiento). RMN (CD_3OD w/ K_2CO_3) δ 200 (q, 2H), 2.07-2.19 (m, 4H), 2.32 (d, 2H), 2.48 (t, 2H), 2.79 (d, 2H), 2.91 (d, 2H), 3.45 (t, 2H), 4.06 (t, 2H), 7.04 (d, 2H), 7.20 (d, 2H), 7.29-7.35 (m, 1H), 7.40 (s, 1H), 7.78 (d, 2H).

[1020] **Parte C. Preparación de:**

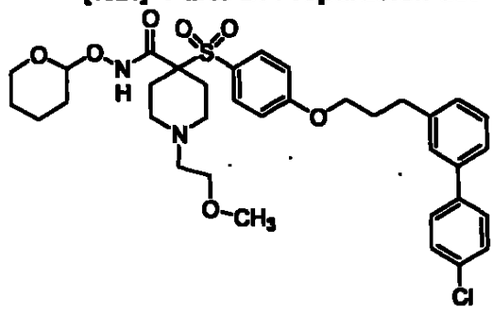


Al ácido de la **Parte B** (5.90, 10.9 mmol), EDC (2.9 g, 15.3 mmol), y HOBt (2.5g, 16.4 mmol) en NMP anhidro (33 mL) se agregó trietilamina (4.5 mL, 32.7 mmol). Después de calentar a 60°C por 1 hr, se agregó THP-hidroxilamina (1.9 g, 16.4 mmol). La solución se agitó por 18 hr a 60°C, y se agregaron más EDC

1016

(2.9 g, 15.3 mmol), HOBt (2.5g, 16.4 mmol), trietilamina (4.5 mL, 32.7 mmol) y THP-hidroxilamina (1.9 g, 16.4 mmol). Después de 2 hr, la reacción se diluyó con agua (300 mL) y se extrajo con acetato de etilo (3x150 mL). Los orgánicos combinados se lavaron con solución salina y se secaron sobre sulfato de magnesio. La cromatografía en gel de sílice (acetato de etilo/hexanos) dio el hidroxamato protegido como un aceite viscoso incoloro impuro (5.70 g). ESMS m/z = 641 $(M+H)^+$.

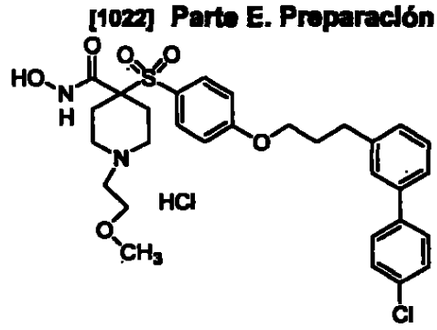
[1021] **Parte D. Preparación de:**



En un recipiente se combinaron el bromuro de arilo de la parte C (0.50 g, 0.78 mmol) en 3 mL de dimetoxietiléter, ácido 4-clorobencenborónico (185 mg, 1.17 mmol), tetrakis(trifenilfosfina)paladio (~45 mg, 0.04 mmol) y carbonato de cesio 2M (1.17 mL, 2.34 mmol). La mezcla se agitó vigorosamente a 80°C por 18 hr. La mezcla de reacción se volcó en un tubo Chem-Elut de 2 mL pre-humedecido con 3 mL de agua y se eluyó con acetato de etilo y cloruro de metileno. La purificación por cromatografía en fase reversa (acetonitrilo/agua/0.05% TFA) dio la sal de TFA del material desprotegido (239.6 mg) que se utilizó en el paso siguiente sin modificaciones.

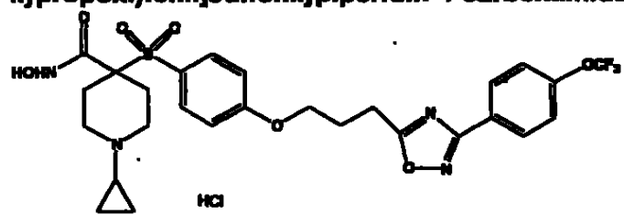
1017

[1022] **Parte E. Preparación de:**



El producto de la **Parte D** (239.6 mg) se recogió en ácido clorhídrico 4M en 1,4-dioxano (2 mL) y metanol (1-2 mL) y se agitó por 0.5 hr, luego se concentró. Este paso se repitió. El producto se desprendió de la solución, se recolectó por filtración, se lavó con dietiléter y se secó bajo alto vacío dando el compuesto del título como un sólido incoloro (170.5 mg, 35% luego de dos pasos). ESMS m/z = 587 $(M+H)^+$. HRMS calculado para $C_{30}H_{36}ClN_2O_6S$: 587.1977 $(M+H)^+$. Hallado: 587.1979.

[1023] **Ejemplo 51. Preparación de clorhidrato de 1-ciclopropil-N-hidroxi-4-{[4-(3-{3-[4-(trifluorometoxi) fenil]-1,2,4-oxadiazol-5-il}propoxi)fenil]sulfonil}piperidin-4-carboxamida.**



[1024] **Parte A.** En un equipo en seco bajo nitrógeno, se disolvió trimetilsilanolato de potasio (35.9 g, 0.28 mol) en dimetilsulfóxido (250 mL) y se agregó gamma-butirolactona (16.14 mL, 0.21 mol) durante 10 min mientras la temperatura de la mezcla de reacción se elevó a 38°C. Después de agitar a temperatura ambiente por 40 min, se agregó hidruro de sodio (8.4 g de una dispersión en aceite al 60%, 0.21 mol) en porciones durante 20 min y la

1018.

temperatura de la reacción se elevó a 43°C. También se observó evolución de gas. Después de agitar a temperatura ambiente por 50 min, se agregó una solución de 1-ciclopropil-4-[(4-fluorofenil)sulfonil]-4-piperidincarboxilato de etilo (49.7g, 0.14 mol) en dimetilsulfóxido (50 mL) durante 10 min mientras la temperatura de la reacción se elevó a 38°C. La mezcla de reacción se agitó a temperatura ambiente por 30 min. La lechada se volcó lentamente en agua de hielo (1.5 L) y luego se extrajo con hexanos (150 mL) 3 veces seguido por una extracción con dietiléter (300 mL). La capa acuosa se enfrió a 5°C y el pH se ajustó a 6 con ácido clorhídrico concentrado. La lechada se filtró y la torta se lavó con 500 mL de agua dos veces. El sólido se secó al vacío para dar el ácido butírico como un sólido blanco (47.5 g, 77%). LCMS m/z = 440 $[M+H]^+$.

[1025] **Parte B.** En un equipo en seco bajo nitrógeno, el ácido butírico de la parte A (3.07 g, 7.0 mmol) se disolvió en dimetilacetamida seca (15 mL) y los reactivos restantes se agregaron a la solución en el orden siguiente: hidrato de N-hidroxibenzotriazol (1.42 g, 10.5 mmol), trietilamina (1.95 mL, 14.0 mmol), 4-(trifluorometoxi)benzamidoxima (2.31 g, 10.5 mmol), y clorhidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (2.68 g, 14.0 mmol). Se agregó más dimetilacetamida seca (5 mL). Después de 24 hr a 70°C, la reacción se concentró al vacío. El residuo se recogió en acetato de etilo, se lavó con agua, $NaHCO_3$ saturado, solución saturada de cloruro de sodio, se secó sobre Na_2SO_4, se filtró, y se concentró al vacío. La cromatografía (sobre sílice, acetato de etilo/metanol/hexanos) dio el oxadiazol como un sólido blanco claro (3.38 g, 78%). LCMS m/z = 624$[M+H]^+$.

[1026] **Parte C.** Una suspensión del oxadiazol de la parte B (3.36 g, 5.39 mmol), hidróxido de sodio 2.5N (6.5 mL, 16.2 mmol) e hidróxido de sodio (0.86 g, 21.6 mmol) en isopropanol (27 mL) se agitó a 75°C por 5 hr. Se

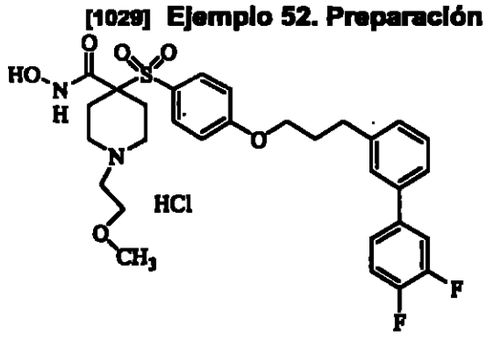
suspendió el calentamiento y la reacción se diluyó con agua (50 mL) y se enfrió a 5°C. Se ajustó el pH en 7 con ácido clorhídrico concentrado. Los sólidos se filtraron, se lavaron con hexanos, y se secaron al vacío para dar el ácido carboxílico como un sólido blanco (3.1 g, 97%). LCMS m/z = 596 $[M+H]^+$.

[1027] **Parte D.** En un equipo en seco bajo nitrógeno, el ácido carboxílico de la parte C (2.9 g, 4.87 mmol) se disolvió en dimetilacetamida seca (10 mL) y los reactivos restantes se agregaron a la solución en el orden siguiente: hidrato de N-hidroxibenzotriazol (0.99 g, 7.3 mmol), trietilamina (2.03 mL, 14.6 mmol), O-(tetrahidro-2H-piran-2-il)hidroxilamina (0.86 g, 7.31 mmol), y clorhidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (1.87 g, 9.75 mmol). Se agregó más dimetilacetamida seca (5 mL). Después de 29 hr a 40°C, la reacción se concentró al vacío. El residuo se recogió en acetato de etilo, se lavó con agua, $NaHCO_3$ saturado, solución saturada de cloruro de sodio, se secó sobre Na_2SO_4, se filtró, y se concentró al vacío. La cromatografía (sobre sílice, acetato de etilo/metanol/hexanos) dio el hidroxamato de THP como una espuma blanca (1.48 g, 44%). LCMS m/z = 695 $[M+H]^+$.

[1028] **Parte E.** Al hidroxamato de THP de la parte D (1.4 g, 2.02 mmol) se agregó solución de HCl 4N en dioxano (5 mL, 20.2 mmol) y metanol (0.5 mL). La lechada se tomó muy espesa. Se agregó dietiléter (50 mL) y después de 1 hr a temperatura ambiente la reacción se filtró bajo nitrógeno. Los sólidos se lavaron con dietiléter (150 mL) bajo nitrógeno y se secó al vacío sobre pentóxido de fósforo para dar el compuesto del título como un sólido blanco (1.4 g, 100%). HRMS (ES+) M+ H $^+$ calculado para $C_{27}H_{29}N_4O_7S_1F_3$ 611.1787, hallado 611.1773.

1020

[1029] **Ejemplo 52. Preparación de:**

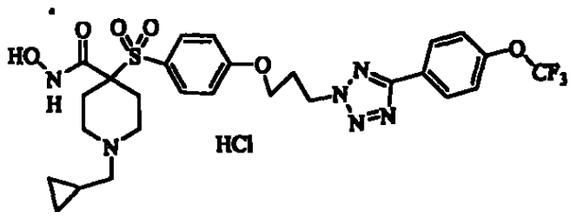


[1030] **Parte A.** En un recipiente se combinaron el bromuro de arilo de la parte C del Ejemplo 50 (0.50 g, 0.78 mmol) en 3 mL de dimetoxietiléter, ácido 3,4-difluorobencenborónico (185 mg, 1.17 mmol), tetrakis(trifenilfosfina)paladio (~45 mg, 0.04 mmol) y carbonato de cesio 2M (1.17 mL, 2.34 mmol). La mezcla se agitó vigorosamente a 80°C por 18 hr. La mezcla de reacción se volcó sobre un tubo Chem-Elut de 2 mL pre-humedecido con 3 mL de agua y se eluyó con acetato de etilo y cloruro de metileno. La purificación por cromatografía en fase reversa (acetonitrilo/agua/0.05% TFA) dio la sal de TFA del material desprotegido (354.8 mg) que se utilizó en el paso siguiente sin modificaciones.

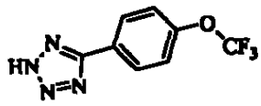
[1031] **Parte B.** El producto de la Parte D (354.8 mg) se recogió en ácido clorhídrico 4M en 1,4-dioxano (2 mL) y metanol (1-2 mL) y se agitó por 30 min y luego se concentró. Este paso se repitió. El producto se desprendió de la solución, se recolectó por filtración, se lavó con dietiléter y se secó bajo alto vacío dando el compuesto del título como un sólido incoloro (298.0 mg, 61% después de dos pasos). ESMS m/z = 589 $(M+H)^+$. HRMS calculado para $C_{30}H_{35}F_2N_2O_6S$: 589.2178 $(M+H)^+$. Hallado: 589.2192.

[1032] **Ejemplo 53. Preparación de**

1021

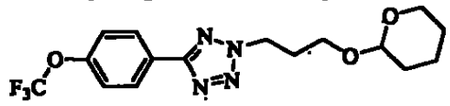


[1033] **Parte A. Preparación de**



Se reflujó una mezcla de cloruro de litio (1.71 g, 40.3 mmol), trifluorometoxibenzonitrilo (5.00 g, 26.7 mmol), y azida sódica (1.75 g, 26.7 mmol) en 2-metoxietanol (26 mL) bajo una atmósfera de N_2 por 4 hr. La mezcla a temperatura ambiente se volcó en una mezcla de hielo (84 g) y ácido clorhídrico concentrado (8.4 mL) y se agitó hasta que se derritió el hielo. El sólido blanco resultante se recolectó por filtración, se lavó con agua, y se secó por 2 hr a 40°C en un horno de vacío para proveer el tetrazol en la forma de un sólido blancuzco (4.86 g, 79% de rendimiento). MS MH^+ calculado para $C_8H_6N_4OF_3$ 231, hallado 231.

[1034] **Parte B. Preparación de:**

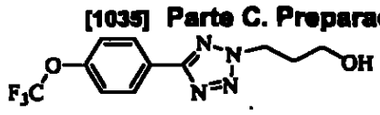


Una solución del tetrazol de la **Parte A** (2.00 g, 8.69 mmol) en NMP (12 mL) se agregó por goteo a una mezcla a temperatura ambiente de hidruro de sodio al 95% (0.438 g, 18.2 mmol) en NMP (12 mL) bajo una atmósfera de N_2. Después de 1 hr de agitación, se agregó 2-(3-cloropropoxi)tetrahidro-2H-pirano (1.58 mL, 9.56 mmol) por goteo. La mezcla se agitó a temperatura ambiente por 18 hr y luego a 70°C por 2 hr. La mezcla se diluyó con una solución de agua (200 mL) y $NaHCO_3$ saturado (100 mL), y se extrajo con acetato de etilo

1012

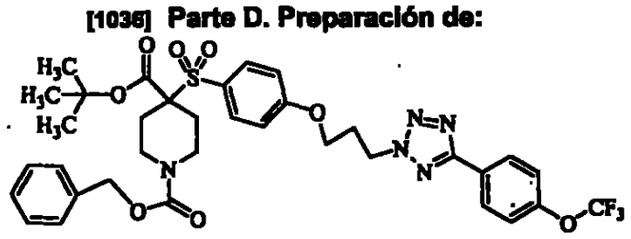
(3x100 mL). La capa orgánica se lavó con agua (2x100 mL) y solución salina (100 mL), se secó sobre $MgSO_4$, y se concentró al vacío para dar un líquido color amarillo. La purificación por cromatografía instantánea (acetato de etilo hexano/gel de sílice) dio el pirano en la forma de un sólido blanco (1.46 g, 45% de rendimiento). Cálculo analítico para $C_{18}H_{18}N_4O_3F_3$: C, 56.34; H, 5.98; N, 7.73; S, 4.42. Hallado C, 56.13; H, 6.08; N, 7.65; S, 4.75.

[1035] Parte C. Preparación de:



A una solución a temperatura ambiente del pirano de la **Parte B** (1.40 g, 3.76 mmol) en MeOH (13.5 mL) se agregó una solución de cloruro de acetilo (0.896 mL, 13.1 mmol) en MeOH (13.5 mL). Después de 15 min la solución se concentró al vacío para dar el alcohol como un sólido (1.02 g, 94% de rendimiento). MS MH^+ calculado para $C_{11}H_{12}N_4O_2F_3$ 289, hallado 289.

[1036] Parte D. Preparación de:

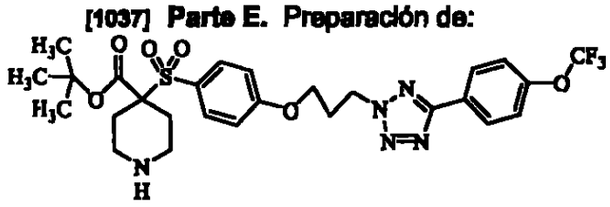


A una mezcla a temperatura ambiente de 95% hidruro de sodio (0.923 g, 38.5 mmol) en NMP (16 mL) bajo una atmósfera de N_2 se agregó por goteo una solución del alcohol de la **Parte C** (8.00 g, 27.7 mmol) en NMP 16 mL), y luego la mezcla se agitó a temperatura ambiente durante 35 minutos.. Se agregó por goteo una solución de 1-bencil-4-tert-butil-4-[(4-fluorofenil)sulfonil]piperidin-1,4-dicarboxilato (12.5 g, 26.3mmol) en NMP (16 mL) a la mezcla de reacción. Luego de 3 horas a 55°C la mezcla a temperatura ambiente se diluyó con agua (700 mL) y se extrajo con acetato de etilo (3x150 mL). La capa orgánica se

1023

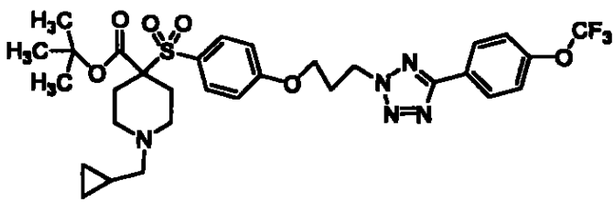
lavó con agua (2x100 mL) y solución salina (100 mL), se secó sobre $MgSO_4$, y se concentró al vacío para formar un aceite amarillo (18.6 g). La purificación por cromatografía (hexano EA/gel de sílice) proveyó la sulfona como de aceite amarillo (10,1 g, 52% de rendimiento). MS MH^+ calculado para $C_{35}H_{39}N_5O_8SF_3$ 746, hallado 746. Anal. Calcd. para $C_{35}H_{38}N_5O_8SF_3$ C,56.37; H, 5.14; N, 9.39; S, 4.30. Hallado C,56.22; H, 4.96; N, 9.22; S, 4.37.

[1037] **Parte E.** Preparación de:



Una mezcla de la sulfona de la parte D (10.0 g, 13.4 mmol) y 10% de paladio sobre carbón (1.43g, 1.34 mmol) in metanol (50 mL) se colocó bajo una atmósfera de H_2 con un balón a temperatura ambiente durante 20 hr. La mezcla se filtró a través de un lecho de celite y se concentró al vacío para proveer la piperidina en forma de un aceite amarillo pálido (7.57 g, 92%). El espectro de RMN protónica confirmó el compuesto deseado.

[1038] **Parte F.** Preparación de:

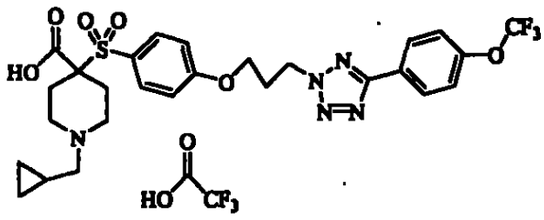


Una mezcla de la piperidina de la **Parte E** (3.50 g, 5.72 mmol), (bromometil)ciclopropano (0.67 mL,6.87 mmol), y carbonato de potasio (2.38 g, 17.2 mmol) en DMF (15 mL) se agitó a temperatura ambiente por 20 hr bajo una atmósfera de N_2. La mezcla se diluyó con agua (700 mL) y se extrajo con acetato de etilo (3x100 mL). La capa orgánica se lavó con agua (2x75 mL) y solución salina (75 mL), se secó sobre $MgSO_4$, y se concentró al vacío para producir un aceite amarillo. Se purificó con cromatografía instantánea

1024

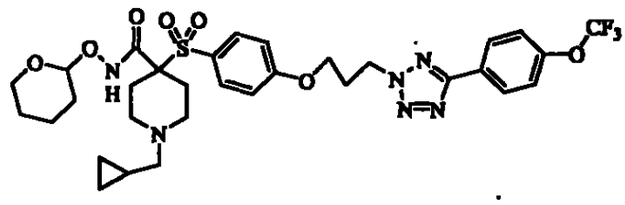
(hexano-EA/gel de sílice) proveyó la alquilpiperidina en la forma de aceite incoloro (2.08 g, 55% de rendimiento): MS MH^+ calculado. para $C_{31}H_{39}N_5O_6SF_3$ 666, hallado 666. Análisis calculado para $C_{31}H_{38}N_5O_6SF_3$: C,55.93; H, 5.75; N, 10.52; S, 4.82. Hallado C,55.85; H, 5.91; N, 10.25; S, 4.99.

[1039] **Parte G.** Preparación de:



Se agitó a temperatura ambiente una solución de la alquilpiperidina de la **Parte F** (2.00 g, 3.00 mmol) en ácido trifluoroacético (10 mL, 130 mmol) por 1.7 hr. La mezcla se concentró al vacío , se trituró dos veces con éter y se secó a 40°C en vacío para proveer el ácido como un sólido blanco (2.21 g, 102%). MS MH^+ calculado para $C_{27}H_{31}N_5O_6SF_3$ 610, hallado 610.

[1040] **Parte H.** Preparación de:

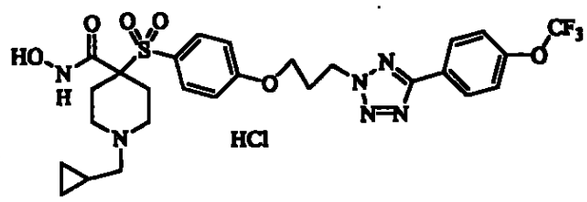


Una mezcla del ácido crudo de la **Parte G** (2.10 g, 3.44 mmol), hidrato de 1-hidroxibenzotriazol (0.820 g, 6.07 mmol), trietilamina(5.57mL, 39.9 mmol), O-(tetrahidro-2H-piran-2-il)hidroxilamina(0.835 g, 7.13mmol), y hidrocloruro de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (1.37 g, 7.13 mmol) en DMF (35 mL) bajo una atmósfera de N_2 se agitó a temperatura ambiente por 20 hr. La mezcla se diluyó con agua (700 mL) y se extrajo con acetato de etilo (3x200 mL). La capa orgánica se lavó con agua (2x100 mL) y solución salina (100 mL), se secó sobre $MgSO_4$, y se concentró al vacío para producir una espuma amarilla. La purificación cromatográfica ($MeOH-CH_2Cl_2$/gel de sílice) produjo el

1025

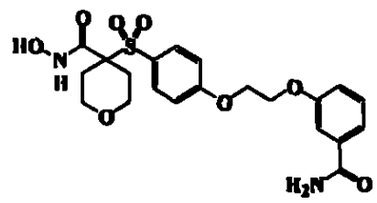
hidroxamato O-protegido en forma de una espuma blanca 1.60 g, 66%). MS MH^+calculado para $C_{32}H_{40}N_6O_7F_3S$ 709, hallado 709.

[1041] **Parte I.** Preparación de:

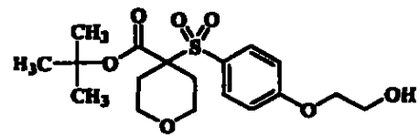


Se agitó a temperatura ambiente una solución del hidroxamato O-protegido de la Parte H (1.50 g, 2.12 mmol) y cloruro de acetilo (0.677 mL, 10.2 mmol) en metanol (23 mL) por 1 hr. La solución se diluyó con éter y se formó un sólido. El sólido se aisló por filtración, se lavó con éter y se secó en un horno de vacío a 40°C para producir el compuesto del título como un sólido blanco (1.55 g, 82% rendimiento). Análisis calculado para $C_{27}H_{31}N_6O_6F_3S{\cdot}HCl$: C, 49.05; H, 4.88; N, 12.71; Cl, 5.36; S, 4.85. Hallado C, 48.94; H, 4.72; N, 12.71; Cl, 5.29; S, 4.94

[1042] **Ejemplo 54. Preparación de:**



[1043] **Parte A.** Preparación de:

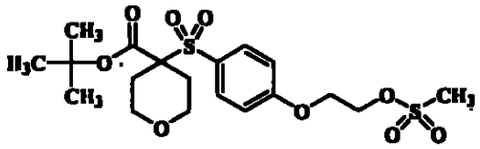


A una solución de tert-butil 4-[(4-fluorofenil)sulfonil]tetrahidro-2H-piran-4-carboxilato (5.0 g, 14.6 mmol) y carbonato de cesio (14.3 g, 43.8 mmol) en DMSO anhidro(30 mL) se agregó etilénglicol (8.1 mL, 146 mmol). La mezcla de reacción resultante se agitó a 80°C por 3 hr. Luego de enfriar a temperatura ambiente, la mezcla se volcó en agua (350 mL) y se extrajo con acetato de etilo (3x). El material orgánico se lavó con solución salina y se secó

1026

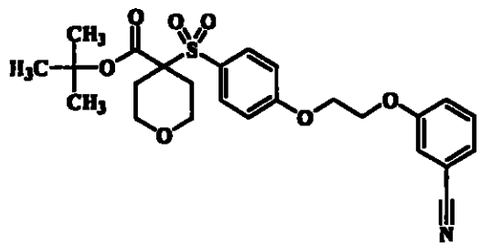
sobre sulfato de magnesio. La cromatografía con Gel de sílice (etilacetato/cloruro de metileno) proveyó el alcohol como un sólido incoloro (2.33 g, 41%). NMR($CDCl_3$) δ 1.45 (s, 9H), 2.13-2.20 (m, 4H), 3.22-3.33 (m, 2H), 3.94-4.03 (m, 4H), 4.16 (q, 2H), 7.02 (d, 2H), 7.73 (d, 2H). ESMS m/z = 404 $(M+NH4)^+$. HRMS calculado para $C_{18}H_{26}O_7S\ NH_4$: 404.1743 $(M+NH_4)^+$. Hallado : 404.1734.

[1044] Parte B. Preparación de:



A una solución del alcohol de la Parte A (0.50 g, 1.3 mmol) en CH_2Cl_2 (2.5 mL) se agregó trietilamina (0.24 mL g, 1.7 mmol), seguida por cloruro de mesilo. La mezcla resultante se agitó a temperatura ambiente por 1.5 hr. La mezcla se diluyó con cloruro de metileno y se lavó con 10% ácido cítrico, se lavó con 5% bicarbonato de sodio, se lavó con solución salina, y se secó sobre $MgSO_4$. La concentración produjo el compuesto deseado en forma de un sólido color tostado (0.62 g, 100%). NMR($CDCl_3$) 1.45 (s, 9H), 2.13-2.22 (m, 4H), 3.07 (s, 3H), 3.22-3.37 (m, 2H), 4.00 (dt, 2H), 4.32-4.37 (m, 2H), 4.58-4.62 (m, 2H), 7.02 (d, 2H), 7.75 (d, 2H): ESMS m/z = 482 $(M+NH4)^+$.

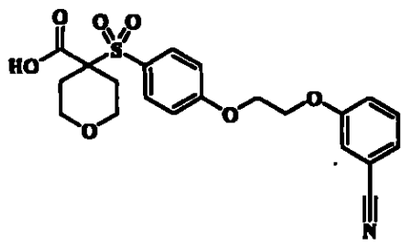
[1045] Parte C. Preparación de:



A una solución del 60% hidruro de sodio (39 mg, 0.98 mmol) en dimetilformamida anhidra (2.5 mL) se agregó 3-cianofenol (108 mg, 0.91 mmol). . Luego de agitar por 15 min, la solución se aclaró. Se agregó el mesilato de la Parte B (0.30 g, 0.65 mmol) en dimetilformamida anhidra (1 mL). Luego de completada la adición, se agitó la mezcla a temperatura ambiente

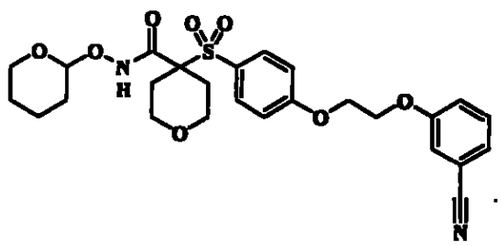
durante la noche. La mañana siguiente, la mezcla se volcó en un tubo de 10 mL Chem-Elut, pre humedecido con 5 mL de agua y se eluyó con acetato de etilo y CH_2Cl_2. Por cromatografía (gel de sílice con acetato de etilo/hexano) produjo el éster deseado (0.27 g, 85%). NMR ($CDCl_3$) δ 1.46 (s, 9H), 2.17-2.21 (m, 4H), 3.22-3.36 (m, 2H), 3.98 (dt, 2H), 4.35-4.43 (m, 4H), 7.04 (d, 2H), 7.15-7.20 (m, 2H), 7.28 (dt, 1H), 7.39 (t, 1H), 7.74 (d, 2H). ESMS m/z = 505 $(M+NH4)^+$. HRMS calculado para $C_{25}H_{33}N_2O_7S$: 505.2008 $(M+NH_4)^+$. Hallado : 505.2019.

[1046] **Parte D.** Preparación de:



El éster de la **Parte C** (0.24 g, 0.49 mmol) se hidrolizó en 5 mL de cloruro de metileno y 5 mL de ácido trifluoroacético. Se concentró y se secó a alto vacío produciéndose el ácido deseado (0.21 g, 100%). NMR (CD_3OD w/ K_2CO_3) δ 201-2.11 (m, 2H), 2.20 (d, 2H), 3.32-3.42 (m, 2H), 3.95 (dt, 2H), 4.38-4.45 (m, 4H), 7.13 (d, 2H), 7.26-7.34 (m, 3H), 7.45 (t, 1H), 7.76 (d, 2H). ESMS m/z = 449 $(M+NH4)^+$. HRMS calculado para $C_{21}H_{21}NO_7S$ NH_4: 449.1382 $(M+NH_4)^+$. Hallado : 449.1407.

[1047] **Parte E.** Preparación de:

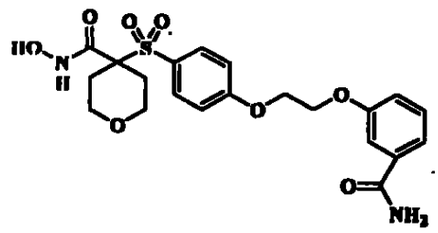


A una lechada del ácido de la **Parte D** (0.20 g, 0.46 mmol), HOBt (76 mg, 0.55 mmol), y EDC (130 mg, 0.68 mmol) se agregó trietilamina (1.4 mmol) y THP-hidroxilamina (167 mg, 1.4 mmol) en un recipiente bajo N_2 en 2 mL DMF

1028

anhidro. La mezcla resultante se agitó a 40°C durante la noche. La mañana siguiente la mezcla se volcó en un tubo de 10 mL Chem-Elut prehumedecido con 6 mL de agua, y se eluyó con acetato de etilo y CH_2Cl_2. Por cromatografía (gel de sílice, acetato de etilo/hexano) se produjo el producto como un aceite incoloro (0.18 g, 74%).

[1048] **Parte F.** Preparación de:



Al producto de la Parte E (0.18 g, 0.34 mmol) en metanol (1-2 mL) se agregó 4M HCl en 1,4-dioxano (2.5 mL). La mezcla resultante se agitó durante la noche. El producto deseado se produjo con cromatografía de fase inversa (agua/acetonitrilo/0.05% TFA) con un sólido cristalino incoloro (25.0 mg 16 %). NMR(DMSO) δ 1.82-1.98 (m, 2H) 215-2.30 (m, 2H), 3.15, (t, 2H), 3.86 (d, 2H), 4.44 (d, 4H), 7.10-7.25 (m, 3H), 7.38 (t, 1H), 7.44-7.52 (m, 2H), 7.68 (d, 2H). ESMS m/z = 465 $(M+H)^+$. HRMS calculado para $C_{21}H_{25}N_2O_8S$: 465.1332 $(M+H)^+$. Hallado : 465.1354.

[1049] **Ejemplos 55-89. Análisis de inhibición de MMP in vitro**

[1050] Se analizaron numerosos hidroxamatos, y las sales de los mismos, en ensayos in vitro con el fin de determinar su capacidad para inhibir el clivaje por MMP de sustratos peptídicos. Las constantes de inhibición (K_i) y los valores IC_{50} se calcularon a partir de las interacciones hidroxamato-MMP evaluadas.

[1051] En este ensayo se usaron las MMP-1, MMP-2, MMP-9, MMP-13 y MMP-14 recombinantes humanas. Todas las enzimas se prepararon en los laboratorios del cesionario utilizando los procedimientos comunes de laboratorio. Los protocolos para la preparación y el uso de estas enzimas se

1029

encuentran disponibles en la literatura científica. Véase, por ejemplo, Enzyme Nomenclature (Academic Press, San Diego, CA, 1992) (y las citas contenidas en la misma). Véase también, Frije et al., J Biol. Chem., 26(24), 16766-73 (1994).

[1052] La proenzima MMP-1 se purificó a partir del medio utilizado para las células HT-1080 transfectadas con MMP-1 provistas por el Dr. Harold Welgus de la Universidad de Washington (St. Louis, MO). La proteína se purificó en una columna quelante de zinc.

[1053] La proenzima MMP-2 se purificó por cromatografía Sepharose gelatina a partir de células p2AHT2 transfectadas con MMP-2 provistas por el Dr. Gregory Goldberg de la Universidad de Washington (St. Louis, MO).

[1054] La proenzima MMP-9 se purificó por cromatografía Sepharose gelatina a partir del medio utilizado para las células HT1080 transfectadas con MMP-9 provistas por el Dr. Howard Welgus de la Universidad de Washington (St. Louis, MO).

[1055] La MMP-13 se obtuvo como una proenzima a partir de un clon de ADNc de longitud completa usando baculovirus, como describe V.A. Luckow, "Insect Cell Expression Technology," Protein Engineering: Principles and Practice, págs. 183-218 (editado por J.L. Cleland et al., Wiley-Liss, Inc., 1996). La proenzima expresada se purificó primero en columna de agarosa heparina y luego en columna quelante de cloruro de zinc. La proenzima se activó después por APMA en el momento del ensayo. Se pueden consultar detalles adicionales sobre los sistemas de expresión en baculovirus en, por ejemplo, Luckow et al., J. Virol., 67, 4566-79 (1993). Véase también, O'Reilly et al, Baculovirus Expression Vectors: A Laboratory Manual (W.H. Freeman y Co., Nueva York, NY, 1992). Véase también, King et al., The Baculovirus

1030

Expression System: A Laboratory Guide (Chapman & Hall, Londres, Inglaterra, 1992).

[1056] El ADNc de longitud completa de MMP-14 fue provisto por el Dr. Gregory Goldberg de la Universidad de Washington (St. Louis, MO). El dominio catalítico de la enzima se expresó en cuerpos de inclusión de E. coli, se solubilizó en urea, se purificó en columna C-14 de fase reversa preparativa para HPLC y luego se replegó en presencia de acetato de zinc y se purificó para su uso.

[1057] Todas las MMP fueron activadas usando acetato 4-aminofenilmercúrico ("APMA", Sigma Chemical, St. Louis, MO) o tripsina. La MMP-9 también se activó usando MMP-3 recombinante humana (purificada en el laboratorio del cesionario mediante técnicas de clonación y purificación estándar).

[1058] Se utilizaron dos sustratos de polipéptidos fluorogénicos que contenían metoxicumarina en los ensayos de inhibición de MMP:

MCA-ProLeuGlileuDpaAlaArgNH$_2$

(I)

MCA-ArgProLeuGlileuDpaAlaArgGluArgNH$_2$

(II)

En este caso, "Dpa" es un grupo 3-(2,4-dinitrofenil)-L-2,3-diaminpropionilo y "MCA" es 7-metoxicumarin-4-ilo, acetilo. El sustrato (I) se obtuvo de Baychem (Redwood City, CA) y el sustrato II se preparó en el laboratorio del cesionario. El sustrato I se utilizó en los ensayos de determinación de la IC_{50}, en tanto el sustrato II se utilizó en los ensayos de determinación de la K_i. En ausencia de actividad inhibidora MMP, ambos sustratos son clivados en el enlace peptídico Gly-Leu. Este clivaje separa el péptido altamente fluorogénico del neutralizador

1031

2,4-dinitrofenilo, dando como resultado un incremento en la intensidad de fluorescencia.

[1059] Las soluciones madre de los hidroxamatos evaluados (o las sales de los mismos) se prepararon en dimetilsulfóxido 1% (DMSO). Estas soluciones madre se diluyeron en Buffer A (Tris-HCl 100 mM, NaCl 100 mM, $CaCl_2$ 10 mM, polioxietilen-23-laurléter 0,05%, pH 7,5) para obtener soluciones con diferentes concentraciones de hidroxamato, es decir, soluciones de ensayo con diferentes concentraciones del compuesto inhibidor MMP evaluado. Los controles del experimento contenían la misma cantidad de buffer A/DMSO que la muestra de prueba, pero no contenían hidroxamato (o sales del mismo).

[1060] Los ensayos con los cuales se efectuaron las determinaciones de IC_{50} se llevaron a cabo de la siguiente manera. Las MMP se activaron ya sea con tripsina o APMA (acetato 4-aminofenilmercúrico, Sigma Chemical, St. Louis, MO). Las muestras de hidroxamato de prueba se incubaron en placas blancas Microfluor™ (Dynatech, Chantilly, VA) y se analizaron con una lectora de placas Perkin Elmer L550 (Norwalk, CT). La longitud de onda de excitación era de 328 nm y la longitud de onda de emisión de 415 nm. Todas las muestras (hidroxamatos de prueba y controles) se incubaron en placas separadas a temperatura ambiente en presencia de sustrato MMP (I) 4 µM. Como se indicó en el párrafo anterior, se prepararon muestras que contenían concentraciones variables del mismo hidroxamato de prueba. La inhibición se midió como una reducción de la intensidad de fluorescencia en función de la concentración de inhibidor MMP.

[1061] Los ensayos con los cuales se efectuaron las determinaciones de la K_i se llevaron a cabo de la siguiente manera. Las muestras de hidroxamato

de prueba se incubaron en cavidades separadas de placas de poliestireno blancas no tratadas (Nunc Nalgene International, Rochester, NY) y se analizaron con una lectora de placas Tecan SpectraFlour Plus. La longitud de onda de excitación era de 330 nm y la longitud de onda de emisión de 420 nm. Todas las muestras (hidroxamatos de prueba y controles) se incubaron en cavidades de placas separadas a temperatura ambiente durante 1 h en presencia de sustrato MMP (II) 4 μM. En ausencia de actividad inhibidora MMP, el sustrato II se clivó en el enlace Gly-Leu dando como resultado un incremento de la fluorescencia relativa. La inhibición se observó como una reducción de este incremento de la fluorescencia relativa. Los diversos hidroxamatos se analizaron usando una sola concentración baja de enzima con una sola concentración de sustrato fija en o por debajo del valor de la K_m. Este protocolo es una modificación del método de Knight et al., FEBS Lett., 296(3), 263-266 (1992). Las constantes de inhibición aparentes se determinaron mediante regresión no lineal de la velocidad de reacción en función de la concentración de inhibidor y enzima usando la ecuación de Morrison, como describe Kuzmic, Anal. Biochem. 286, 45-50 (2000). Las modificaciones del método de regresión no lineal se efectuaron con el fin de obtener una velocidad de reacción control común y una concentración de enzima efectiva para todas las relaciones de dosis-respuesta de una placa de ensayo dada. Dado que la concentración de sustrato se eligió en o debajo del valor de la K_m, los valores de las K_i aparentes obtenidos con este análisis se expresaron como K_i sin una corrección por el efecto del sustrato.

[1082] Los protocolos anteriores se usaron para determinar las constantes de IC_{50} y los valores K_i de varios de los compuestos de los Ejemplos 1-52 descriptos anteriormente. Los resultados se muestran en la

1033

Tabla 5. Todos los valores de la Tabla 5 están expresados como unidades nM.

Las mediciones K_i están entre paréntesis.

Tabla 5

Ej. #	Compuesto	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
55	Ejemplo 17		550		1.8	
56	Ejemplo 18	>10000	537	6000	1.8	>10000
57	Ejemplo 19	>10000	9000	5190	15	>10000
58	Ejemplo 20	>10000	1.8	498	1.8	>10000
59	Ejemplo 21	>10000	450	>10000	3.5	>10000
60	Ejemplo 22	>10000	1000	>10000	4.9	>10000
61	Ejemplo 25	>10000	247.2	8498	1.8	>10000
62	Ejemplo 26	>10000	52.0	4429	3.4	>10000
63	Ejemplo 27	>10000	83.9	9366	0.2	>10000
64	Ejemplo 28	>10000	76.4	3710	7.0	>10000
65	Ejemplo 30	>10000	22.6	809	1.3	>10000
66	Ejemplo 31	>10000 (>10000)	346.3 (412.93)	5651 (1596.8)	2.1 (1.503)	>10000 (>10000)
67	Ejemplo 32	>10000	217.7	4076	0.8	>10000
68	Ejemplo 33	>10000	16	7.9	1	4936
69	Ejemplo 34	429	36.6	>10000	3.0	>10000
70	Ejemplo 35	>10000	600	>10000	3	>10000
71	Ejemplo 36		95		2.4	
72	Ejemplo 37	8708	30.3	449	1.4	>10000
73	Ejemplo 38	>10000 (>10000)	157.5	1026.3 (369.98)	0.9 (6.55)	>10000 (4451.2)
74	Ejemplo 39	(>10000)	1299 (1640)	(2360)	0.9 (3.04)	(>10000)
75	Ejemplo 40	>10000 (>10000)	112.4 (215.98)	413 (585.44)	0.5 0.58)	>10000 (>10000)
76	Ejemplo 41	>10000 (>10000)	357.5 (414.99)	1597 (1485.7)	2.0 (1.056)	>10000 (>10000)
77	Ejemplo 42	>10000 (>10000)	100.3 (186.26)	382.5 (661.7)	0.3 (0.486)	>10000 (>10000)
78	Ejemplo 43	>10000	4.8	1.0	1.0	2084
79	Ejemplo 44	>10000	133.2	154.5	1.4	4976
80	Ejemplo 45	(>10000)	(224.78)	(499.18)	(0.62)	(>10000)
81	Ejemplo 46	>10000 (>10000)	320.9 (786.36)	1986 (417.51)	3.1 (2.29)	>10000 (>10000)
82	Ejemplo 47	(>10000)	18.2 (19.15) (46.49)	(118.75) (308.77)	0.2 (0.304) (0.423)	(3317.66) (5293)
83	Ejemplo 48	>10000 (>10000)	104.6 (227.54)	4450.3 (159.2)	0.2 (0.127)	>10000 (>10000)
84	Ejemplo 49	>10000 (>10000)	273.9 (439.76)	4056 (1947.90)	0.3 (0.439)	>10000 (>10000)
85	Ejemplo 50	(>10000)	(1127.89)	(304.41)	(0.60)	(>10000)
86	Ejemplo 51	>10000 (5160.20)	251.6 (93.68)	7983 (98.72)	0.2 (1.697)	>10000 (687.93)
87	Ejemplo 52	(>10000)	(542.89)	(617.14)	(0.81)	(>10000)

Ej. #	Compuesto	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
88	Ejemplo 53	>10000 (>10000)	383.5 (697)	75.5 (2900)	1.0 (0.662)	>10000 (>10000)
89	Ejemplo 54	(>10000)	35.5 (64.8)	(368)	10.5	(4120)

[1063] Ejemplo 90. Ensayo de angiogénesis in vivo

[1064] El estudio de angiogénesis depende de un modelo confiable y reproducible de estimulación e inhibición de una respuesta neovascular. El ensayo de microbolsillos de cornea provee dicho modelo de angiogénesis en la córnea de ratón. Véase, A Model of Angiogenesis in the Mouse Cornea; Kenyon, BM, et al., Investigative Oftalmology & Visual Science, Julio 1996, Vol. 37, Nº 8.

[1065] En este ensayo, se prepararon pellets Hidron™ de tamaño uniforme que contenían bFGF y sucralfato y luego se implantaron quirúrgicamente en el estroma de córneas de ratón, adyacentes al limbo temporal. Los pellets se formaron con una suspensión de 20 µl de salina estéril que contenía 10 µg de bFGF recombinante, 10 mg de sucralfato y 10 µl de Hidron™ 12% en etanol. La lechada se depositó después sobre una sección de malla de nylon estéril de 10 x 10 mm. Después de dejarla secar, se separaron las fibras de nylon de la malla para liberar los pellets.

[1066] El bolsillo en la córnea se realizó luego de anestesiar un ratón C57Bl/6 hembra de 7 semanas, por proptosis del ojo con un fórceps de joyería. Bajo microscopio de disección, se efectuó una queratotomía lineal central, intraestromática de aproximadamente 0,6 mm de longitud con una hoja quirúrgica Nº 15, en posición paralela a la inserción del músculo recto lateral. A continuación se disecó un microbolsillo lamelar hacia el limbo temporal usando un bisturí de cataratas modificado. El bolsillo se extendió hasta 1,0 mm del limbo temporal. Se colocó un solo pellet sobre la superficie de la córnea en la base del bolsillo usando para ello un fórceps de joyería. El pellet se empujó

1035

después hacia el extremo temporal del bolsillo. A continuación se aplicó un ungüento antibiótico al ojo.

[1067] Los ratones recibieron dosis diarias durante el transcurso de todo el ensayo. La dosificación de los animales se basó en la biodisponibilidad y la potencia general del compuesto. Un ejemplo de dosis era de 10 ó 50 mg/kg (mpk) bid, po. Se permitió que avanzara la neovascularización del estroma córneo bajo el efecto del compuesto de prueba durante 2 días. En ese momento se registró el grado de inhibición angiogénica por visualización del avance neovascular con un microscopio de difracción.

[1068] Los ratones se anestesiaron y nuevamente se efectuó una proptosis del ojo estudiado. Se midió la longitud máxima de los vasos de la neovascularización, que se extendían desde el plexo vascular del limbo hacia pellet. Además, se midió también la zona de neovascularización contigua circunferencial expresada como horas de reloj, donde 30 grados de arco representan la una del reloj. El área de angiogénesis se calculó de la siguiente manera.

i. área = $\frac{(0,4 \times \text{horas reloj} \times 3,14 \times \text{longitud del vaso (en mm)})}{2}$

[1069] Se deben utilizar cinco a seis ratones para cada compuesto en cada estudio. Los ratones estudiados se compararon después con ratones control y se registró la diferencia de área de neovascularización como un valor promediado. Cada grupo de ratones estudiado constituye un valor "n" de uno, de modo que "n" valores mayores que uno representan estudios múltiples cuyos resultados promediados se muestran en la tabla. El compuesto contemplado exhibe típicamente entre un 25 y 75 por ciento aproximadamente

1036

de inhibición, mientras que el vehículo control muestra cero por ciento de inhibición.

[1070] Ejemplo 91. Ensayos con el Factor de Necrosis Tumoral

[1071] Cultivo de células.

[1072] Las células utilizadas en el ensayo pertenecen a la línea monocítica humana U-937 (ATCC CRL-1593). Las células se cultivan en medio RPMI w/FCS 10% y suplemento PSG (R-10) y no se permite el sobrecrecimiento. El ensayo se lleva a cabo de la siguiente manera:

[1073] 1. Se cuentan y luego se cosechan células por centrifugación. Se vuelve a suspender el pellet en suplemento R-10 hasta una concentración de 1.540×10^6 células/ml.

[1074] 2. El compuesto de prueba, en 65 µl de R-10, se introduce en las cavidades apropiadas de una placa para cultivo tisular de fondo plano de 96 cavidades. La dilución inicial de una solución madre de DMSO (compuesto 100 mM) provee una solución 400 µM, a partir de la cual se elaboran cinco diluciones adicionales 3X. Cada dilución de 65 µl (por triplicado) permite obtener concentraciones finales de compuesto de 100 µM, 33,3 µM, 11,1 µM, 3,7 µM, 1,2 µM y 0,4 µM.

[1075] 3. Las células contadas, lavadas y resuspendidas (200.000 células/cavidad), en 130 µl se agregan a las cavidades.

[1076] 4. Se incuban durante 45 minutos a una hora a 37 °C en CO_2 5% en un contenedor saturado con agua.

[1077] 5. Se añade R-10 (65 µl) que contiene PMA 160 ng/ml (Sigma) a cada cavidad.

[1078] 6. El sistema de prueba es incubado a 37 °C en CO_2 5% durante toda la noche (18-20 horas) bajo un 100% de humedad.

1037

[1079] 7. Se retira cuidadosamente el sobrenadante, 150 µl, de cada cavidad para su uso en el ensayo ELISA.

[1080] 8. Para verificar la toxicidad, se toma una alícuota de 50 µl de la solución de trabajo que contiene 5 ml de R-10, 5 ml de solución MTS [CellTiter 96, Aqueous One Solution Cell Proliferation Assay (Solución acuosa única para ensayos de proliferación celular) N° Catálogo G358/0,1 (Promega Biotech)] y 250 µl de solución PMS y se agrega a cada cavidad que contiene el sobrenadante restante y las células y luego se incuban las células 37 °C en CO_2 5% hasta que se observa desarrollo de color. El sistema es excitado a 570 nm y leído a 630 nm.

[1081] Ensayo ELISA del Receptor TNF II

[1082] 1. Se plaquearon, a razón de 100 µl/cavidad, anticuerpos TNFrII anti-humanos de ratón 2 µg/ml (R&D Systems N° MAB226) en PBS 1 x (pH 7.1, Gibco) sobre una placa NUNC-Immuno Maxisorb. La placa se incubó a 4 °C durante toda la noche (18-20 hs aproximadamente).

[1083] 2. La placa se lavó con PBS-Tween (1 x PBS w/Tween 0,05%).

[1084] 3. Se agregaron 200 µl de BSA 5% en PBS y se bloqueó a 37 °C bajo atmósfera saturada con agua durante 2 horas.

[1085] 4. La placa se lavó con PBS-Tween.

[1086] 5. Se agregaron muestras y controles (100 µl de cada uno) a cada cavidad. Los estándares son 0, 50, 100, 200, 300 y 500 pg de TNFrII humano recombinante (R&D Systems N° 226-B2) en 100 µl de BSA 0,5% en PBS. El ensayo es lineal hasta 400-500 pg de estándar.

[1087] 6. Se incubó a 37 °C bajo atmósfera saturada durante 1,5 horas.

[1088] 7. La placa se lavó con PBS-Tween.

[1089] 8. Se agregaron 100 µl de anticuerpo policlonal TNFrII anti-

1038

humano de cabra (1,5 µg/ml, R&D Systems Nº AB226-PB en BSA 0,5% en PBS).

[1090] 9. Se incubó a 37 °C bajo atmósfera saturada durante 1 hora.

[1091] 10. La placa se lavó con PBS-Tween.

[1092] 11. Se agregaron 100 µl de IgG anticabra-peroxidasa (1:50.000 en BSA 0,5% en PBS, Sigma Nº A5420).

[1093] 12. Se incubó a 37 °C bajo atmósfera saturada durante 1 hora.

[1094] 13. La placa se lavó con PBS-Tween.

[1095] 14. Se añadieron 10 µl de revelador KPL TMB, se desarrolló a temperatura ambiente (habitualmente 10 minutos aproximadamente), luego se terminó con ácido fosfórico y se excitó a 450 nm con lectura a 570 nm.

[1096] Ensayo ELISA TNFα

[1097] Se recubrieron placas Immulon® 2, a razón de 0,1 ml/cavidad, con Genzyme mAb 1 µg/ml en buffer $NaHCO_3$ 0,1 M pH 8,0 durante toda la noche (18-20 horas aproximadamente) a 4 °C, envueltas firmemente en una envoltura Saran®.

[1098] Se retiró rápidamente la solución de recubrimiento y las placas se bloquearon con buffer de bloqueo 0,3 ml/cavidad durante toda la noche a 4 °C, envueltas en Saran®.

[1099] Las cavidades se lavaron exhaustivamente con buffer de lavado 4X y se retiró por completo todo el buffer de lavado. Se agregaron todas las muestras o el estándar rhTNFα a razón de 0,1 ml/cavidad. Las muestras se diluyeron, si era necesario, en un diluyente apropiado (por ejemplo, medio de cultivo tisular). Los estándares se diluyeron con el mismo diluyente. Los estándares y las muestras se elaboraron por triplicado.

[1100] Se incubaron a 37 °C durante 1 hora en un contenedor con

1039

humedad.

[1101] Las placas se lavaron como antes. Se agregó una dilución 1:200 de anti-hTNFα de conejo Genzyme a razón de 0,1 ml/cavidad.

[1102] Se repitió la incubación.

[1103] Se repitió el lavado. Se agregaron 0,1 ml/cavidad de (H+L) IgG anti-conejo de cabra Jackson-peroxidasa 1 µg/ml.

[1104] Se incubó a 37 °C durante 30 minutos.

[1105] Se repitió el lavado. Se añadió solución de peróxido ABTS a razón de 0,1 ml/cavidad.

[1106] Se incubó a temperatura ambiente durante 5-20 minutos.

[1107] La DO se leyó a 405 nm.

[1108] 12. Los reactivos son:

Anticuerpos monoclonales TNF anti-humano de ratón Genzyme (Nº Catálogo 80-3399-01)

Anticuerpos policlonales TNF anti-humano de conejo Genzyme (Nº Catálogo IP-300)

TNF humano recombinante Genzyme (Nº Catálogo TNF-H).

(H+L) IgG anti-conejo de cabra conjugado con peróxido Jackson Immunoresearch (Nº Catálogo 111-035-144).

Solución ABTS peróxido Kirkegaard/Perry (Nº Catálogo 50-66-01).

Placas para microtitulación de 96 cavidades Immulon 2.

La solución de bloqueo es gelatina 1 mg/ml en PBS con timerasol 1X.

El buffer de lavado es 0,5 ml de Tween 20 en 1 litro de PBS.

[1109] **Ejemplo 92. Análisis de inhibición por agrecanasa in vitro**

[1110] Los ensayos para medir la potencia (IC_{50}) de un compuesto con respecto a la inhibición de agrecanasa son conocidos en el arte.

1040

[1111] Uno de dichos ensayos se describe, por ejemplo, en la publicación de la Solicitud de Patente Europea Nº EP 1 081 137 A1. En este ensayo, se aislaron condrocitos primarios porcinos del cartílago articular por digestión secuencial con tripsina y colagenaza, seguido de digestión con colagenasa durante la noche y se plaquearon a razón de $2x10^5$ células por cavidad en placas de 48 cavidades con azufre 5 µCi/ml ^{35}S (1000 Ci/mmol) en placas recubiertas con colágeno de tipo 1. Se dejó que las células incorporaran la marca en su matriz de proteoglicanos (aproximadamente 1 semana) a 37 °C bajo atmósfera de CO_2 5%. La noche antes de comenzar el ensayo, las monocapas de condrocitos se lavaron 2 veces con DMEM/PSF 1%/G y luego se incubaron durante toda la noche en DMEM/FBS 1% recién preparado. La mañana siguiente los condrocitos se lavaron una vez con DMEM/PSF 1%/G. El lavado final se dejó sobre las placas en incubadora mientras se elaboraban las diluciones. Los medios y las diluciones se elaboraron como se describe en la siguiente Tabla 6:

Tabla 6

Medio control	DMEM solamente
Medio IL-1	DMEM + IL-1 (5ng/ml)
Diluciones de fármaco	Llevar las soluciones madre de los compuestos a 10 mM en DMSO. Obtener una solución madre 100 µM de cada compuesto en DMEM en placas de 96 cavidades. Congelar durante la noche. Al día siguiente, obtener diluciones seriadas en DMEM con IL-1 de 5 µM, 500 nM y 50 nM. Aspirar los lavados finales de las cavidades y agregar 50 µM de compuesto de las diluciones anteriores hasta 450 µl de medio IL-1 en las cavidades correspondientes de las placas de 48 cavidades.

1041

	Las concentraciones finales de compuesto son de 500 nM, 50 nM y 5 nM. Obtener todas las muestras por triplicado con control e IL-1 solo, en cada placa.

Las placas se marcaron y solamente se usaron las 24 cavidades interiores de cada placa. En una de las placas, varias columnas fueron asignadas a IL-1 (sin fármaco) y control (sin IL-1, sin fármaco). Se efectúa un recuento periódico de estas columnas control con el fin de monitorear la liberación de 35S-proteoglicano. Se agregan los medios de control e IL-1 a las cavidades (450 µl) seguido de los compuestos (50 µl) para así iniciar el ensayo. Las placas se incubaron a 37 °C bajo atmósfera de CO_2 5%. El ensayo se terminó (entre 9 y 12 horas aproximadamente) con un 40-50% de liberación (cuando el valor de CPM del medio IL-1 representa 4-5 veces el medio control), evaluado por conteo de centelleo líquido (LSC) de las muestras de medio. Se retiró el medio de todas las cavidades y se colocó en tubos de centelleo. Se agregó el compuesto de centelleo y luego se obtienen los recuentos radioactivos (LSC). Con el fin de solubilizar las capas de células, se agregaron 500 µl de buffer de digestión de papaína (Tris 0,2 M, pH 7,0, DTT 5 mM y papaína 1 mg/ml) a cada cavidad. Las placas con la solución de digestión se incubaron a 60 °C durante la noche. Al día siguiente se retiró la capa de células de las placas y se colocaron en tubos de centelleo. A continuación se agregó el líquido de centelleo y se efectuó el recuento de las muestras (LSC). Se determinó el porcentaje de cuentas liberadas del total de cuentas presentes en cada cavidad. Se efectuaron los promedios de los triplicados, restándole el valor basal control de cada cavidad. El porcentaje de inhibición de compuesto se basa en las muestras IL-1 como 0% de inhibición (100% de cuentas totales).

[1112] Otro ensayo para medir la inhibición de agrecanasa se describe en la publicación de Patente Internacional WIPO Nº WO 00/59874. En dicho

1042

ensayo se describe el uso de agrecanasa activa acumulada en el medio de cartílago bovino estimulado (BNC) o fuentes de cartílago relacionadas y monómeros de agrecano de cartílago purificado o de un fragmento de los mismos como sustrato. La agrecanasa es generada por estimulación de cortes de cartílago con interleuquina-1 (IL-1), factor de necrosis tumoral alfa (TNF-α) u otros estímulos. Para acumular agrecanasa BNC en el medio de cultivo, primero se elimina el agrecano endógeno del cartílago por estimulación con IL-β recombinante humana 500 ng/ml durante 6 días, con cambios de medio cada 2 días. Luego se estimula el cartílago durante otros 8 días sin cambiar el medio con el fin de permitir la acumulación de agrecanasa activa soluble en el medio de cultivo. Con el fin de disminuir la cantidad de metaloproteinasas de matriz liberadas hacia el medio durante la acumulación de agrecanasa, se incluyeron agentes inhibidores de la biosíntesis de las MMP-1, -2, -3 y -9 durante el período de estimulación. Este medio acondicionado con BNC que presenta actividad agrecanasa se usó después como fuente de agrecanasa en el ensayo. La actividad enzimática de la agrecanasa se detectó por monitoreo de la producción de fragmentos de agrecano producidos exclusivamente por clivaje del enlace Glu373-Ala374 de la proteína agrecano mediante análisis Western usando el anticuerpo monoclonal, BC-3 (Hughes, et al., Biochem J, 306:799-804 (1995)). Este anticuerpo reconoce los fragmentos de agrecano con extremo N-terminal, 374ARGSVIL, generados luego del clivaje con agrecanasa. El anticuerpo BC-3 solamente reconoce este neoepítope cuando se encuentra en el extremo N-terminal y no cuando está presente en el interior de los fragmentos de agrecano o de la proteína agrecano. Solamente se detectan los productos producidos después de clivaje por la agrecanasa. Los estudios cinéticos llevados a cabo usando este ensayo permite obtener una

1043

Km de 1,5 +/- 0,35 µM para la agrecanasa. Para evaluar la inhibición de agrecanasa, los compuestos se prepararon como soluciones madre 10 mM en DMSO, agua u otros solventes y se diluyeron hasta las concentraciones apropiadas en agua. A continuación se agregaron los fármacos (50 µl) al medio que contenía 50 µl de agrecanasa y 50 µl de sustrato agrecano 2 mg/ml y se llevó todo a un volumen final de 200 µl en Tris 0,2 M, pH 7,6, que contenía NaCl 0,4 M y $CaCl_2$ 40 mM. El ensayo se corrió durante 4 hs a 37 °C, se detuvo con EDTA 20 mM y se analizaron los productos generados por la agrecanasa. Se incluyó una muestra que contenía enzima y sustrato sin fármaco como control positivo y la enzima incubada en ausencia de sustrato sirvió como una medida del nivel basal. Es necesario eliminar las cadenas laterales de glicosaminglicano del agrecano para que el anticuerpo BC-3 reconozca el epitope ARGSVIL de la proteína principal. Por lo tanto, para analizar los fragmentos de agrecano generados por clivaje en el sitio Glu373-Ala374, de deglicosilaron enzimáticamente los fragmentos de proteoglicanos y los proteoglicanos con condroitinasa ABC (0,1 unidades/10 µg de GAG) durante 2 hs a 37 °C y luego con queratanasa (0,1 unidades/10 µg de GAG) y queratanasa II (0,002 unidades/10 µg de GAG) durante 2 hs a 37 °C en buffer que contenía acetato de sodio 50 mM, Tris/HCl 0,1 M, pH 6,5. Después de la digestión, se hizo precipitar el agrecano contenido en las muestras con 5 volúmenes de acetona y se luego se resuspendió en 30 µl de buffer para muestras de Tris glicina SDS (Novex) que contenía beta-mercaptoetanol 2,5%. Las muestras se cargaron y luego se separaron por SDS-PAGE bajo condiciones reductoras con gradientes de 4-12%, se transfirieron a nitrocelulosa y se inmunolocalizaron con una dilución 1:500 de anticuerpo BC3. A continuación, se incubaron las membranas con una dilución 1:5000 de

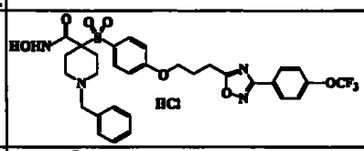
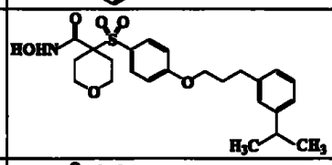
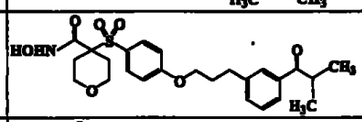
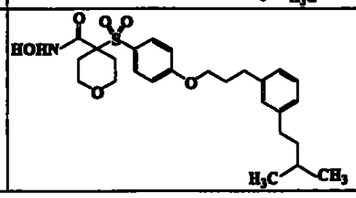
1044

segundo anticuerpo IgG antirratón de cabra-fosfatasa alcalina y los catabolitos de agrecano se visualizaron por incubación con el sustrato apropiado durante 10-30 minutos para lograr el revelado óptimo del color. Los transferidos fueron cuantificados por densitometría de barrido y la inhibición de agrecanasa se determinó comparando la cantidad de producto producido en presencia versus ausencia de compuesto.

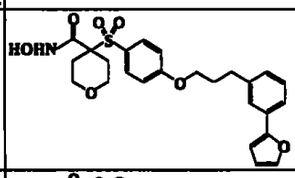
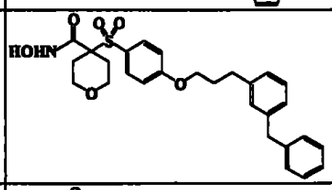
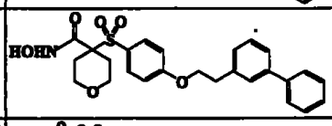
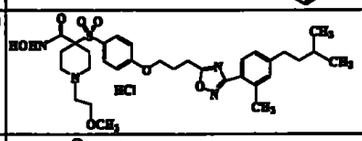
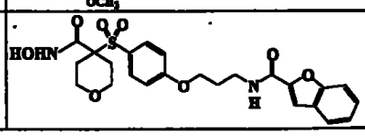
[1113] **Ejemplos 93-645.**

[1114] El especialista en el arte podrá preparar otros compuestos de hidroxamatos (y las sales de los mismos) utilizando solamente los métodos similares a los que se describieron en los **Ejemplos 1-54** solamente o en combinación con técnicas bien conocidas en el arte. Dichos compuestos incluyen, por ejemplo, los compuestos que se resumen en la siguiente **Tabla 7**. En la **Tabla 7** también se resumen los resultados de la inhibición de MMP in vitro que obtuvieron los solicitantes con los hidroxamatos enumerados. Al igual que en la **Tabla 5**, todos los resultados K_i e IC_{50} obtenidos in vitro que se muestran en la **Tabla 7** están expresados en unidades nM. Las mediciones Ki están entre paréntesis.

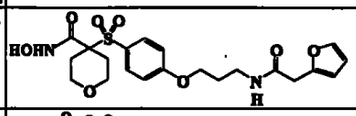
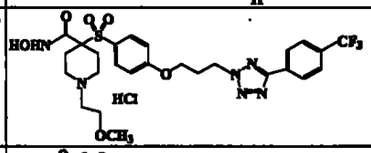
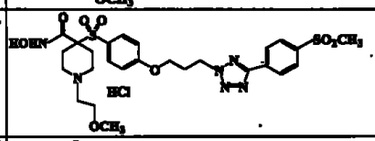
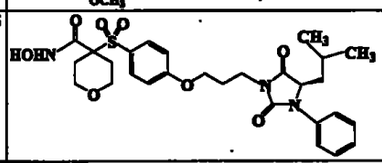
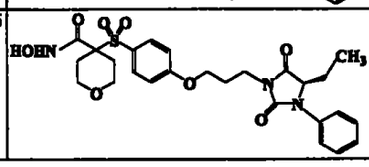
Tabla 7

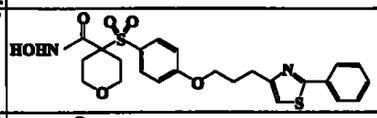
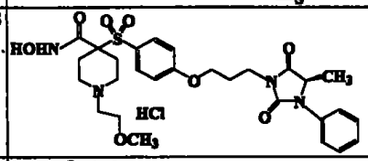
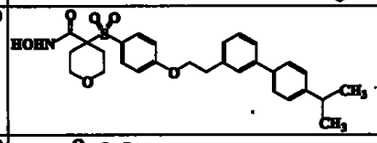
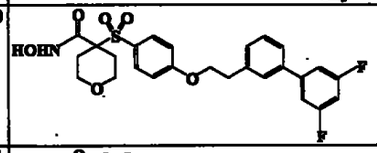
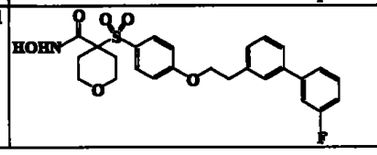
Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
93				(>10000)	746,6 (676)	(1120)	15,5 (9,29)	(>10000)
94					17,8		3,7	
95				>10000 (>10000)	81,4 (149)	1204,6 (788)	2,7	>10000 (5410)
96					39,1		15,3	

1090

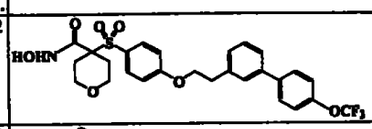
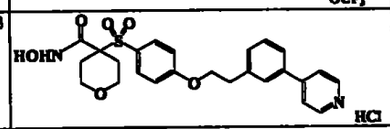
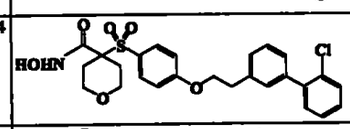
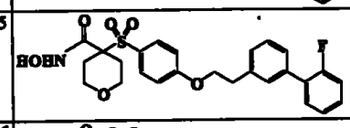
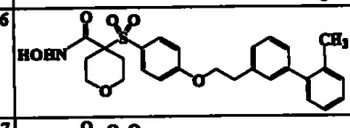
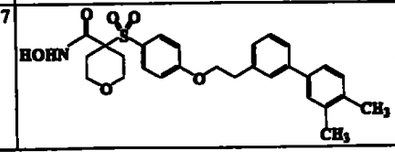
Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
97		486,1586	486,1602	(7360)	185,0 (295)	(473)	3,3 (5,57)	(>10000)
98		510,1950	510,1947	>10000 (>10000)	316,2 (625)	2418 (1450)	1,8 (9,15)	>10000 (>10000)
99		482,1637	482,1661	>10000	245,8	3435	0,4	>10000
100					1691,4		152,6	
101		503,1480	503,1485		18,2		0,2	

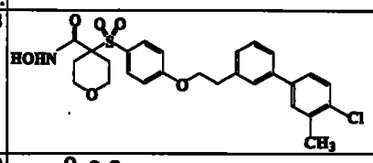
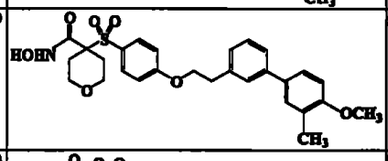
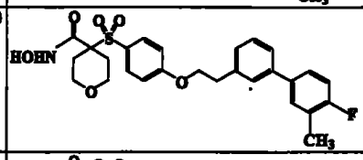
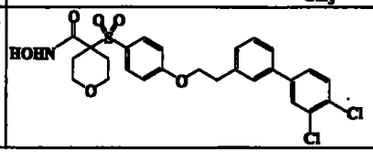
1091

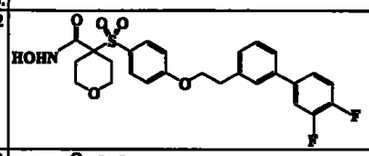
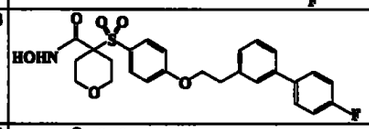
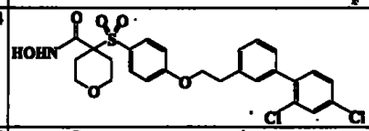
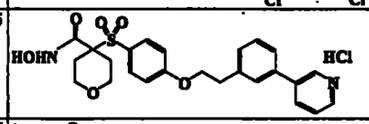
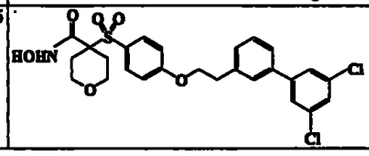
Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
102		483,1260	483,1264		12,4		1,2	
103		813	813	>10000	85,8	1134	0,4	>10000
104					44,2		0,8	
105				>10000	1368,6	7694	9,7	>10000
106				>10000	1048,6	>10000	3,5	>10000

Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
107					34,0		5,5	
108					433,7		20,0	
109		524,2107	524,2136	(>10000)	5410,3 (8100)	(>10000)	152,1 (93,1)	(>10000)
110		518,1449	518,1505	(>10000)	1198,5 (1120)	(4340)	7,6 (11,4)	(>10000)
111		500,1543	500,1561	(>10000)	559,4 (769)	(2680)	2,0 (6,39)	(>10000)

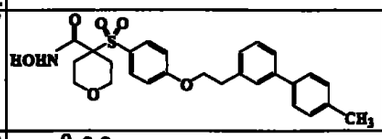
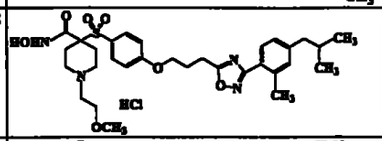
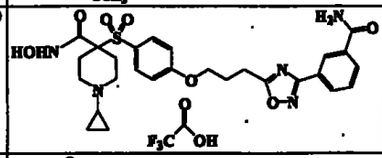
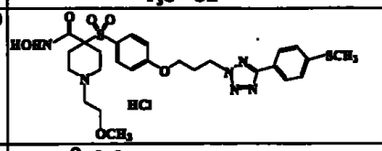
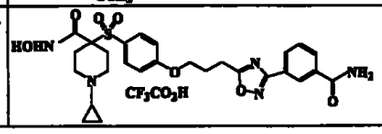
1053

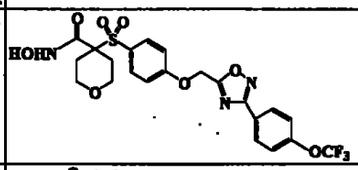
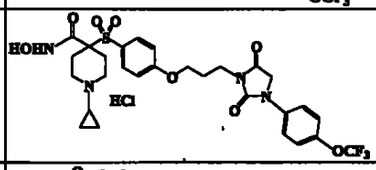
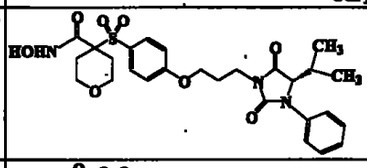
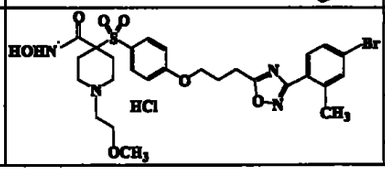
Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
112		566,1480	566,1500	(>10000)	66,4 (3970)	(8850)	37,9 (51,2)	(>10000)
113		483,1590	483,1597	>10000 (>10000)	20,3 (42,30)	1980,5 (161,22)	0,2 (0,312)	7725 (3481,8)
114		516,1248	516,1259	(>10000)	1010,6 (1500)	(4870)	5,2 (4,2)	(>10000)
115		500,1543	500,1550	>10000 (>10000)	311,9 (807)	>10000 (1980)	0,9 (2,24)	>10000 (>10000)
116		496,1794	496,1811	(>10000)	1053,2 (1250)	(5550)	11,2 (5,1)	(>10000)
117		510,1950	510,1985	(>10000)	1744,7 (3640)	(9910)	16,0 (21)	(>10000)

Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
118		530,1404	530,1418	(>10000)	1862,0 (2650)	(>10000)	29,8 (16,8)	(>10000)
119		526,1899	526,1920	(>10000)	1187,6 (1680)	(3950)	18,3 (31,4)	(>10000)
120		514,1700	514,1724	>10000	1171,6	>10000	5,6	>10000
121		550,0858	550,0848	(>10000)	2469,3 (4620)	(>10000)	21,6 (26,9)	(>10000)

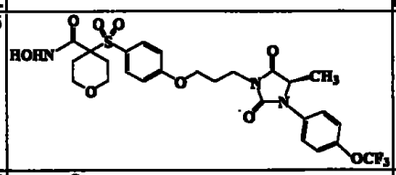
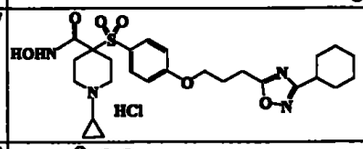
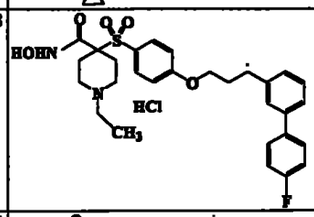
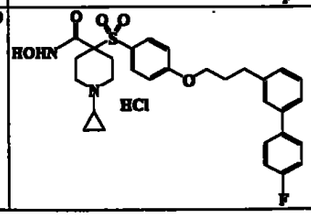
Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
122		518,1449	518,1470	>10000	759,7	7668	1,9	>10000
123		500,1543	500,1545	>10000 (>10000)	383,0 (793)	>10000 (2130)	1,4 (7,35)	>10000 (>10000)
124		550,0858	550,0898	(>10000)	2151,5 (5730)	(>10000)	21,9 (20,1)	(>10000)
125				2937 (3584,24)	27,3 (51,34)	962,9 (146,43)	0,2 (0,17)	5825 (1666,65)
126		550,0858	550,0881	(>10000)	3280,4 (6360)	(>10000)	349,0 (81,3)	(>10000)

1025

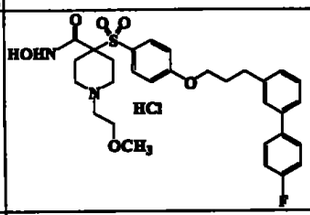
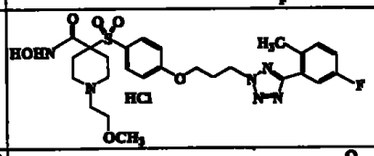
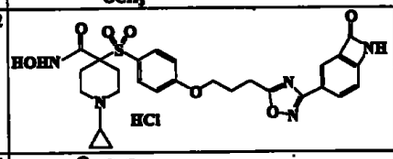
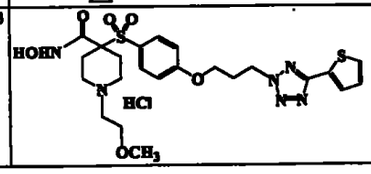
Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
127		496,1794	496,1800	>10000 (>10000)	1380,0 (2180)	>10000 (4230)	5,5 (16,2)	>10000 (>10000)
128		815,2802	815,2852	(>10000)	858,7 (1130)	(3550)	23,7 (13,8)	(>10000)
129				(>10000)	41,4 (50)	(110)	1,9 (0,27)	(>10000)
130				4811	4,7	50,2	0,3	499,8
131					107,9		4,5	

Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
132					81,7		3,7	
133					84,4		4,3	
134				>10000	2382	>10000	7,7	>10000
135		637,1332	637,1315	(>10000)	24,3 (58,5)	(457)	2,9 (0,761)	(9510)

1027

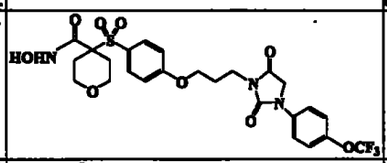
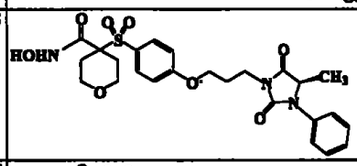
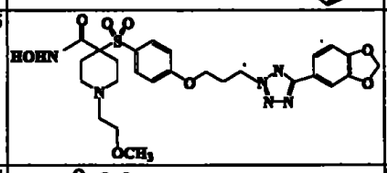
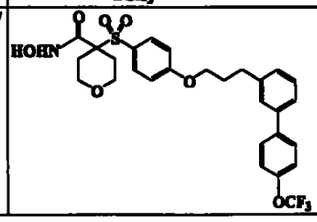
Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
136					229,4		4,4	
137				(>10000)	20,4 (36,6)	(804)	7,0 (0,976)	(>10000)
138				>10000	247,3	1896	2,1	>10000
139		553,2172	553,2176	>10000 (>10000)	207,7 (1410)	4514 (1390)	0,4 (2,89)	>10000 (>10000)

1027

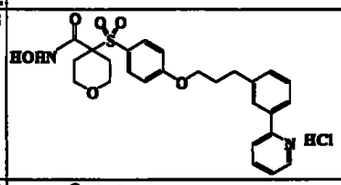
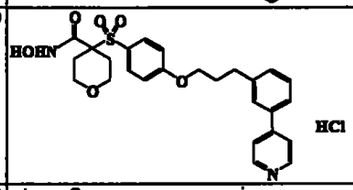
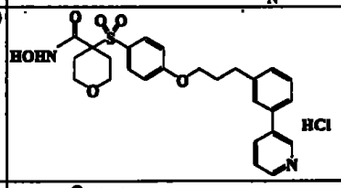
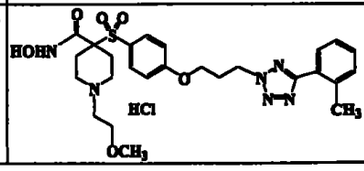
Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
140				>10000 (>10000)	48,0 (708)	1692 (754)	0,5 (0,895)	>10000 (>10000)
141		577	577		32,5		3,8	
142				(>10000)	58,6 (86,4)	(310)	7,5 (1,34)	(>10000)
143					4,9		1,4	

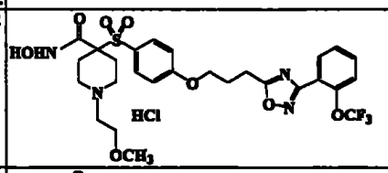
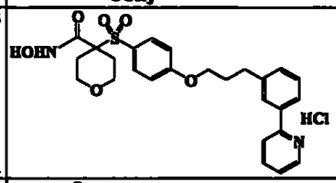
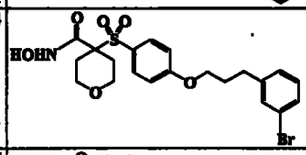
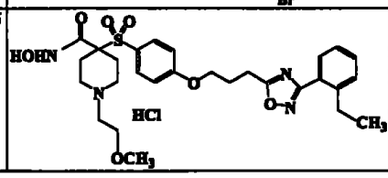
1055

1029

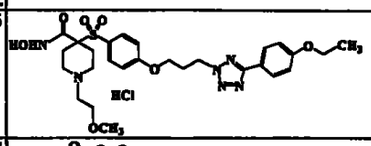
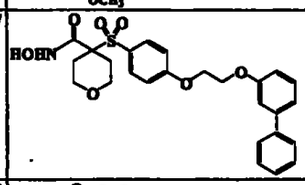
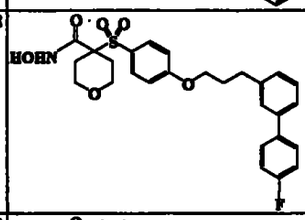
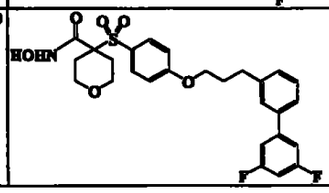
Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
144				>10000	238,6	5989	2,5	>10000
145				>10000	816,9	9438	2,0	>10000
146					11,1		0,4	
147		580,1617	580,1620	(>10000)	4746,8 (>10000)	(7970)	26,3 (23,9)	(>10000)

1030

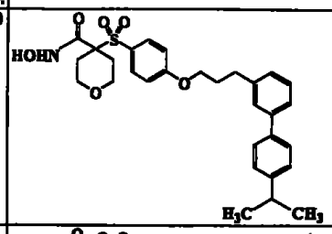
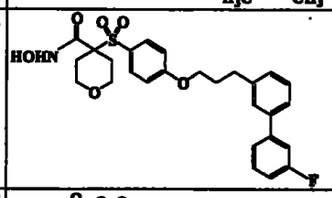
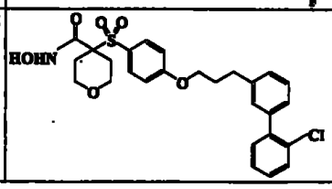
Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
148				(8790)	272,0 (213)	(427)	3,1 (1,72)	(5150)
149				(>10000)	77,1 (84,1)	(94,5)	1,3 (1,18)	(2530)
150				>10000 (>10000)	135,5 (159)	529,9 (125)	0,6 (0,587)	8630 (5510)
151		559	559		38,4		2,6	

Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
152		629,1893	629,1885	>10000 (>10000)	58,6 (149)	72,3 (44,5)	11,8 (2,66)	>10000 (>10000)
153					192,5		7,6	
154		498,0586	498,0591	>10000 (>10000)	10,9 (33,9)	111 (151)	0,8 (0,95)	9123 (3910)
155		573,2383	573,2413	>10000 (>10000)	13,8 (37,9)	1173,7 (172)	9,7 (1,58)	>10000 (9370)

1032

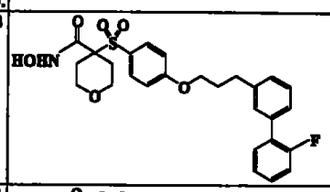
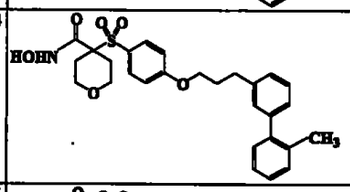
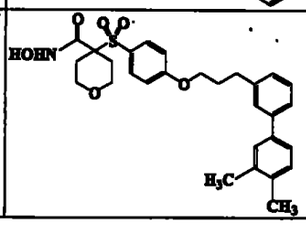
Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
156					32,1		1,0	
157				>10000 (>10000)	182,1 (419)	2473 (1390)	3,5 (4,01)	>10000 (>10000)
158		530,1404	530,1446	>10000 (>10000)	2184 (2730)	5830 (3950)	3,6 (5,1)	>10000 (>10000)
159		532,1605	532,1632		1368,6		24,4	

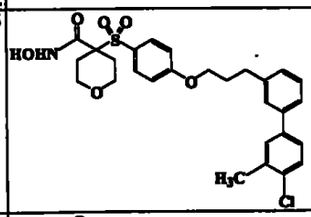
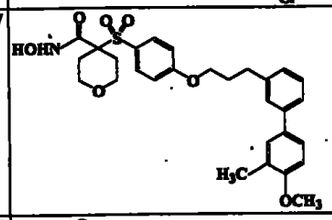
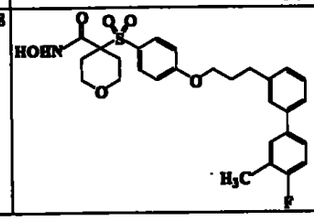
~~7033~~

Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
160		538,2263	538,2275	>10000 (>10000)	>10000 (>10000)	(>10000)	505,1	(>10000)
161		514,1700	514,1708	>10000 (>10000)	1001,1 (1760)	2625 (1730)	2,6 (20,3)	>10000
162		530,1404	530,1428	(>10000)	1586,6 (2370)	(3150)	15,6 (12)	(>10000)

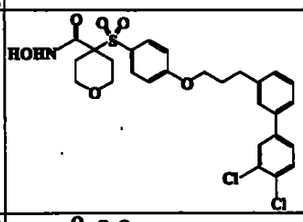
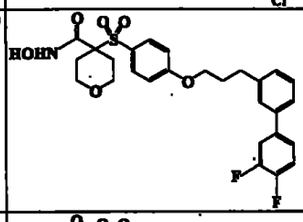
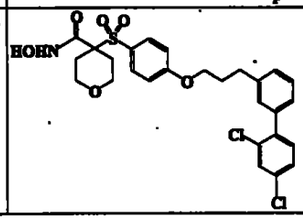
1060

~~1034~~

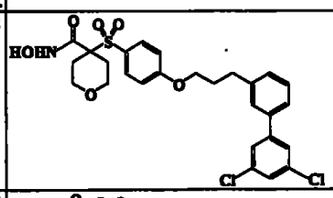
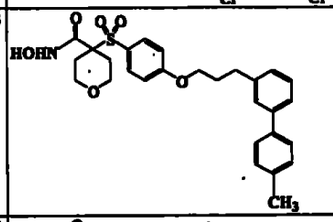
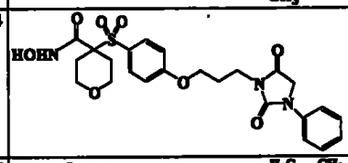
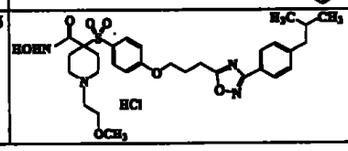
Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
163		514,1700	514,1680	>10000 (>10000)	1370,7 (1010)	2880 (2500)	2,5 (11,6)	>10000 (>10000)
164		510,1950	510,1940	(>10000)	1073,2 (978)	(2720)	20,0 (6,85)	(>10000)
165		524,2107	524,2112	(>10000)	3396,2 (>10000)	(9750)	146,9 (144)	(>10000)

Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
166		544,1581	844,1606	(>10000)	3081,7 (8090)	(8690)	135,9 (63,4)	(>10000)
167		540,2056	540,2029	(>10000)	3739,4 (128)	(68,1)	147,0 (78,9)	(>10000)
168		528,1856	528,1863	(>10000)	3428,2 (5500)	(6500)	34,3 (27,3)	(>10000)

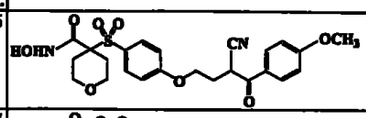
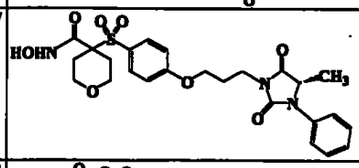
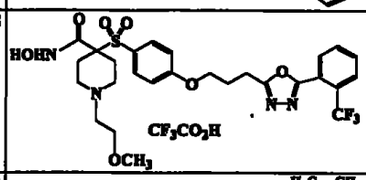
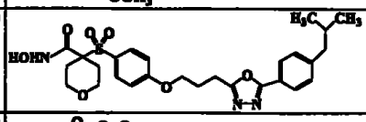
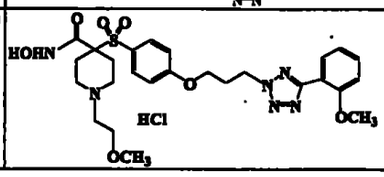
~~1036~~

Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
169		564,1014	564,1028	(>10000)	4383,5 (5360)	(6600)	70,7 (20,4)	(>10000)
170		532,1605	532,1618	(>10000)	1608,7 (1410)	(1500)	3,3 (6,79)	(>10000)
171		564,1014	564,1028	(>10000)	2288,8 (3190)	(6600)	82,8 (12,5)	(>10000)

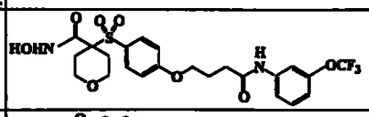
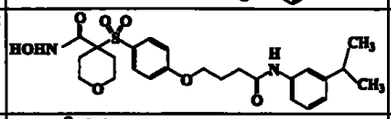
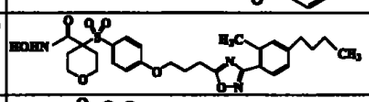
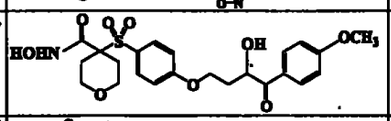
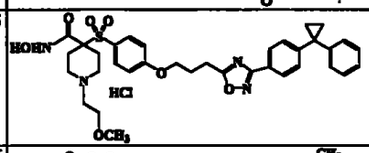
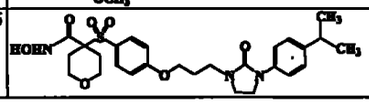
1074

Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
172		564,1014	564,1032	(>10000)	5163,1 (>10000)	(9440)	377,0 (71,1)	(>10000)
173		509,1950	509,1954	(>10000)	2120,4 (4090)	(3480)	12,2 (11,5)	(>10000)
174				>10000	708,6	4017	5,2	>10000
175		801,2696	801,2657	>10000 (>10000)	438,0 (872)	7296,6 (1390)	1,4 (2,01)	>10000 (>10000)

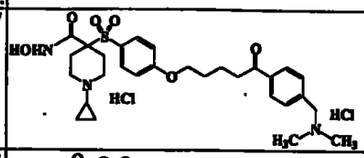
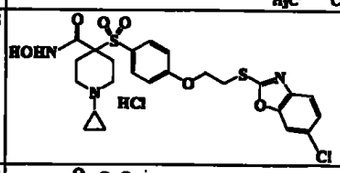
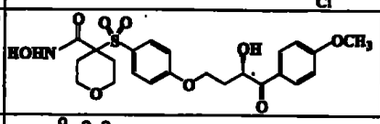
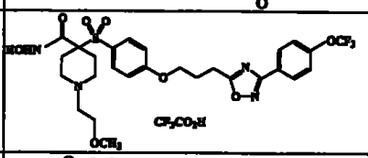
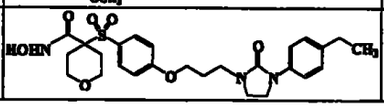
1038

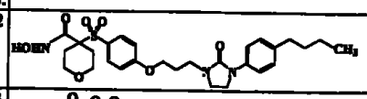
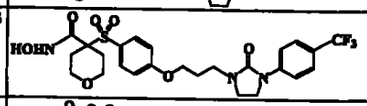
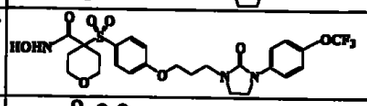
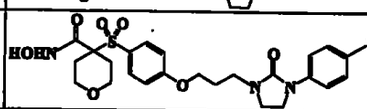
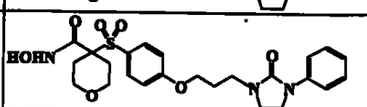
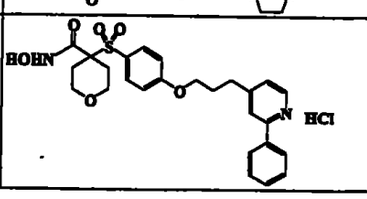
Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
176					108,9		7,8	
177					333,2		17,0	
178				>10000 (>10000)	28,4 (39,3)	1166,4 (306)	7,8 (1,71)	>10000 (>10000)
179					246,9		1,1	
180					443,0		17,0	

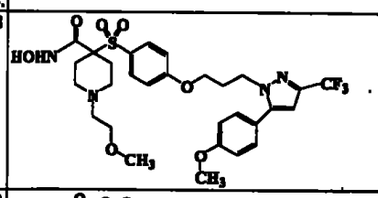
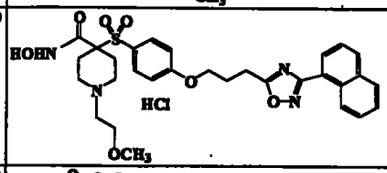
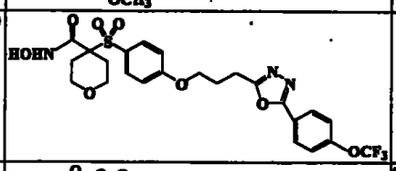
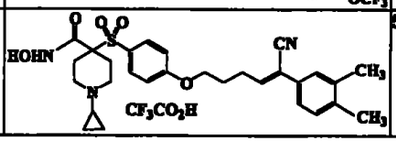
~~1039~~

Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
181				>10000 (1850)	13,9 (15,8)	26,4 (40,5)	0,3 (0,27)	8059 (4830)
182				>10000 (8540)	33,1 (34,3)	82,1 (85,4)	0,5 (0,212)	>10000 (5850)
183				(>10000)	708,0 (843)	(2510)	21,0 (15,1)	(>10000)
184				1528,7	30,4	103,6	3,9	2715,4
185				(>10000)	84,7 (116)	(220)	12,4 (3,73)	(>10000)
186					809,9		13,5	

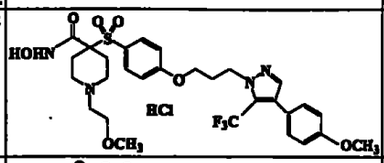
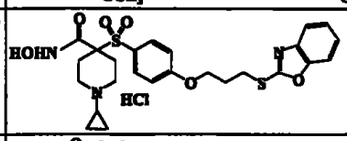
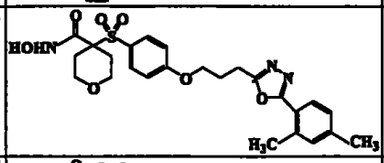
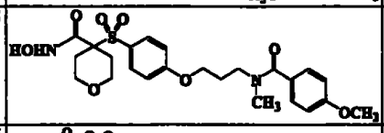
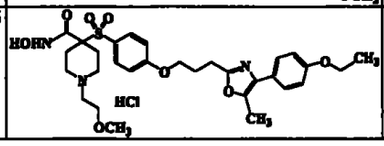
1040

Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
187				3868	3,6	11,2	1,8	1425
188				>10000	4,7	48,2	0,3	3537,7
189				1070	19,3	24,1	1,9	4316
190				>10000 (>10000)	165,9 (283)	1742,6 (669)	0,5 (0,6)	>10000 (>10000)
191				9956	341,2	383,4	9,5	>10000

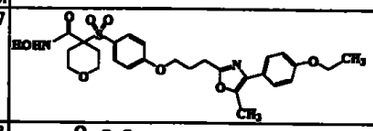
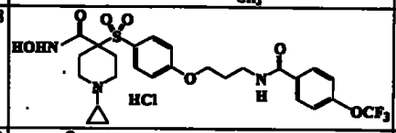
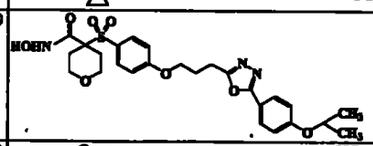
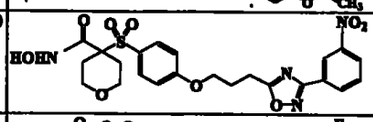
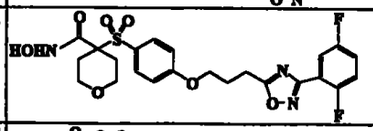
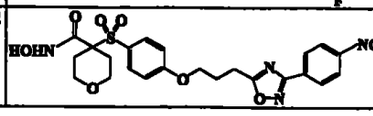
Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
192					1258,4		15,4	
193				5931,6	312,3	272,5	8,8	>10000
194				>10000	221,6	515,7	8,2	>10000
195				4381,7	20,8	45,8	7,5	2741,5
196					32,2		11,4	
197				>10000 (>10000)	13,2 (30,7)	432,2 (334)	0,5 (0,37)	>10000 (>10000)

Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
198					4527,4		834,9	
199				(>10000)	133,2 (228)	(59,5)	7,4 (3,09)	(>10000)
200				7498	84,0	1207,2	0,8	>10000
201		538,2376	538,2362	>10000	127,7	4509,5	0,7	>10000

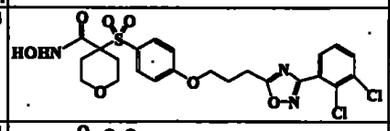
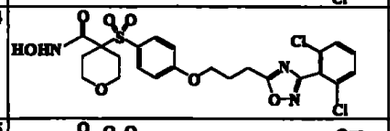
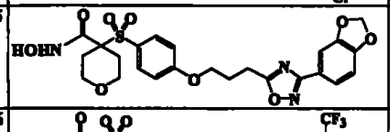
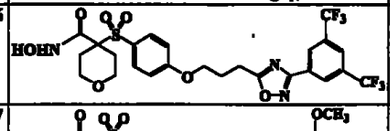
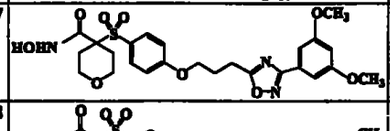
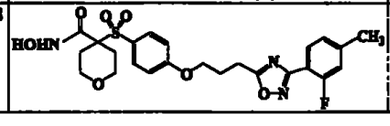
~~1073~~

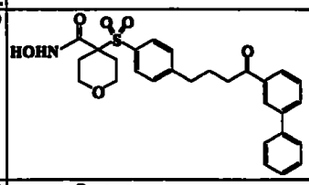
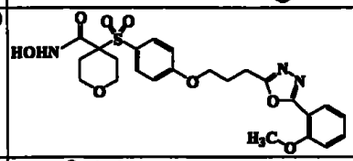
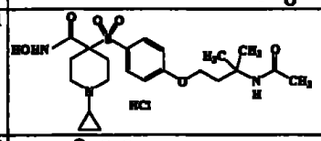
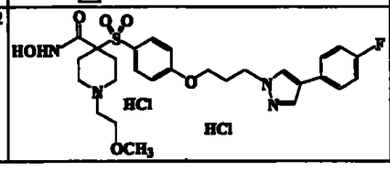
Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
202					1604,4		41,9	
203				>10000	4,2	8,0	1,0	>10000
204				>10000	145,7	1824,8	0,8	>10000
205					4780,2		17,6	
206				>10000	82,6	59,4	15,8	3112

1044

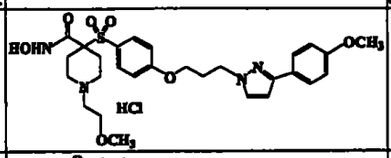
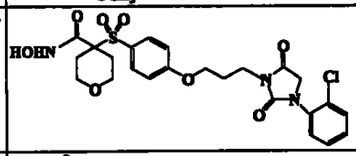
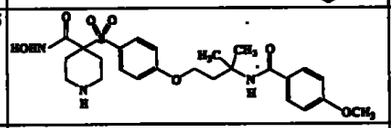
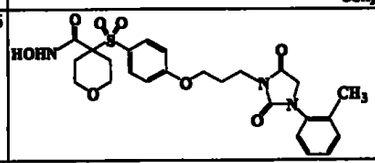
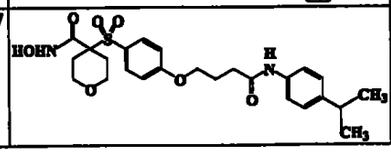
Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
207				>10000	114,3	126,7	3,7	>10000
208				>10000	230,2	8587,6	0,6	>10000
209				>10000	172,5	905,6	1,4	>10000
210				>10000	8,9	284,6	1,3	>10000
211				9853	26,2	863,5	0,4	>10000
212				1408	4,1	212,2	0,3	>10000

1045

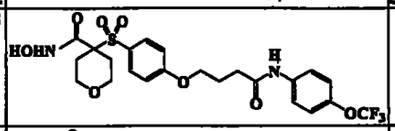
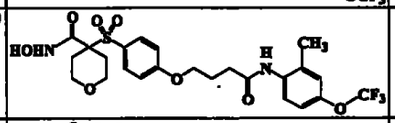
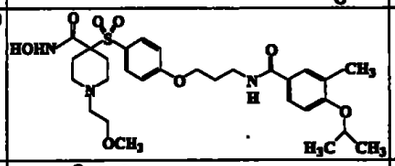
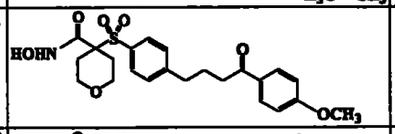
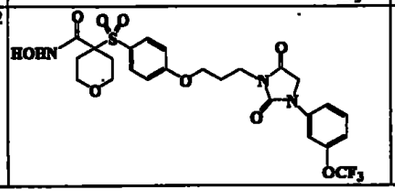
Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
213				>10000	54,8	2204	2,2	>10000
214				>10000	15,8	4239	3,3	>10000
215				>10000	20,3	767,9	0,3	>10000
216					1952,2		51,2	
217				>10000	48,9	5179	4,6	>10000
218				>10000	40,4	2973	1,4	>10000

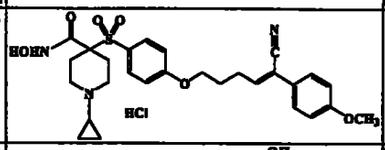
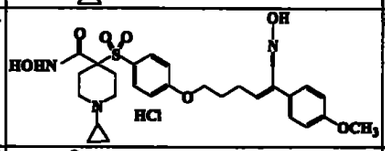
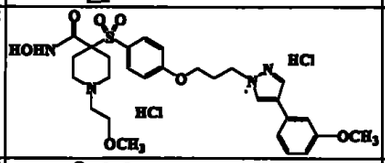
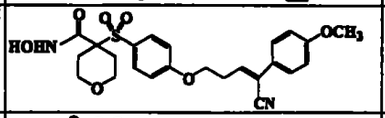
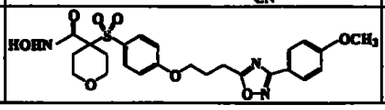
Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
219				>10000 (5800)	50,8 (105)	77,7 (59,5)	0,4 (0,355)	>10000 (7840)
220				>10000	409,7	1466,8	5,7	>10000
221					8796,4		243,8	
222					138,1		13,3	

1073

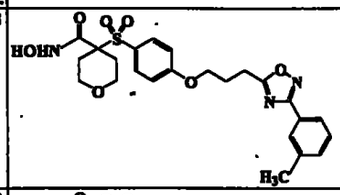
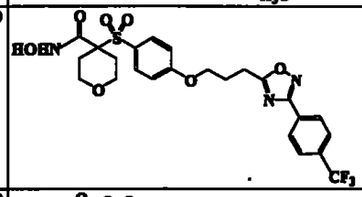
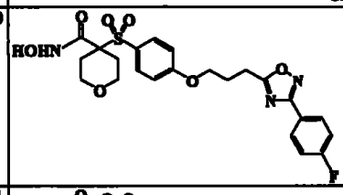
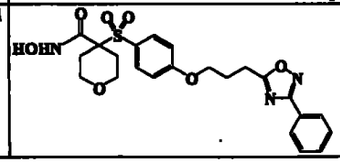
Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
223					89,7		11,9	
224				>10000	193,5	1466,8	4,7	>10000
225					2332,3		17,8	
226				>10000	222,0	2144,0	4,3	>10000
227					2,7		0,2	

1098

Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
228				6871 (3940)	11,4 (22,4)	180,4 (247)	0,2 (0,324)	>10000 (6290)
229				5033 (955)	12,2 (10,4)	293,7 (281)	1,7 (0,27)	>10000 (7870)
230				>10000	555,2	1017,7	1,1	>10000
231				>10000	1,6	10,2	0,2	841,7
232				>10000	74,2	877,7	5,6	>10000

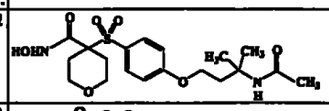
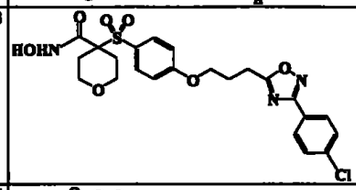
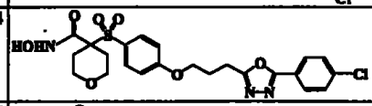
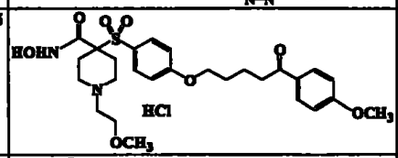
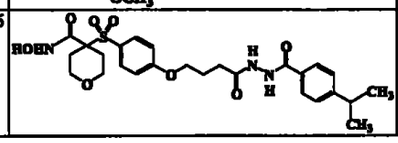
Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
233				>10000 (>10000)	25,5 (80,18)	831,8 (509,42)	0,1 (0,137)	>10000 (>10000)
234		598,2430	598,2441		213,4		10,3	
235					421,7		26,0	
236					7,6		3,4	
237				>10000	42,5	1111	0,7	>10000

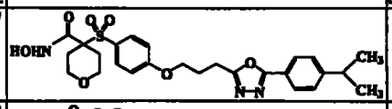
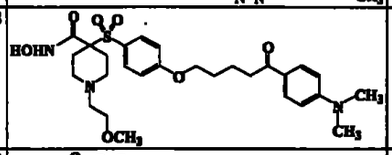
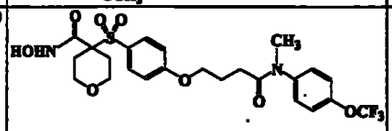
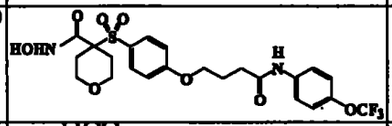
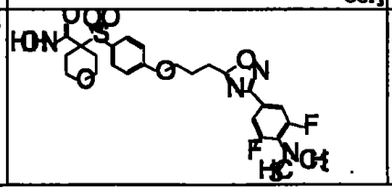
1050

Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
238				>10000	78,7	1188,1	1,2	>10000
239					236,9		2,5	
240				>10000	84,0	1428,4	0,7	>10000
241				>10000	80,2	944,2	1,3	>10000

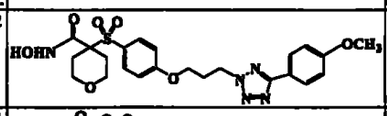
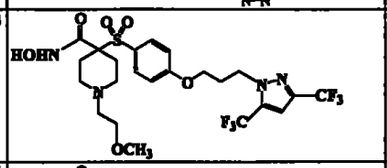
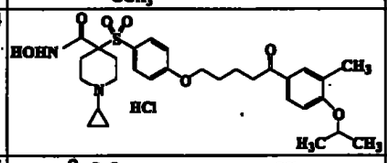
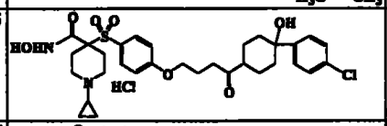
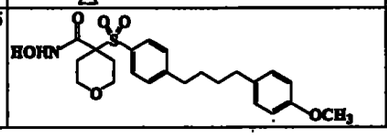
1077

1057

Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
242					2720,2		203,0	
243				9313,6	49,4	2101,9	0,5	>10000
244				3250,6	18,8	108,2	0,7	>10000
245				>10000	8,6	81,1	0,2	>10000
246				1166,7	7,5	104,7	3,0	>10000

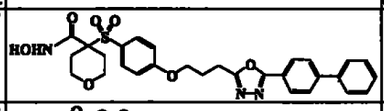
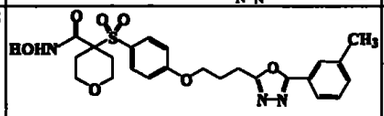
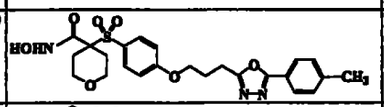
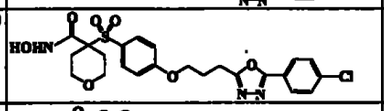
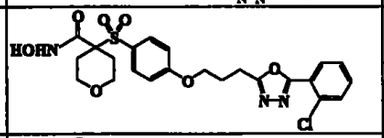
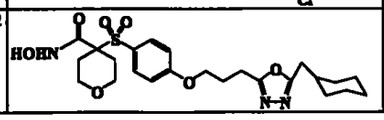
Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
247				3610,8	445,1	341,1	1,1	>10000
248				>10000	15,7	105,6	0,2	1704,1
249				>10000 (>10000)	228 (333)	3628,6 (1490)	5,09 (1,49)	>10000 (>10000)
250				4406,1 (1440)	2,5 (3,12)	22,5 (12,5)	0,3 (0,127)	7830,2 (1700)
251					182,4		5,4	

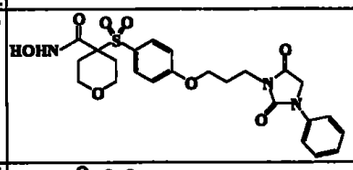
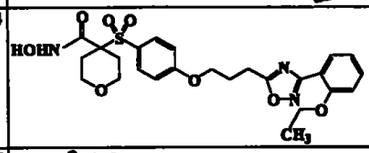
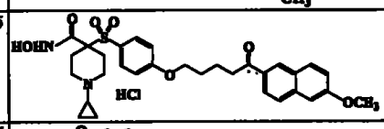
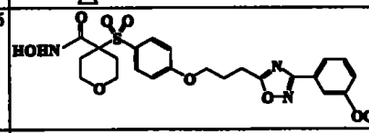
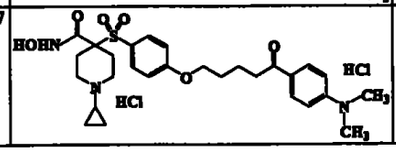
1055

Ej. Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
252				5602,7	47,9	1052,4	0,2	>10000
253					1448,2		32,4	
254				>10000	138,3	968,2	1,7	>10000
255					51,3		1,9	
256				>10000	0,1	37,9	<0,1	>10000

1080

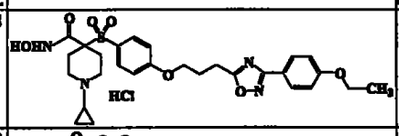
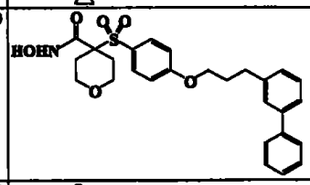
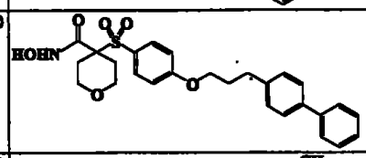
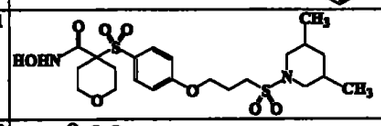
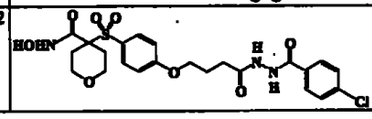
~~1054~~

Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
257				>10000	173,8	8227	0,5	>10000
258				>10000	173,5	1956	1,7	>10000
259				7256	201,1	1876	0,7	>10000
260				1159	13,2	391,0	1,8	>10000
261				>10000	178,3	1185,0	1,9	>10000
262				>10000	118,3	1702,3	3,0	>10000

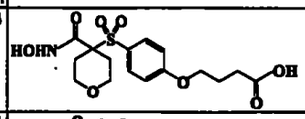
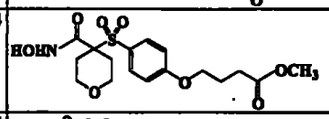
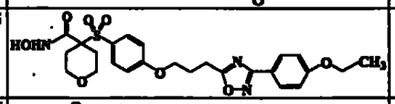
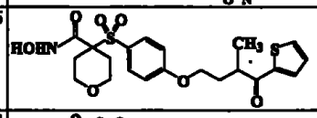
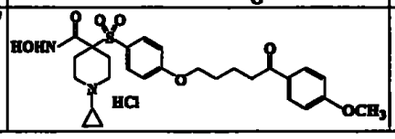
Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
263				>10000	87,7	3267,5	3,8	>10000
264				>10000	162,8	287,1	5,3	>10000
265					40,0		0,2	
266				>10000	391,2	202,6	9,1	>10000
267				>10000	18,5	108,7		>10000

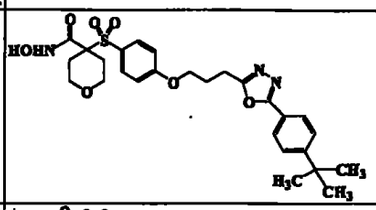
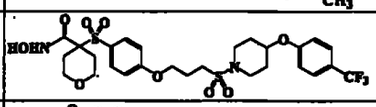
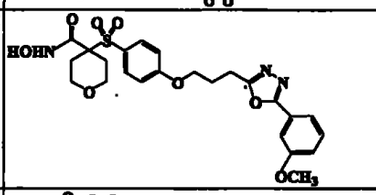
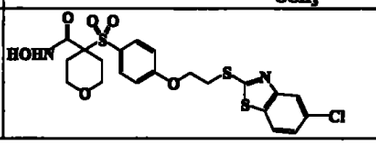
1082

1056

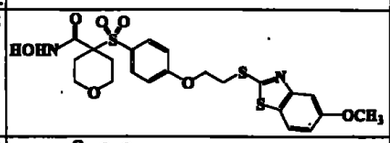
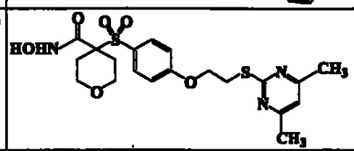
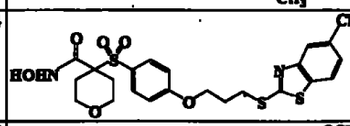
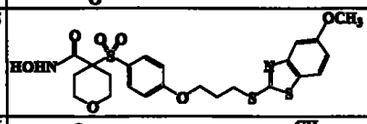
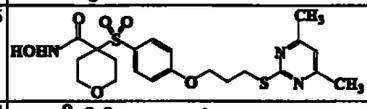
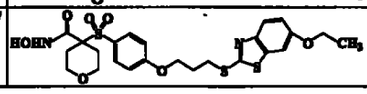
Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
268				>10000	125,9	874,0	2,5	>10000
269				>10000	897,9	2755	1,8	>10000
270					521,8		8,1	
271				>10000	8,7	531,8	2,9	>10000
272				399	4,2	152,1	2,8	>10000

~~1054~~

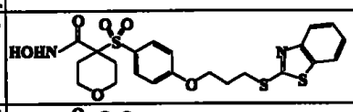
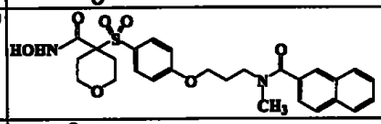
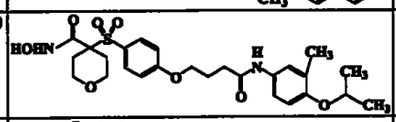
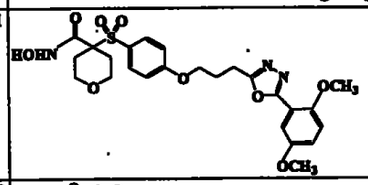
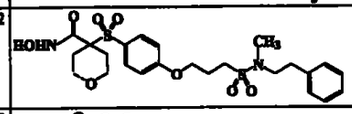
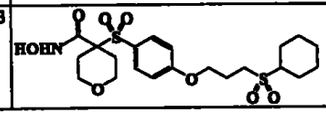
Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
273		405,1332	405,1335		1010,7		304,0	
274		402,1223	402,1225	9864	15,4	33,6	4,1	>10000
275					115,2		1,7	
276				9870,4	17,4	196,3	2,8	7019,9
277				>10000	3,5	41,5	0,2	>10000

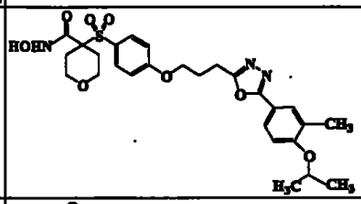
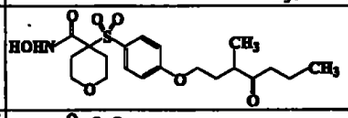
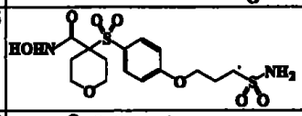
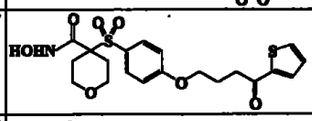
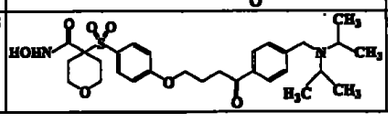
Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
278		544,2117	544,2104	>10000	207,9	494	3,7	>10000
279					15,9		9,4	
280		518,1597	518,1578	>10000	170,1	2034	1,5	>10000
281		529,0329	529,0353	>10000	70,4	278,1	1,3	>10000

~~1054~~

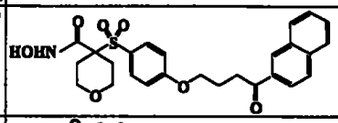
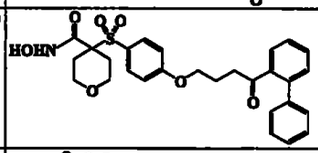
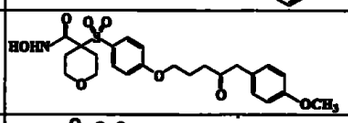
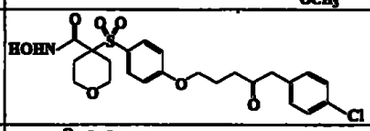
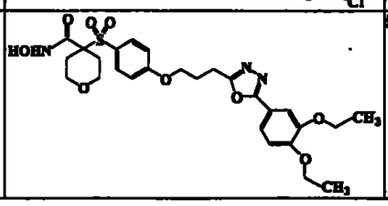
Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
282		525,0824	525,0827	>10000	43,3	704,3	2,6	>10000
283		468,1283	468,1257		186,2		29,3	
284		543,0485	543,0500	>10000	10,1	18,5	1,1	>10000
285		539,0880	539,0978	>10000	16,7	23,6	1,8	>10000
286		482,1420	482,1421	>10000	74,9	1134,5	4,0	>10000
287		553,1137	553,1137	>10000	3,6	16,4	0,8	>10000

~~1060~~

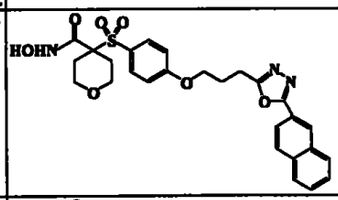
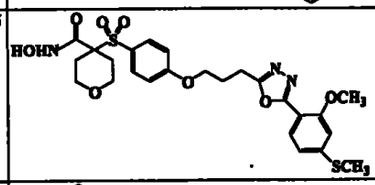
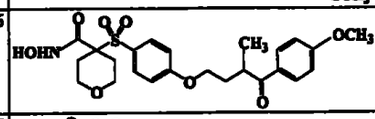
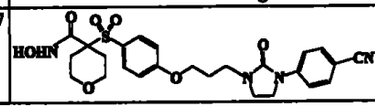
Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
288		509,0875	509,0880	>10000	2,3	10,6	0,8	>10000
289		527,1852	527,1838	>10000	2720,2	>10000	10,1	>10000
290				>10000 (>10000)	590,2 (1009,04)	>10000 (>10000)	1,1 (0,547)	>10000 (>10000)
291					100		8,0	
292				970	14,4	163,5	2,4	>10000
293				6147	2,3	447,9	2,6	>10000

Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
294				4823	100,0	447,9	4,3	>10000
295				>10000	15,6	172,1	2,6	>10000
296					1335,9		564,6	
297		454,0944	454,0986	8812	8,1	84,6	0,5	8562
298		561,2634	561,2641		11,9		18,1	

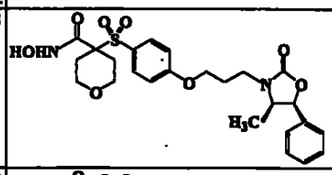
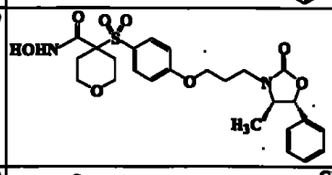
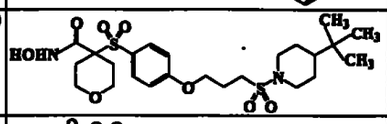
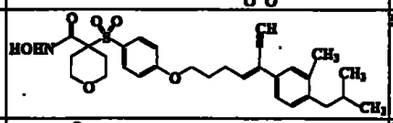
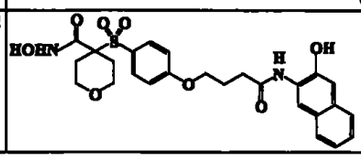
1062

Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
299		498,1586	498,1588		3,2		0,1	
300		524,1743	524,1729		12,5		8,7	
301		492,1692	492,1687	3655,3	0,2	9,1	<0,1	319,9
302		496,1197	496,1192	2728,9	0,2	2,9	0,1	94,9
303		576,2016	576,2198		50,0		9,9	

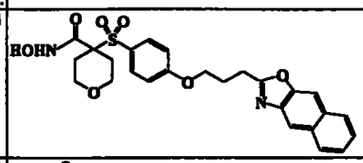
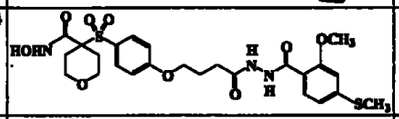
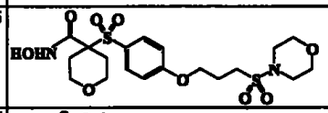
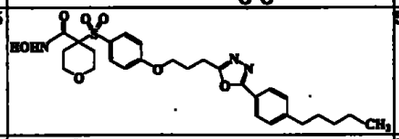
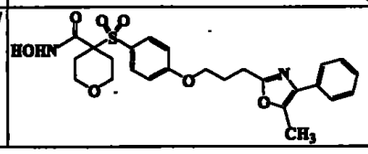
~~1063~~

Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
304		538,1648	538,1629		138,6		0,2	
305		569,1474	569,1444		175,9		3,9	
306				>10000	92,9	185,2	1,7	>10000
307				9135	135	139,5	4,5	>10000

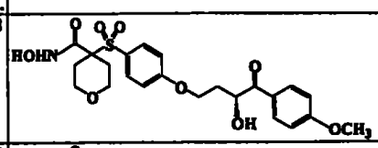
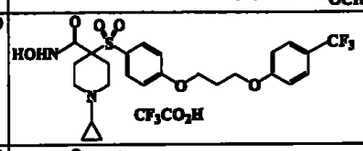
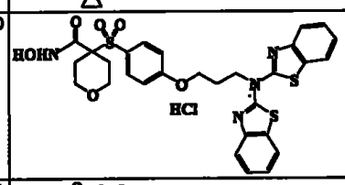
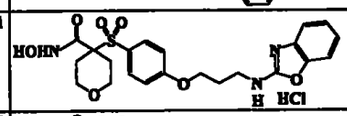
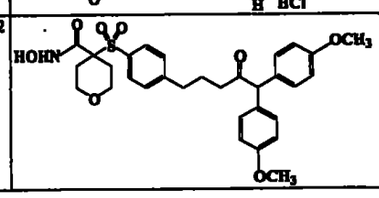
1064

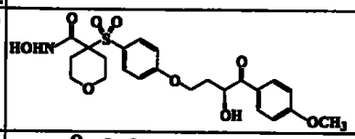
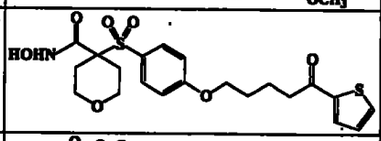
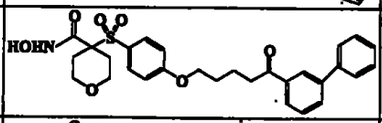
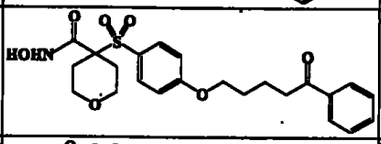
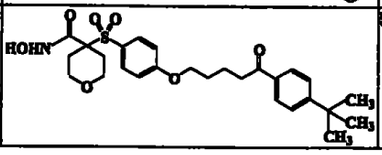
Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
308		519,1801	519,1780	>10000	175,8	1601,1	3,7	>10000
309		519,1801	519,1772	>10000	135,3	1557,8	1,8	>10000
310				>10000	32,0	1980,5	3,0	>10000
311		543,2185	543,2185		25,6		2,6	
312		529,1645	529,1635		9,1		0,2	

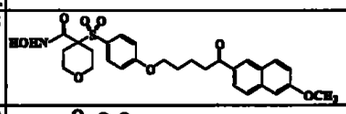
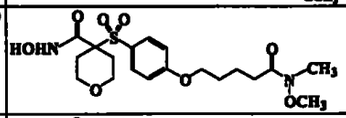
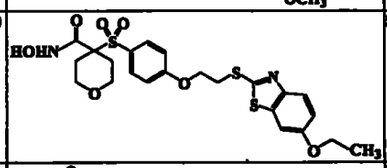
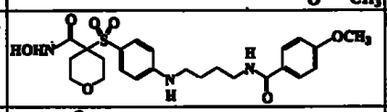
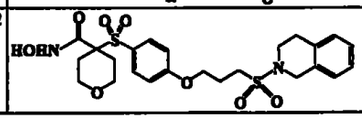
~~1065~~

Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
313		511,1539	511,1535		18,1		<0,1	
314					7,8		2,5	
315					12,8		12,7	
316		558,2274	558,2274	2878	2842	892,0	13,8	>10000
317		501,1695	501,1693	>10000	120,4	244,3	3,1	>10000

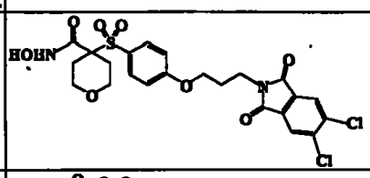
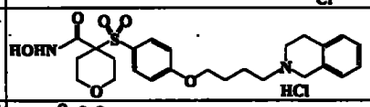
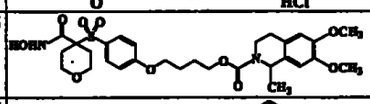
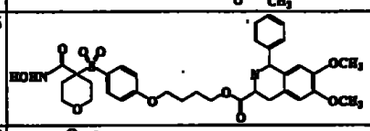
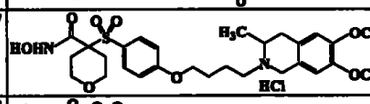
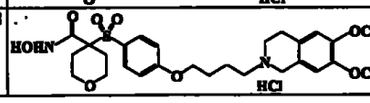
~~1066~~

Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
318					815		97,3	
319				>10000	5,8	258	1,0	4225
320					5864		8110	
321				>10000	1701	825,8	3,7	>10000
322		801,2220	801,2226		354		233	

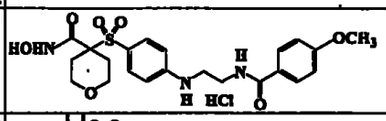
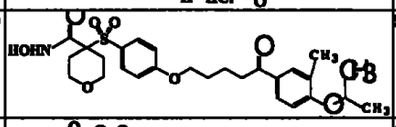
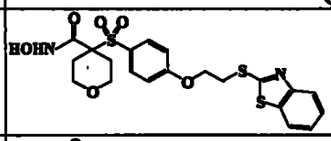
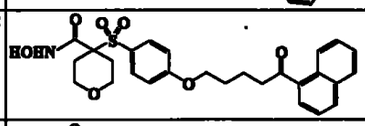
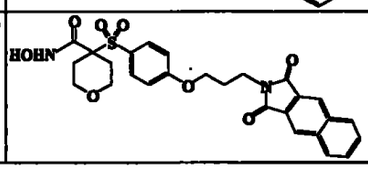
Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
323					358,8		108	
324		488,1151	488,1148	2990	4,2	500	0,5	8002
325		538,1899	538,1918	>10000	11,0	4042	0,5	>10000
326		482,1586	482,1582	>10000	7,4	263	0,3	8316
327		518,2212	518,2203	>10000	50,7	5284	0,9	>10000

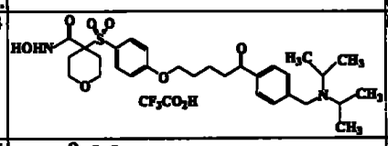
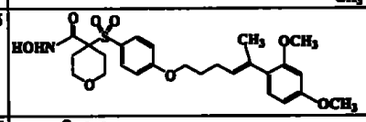
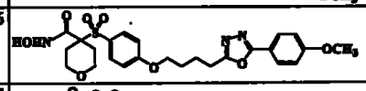
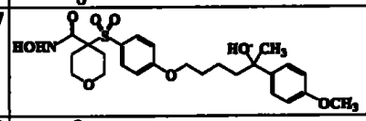
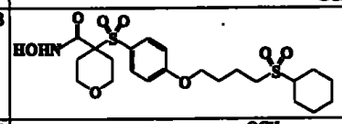
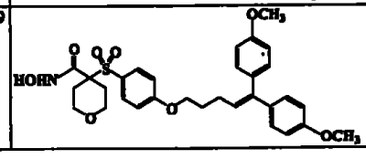
Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
328		542,1849	542,1868		81,3		<0,1	
329					103,1		8,6	
330		539,0980	539,0985	>10000	261,7	216	16,0	592
331		506,1961	506,1954		386		261,4	
332				2459	3,6	132,4	2,6	>10000

~~1069~~

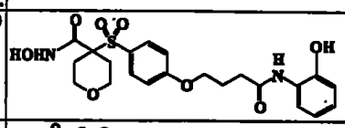
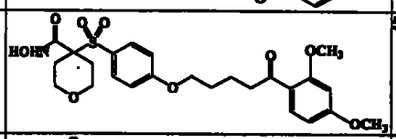
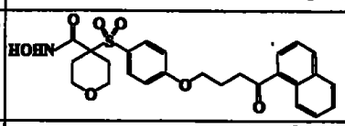
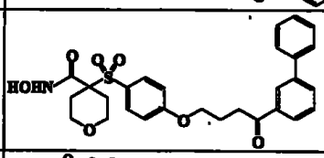
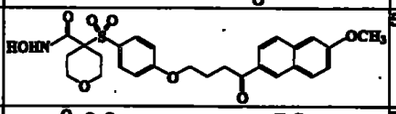
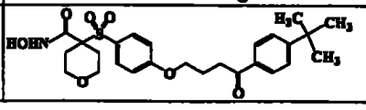
Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
333		557,0552	557,0582	>10000	856,3	3240	1,8	>10000
334		489,2059	489,2073	>10000	16,4	866	5,1	2876
335		607,2325	607,233	>10000	2,3	172,3	8,5	>10000
336		669,2482	669,2483		300,6		19,8	
337		563,2427	563,2414		41,9		12,2	
338		549,2271	549,2242		20,6		137,7	

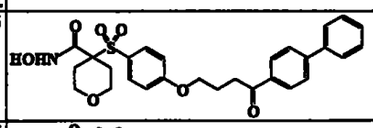
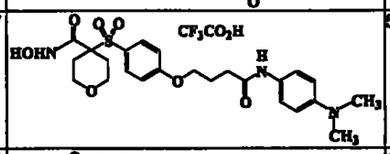
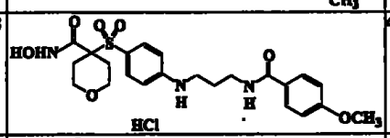
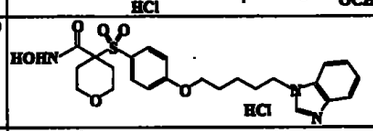
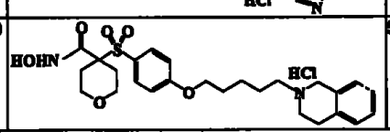
1076

Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
339		478,1648	478,1631		1205,8		932,9	
340		534,2162	534,2161	>10000	253,0	5590	1,9	>10000
341		495,0718	495,0689	>10000	16,8	1122	0,5	8400
342		512,1743	512,1769	>10000	41,2	2165	2,0	>10000
343					7702,4		2,4	

Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
344		575,2791	575,2819		12,7		4,6	
345		520,2005	520,1988		271,1		14,3	
346		532,1754	532,171	>10000	2,6	2010	0,9	>10000
347					10,3		1,8	
348				>10000	81,8	>10000	4,4	>10000
349					505,3		39,0	

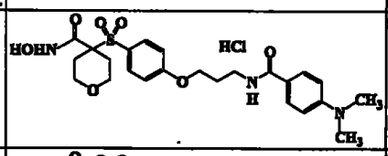
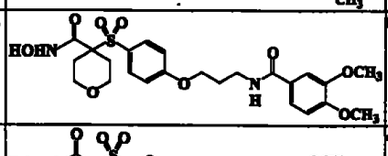
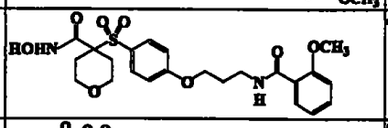
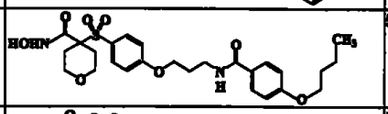
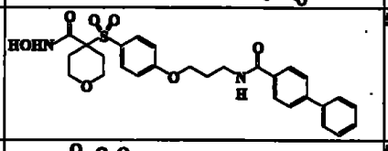
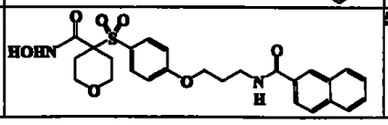
1072

Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
350		479,1488	479,1484	3283	2,8	271	0,5	2870
351		522,1798	522,1791	>10000	34,1	2225	1,0	>10000
352		498,1586	498,1576	>10000	33,6	3601	2,0	8238
353		524,1743	524,1703	>10000	25,1	1152	1,8	>10000
354		528,1692	528,1658					
355		504,2058	504,2017	>10000	17,4	1072	1,1	3622

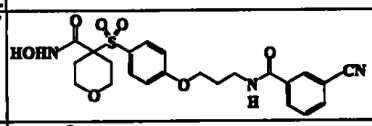
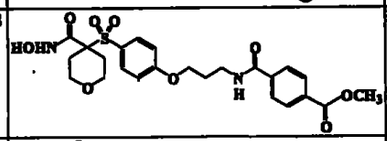
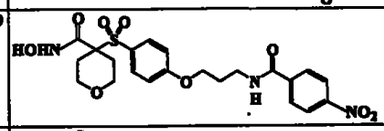
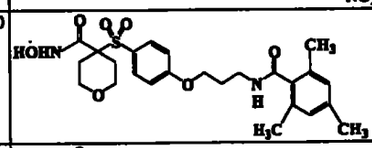
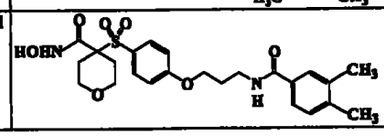
Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
356		524,1743	524,1731	>10000	33,1	1650	0,8	>10000
357		508,1961	508,1964	>10000	10,2	952	1,7	>10000
358		492,1804	492,1813		788,4		14,6	
359		486,1855	486,1862	>10000	2,3	1183	1,0	7956
360		503,2216	503,2226	>10000	9,7	547	8,4	962

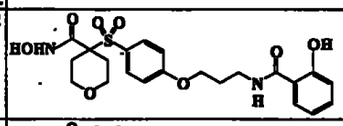
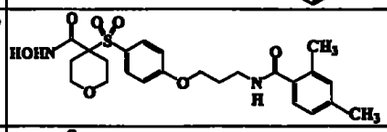
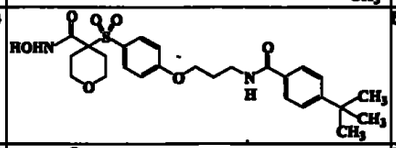
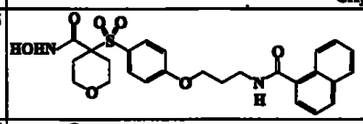
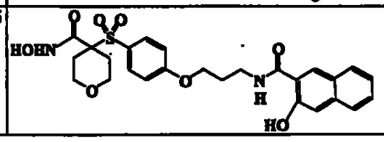
1100

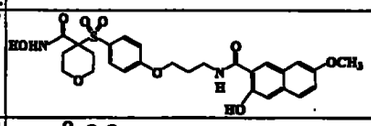
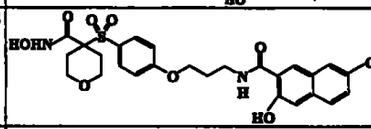
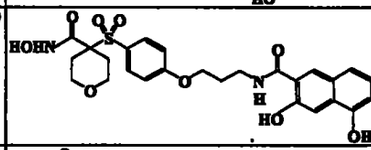
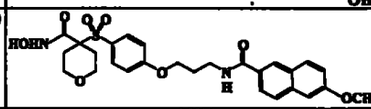
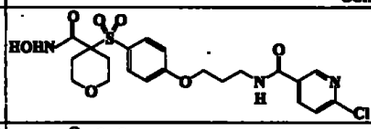
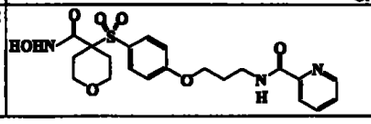
1074

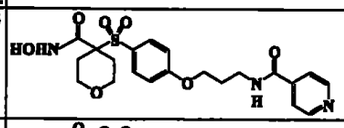
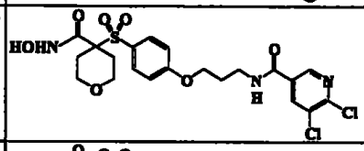
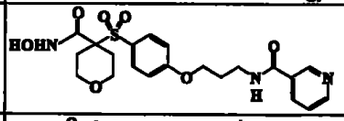
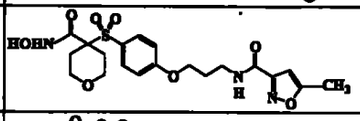
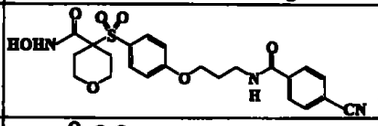
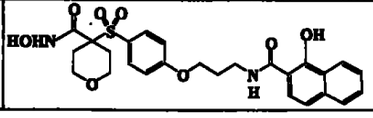
Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
361		508,1981	516,1985	8000	500	>10000	0,5	>10000
362		523,1750	523,1763		347		3,7	
363		493,1645	493,1660		430		7	
364		535,2114	535,2105	>10000	250	>10000	1,8	>10000
365		539,1852	539,1846		21		0,8	
366		513,1695	513,1699		347		0,3	

1075

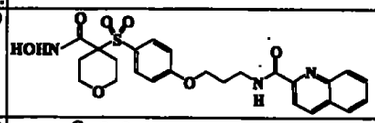
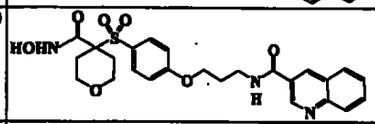
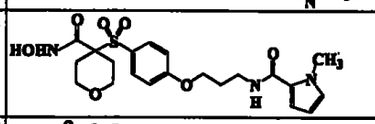
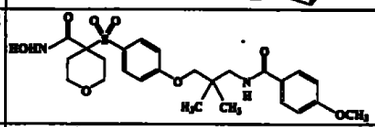
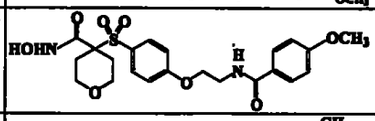
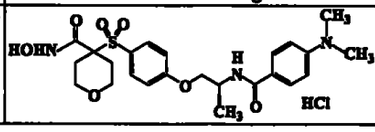
Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
367		488,1491	488,1496		235		4,5	
368		521,1594	521,1594	>10000	150	9000	0,8	>10000
369		508,1390	508,1390		155		1,5	
370		505,2008	505,1990		900		37	
371		491,1852	491,1894	>10000	1100	9600	2,4	>10000

Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
372		479,1488	479,1491		210		6	
373		491,1852	491,1843	>10000	940	3945	7	>10000
374		519,2165	519,2148		800		8	
375		513,1695	513,1695		425		17	
376		529,1645	529,1625	>10000	360	>10000	0,8	>10000

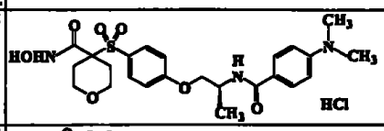
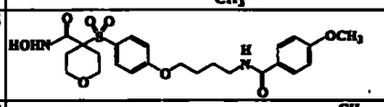
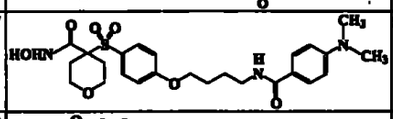
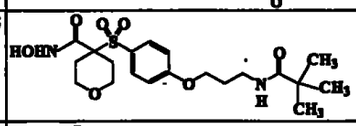
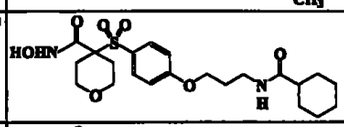
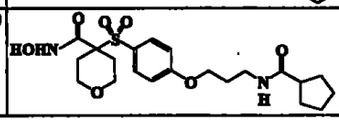
Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
377		559,1750	559,1761		1271		5,9	
378		545,1594	545,1586		855		2,7	
379		545,1594	545,1585		258		10	
380		543,1801	543,1835		450		0,2	
381		498,1102	498,1090		193		1,4	
382		464,1491	464,1475		59		1,7	

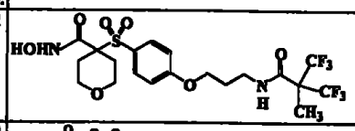
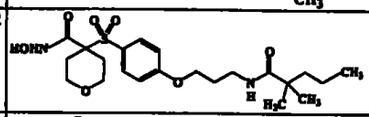
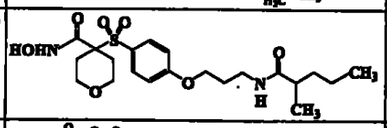
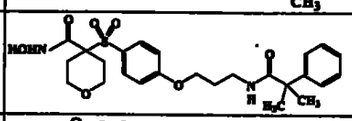
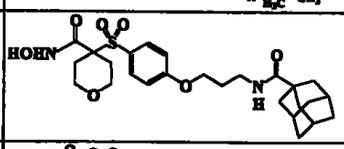
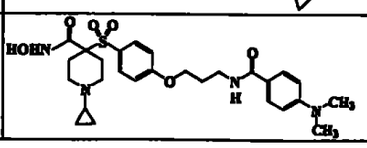
Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
383		484,1491	484,1487		351		7,5	
384		532,0712	532,0709	>10000	176	2628	0,8	>10000
385		484,1491	484,1490	4341	253	>10000	3,3	>10000
386		488,1441	488,1459	>10000	131	35,3	1,2	9725
387		488,1491	488,1508		83		2,2	
388		529,1645	529,1640		185		2	

~~F078~~

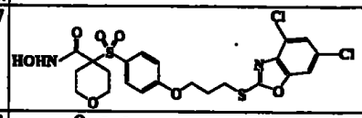
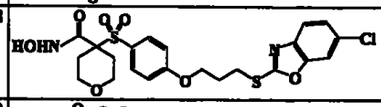
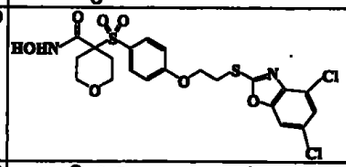
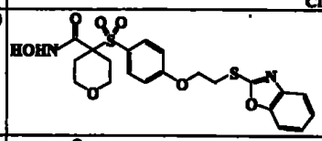
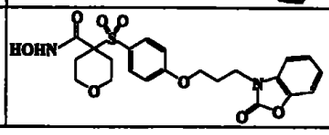
Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
389		514,1648	514,1623		47		0,5	
390		514,1648	514,1641	>10000	907	>10000	2,7	>10000
391		466,1648	466,1647		900		7	
392		521,1958	521,1947	>10000	>10000	>10000	40	>10000
393		479,1488	479,1497		50		45	
394		508,1961	508,1981		3200		1900	

~~1080~~

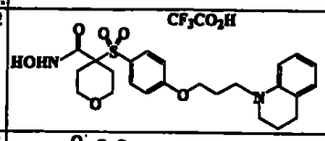
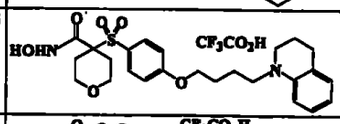
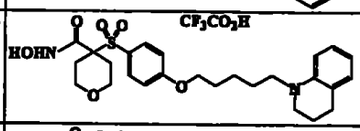
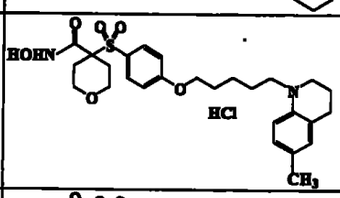
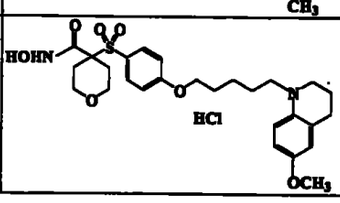
Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
395		506,1981	506,1947		8000		305	
396		507,1801	507,1807		4		4	
397		520,2117	520,2093		3		14	
398		433	433		730		22	
399		469,2008	469,1988		850		8	
400		455,1852	455,1843		326		9	

Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
401		551,1287	551,1284		700		25	
402		471,2185	471,2144		454		30	
403		457,2008	457,1997	>10000	454	>10000	5,2	>10000
404		505,2008	505,1992		254		15	
405		521,5321	521,2323	>10000	2352	>10000	1,9	>10000
406		545,2434	545,2441	>10000	2200	>10000	4	>10000

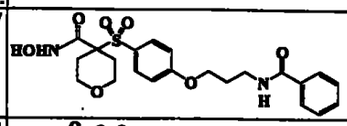
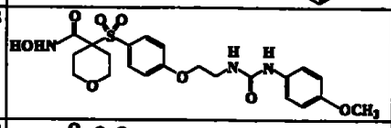
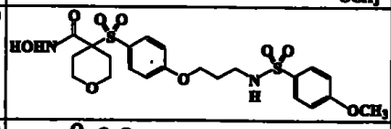
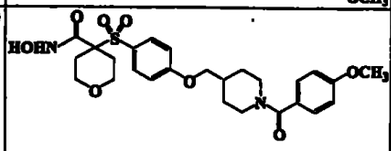
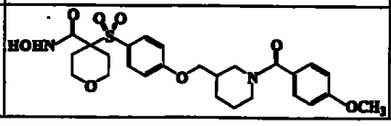
~~1082~~

Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
407		561,0324	561,0368		285		25	
408		527,0713	527,0694	>10000	90	49	2,5	8813
409		547,0167	547,0196	>10000	23	160	1	5644
410		479,0947	479,0978	4700	12	202	1,1	515
411		483,1175	483,1204	>10000	1517	>10000	587	>10000

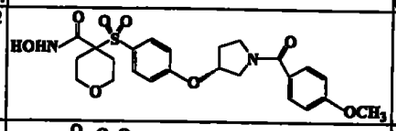
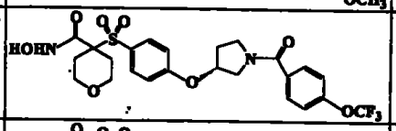
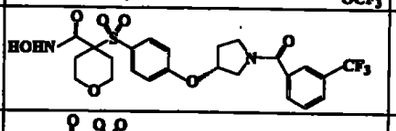
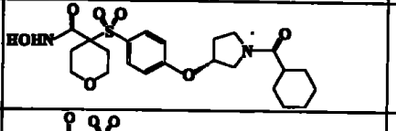
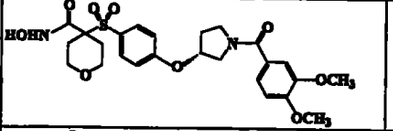
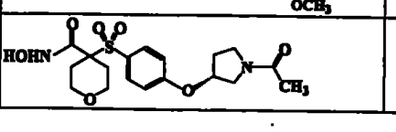
1083

Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
412		475,1903	475,0916		313		41	
413		489,2059	489,2068		81		8	
414		503,2216	503,2215		37		14	
415		517,2372	517,2377	>10000	51	1784	15	>10000
416		533,2321	533,2314		17		8,6	

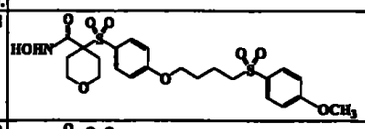
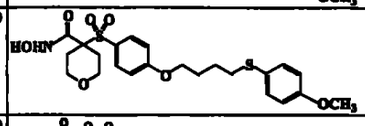
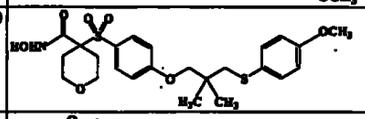
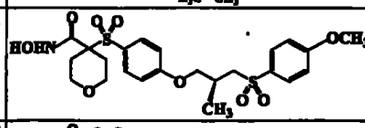
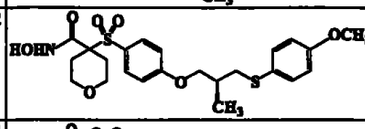
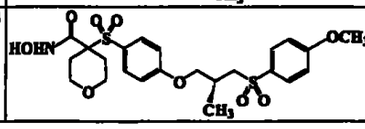
~~1087~~

Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
417		463,1539	463,1546		315		2,8	
418				>10000	1500	>10000	84	>10000
419					120		4	
420				>10000	87	>10000	4	>10000
421					849		256	

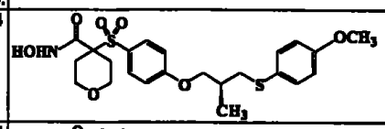
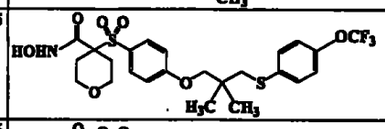
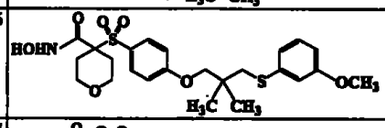
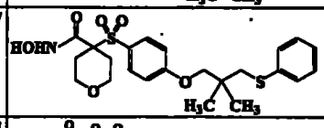
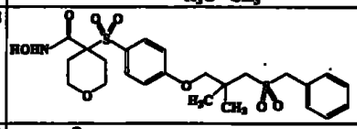
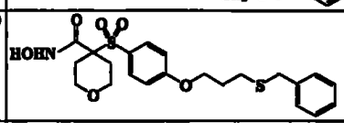
~~1085~~

Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
422					7200		1484	
423					9000		1585	
424					485		192	
425					>10000		3308	
426					>10000		5151	
427					251		114	

~~1086~~

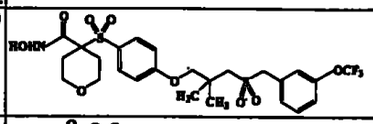
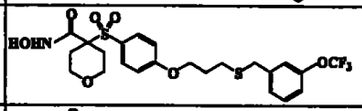
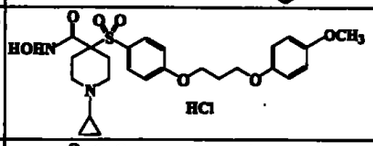
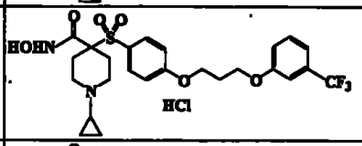
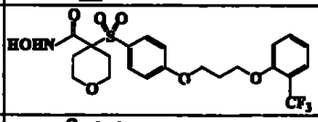
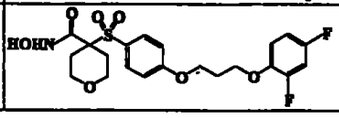
Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
428					20		1,4	
429					8,5	>10000	0,5	>10000
430					2700		195	
431					115		4	
432					7		1,5	
433					220		7	

~~1077~~

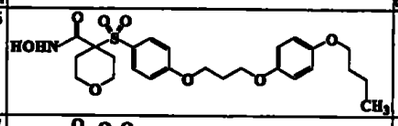
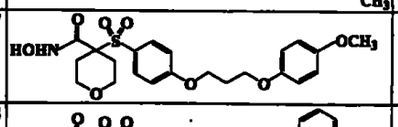
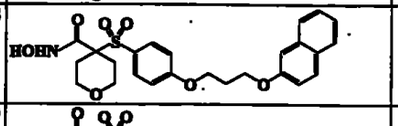
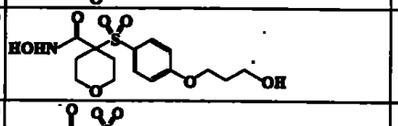
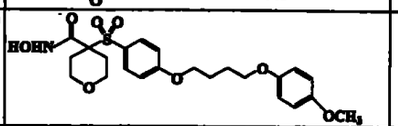
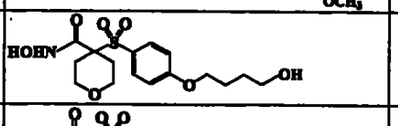
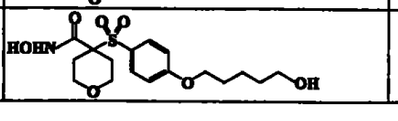
Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
434					1,1		0,6	
435				>10000	>10000		500	
436				>10000	1500		100	
437				>10000	>10000	>10000	90	>10000
438				>10000	505	3800	11	>10000
439				>10000	2000	8000	25	>10000

1114

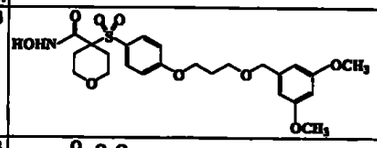
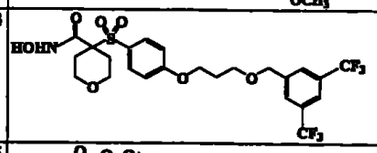
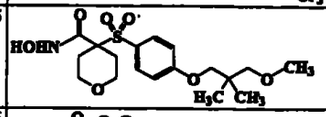
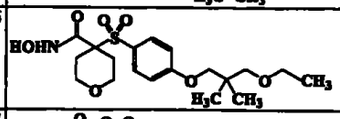
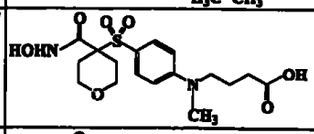
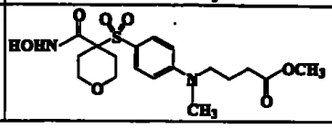
1077

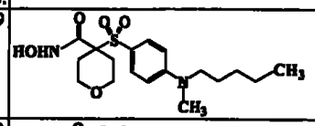
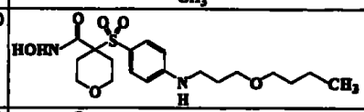
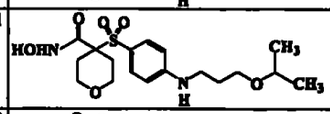
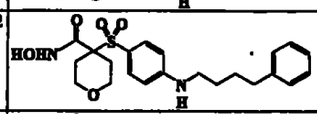
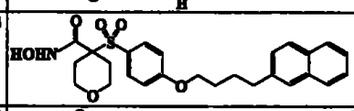
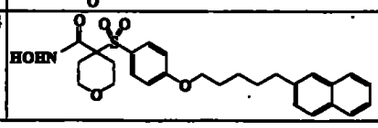
Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
440				>10000	4	140	1	2500
441				9000	13	110	2	2290
442				>10000	8,2	5,4	1,8	997
443				>10000	25	375	3,5	2429
444					8,9		7,6	
445				3325	2,2	44	0,5	548

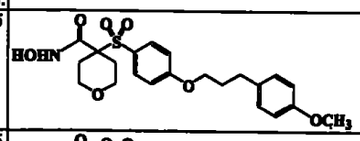
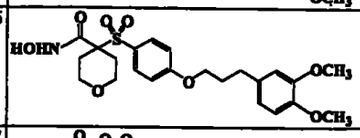
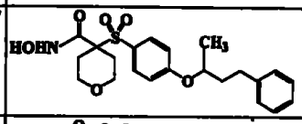
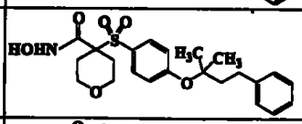
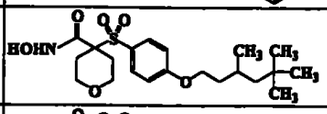
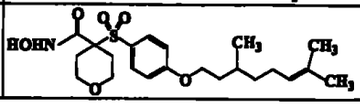
~~1089~~

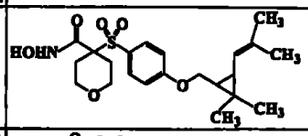
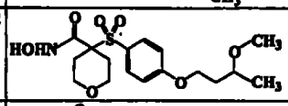
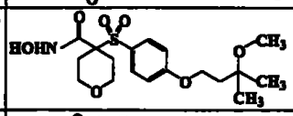
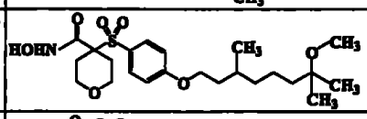
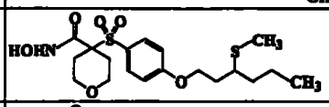
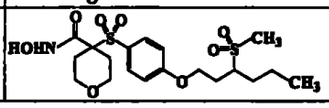
Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
446					76		6,6	
447				>10000	8,9	12,2	2	1360
448				3080	9	116	2,7	832
449				1929	3,7	41	7	58
450				>10000	6,6	44	0,9	4937
451					4,7		9	
452					2,2		14,8	

~~1096~~

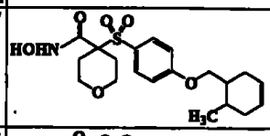
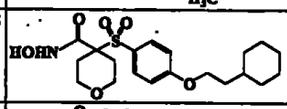
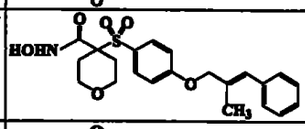
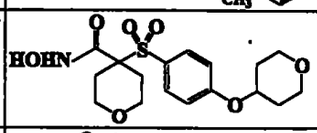
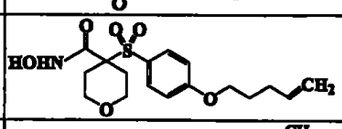
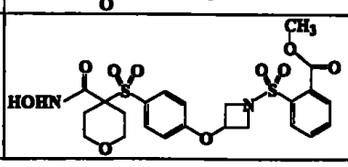
Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
453				>10000	13	800	3	5000
454				>10000	165		27	
455					900		890	
456					425		350	
457				>10000	>10000		>10000	
458				>10000	3500		1400	

Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
459				>10000	700		670	
460				>10000	145	700	25	>10000
461				>10000	2200		590	
462				>10000	11	18	7	8500
463		484,1794	484,1776		17		7	
464		498,195	498,1925		46		1,4	

Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
465		450,1586	450,1577	>10000	4	180	0,3	1800
466		480,1692	480,1732	>10000	110	45	15	>10000
467				>10000	940	450	120	>10000
468				>10000	2500		1500	
469				>10000	145		80	
470				>10000	7		3	

Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
471				>10000	270		120	
472				>10000	3	40	8	400
473				>10000	5	45	5	800
474				>10000	12		3	
475				>10000	30	120	2	3600
476				>10000	2500	>10000	230	>10000

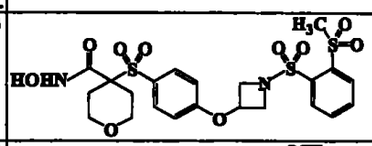
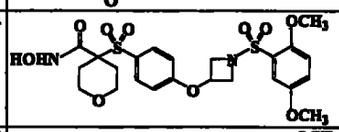
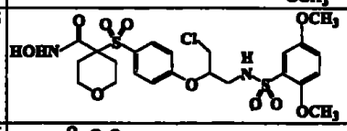
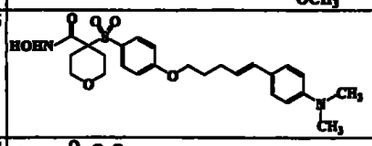
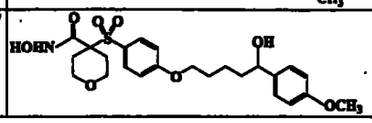
~~Lo que~~

Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
477				1300	1,5		2	
478				>10000	1	34	5	1450
479				2700	4	14	3	2000
480				4200	18	80	11	1400
481					1,3		2	
482					3300		40	

1121

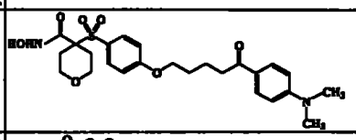
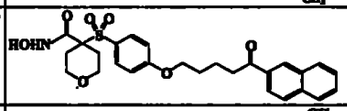
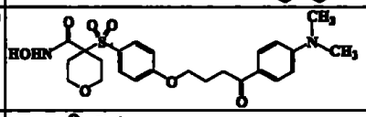
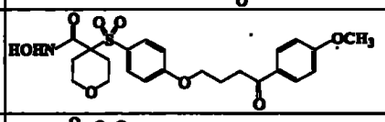
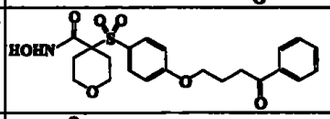
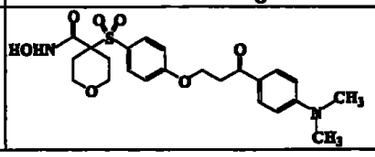
~~1095~~

1122

Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
483					2000		29	
484					840		12	
485					4000		84	
486				>10000	106	255	4,6	>10000
487				>10000	3,1	169	0,5	1570

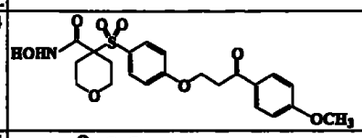
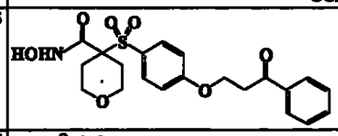
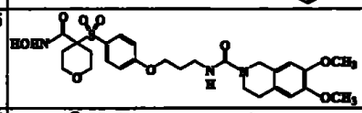
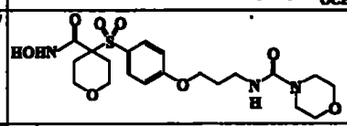
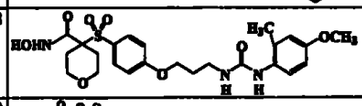
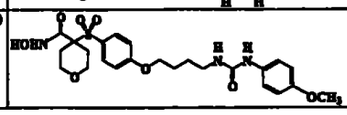
~~1096~~

1123

Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
488		505,2008	505,1991					
489		512,1743	512,1788	>10000	58,2	>10000	0,4	>10000
490		491,1852	491,1856	>10000	18,2	928	0,2	5630
491		478,1536	478,1540	7310	8,8	94,2	0,8	981
492		448,1430	448,1428	3550	3,5	87,3	0,7	574
493		471,1695	471,1695	4770	15,9	752	0,9	3230

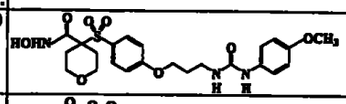
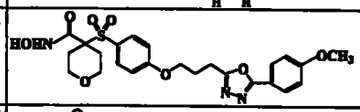
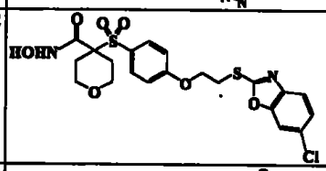
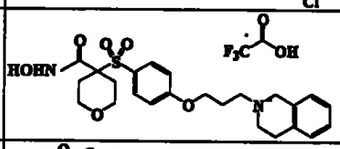
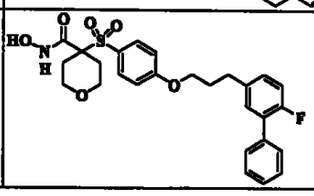
~~6047~~

1124

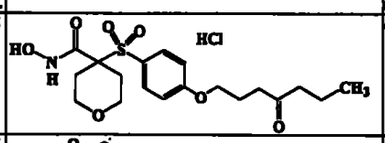
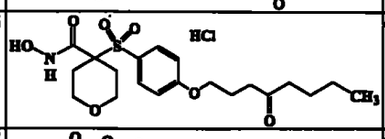
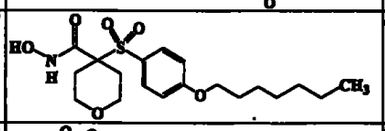
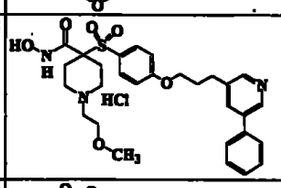
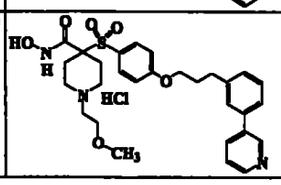
Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
494		484,1392	484,1379	1620	<0,1	13,8	<0,1	197
495		434,1273	434,1277	815	1,9	25,8	1,7	505
496		578,2172	578,2164		242		9,4	
497		472,1754	472,1769		1450		23,5	
498		522,191	522,1915		160		14,8	
499		508,1754	508,1753		56,2		7,0	

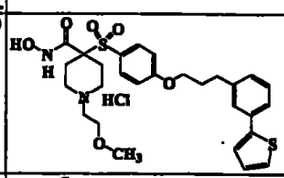
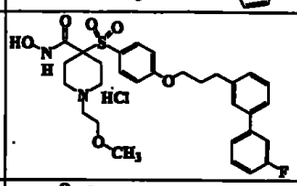
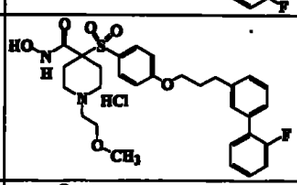
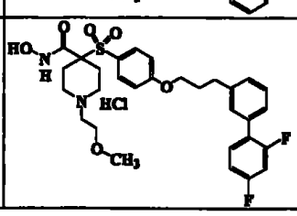
~~1098~~

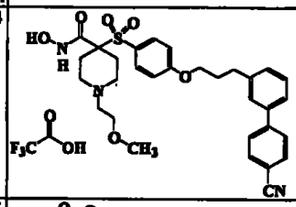
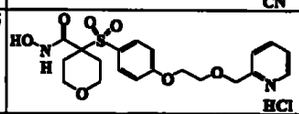
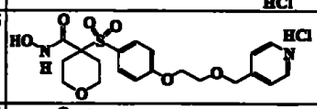
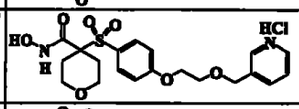
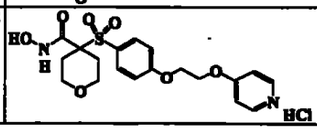
1125

Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
500		494,1597	494,1596	2390	1,9	83,2	8,5	2960
501		518,1597	518,158	>10000	184	7710	1,4	>10000
502		513,0567	513,0574	>10000	22,7	160	1,0	5840
503		475,1903	475,1907					
504		514,1700	514,1735	(>10000)	(434)	(2310)	(4,65)	(>10000)

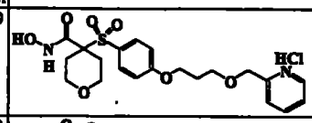
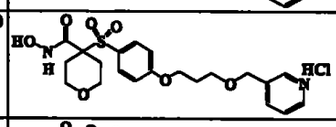
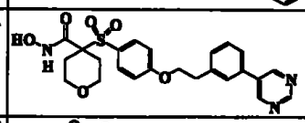
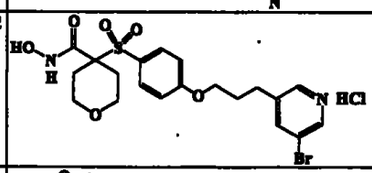
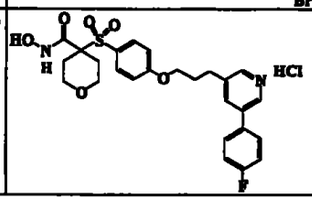
1049

Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
505		414,1581	414,1586	(850)	(2,58)	(10,2)	(0,81)	(982)
506		428,1738	428,1751	(1485)	(1,92)	(11,4)	(0,23)	(681)
507		400,1787	400,1788	(3590)	(0,84)	(0,44)	(0,19)	(444)
508		554,2319	554,2347	(4850)	(22,8)	(160)	(0,141)	(2790)
509		554,2319	554,2308	(>10000)	(89,26)	(50,85)	(0,297)	(4158,92)

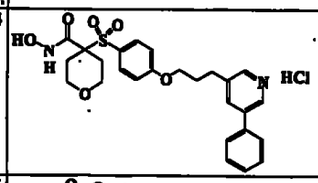
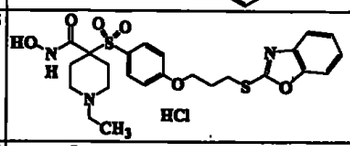
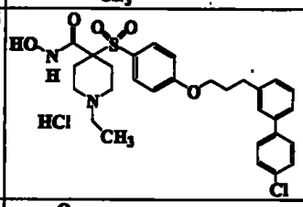
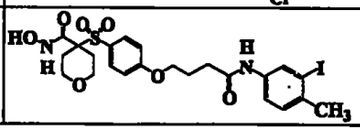
Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
510				(>10000)	(7,85)	(39,82)	(0,25)	(2183,66)
511		571,2273	571,2255	(>10000)	(525,76)	(38,53)	(1,36)	(>10000)
512		571,2273	571,2281	(>10000)	(757,99)	(25,71)	(1,07)	(>10000)
513		589,2178	589,2193	(>10000)	(879,71)	(254,58)	(0,98)	(9274,4)

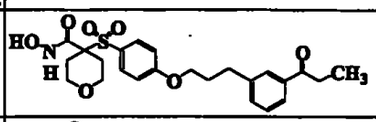
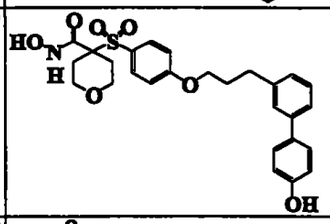
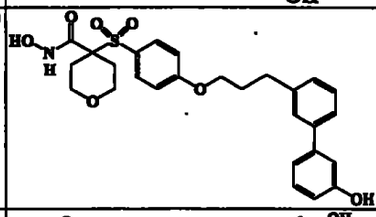
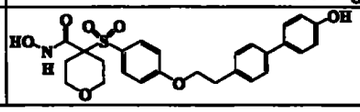
Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
514		578,2319	578,2305	(>10000)	(282,63)	(223,53)	(0,28)	(4082,05)
515				>10000	89,76	154,32	24,23	>10000
516				>10000	41,94	119,72	9,55	9434,24
517				>10000	34,66	137,63	8,19	>10000
518				>10000	26,35	115,39	169,48	967,13

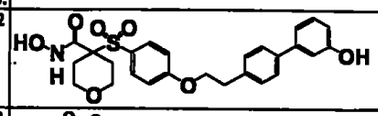
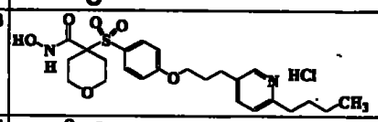
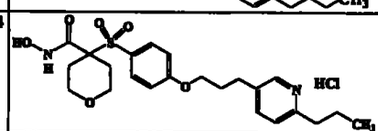
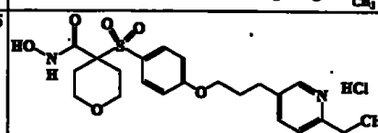
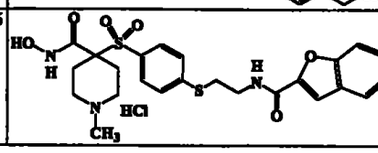
HOE

Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
519				>10000	170,25	421,64	2,18	>10000
520				>10000	54,24	36,38	0,62	4296,13
521					82,0		5,8	
522				(>10000)	12,9 (32,1)	(135)	0,3	(6290)
523		515,1647	515,1690	8069 (3213)	161,6 (196,7)	1647,2 (1253)	0,3 (0,234)	>10000 (>10000)

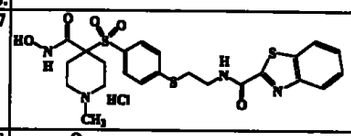
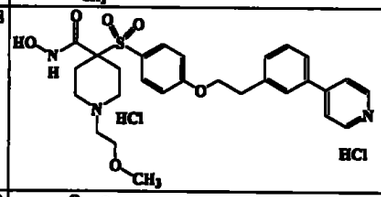
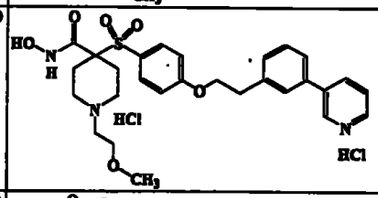
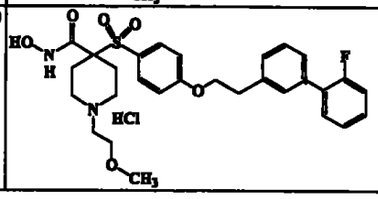
~~403~~

Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
524		497,1741	497,1763	>10000	38,3 (51,8)	1841,5 (739,5)	0,2 (0,244)	>10000 (>10000)
525		520,1576	520,1581		7,5		1,5	
526		557,1871	557,1863 557,1843	(>10000)	(1680)	(2070)	(3,98)	(>10000)
527				(5100)	(21,3)	(30,4)	(,044)	(1360)

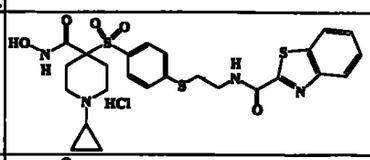
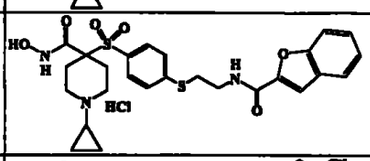
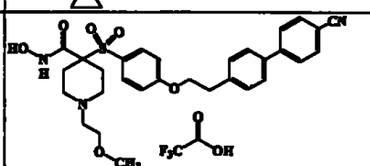
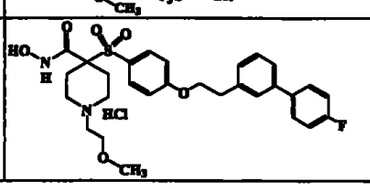
Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
528				(>10000)	(83,5)	(238)	(2,67)	(5700)
529		529,2003	529,1982	(>10000)	(3550)	(1870)	(20,2)	(>10000)
530		512,1738	512,1774	(>10000)	(899)	(220)	(7,33)	(>10000)
531		498,1581	498,1614	(>10000)	(337)	(774)	(2,72)	(>10000)

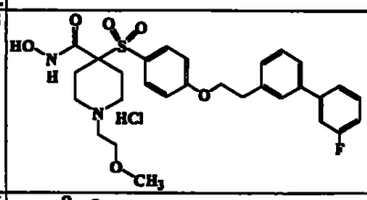
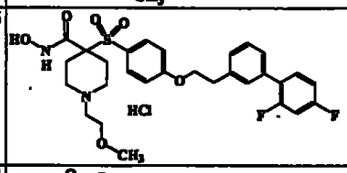
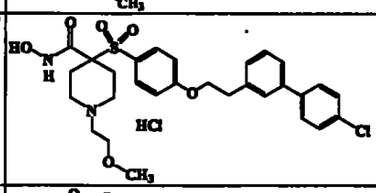
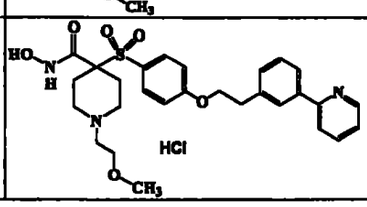
Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
532		498,1581	498,1610	(>10000)	(739)	(1320)	(1,02)	(>10000)
533				(>10000)	(29,3)	(141)	(0,226)	(6880)
534				(>10000)	(25,4)	(324)	(0,493)	(6810)
535				(>10000)	(23,2)	(128)	(0,261)	(3870)
536				(>10000)	(744)	(3400)	(3,4)	(>10000)

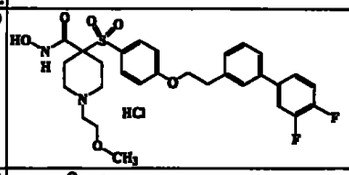
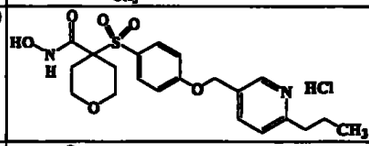
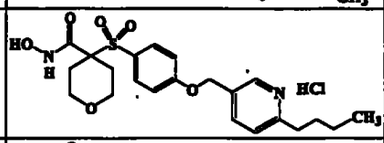
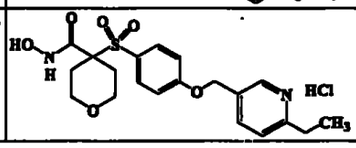
~~1106~~

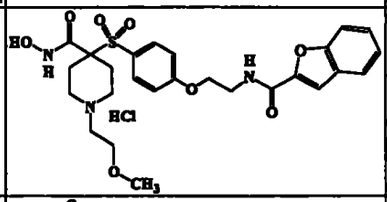
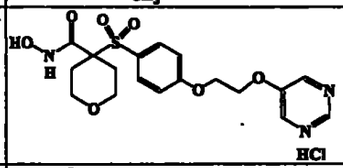
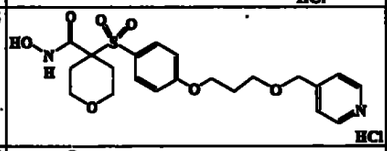
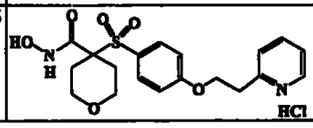
Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
537		535,1138	535,1160	(>10000)	(985)	(900)	(0,857)	(>10000)
538		540,2163	540,2142	(>10000)	(24,8)	(117)	(0,184)	(1700)
539		540,2163	540,2160	(9130)	(38,6)	(85,5)	(0,21)	(1180)
540		557,2116	557,2132	(>10000)	(270)	(689)	(0,58)	(>10000)

HOF

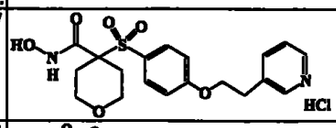
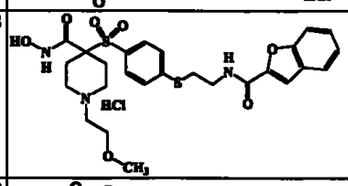
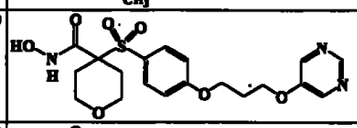
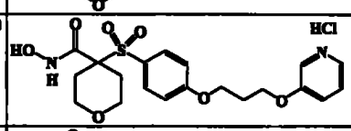
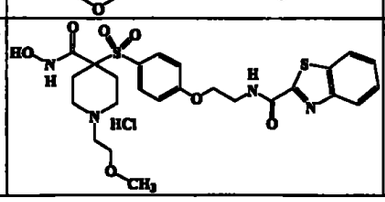
Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KJ)	MMP-14 IC_{50} (KI)
541		561,1295	561,1266	(>10000)	(302,15)	(269,03)	(0,24)	(>10000)
542		544,1571	544,1566	(>10000)	(234,13)	(921,73)	(0,86)	(>10000)
543		584,2163	584,2192	(>10000)	(124,15)	(207,41)	(0,23)	(3094,73)
544		557,2116	557,2087	(>10000)	(302,23)	(787,01)	(0,898)	(>10000)

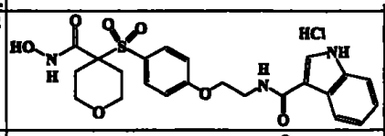
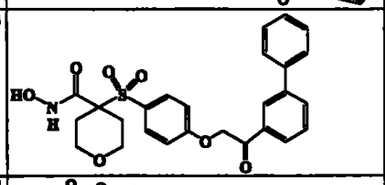
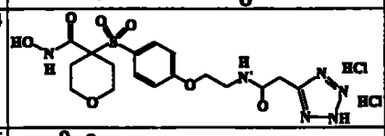
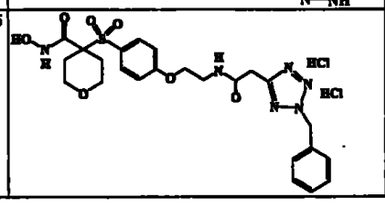
Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
545		557,2116	557,2101	(>10000)	(309,81)	(922,55)	(1,11)	(>10000)
546		575,2022	557,5023	(>10000)	(426,17)	(1269,5)	(1,06)	(>10000)
547		573,1821	573,1848	(>10000)	(727,08)	(1863,44)	(2,28)	(>10000)
548		540,2163	540,2193	(>10000)	(1,58)	(278,57)	(0,38)	(7415,08)

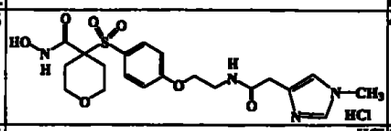
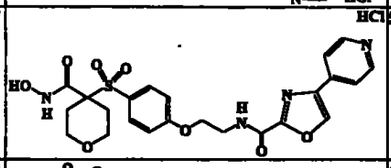
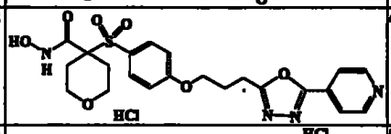
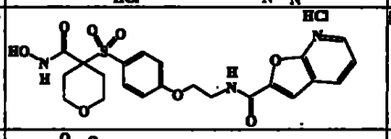
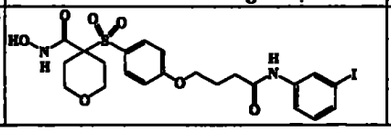
Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
549		575,2022	575,2042	(>10000)	(503,95)	(1770,79)	(1,87)	(>10000)
550				(>10000)	(5,49)	(7,51)	(0,52)	(2180)
551				(>10000)	(5,07)	(48,2)	(0,82)	(2055)
552				(>10000)	(4,94)	(2,22)	(1,78)	(2440)

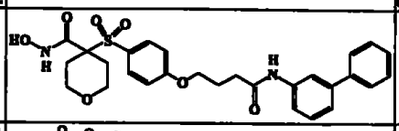
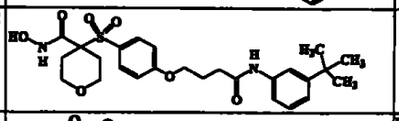
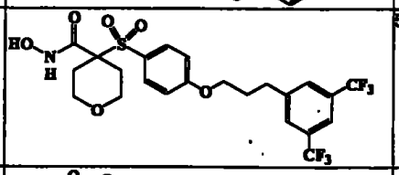
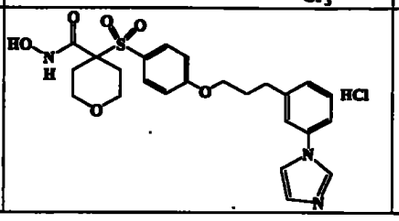
Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
553		546,1905	546,1896	(>10000)	(7,797)	(71,205)	(0,259)	(2257,112)
554				(>10000)	(81,27)	(442,07)	(14,50)	(>10000)
555				(>10000)	(3,383)	(50,012)	(0,261)	(686,63)
556				(6972,84)	(68,058)	(211,92)	(53,22)	(3496,68)

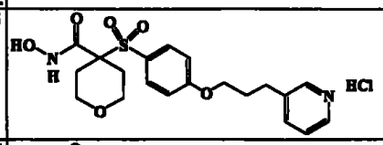
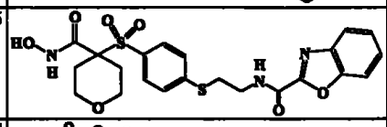
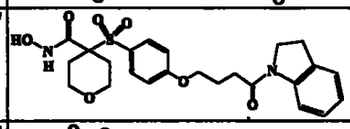
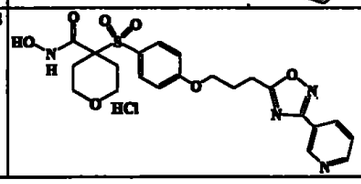
444

Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
557				(>10000)	(6,46)	(33,57)	(3,66)	(52,23)
558		562,1676	562,1714	(>10000)	(352,06)	(1357,7)	(2,163)	(>10000)
559				(>10000)	(11,65)	(57,58)	(1,51)	(845,5)
560				(>10000)	(10,26)	(7,17)	(0,616)	(549,16)
561		579,1400	579,1389	(>10000)	(336,04)	(467,44)	(0,31)	(>10000)

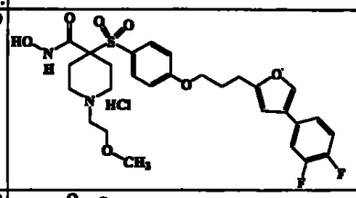
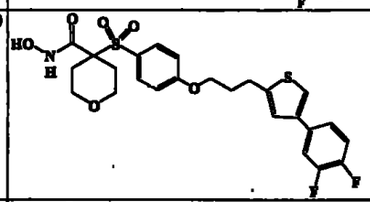
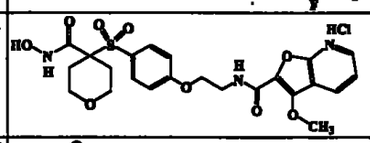
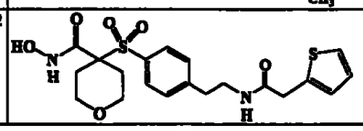
Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
562		488,1486	488,1476	(2738,33)	(241,03)	(785,83)	(2,87)	(9265,87)
563		496,1425	496,1453	(>10000)	73,5 (70,11)	(132,06)	1,1 (0,70)	(4400,5)
564		455,1343	455,1345		144,9		19,4	
565		545,1813	545,1825		14,0		1,8	

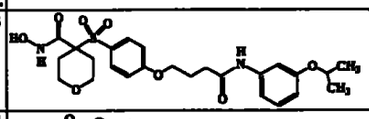
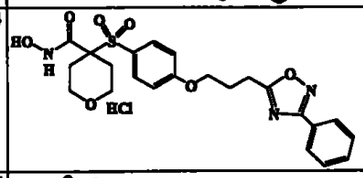
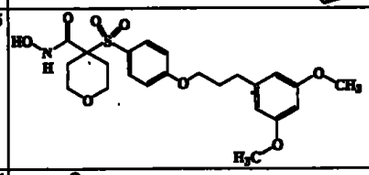
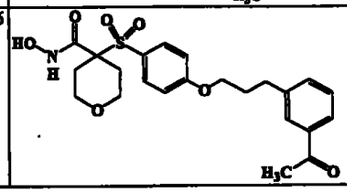
Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
566		467,1595	467,1643		35,7		18,8	
567		549,0931	549,0955		880,5		21,9	
568		489,1438	489,1435		21,0		1,5	
569		506,1050	506,1028		1405		171,8	
570				(3061,49)	4,8 (10,09)	(6,15)	0,2 (0,142)	(1357,48)

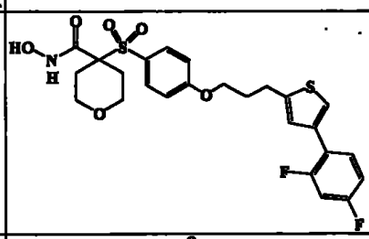
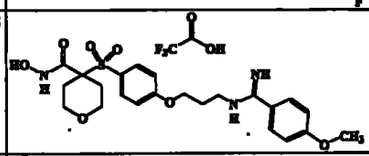
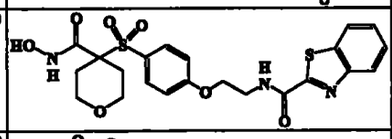
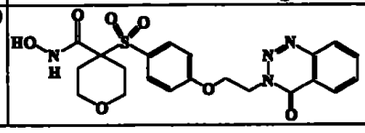
Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
571					11,9		1,6	
572					37,3		4,7	
573		556,1223	556,1214		1707,7		75,1	
574				(>10000)	29,4 (112,25)	(83,02)	0,7 (1,32)	(5366,06)

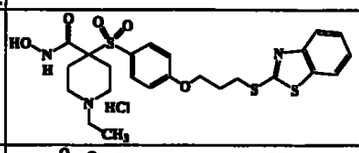
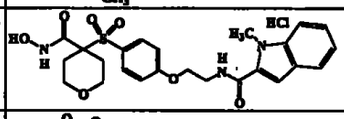
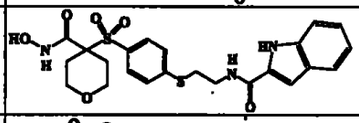
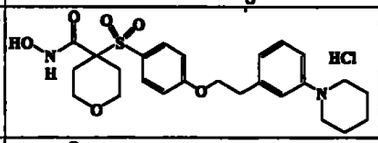
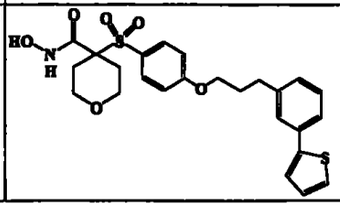
Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
575					8,4		2,0	
576		506,1050	506,1069	>10000	232,7	397,0	0,3	>10000
577					48,2		1,2	
578		489,1438	489,1428	(>10000)	20,5 (72,1)	(578)	2,9 (1,72)	(>10000)

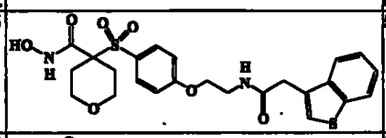
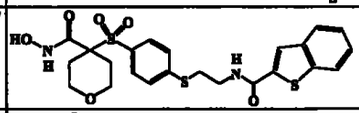
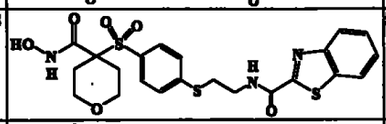
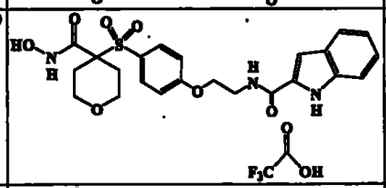
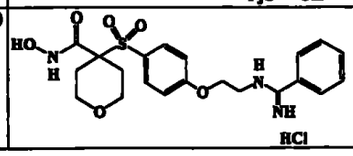
1116

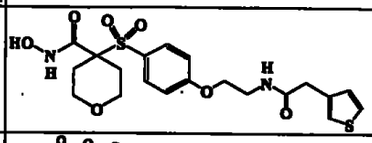
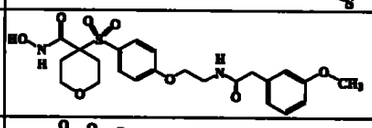
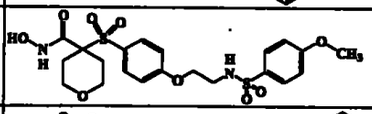
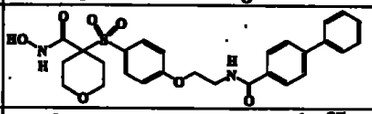
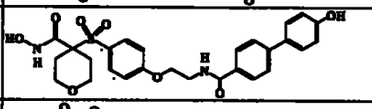
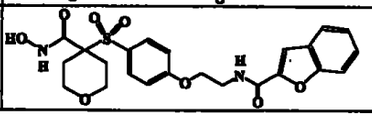
Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
579		595,1743	595,1767	>10000	37,8	136,0	0,4	>10000
580		555,1430	555,1454	>10000	136,0	417,2	0,6	>10000
581		536,1156	536,1173		2534,3		29,8	
582		460,1571	460,1573		55,7		25,3	

Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
583					15,7		1;6	
584				(2780)	72,9 (20,8)	(12,6)	3,6 (0,944)	(6630)
585					85,4		4,0	
586					10,1		0,6	

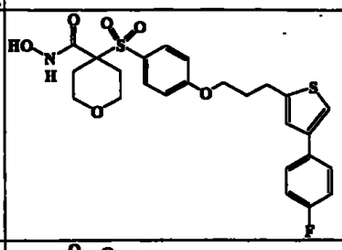
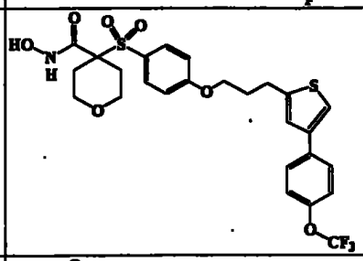
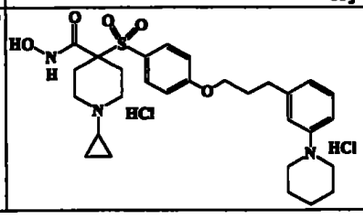
Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
587		538,1164	538,1191	>10000 (>10000)	81,7 (124,9)	1372,9 (8180)	0,1 (1,424)	>10000 (4154)
588		492,1804	492,1773		94,9		16,0	
589		508,1050	508,1054		9,9		0,4	
590					857,7		48,0	

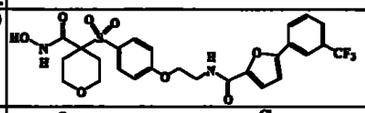
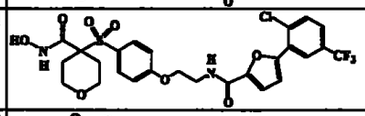
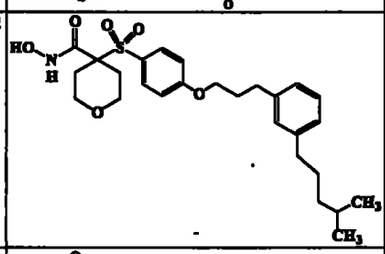
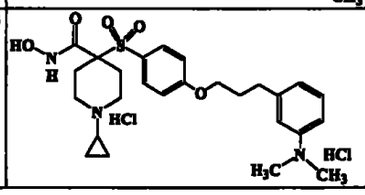
Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
591		536,1348	536,1372	>10000 (>10000)	3,5 (4,4)	12,0 (4,22)	0,3 (0,19)	>10000 (8742,7)
592		502,1648	502,1639		336,4		36,7	
593		504,1263	504,1254		6,5		15,6	
594					140,1		3,8	
595		502,1353	502,1359	>10000 (>10000)	482,5 (586,2)	1733 (2056,6)	1,0 (7,245)	>10000 (>10000)

Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (Ki)	MMP-2 IC_{50} (Ki)	MMP-9 IC_{50} (Ki)	MMP-13 IC_{50} (Ki)	MMP-14 IC_{50} (Ki)
596		519,1260	519,1265	>10000 (>10000)	10,3 (11,2)	194,5 (307,7)	2,7 (0,398)	2491 (1160)
597		521,0875	521,0910		471,1		12,1	
598		522,0827	522,0932	(>10000)	(589,35)	(705,33)	(0,27)	(>10000)
599		488,1491	488,1491	>10000 (>10000)	<0,1 (0,38)	11,6 (11,34)	0,1 (0,24)	57,01
600		448,1542	448,1542		205,7		214,4	

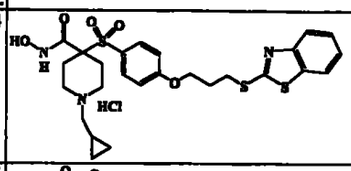
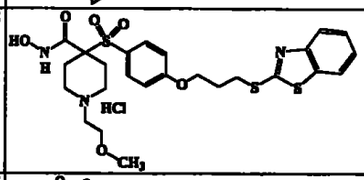
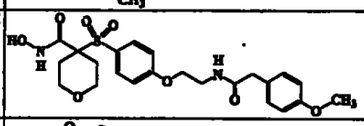
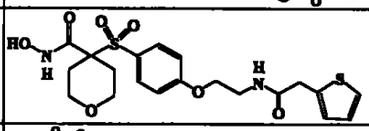
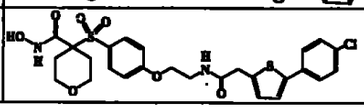
Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
601		469,1103	469,1093	4916	1,9	42,6	1,3	2062
602		493,1639	493,1608		13,7		3,6	
603		515,1158	515,1145		34,0		2,4	
604					36,6		3,3	
605					44,0		3,8	
606		469,1332	469,1326	>10000 (>10000)	5,0 (11,574)	234,0 (105,89)	0,4 (0,432)	2566 (2053,20)

~~X 22~~

Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
607		520,1284	520,1297	>10000	45,2	2298	0,1	>10000
608		586,1181	586,1160	>10000 (>10000)	342,1 (723,95)	1794 (1368,3)	8,6 (9,34)	>10000 (>10000)
609				>10000	579,9	8887	7,7	>10000

Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
610					488,3		4,1	
611					733,2		13,6	
612		504,2414	504,2413		1232,2		16,1	
613					34,3		8,6	

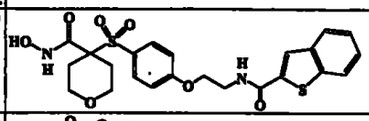
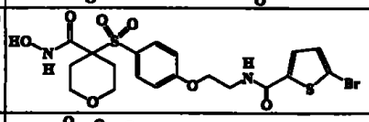
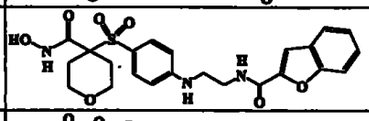
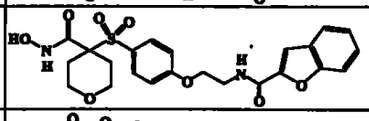
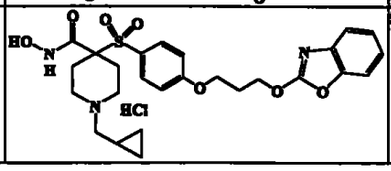
1127

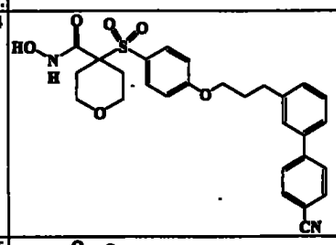
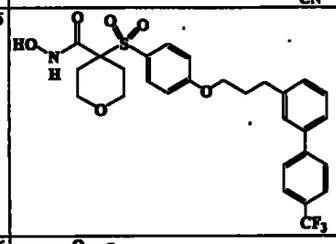
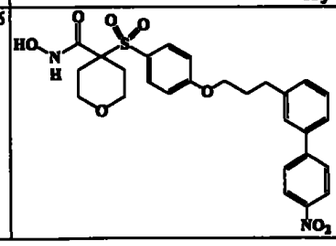
Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
614		562,1504	562,1516	>10000	1,8	8,5	0,7	9440
615		566,1443	566,1453	>10000	1,1	3,6	0,4	8696
616		493,1645	493,1617	1584	5,3	54,6	2,0	1969
617		469,1103	469,1086	2074 1112	0,8	413	0,6	4133
618					822,1		27,5	

1151

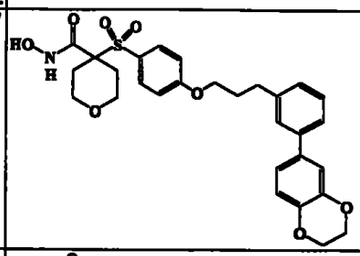
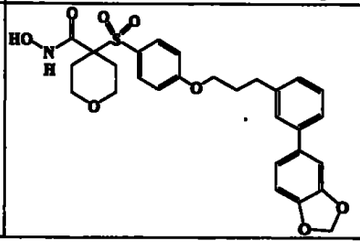
1124

1152

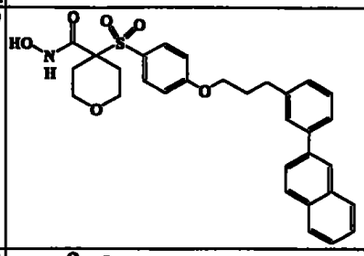
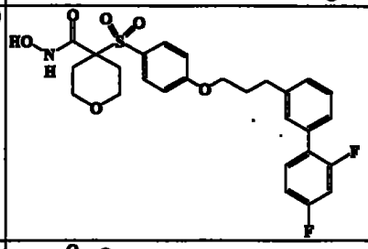
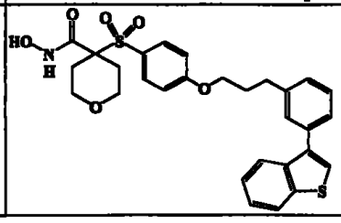
Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
619					86,2		1,5	
620					16,2		4,1	
621		488,1491	488,1489		367,6		17,8	
622		505,1103	505,1120	>10000 (>10000)	273,1 (450,85)	1758 (2077,1)	1,5 (2,68)	>10000 (>10000)
623		548,1733	548,1728	>10000	5,2	3,1	1,2	5520

Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
624		521,1746	521,1753	>10000 (>10000)	214,4 (623)	1029 (443)	0,3 (0,9)	>10000 (7580)
625		564,1668	564,1643	(>10000)	3499,5 (6880)	(4600)	33,6 (43,6)	(>10000)
626		558,191	558,1925	>10000 (>10000)	142,8 (645)	885 (1100)	0,4 (7,5)	>10000 (>10000)

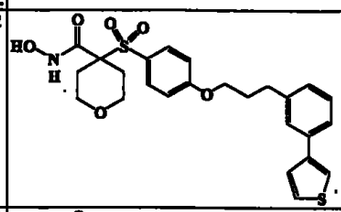
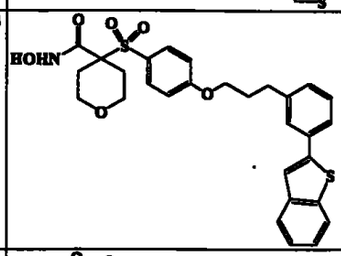
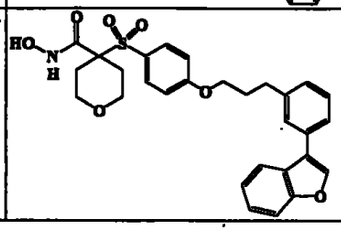
~~1126~~

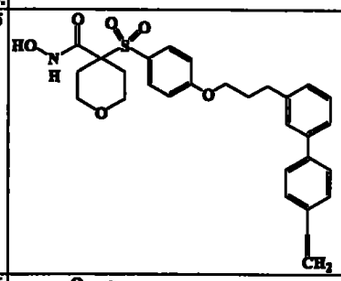
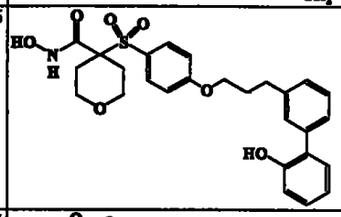
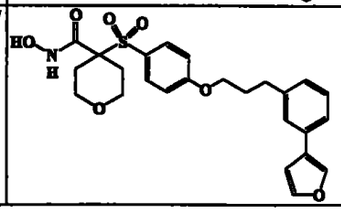
Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
627		554,1849	554,1884	(>10000)	2072,7 (3950)	(3150)	14,9 (40,9)	(>10000)
628		540,1692	540,1712	>10000 (>10000)	1701,3 (2750)	1754 (1930)	3,3 (19,8)	>10000 (>10000)

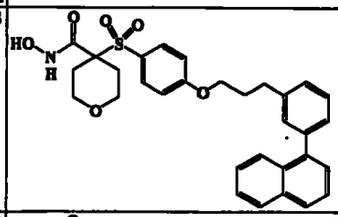
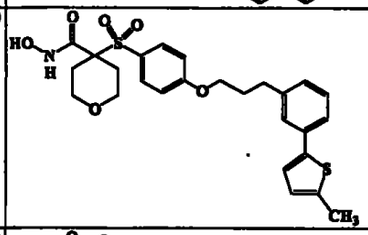
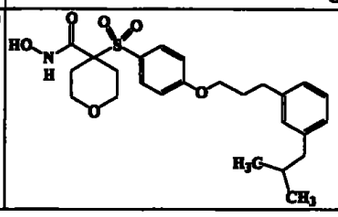
~~1127~~

Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
629		548,1950	548,1985	(>10000)	536,8 (1020)	(1300)	78,6 (89,1)	(>10000)
630		532,1605	532,1598	>10000 (>10000)	1166,6 (2070)	5890 (2280)	0,4 (6,02)	>10000 (>10000)
631		552,1515	552,1520	(>10000)	2143,2 (4960)	(5810)	117,7 (57,8)	(>10000)

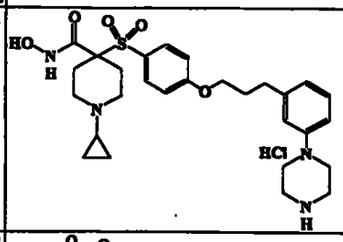
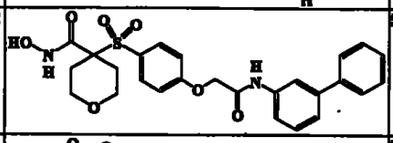
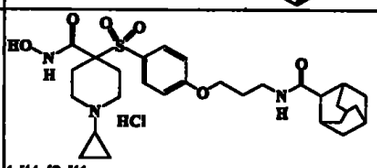
~~428~~

Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
632		502,1358	502,1387	>10000 (>10000)	91,0 (279)	411 (716)	1,6 (8,54)	>10000 (>10000)
633		552,1515	552,1510	(>10000)	2828,1 (4580)	(6780)	117,0 (92,4)	(>10000)
634		536,1743	536,1730	(>10000)	486,4 (983)	(1300)	16,3 (19,4)	(>10000)

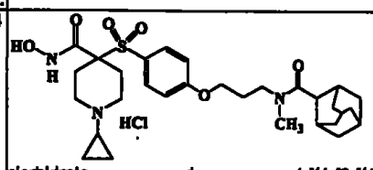
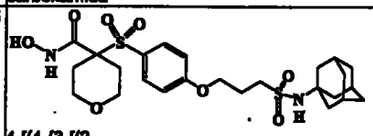
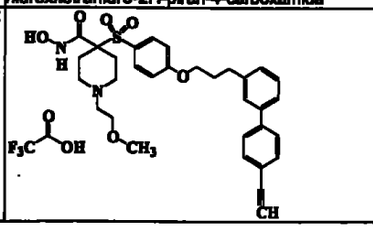
Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
635		522,1950	522,1973	(>10000)	2309,5 (4680)	(4830)	20,0 (28,2)	(>10000)
636		512,1743	512,1756	(>10000)	195,0 (627)	(763)	3,2 (3,21)	(>10000)
637		486,1586	486,1576	>10000 (>10000)	137,6 (498)	830 (881)	1,8 (4,63)	>10000 (>10000)

Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
638		546,1950	546,1950	(>10000)	4400,9 (8120)	(8770)	400,4 (68,1)	(>10000)
639		516,1515	516,1501	(>10000)	247,1 (505)	(888)	4,3 (12,5)	(>10000)
640		476,2101	476,2114		324,5		10,4	

~~437~~

Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
641					134,7		5,0	
642		528,1799	528,1771		2869,0		36,9	
643	 4-[(4-{3-[(1-adamantilcarbonil)amino]propoxi}fenil)sulfonil]-1-ciclopropil-N-hidroxipiperidina-4-carboxamida hidrocloride	560,2794	560,2793		1134,1		11,4	

~~43~~

Ej Nro.	Estructura	Masa calculada	Masa observada	MMP-1 IC_{50} (KI)	MMP-2 IC_{50} (KI)	MMP-9 IC_{50} (KI)	MMP-13 IC_{50} (KI)	MMP-14 IC_{50} (KI)
644	 clorhidrato de 4-[(4-[3-[(1-adamantilcarbonil)(metil)amino]propoxi}fenil)sulfonil]-1-ciclopropil-N-hidroxipiperidin-4-carboxamida	574,2951	574,2943		2633,4		20,9	
645	 4-[(4-{3-[(2-adamantilamino)sulfonil]propoxi}fenil)sulfonil]-N-hidroxitetrahidro-2H-piran-4-carboxamida	557	557	9283	22,9	1726	4,3	>10000
646				(>10000)	(288,84)	(76,21)	(0,16)	(4298,95)

433

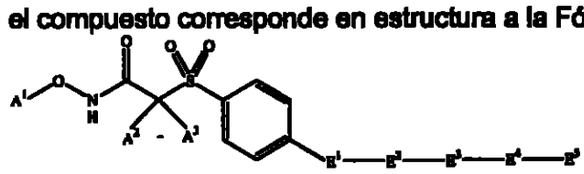
[1115] La descripción detallada de las realizaciones preferidas que antecede tiene como objeto solamente familiarizar a aquellos familiarizados con el arte con la invención, sus principios y su aplicación práctica, de modo que dichos especialistas puedan adaptar y aplicar la invención en sus numerosas formas, según se ajuste de mejor manera a los requerimientos de un uso específico. Esta invención, por lo tanto, no se limita a las realizaciones precedentes, y podrá ser modificada de diversas maneras.

1162

REIVINDICACIONES

1. Un compuesto o sal del mismo en el cual:

el compuesto corresponde en estructura a la Fórmula 1-1:



(1-1); y

A^1 se selecciona del grupo formado por -H, alquilcarbonilo, alcoxicarbonilo, carbociclilcarbonilo, carbociclilalquilcarbonilo, heterociclilcarbonilo, heterociclilalquilcarbonilo, carbocicliloxicarbonilo, carbociclilalcoxicarbonilo, aminoalquilcarbonilo, alquil(tiocarbonilo), alcoxi(tiocarbonilo), carbociclil(tiocarbonilo), carbociclilalquil(tiocarbonilo), heterociclil(tiocarbonilo), heterociclilalquil(tiocarbonilo), carbocicliloxi(tiocarbonilo), carbociclilalcoxi(tiocarbonilo), y aminoalquil(tiocarbonilo), donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido; y

A^2 y A^3, junto con el átomo de carbono al cual ambos están unidos, forman un heterociclilo optativamente sustituido que contiene entre 5 y 8 miembros en el anillo; y

E^1 se selecciona del grupo formado por -O-, $-S(O)_2-$, -S(O)-, -S-, $-N(R^1)-$, $-C(O)-N(R^1)-$, $-N(R^1)-C(O)-$, y $-C(R^1)(R^2)-$; y

E^2 se selecciona del grupo formado por alquilo, cicloalquilo, alquilcicloalquilo, cicloalquilalquilo, y alquilcicloalquilalquilo donde cualquier miembro de dicho grupo es optativamente sustituido; y

E^2 forma un enlace de al menos 2 átomos de carbono entre E^1 y E^3; y

E^3 se selecciona del grupo formado por -C(O)-, -O-(CO)-, -C(O)-O-, -C(NR^3)-, -N(R^4)-, -N(R^4)-C(NR^3)-, -C(NR^3)-N(R^4)-, -C(O)-N(R^4)-, -N(R^4)-C(O)-, -N(R^4)-C(O)-N(R^5)-, -S-, -S(O)-, -N(R^4)-S(O)$_2$-, -S(O)$_2$-N(R^4)-, -C(O)-N(R^4)-N(R^5)-C(O)-, -C(R^4)(R^6)-C(O)-, -C(R^7)(R^8)-; y

E^4 se selecciona del grupo formado por un enlace, alquilo, y alquenilo donde el alquilo o alquenilo es optativamente sustituido; y

E^5 se selecciona del grupo formado por -H, -OH, alquilo, alquenilo, alquinilo, alcoxi, alcoxialquilo, carbociclilo, y heterociclilo donde cualquier miembro (excepto -H o, -OH) de dicho grupo es optativamente sustituido; y

R^1 y R^2 se seleccionan independientemente del grupo formado por -H y alquilo donde el alquilo es optativamente sustituido; y

R^3 se selecciona del grupo formado por -H y -OH; y

R^4 y R^5 se seleccionan independientemente del grupo formado por -H, alquilo, carbociclilo, carbociclilalquilo, heterociclilo, y heterociclilalquilo donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido; y

R^6 se selecciona del grupo formado por -CN y -OH; y

R^7 se selecciona del grupo formado por -H, halógeno, -OH, alquilo, alcoxi, y alcoxialquilo donde el alquilo , alcoxi, o alcoxialquilo es optativamente sustituido; y

R^8 se selecciona del grupo formado por -OH y alcoxi donde el alcoxi es optativamente sustituido; y

ni R^1 ni R^2 forman una estructura de anillo con E^2, E^3, E^4, o E^5; y

ni R^4 ni R^5 forman una estructura de anillo con E^2, E^4, o E^5; y

E^5 no es -H cuando E^3 es -C(R^7)(R^8)- y E^4 es un enlace.

1164

2. Un compuesto o sal del mismo de acuerdo con la cláusula 1 en el cual

A^1 se selecciona del grupo formado por -H, C_1-C_8-alquilcarbonilo, C_1-C_8-alcoxicarbonilo, carbociclilcarbonilo, carbociclil-C_1-C_8-alquilcarbonilo, heterociclilcarbonilo, heterociclil-C_1-C_8-alquilcarbonilo, carbocicliloxicarbonilo, carbociclil-C_1-C_8-alcoxicarbonilo, $N(R^9)(R^{10})$-C_1-C_8-alquilcarbonilo, C_1-C_8-alquil(tiocarbonilo), C_1-C_8-alcoxi(tiocarbonilo), carbociclil(tiocarbonilo), carbociclil-C_1-C_8-alquil(tiocarbonilo), heterociclil(tiocarbonilo), heterociclil-C_1-C_8-alquil(tiocarbonilo), carbociclilox(tiocarbonilo), carbociclil-C_1-C_8-alcoxi(tiocarbonilo), y $N(R^9)(R^{10})$-C_1-C_8-alquil(tiocarbonilo); y

E^2 se selecciona del grupo formado por C_2-C_{20}-alquilo, cicloalquilo, C_1-C_{10}-alquilcicloalquilo, cicloalquil-C_1-C_{10}-alquilo, y C_1-C_{10}-alquilcicloalquil-C_1-C_{10}-alquilo donde cualquier miembro de dicho grupo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, C_1-C_8-alquilo, y halo-C_1-C_8-alquilo; y

E^4 se selecciona del grupo formado por un enlace, C_1-C_{20}-alquilo, y C_2-C_{20}-alquenilo donde el C_1-C_{20}-alquilo o C_2-C_{20}-alquenilo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por:

halógeno, y

carbociclilo optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_8-alquilo, C_1-C_8-alcoxi, C_1-C_8-alcoxi-C_1-C_8-alquilo, carbociclilo, carbociclil-C_1-C_8-alquilo, halo-C_1-C_8-alquilo, halo-C_1-C_8-alcoxi, C_1-C_8-alcoxi-C_1-

1165

C_8-alquilo sustituido con halógeno , halocarbociclilo, y carbociclil-C_1-C_8-alquilo sustituido con halógeno; y

E^5 se selecciona del grupo formado por -H, -OH, C_1-C_{20}-alquilo, C_2-C_{20}-alquenilo, C_2-C_{20}-alquinilo, C_1-C_{20}-alcoxi, C_1-C_{20}-alcoxi-C_1-C_{20}-alquilo, carbociclilo, y heterociclilo donde:

el C_1-C_{20}-alquilo, C_2-C_{20}-alquenilo, C_2-C_{20}-alquinilo, C_1-C_{20}-alcoxi, o C_1-C_{20}-alcoxi-C_1-C_{20}-alquilo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, y -CN, y

el carbociclilo o heterociclilo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, -CN, C_1-C_8-alquilo, C_1-C_8-alcoxi, C_1-C_8-alcoxi-C_1-C_8-alquilo, $-N(R^{11})(R^{12})$, $-C(O)(R^{13})$, $-S-R^{11}$, $-S(O)_2-R^{11}$, carbociclilo, carbociclil-C_1-C_8-alquilo, halo-C_1-C_8-alquilo, halo-C_1-C_8-alcoxi, C_1-C_8-alcoxi-C_1-C_8-alquilo sustituido con halógeno , halocarbociclilo, carbociclil-C_1-C_8-alquilo sustituido con halógeno, C_1-C_8-alquilcarbociclilo, C_1-C_8-alquilcarbociclilo sustituido con halógeno, hidroxicarbociclilo, y heterociclilo ; y

R^1 y R^2 se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, y halo-C_1-C_8-alquilo; y

R^4 y R^5 se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, carbociclilo, carbociclil-C_1-C_8-alquilo, heterociclilo, y heterociclil-C_1-C_8-alquilo donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido con uno o más halógenos; y

1166

R^7 se selecciona del grupo formado por -H, halógeno, -OH, C_1-C_8-alquilo, C_1-C_8-alcoxi, C_1-C_8-alcoxi-C_1-C_8-alquilo, halo-C_1-C_8-alquilo, halo-C_1-C_8-alcoxi, y C_1-C_8-alcoxi-C_1-C_8-alquilo sustituido con halógeno ; y

R^8 se selecciona del grupo formado por -OH, C_1-C_8-alcoxi, y halo-C_1-C_8-alcoxi; y

R^9 y R^{10} se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, C_1-C_8-alcoxicarbonilo, C_1-C_8-alquilcarbonilo, carbociclil-C_1-C_8-alquilo, y carbociclil-C_1-C_8-alcoxicarbonilo; y

R^{11} y R^{12} se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, carbociclilo, carbociclil-C_1-C_8-alquilo, heterociclilo, y heterociclil-C_1-C_8-alquilo donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido con uno o más halógenos; y

R^{13} se selecciona del grupo formado por -H, C_1-C_8-alquilo, -O-R^{14}, -N(R^{14})(R^{15}), carbociclil-C_1-C_8-alquilo, heterociclil-C_1-C_8-alquilo, halo-C_1-C_8-alquilo, carbociclil-C_1-C_8-alquilo sustituido con halógeno, y heterociclil-C_1-C_8-alquilo sustituido con halógeno; y

R^{14} y R^{15} se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, carbociclilo, carbociclil-C_1-C_8-alquilo, heterociclilo, y heterociclil-C_1-C_8-alquilo donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido con uno o más halógenos; y

E^5 no es -H cuando E^3 es -C(R^7)(R^8)- y E^4 es un enlace.

3. Un compuesto o sal del mismo de acuerdo con la cláusula 2 en el cual A^1 es -H.

4. Un compuesto o sal del mismo de acuerdo con la cláusula 3 en el cual:

E^2 es C_2-C_6-alquilo optativamente sustituido con uno o más halógenos; y

E^4 se selecciona del grupo formado por un enlace, C_1-C_3-alquilo, y C_2-C_3-alquenilo donde cualquier miembro (excepto el enlace) de dicho grupo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por:

halógeno, y

carbociclilo optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, halocarbociclilo, y carbociclil-C_1-C_6-alquilo sustituido con halógeno; y

E^5 se selecciona del grupo formado por -H, -OH, C_1-C_6-alquilo, C_2-C_6-alquenilo, C_2-C_6-alquinilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, carbociclilo, y heterociclilo donde:

el C_1-C_6-alquilo, C_2-C_6-alquenilo, C_2-C_6-alquinilo, C_1-C_6-alcoxi, o C_1-C_6-alcoxi-C_1-C_6-alquilo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, y -CN, y

el carbociclilo o heterociclilo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-

1168

alquilo, -N(R^{11})(R^{12}), -C(O)(R^{13}), -S-R^{11}, -S(O)$_2$-R^{11}, carbociclilo, carbociclil-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, halocarbociclilo, carbociclil-C_1-C_6-alquilo sustituido con halógeno, C_1-C_6-alquilcarbociclilo, halógeno-sustituido C_1-C_6-alquilcarbociclilo, hidroxicarbociclilo, y heteroarilo-; y

R^1 y R^2 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, y halo-C_1-C_6-alquilo; y

R^4 y R^5 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido con uno o más halógenos; y

R^7 se selecciona del grupo formado por -H, halógeno, -OH, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, y C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno; y

R^8 se selecciona del grupo formado por -OH, C_1-C_6-alcoxi, y halo-C_1-C_6-alcoxi; y

R^{11} y R^{12} se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido con uno o más halógenos; y

R^{13} se selecciona del grupo formado por -H, C_1-C_6-alquilo, -O-R^{14}, -N(R^{14})(R^{15}), carbociclil-C_1-C_6-alquilo, y heterociclil-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, carbociclil-C_1-C_6-alquilo sustituido con halógeno, y heterociclil-C_1-C_6-alquilo sustituido con halógeno; y

1169

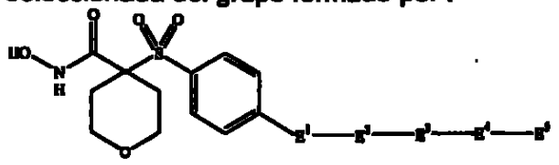
R^{14} y R^{15} se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido con uno o más halógenos; y

E^5 no es -H cuando E^3 es $-C(R^7)(R^8)-$ y E^4 es un enlace.

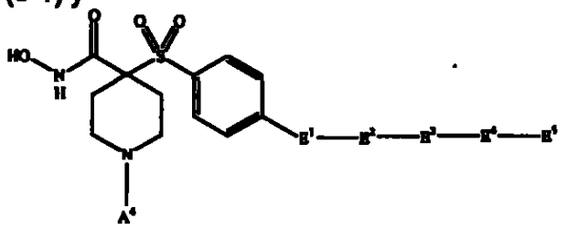
5. Un compuesto o sal del mismo de acuerdo con la cláusula 4 en el cual A^2 y A^3, junto con el átomo de carbono al cual están ambos unidos, forman un heterociclilo optativamente sustituido que contiene ya sea 5 o 6 miembros en el anillo.

6. Un compuesto o sal del mismo de acuerdo con la cláusula 5 en el cual:

el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



(6-1) y



(6-2); y

A^4 se selecciona del grupo formado por -H, alquilo, alquilcarbonilo, alquilcarbonilalquilo, alquilcarbonilalquilcarbonilo, alcoxicarbonilo, alcoxicarbonilalquilo, alcoxicarbonilalquilcarbonilo, alquilsulfonilo, alquiliminocarbonilo, alquenilo, alquinilo, alcoxialquilo, alquiltioalquilo,

1170

alquilsulfonilalquilo, alquilsufoxidoalquilo, alquiltioalquenilo, alquilsulfoxidoalquenilo, alquilsulfonilalquenilo, carbociclilo, carbociclilalquilo, carbociclilalcoxialquilo, carbociclilcarbonilo, carbociclilsulfonilo, carbociclliminocarbonilo, carbocicliloxicarbonilo, carbociliitioalquilo, carbocilisulfoxidoalquilo, carbocilisulfonilalquilo, carbociclitioalquenilo, carbociclilsulfoxidoalquenilo, carbociclilsulfonilalquenilo, heterociclilo, heterociclilalquilo, heterociclilalcoxialquilo, heterociclilcarbonilo, heterociclitioalquilo, heterociclilsulfoxidoalquilo, heterociclilsulfonilalquilo, heterociclitioalquenilo, heterociclilsulfoxidoalquenilo, heterociclilsulfonilalquenilo, heterociclilsulfonilo, heterociclliminocarbonilo, heterociclilalquilcarbonilo, heterociclilcarbonilalquilcarbonilo, heterociclilsulfonilo, heterocicilcarbonilalquilo, aminoalquilcarbonilo, aminocarbonilo, aminocarbonilalquilcarbonilo, aminosulfonilo, aminosulfonilalquilo, aminoalquilo, aminocarbonilalquilo, y aminoalquilsulfonilo donde:

cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido.

7. Un compuesto o sal del mismo de acuerdo con la cláusula 6 en el cual:

A^4 se selecciona del grupo formado por -H, C_1-C_8-alquilo, C_1-C_8-alquilcarbonilo, C_1-C_8-alquilcarbonil-C_1-C_8-alquilo, C_1-C_8-alquilcarbonil-C_1-C_8-alquilcarbonilo, C_1-C_8-alcoxicarbonilo, C_1-C_8-alcoxicarbonil-C_1-C_8-alquilo, C_1-C_8-alcoxicarbonil-C_1-C_8-alquilcarbonilo, C_1-C_8-alquilsulfonilo, C_1-C_8-alquilliminocarbonilo, C_2-C_8-alquenilo, C_2-C_8-alquinilo, C_1-C_8-alcoxi-C_1-C_8-alquilo, C_1-C_8-alquiltio-C_1-C_8-alquilo, C_1-C_8-alquiltio-C_2-C_8-alquenilo, C_1-C_8-

alquilsulfóxido-C_1-C_6-alquilo, C_1-C_6-alquilsulfóxido-C_2-C_6-alquenilo, C_1-C_6-alquilsulfonil-C_1-C_6-alquilo, C_1-C_6-alquilsulfonil-C_2-C_6-alquenilo, carbociclilo, carbociclil-C_1-C_6-alquilo, carbociclil-C_1-C_6-alcoxi-C_1-C_6-alquilo, carbociclilcarbonilo, carbociclilsulfonilo, carbociclliminocarbonilo, carbociclioxicarbonilo, carbociclitio-C_1-C_6-alquilo, carbociclitio-C_2-C_6-alquenilo, carbociclilsulfóxido-C_1-C_6-alquilo, carbociclilsulfóxido-C_2-C_6-alquenilo, carbociclilsulfonil-C_1-C_6-alquilo, carbociclilsulfonil-C_2-C_6-alquenilo, heterociclilo, heterociclil-C_1-C_6-alquilo, heterociclil-C_1-C_6-alcoxi-C_1-C_6-alquilo, heterociclilcarbonilo, heterociclitio-C_1-C_6-alquilo, heterociclilsulfóxido-C_1-C_6-alquilo, heterociclilsulfonil-C_1-C_6-alquilo, heterociclitio-C_2-C_6-alquenilo, heterociclilsulfóxido-C_2-C_6-alquenilo, heterociclilsulfonil-C_2-C_6-alquenilo, heterociclilsulfonilo, heterocicliliminocarbonilo, heterociclil-C_1-C_6-alquilcarbonilo, heterociclilcarbonil-C_1-C_6-alquilcarbonilo, heterociclilsulfonilo, heterociclilcarbonil-C_1-C_6-alquilo, N(R^{16})(R^{17})-C_1-C_6-alquilcarbonilo, N(R^{16})(R^{17})-carbonilo, N(R^{16})(R^{17})-carbonil-C_1-C_6-alquilcarbonilo, N(R^{16})(R^{17})-sulfonilo, N(R^{16})(R^{17})-sulfonil-C_1-C_6-alquilo, N(R^{16})(R^{17})-C_1-C_6-alquilo, N(R^{16})(R^{17})-carbonil-C_1-C_6-alquilo, y N(R^{16})(R^{17})-C_1-C_6-alquilsulfonilo donde:

cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -CN, -C(O)-OH, -SH, $-SO_3H$, y NO_2; y

R^{16} y R^{17} se seleccionan independientemente del grupo formado por -H, -OH, C_1-C_6-alquilo, C_1-C_6-alquil-carbonilo, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_2-C_6-alquenilo, C_2-C_6-alquinilo, C_1-C_6-alquil-tio-C_1-C_6-alquilo, C_1-C_6-alquil-sulfóxido-C_1-C_6-alquilo, C_1-C_6-alquil-sulfonil-C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-

alquilo, carbociclilcarbonilo, carbociclil-C_1-C_8-alcoxi-C_1-C_8-alquilo, carbociclil-tio-C_1-C_8-alquilo, carbociclilsulfóxido-C_1-C_8-alquilo, carbociclilsulfonil-C_1-C_8-alquilo, heterociclilo, heterociclil-C_1-C_8-alquilo, heterociclil-C_1-C_8-alcoxi-C_1-C_8-alquilo, heterociclilcarbonilo, heterociclil-tio-C_1-C_8-alquilo, heterociclilsulfóxido-C_1-C_8-alquilo, heterociclilsulfonil-C_1-C_8-alquilo, aminocarbonil-C_1-C_8-alquilo, C_1-C_8-alquiloxicarbonilamino-C_1-C_8-alquilo, y amino-C_1-C_8-alquilo donde:

cualquier miembro (excepto -H o OH) de dicho grupo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -CN, -C(O)-OH, -SH, $-SO_3H$, y NO_2, y

el nitrógeno del amino-C_1-C_8-alquilo es optativamente sustituido con 1 o 2 sustituyentes seleccionados independientemente del grupo formado por C_1-C_8-alquilo, C_1-C_8-alquilcarbonilo, carbociclilo, y carbociclil-C_1-C_8-alquilo, y

no más de uno de R^{16} o R^{17} es -OH.

8. Un compuesto o sal del mismo de acuerdo con la cláusula 7 en el cual A^4 se selecciona del grupo formado por -H, C_1-C_8-alquilo, C_1-C_8-alcoxi-C_1-C_8-alquilo, carbociclilo, carbociclil-C_1-C_8-alquilo, C_1-C_8-alquilsulfonilo, C_3-C_8-alquenilo, C_3-C_8-alquinilo donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido con halógeno.

9. Un compuesto o sal del mismo de acuerdo con la cláusula 8 en el cual A^4 se selecciona del grupo formado por -H, C_1-C_4-alquilo, C_1-C_2-alcoxi-C_1-C_3-alquilo, C_3-C_8-cicloalquilo, C_3-C_8-cicloalquil-C_1-C_3-alquilo, fenilo, fenil-C_1-C_3-alquilo, C_1-C_2-alquilsulfonilo, C_3-C_4-alquenilo, C_3-C_4-alquinilo donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido con halógeno.

1173

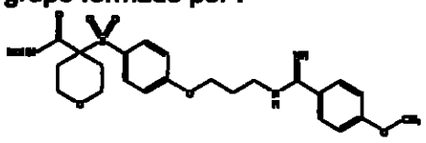
10. Un compuesto o sal del mismo de acuerdo con la cláusula 9 en el cual A^4 se selecciona del grupo formado por -H, etilo, metoxietilo, ciclopropilo, ciclopropilmetilo, bencilo, metilsulfonilo, C_3-alquenilo, y C_3-alquinilo donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido con halógeno.

11. Un compuesto o sal del mismo de acuerdo con la cláusula 10 en el cual A^4 se selecciona del grupo formado por -H, etilo, metoxietilo, ciclopropilo, ciclopropilmetilo, y bencilo donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido con halógeno.

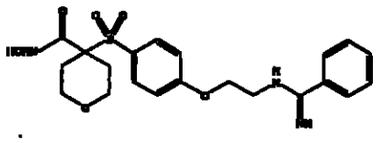
12. Un compuesto o sal del mismo de acuerdo con la cláusula 7 en el cual la sal comprende un ácido seleccionado del grupo formado por HCl y CF_3COOH.

13. Un compuesto o sal del mismo de acuerdo con la cláusula 7 en el cual E^3 es $-N(R^4)-C(NR^3)-$.

14. Un compuesto o sal del mismo de acuerdo con la cláusula 13 en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



y



(14-1) (14-2).

15. Un compuesto o sal del mismo de acuerdo con la cláusula 7 en el cual E^3 es -C(O)-.

16. Un compuesto o sal del mismo de acuerdo con la cláusula 15 en el cual E^5 es carbociclilo optativamente sustituido con uno o más sustituyentes

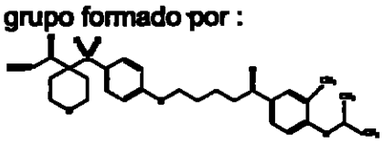
independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, -$N(R^{11})(R^{12})$, -$C(O)(R^{13})$, -S-R^{11}, -$S(O)_2$-R^{11}, arilo, aril-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, haloarilo, C_1-C_6-alquilo sustituido con halógeno, C_1-C_6-alquilarilo, C_1-C_6-alquilarilo sustituido con halógeno, hidroxiarilo, y heteroarilo.

17. Un compuesto o sal del mismo de acuerdo con la cláusula 16 en el cual E^5 es arilo optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, -$N(R^{11})(R^{12})$, -$C(O)(R^{13})$, -S-R^{11}, -$S(O)_2$-R^{11}, arilo, aril-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, haloarilo, C_1-C_6-alquilo sustituido con halógeno, C_1-C_6-alquilarilo, C_1-C_6-alquilarilo sustituido con halógeno, hidroxiarilo, y heteroarilo.

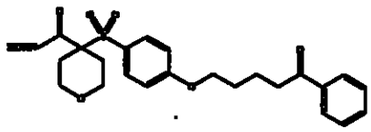
18. Un compuesto o sal del mismo de acuerdo con la cláusula 17 en el cual E^5 es fenilo optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, -$N(R^{11})(R^{12})$, -$C(O)(R^{13})$, -S-R^{11}, -$S(O)_2$-R^{11}, arilo, aril-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, haloarilo, C_1-C_6-alquilo sustituido con halógeno, C_1-C_6-alquilarilo, C_1-C_6-alquilarilo sustituido con halógeno, hidroxiarilo, y heteroarilo.

1175

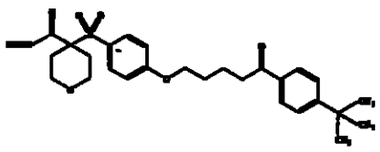
19. Un compuesto o sal del mismo de acuerdo con la cláusula 18 en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



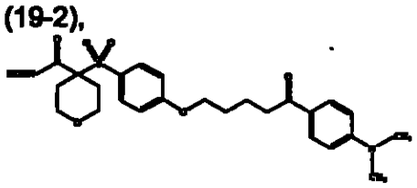
(19-1),



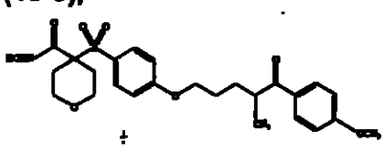
(19-2),



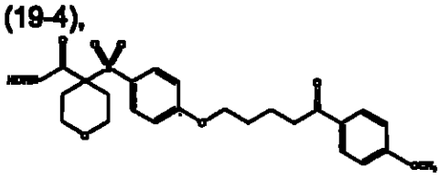
(19-3),



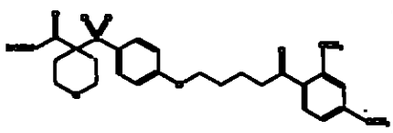
(19-4),



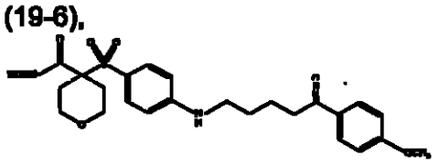
(19-5),



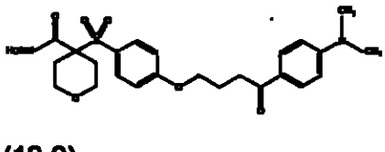
(19-6),



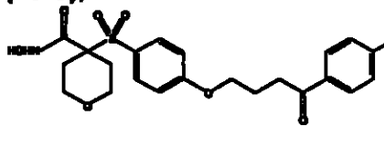
(19-7),



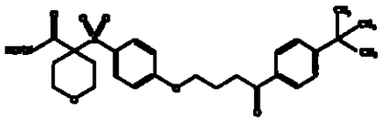
(19-8),



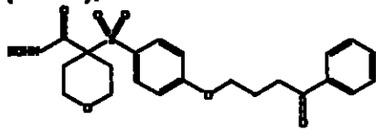
(19-9),



(19-10),

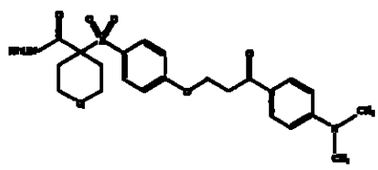


(19-11),

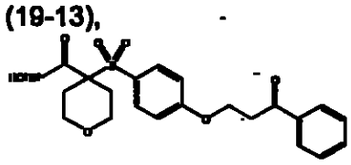


(19-12),

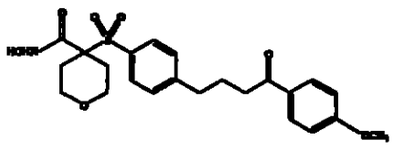
1176



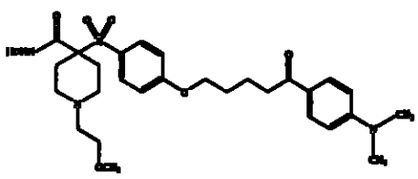
(19-13),



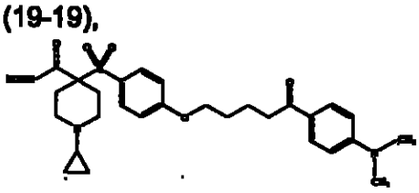
(19-15),



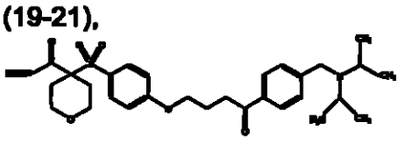
(19-17),



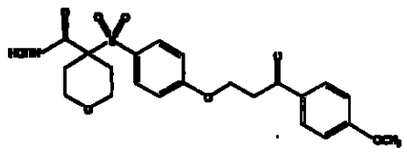
(19-19),



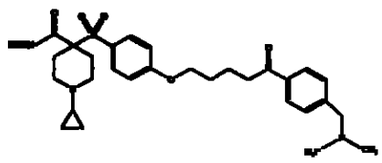
(19-21),



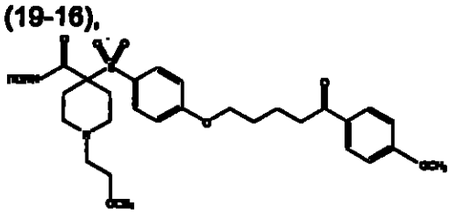
(19-23),



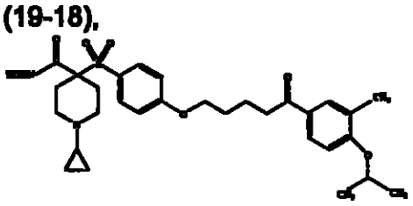
(19-14),



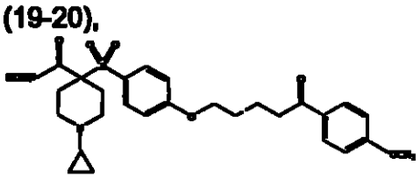
(19-16),



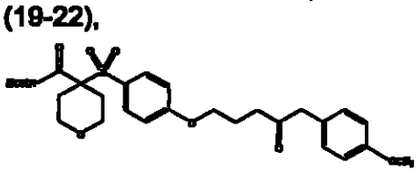
(19-18),



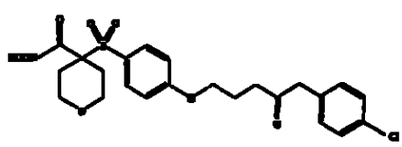
(19-20),



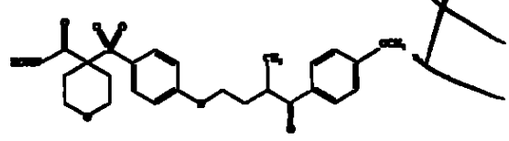
(19-22),



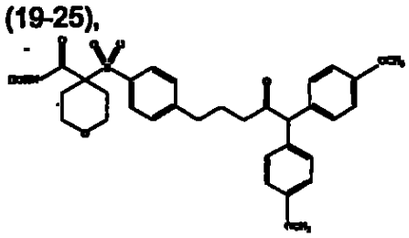
(19-24),



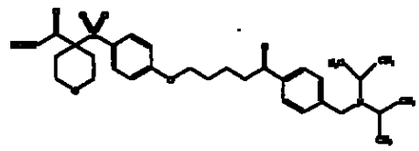
(19-25),



(19-26),



(19-27), y



(19-28).

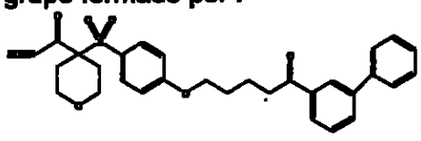
20. Un compuesto o sal del mismo de acuerdo con la cláusula 17 en el cual E^5 es fenilo que es:

sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por arilo, haloarilo, aril-C_1-C_6-alquilo, y C_1-C_6-alquilo sustituido con halógeno; y

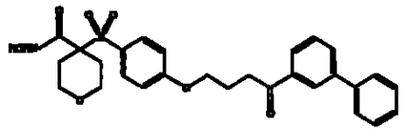
optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, -N(R^{11})(R^{12}), -C(O)(R^{13}), -S-R^{11}, -S(O)$_2$-R^{11}, arilo, aril-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, haloarilo, C_1-C_6-alquilo sustituido con halógeno, C_1-C_6-alquilarilo, C_1-C_6-alquilarilo sustituido con halógeno, hidroxiarilo, y heteroarilo.

1178

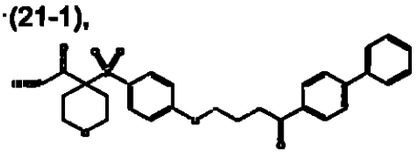
21. Un compuesto o sal del mismo de acuerdo con la cláusula 20 en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



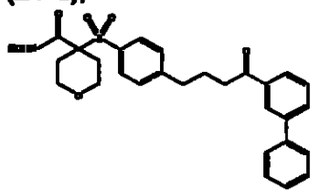
(21-1),



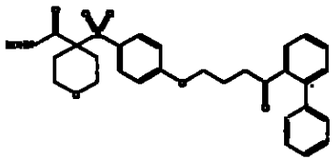
(21-2),



(21-3),



(21-4), y

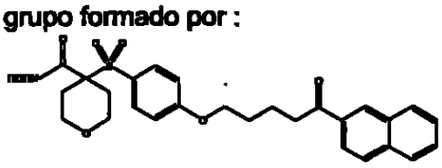


(21-5).

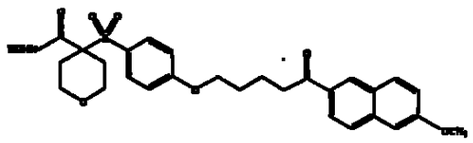
22. Un compuesto o sal del mismo de acuerdo con la cláusula 17 en el cual E^5 es naftalenilo optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, -$N(R^{11})(R^{12})$, -$C(O)(R^{13})$, -S-R^{11}, -$S(O)_2$-R^{11}, arilo, aril-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, haloarilo, C_1-C_6-alquilo sustituido con halógeno, C_1-C_6-alquilarilo, C_1-C_6-alquilarilo sustituido con halógeno, hidroxiarilo, y heteroarilo.

1179

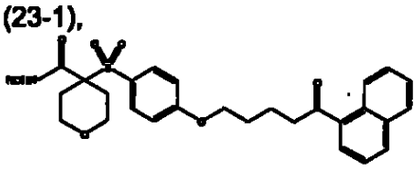
23. Un compuesto o sal del mismo de acuerdo con la cláusula 22 en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



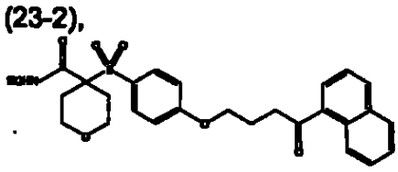
(23-1),



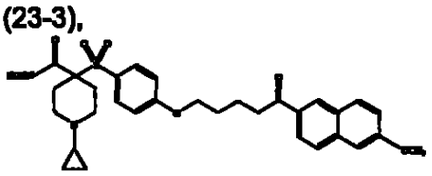
(23-2),



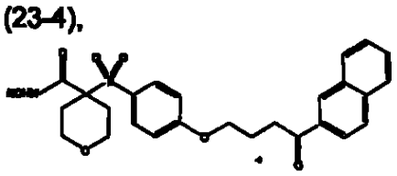
(23-3),



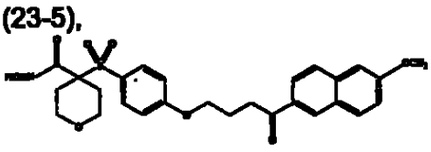
(23-4),



(23-5),



(23-6), y

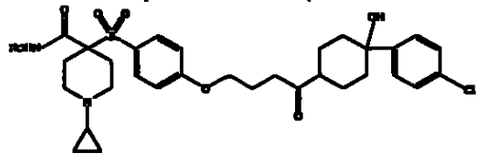


(23-7).

24. Un compuesto o sal del mismo de acuerdo con la cláusula 16 en el cual E^5 es C_5-C_6-cicloalquilo optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, -$N(R^{11})(R^{12})$, -$C(O)(R^{13})$, -S-R^{11}, -$S(O)_2$-R^{11}, arilo, aril-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, haloarilo, C_1-C_6-alquilo sustituido con halógeno, C_1-C_6-alquilarilo, C_1-C_6-alquilarilo sustituido con halógeno, hidroxiarilo, y heteroarilo.

1180

25. Un compuesto o sal del mismo de acuerdo con la cláusula 24 en el cual el compuesto corresponde en estructura a la siguiente fórmula:



(25-1).

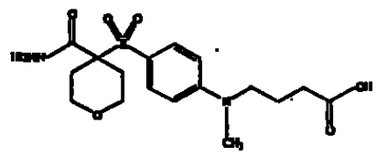
26. Un compuesto o sal del mismo de acuerdo con la cláusula 15 en el cual E^5 se selecciona del grupo formado por -H, -OH, C_1-C_6-alquilo, C_2-C_6-alquenilo, C_2-C_6-alquinilo, C_1-C_6-alcoxi, y C_1-C_6-alcoxi-C_1-C_6-alquilo donde:

el C_1-C_6-alquilo, C_2-C_6-alquenilo, C_2-C_6-alquinilo, C_1-C_6-alcoxi, o C_1-C_6-alcoxi-C_1-C_6-alquilo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, y, -CN.

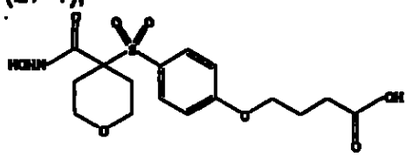
27. Un compuesto o sal del mismo de acuerdo con la cláusula 26 en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



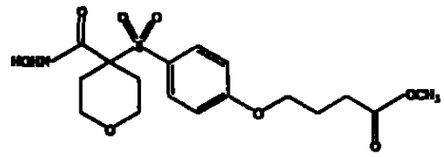
(27-1),



(27-2),

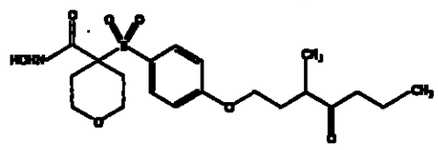


(27-3),



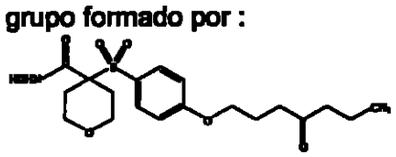
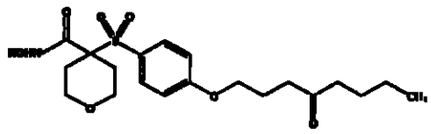
(27-4), y

1181



(27-5).

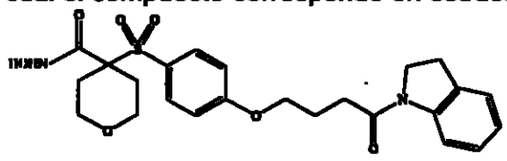
28. Un compuesto o sal del mismo de acuerdo con la cláusula 26 en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :

 y 

(28-1) (28-2).

29. Un compuesto o sal del mismo de acuerdo con la cláusula 15 en el cual E^5 es heterociclilo optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, -$N(R^{11})(R^{12})$, -$C(O)(R^{13})$, -S-R^{11}, -$S(O)_2$-R^{11}, arilo, aril-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, haloarilo, C_1-C_6-alquilo sustituido con halógeno, C_1-C_6-alquilarilo, C_1-C_6-alquilarilo sustituido con halógeno, hidroxiarilo, y heteroarilo.

30. Un compuesto o sal del mismo de acuerdo con la cláusula 29 en el cual el compuesto corresponde en estructura a la siguiente fórmula:



(30-1).

1182

31. Un compuesto o sal del mismo de acuerdo con la cláusula 29 en el cual E^5 se selecciona del grupo formado por furanilo, tetrahidropiranilo, dihidrofuranilo, tetrahidrofuranilo, tiofenilo, dihidrotiofenilo, tetrahidrotiofenilo, pirrolilo, isopirrolilo, pirrolinilo, pirrolidinilo, imidazolilo, isoimidazolilo, imidazolinilo, imidazolidinilo, pirazolilo, pirazolinilo, pirazolidinilo, triazolilo, tetrazolilo, ditiolilo, oxatiolilo, oxazolilo, isoxazolilo, oxazolidinilo, isoxazolidinilo, tiazolilo, isotiazolilo, tiazolinilo, isotiazolinilo, tiazolidinilo, isotiazolidinilo, tiodiazolilo, oxatiazolilo, oxadiazolilo, oxatriazolilo, dioxazolilo, oxatiazolilo, oxatiolilo, oxatiolanilo, piranilo, dihidropiranilo, piridinilo, piperidinilo, diazinilo, piperazinilo, triazinilo, oxazinilo, isoxazinilo, oxatiazinilo, oxadiazinilo, morfolinilo, azepinilo, oxepinilo, tiepinilo, diazepinilo, indolizinilo, pirindinilo, piranopirrolilo, 4H-quinolizinilo, purinilo, naftiridinilo, piridopiridinilo, pteridinilo, indolilo, isoindolilo, indoleninilo, isoindazolilo, benzazinilo, ftalazinilo, quinoxalinilo, quinazolinilo, benzodiazinilo, benzopiranilo, benzotiopiranilo, benzoxazolilo, indoxazinilo, antranililo, benzodioxolilo, benzodioxanilo, benzoxadiazolilo, benzofuranilo, isobenzofuranilo, benzotienilo, isobenzotienilo, benzotiazolilo, benzotiadiazolilo, bencimidazolilo, benzotriazolilo, benzoxazinilo, bencisoxazinilo, tetrahidroisoquinolinilo, carbazolilo, xantenilo, y acridinilo donde:

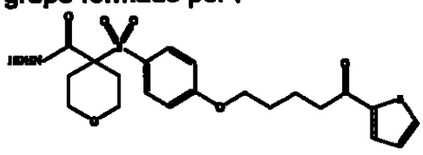
cualquier miembro de dicho grupo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, -CN, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, $-N(R^{11})(R^{12})$, $-C(O)(R^{13})$, $-S-R^{11}$, $-S(O)_2-R^{11}$, arilo, aril-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con

1183

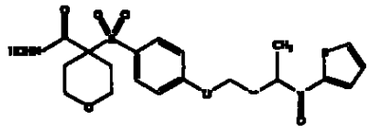
halógeno, haloarilo, C_1-C_6-alquilo sustituido con halógeno, C_1-C_6-alquilarilo, C_1-C_6-alquilarilo sustituido con halógeno, hidroxiarilo, y heteroarilo.

32. Un compuesto o sal del mismo de acuerdo con la cláusula 31 en el cual E^5 es tiofenilo-optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, -N(R^{11})(R^{12}), -C(O)(R^{13}), -S-R^{11}, -S(O)$_2$-R^{11}, arilo, aril-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, haloarilo, C_1-C_6-alquilo sustituido con halógeno, C_1-C_6-alquilarilo, C_1-C_6-alquilarilo sustituido con halógeno, hidroxiarilo, y heteroarilo.

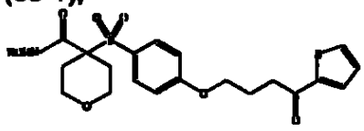
33. Un compuesto o sal del mismo de acuerdo con la cláusula 32 en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



(33-1),



(33-2), y



(33-3).

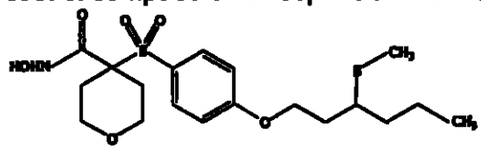
34. Un compuesto o sal del mismo de acuerdo con la cláusula 7 en el cual E^3 es -S-.

1184

35. Un compuesto o sal del mismo de acuerdo con la cláusula 34 en el cual E^5 se selecciona del grupo formado por -H, -OH, C_1-C_6-alquilo, C_2-C_6-alquenilo, C_2-C_6-alquinilo, C_1-C_6-alcoxi, y C_1-C_6-alcoxi-C_1-C_6-alquilo donde:

el C_1-C_6-alquilo, C_2-C_6-alquenilo, C_2-C_6-alquinilo, C_1-C_6-alcoxi, o C_1-C_6-alcoxi-C_1-C_6-alquilo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, y -CN.

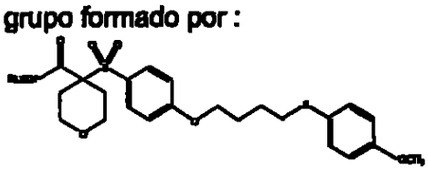
36. Un compuesto o sal del mismo de acuerdo con la cláusula 35 en el cual el compuesto corresponde en estructura a la siguiente fórmula:



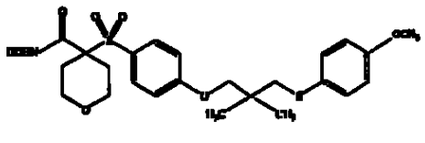
(36-1).

37. Un compuesto o sal del mismo de acuerdo con la cláusula 34 en el cual E^5 es fenilo optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, -N(R^{11})(R^{12}), -C(O)(R^{13}), -S-R^{11}, -S(O)$_2$-R^{11}, arilo, aril-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, haloarilo, C_1-C_6-alquilo sustituido con halógeno, C_1-C_6-alquilarilo, C_1-C_6-alquilarilo sustituido con halógeno, hidroxiarilo, y heteroarilo.

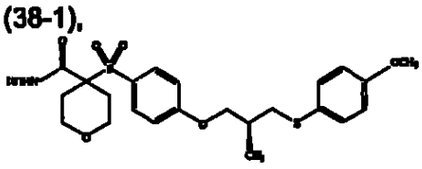
38. Un compuesto o sal del mismo de acuerdo con la cláusula 37 en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



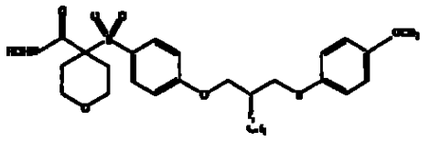
(38-1),



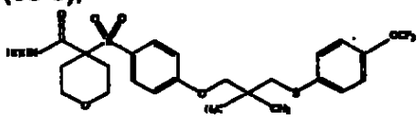
(38-2),



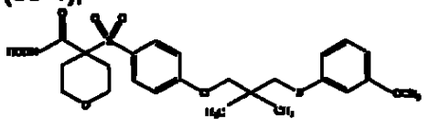
(38-3),



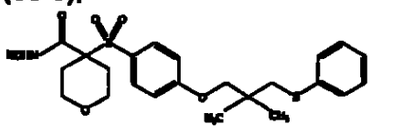
(38-4),



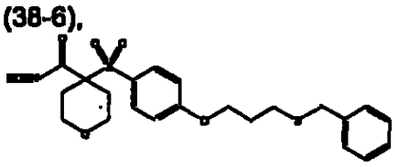
(38-5),



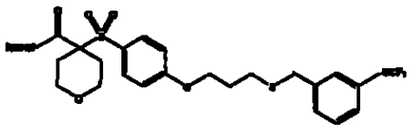
(38-6),



(38-7),



(38-8), y



(38-9).

39. Un compuesto o sal del mismo de acuerdo con la cláusula 34 en el cual E^5 es heterociclilo optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, -$N(R^{11})(R^{12})$, -$C(O)(R^{13})$, -S-R^{11}, -$S(O)_2$-R^{11}, arilo, aril-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-

C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, haloarilo, C_1-C_6-alquilo sustituido con halógeno, C_1-C_6-alquilarilo, C_1-C_6-alquilarilo sustituido con halógeno, hidroxiarilo, y heteroarilo.

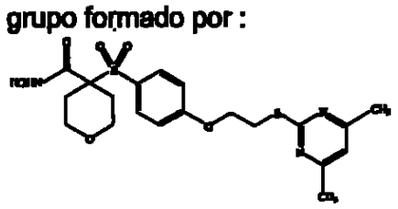
40. Un compuesto o sal del mismo de acuerdo con la cláusula 39 en el cual E^5 se selecciona del grupo formado por furanilo, tetrahidropiranilo, dihidrofuranilo, tetrahidrofuranilo, tiofenilo, dihidrotiofenilo, tetrahidrotiofenilo, pirrolilo, isopirrolilo, pirrolinilo, pirrolidinilo, imidazolilo, isoimidazolilo, imidazolinilo, imidazolidinilo, pirazolilo, pirazolinilo, pirazolidinilo, triazolilo, tetrazolilo, ditiolilo, oxatiolilo, oxazolilo, isoxazolilo, oxazolidinilo, isoxazolidinilo, tiazolilo, isotiazolilo, tiazolinilo, isotiazolinilo, tiazolidinilo, isotiazolidinilo, tiodiazolilo, oxatiazolilo, oxadiazolilo, oxatriazolilo, dioxazolilo, oxatiazolilo, oxatiolilo, oxatiolanilo, piranilo, dihidropiranilo, piridinilo, piperidinilo, diazinilo, piperazinilo, triazinilo, oxazinilo, isoxazinilo, oxatiazinilo, oxadiazinilo, morfolinilo, azepinilo, oxepinilo, tiepinilo, diazepinilo, indolizinilo, pirindinilo, piranopirrolilo, 4H-quinolizinilo, purinilo, naftiridinilo, piridopiridinilo, pteridinilo, indolilo, isoindolilo, indoleninilo, isoindazolilo, benzazinilo, ftalazinilo, quinoxalinilo, quinazolinilo, benzodiazinilo, benzopiranilo, benzotiopiranilo, benzoxazolilo, indoxazinilo, antranililo, benzodioxolilo, benzodioxanilo, benzoxadiazolilo, benzofuranilo, isobenzofuranilo, benzotienilo, isobenzotienilo, benzotiazolilo, benzotiadiazolilo, bencimidazolilo, benzotriazolilo, benzoxazinilo, bencisoxazinilo, tetrahidroisoquinolinilo, carbazolilo, xantenilo, y acridinilo donde:

cualquier miembro de dicho grupo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-

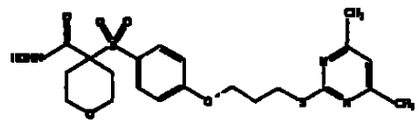
alquilo, -N(R^{11})(R^{12}), -C(O)(R^{13}), -S-R^{11}, -S(O)$_2$-R^{11}, arilo, aril-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, haloarilo, C_1-C_6-alquilo sustituido con halógeno, C_1-C_6-alquilarilo, C_1-C_6-alquilarilo sustituido con halógeno, hidroxiarilo, y heteroarilo.

41. Un compuesto o sal del mismo de acuerdo con la cláusula 40 en el cual E^5 es pirimidinilo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, -N(R^{11})(R^{12}), -C(O)(R^{13}), -S-R^{11}, -S(O)$_2$-R^{11}, arilo, aril-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, haloarilo, C_1-C_6-alquilo sustituido con halógeno, C_1-C_6-alquilarilo, C_1-C_6-alquilarilo sustituido con halógeno, hidroxiarilo, y heteroarilo.

42. Un compuesto o sal del mismo de acuerdo con la cláusula 41 en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



y



(42-1)

(42-2).

43. Un compuesto o sal del mismo de acuerdo con la cláusula 39 en el cual E^5 es heterociclilo de 2 anillos fusionados optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, -N(R^{11})(R^{12}), -C(O)(R^{13}), -S-R^{11}, -S(O)$_2$-R^{11}, arilo, aril-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con

halógeno, haloarilo, C_1-C_6-alquilo sustituido con halógeno, C_1-C_6-alquilarilo, C_1-C_6-alquilarilo sustituido con halógeno, hidroxiarilo, y heteroarilo.

44. Un compuesto o sal del mismo de acuerdo con la cláusula 43 en el cual E^5 se selecciona del grupo formado por indolizinilo, pirindinilo, piranopirrolilo, 4H-quinolizinilo, purinilo, naftiridinilo, piridopiridinilo, pteridinilo, indolilo, isoindolilo, indoleninilo, isoindazolilo, benzazinilo, ftalazinilo, quinoxalinilo, quinazolinilo, benzodiazinilo, benzopiranilo, benzotiopiranilo, benzoxazolilo, indoxazinilo, antranililo, benzodioxolilo, benzodioxanilo, benzoxadiazolilo, benzofuranilo, isobenzofuranilo, benzotienilo, isobenzotienilo, benzotiazolilo, benzotiadiazolilo, bencimidazolilo, benzotriazolilo, benzoxazinilo, bencisoxazinilo, y tetrahidroisoquinolinilo donde:

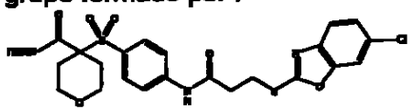
cualquier miembro de dicho grupo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, -CN, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, $-N(R^{11})(R^{12})$, $-C(O)(R^{13})$, $-S-R^{11}$, $-S(O)_2-R^{11}$, arilo, aril-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, haloarilo, C_1-C_6-alquilo sustituido con halógeno, C_1-C_6-alquilarilo, C_1-C_6-alquilarilo sustituido con halógeno, hidroxiarilo, y heteroarilo.

45. Un compuesto o sal del mismo de acuerdo con la cláusula 44 en el cual E^5 se selecciona del grupo formado por benzoxazolilo y benzotiazolilo donde cualquier miembro de dicho grupo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, -CN, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, $-N(R^{11})(R^{12})$, $-C(O)(R^{13})$, $-S-R^{11}$, $-S(O)_2-R^{11}$, arilo, aril-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con

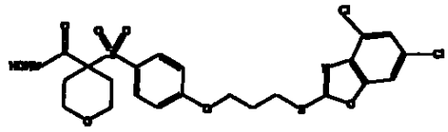
1189

halógeno, haloarilo, C_1-C_6-alquilo sustituido con halógeno, C_1-C_6-alquilarilo, C_1-C_6-alquilarilo sustituido con halógeno, hidroxiarilo, y heteroarilo.

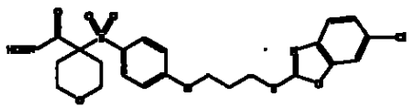
46. Un compuesto o sal del mismo de acuerdo con la cláusula 45 en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



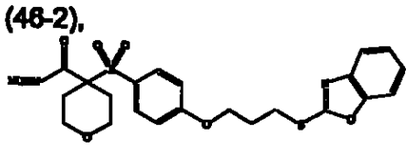
(46-1),



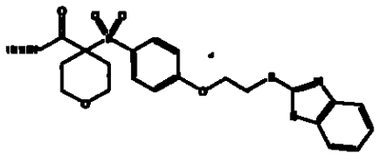
(46-2),



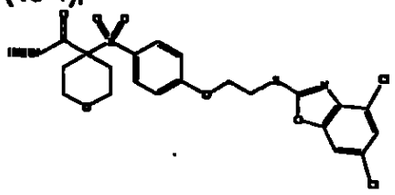
(46-3),



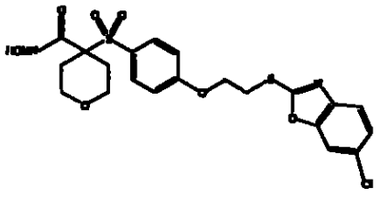
(46-4),



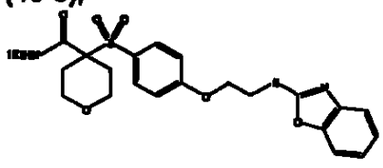
(46-5),



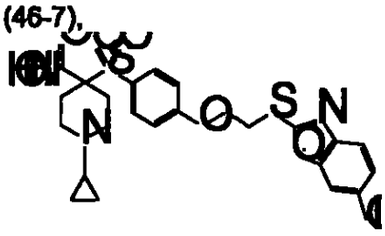
(46-6),



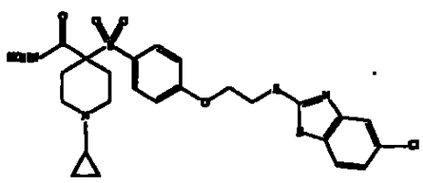
(46-7),



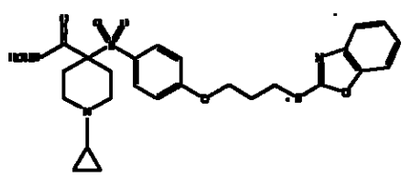
(46-8),



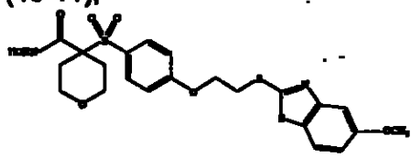
(46-9),



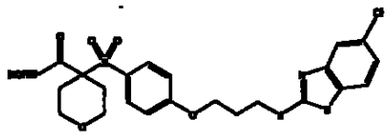
(46-10),



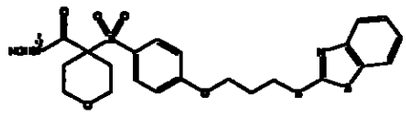
(46-11),



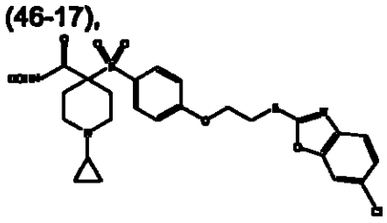
(46-13),



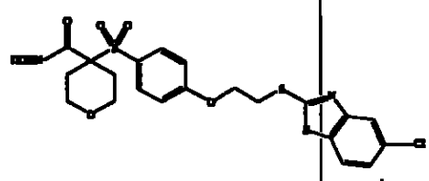
(46-15),



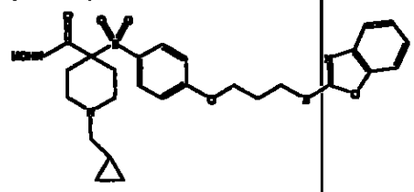
(46-17),



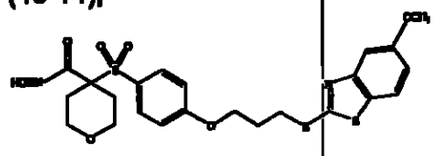
(46-19), y



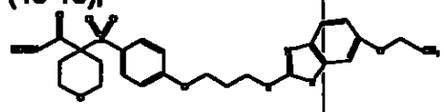
(46-12),



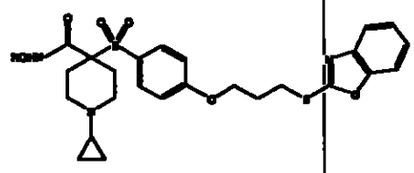
(46-14),



(46-16),



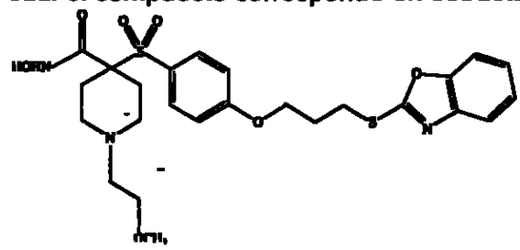
(46-18),



(46-20)

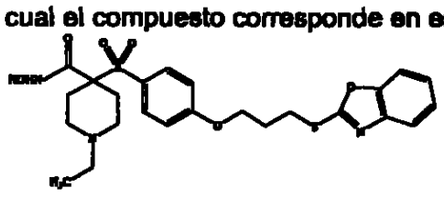
1191

47. Un compuesto o sal del mismo de acuerdo con la cláusula 45 en el cual el compuesto corresponde en estructura a la siguiente fórmula:

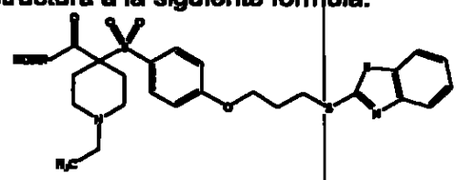


(47-1).

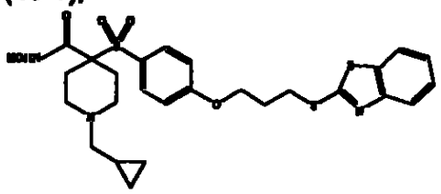
48. Un compuesto o sal del mismo de acuerdo con la cláusula 45 en el cual el compuesto corresponde en estructura a la siguiente fórmula:



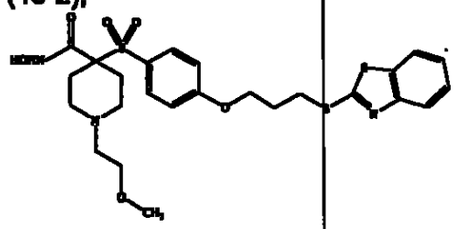
(48-1),



(48-2),



(48-3), y



(48-4).

49. Un compuesto o sal del mismo de acuerdo con la cláusula 7 en el cual E^3 es $-N(R^4)-C(O)-$.

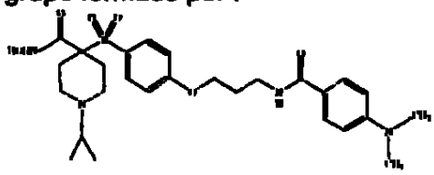
50. Un compuesto o sal del mismo de acuerdo con la cláusula 49 en el cual E^5 es carbociclilo optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, -CN, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, $-N(R^{11})(R^{12})$, $-C(O)(R^{13})$, $-S-R^{11}$, $-S(O)_2-R^{11}$, arilo, aril-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-

1192

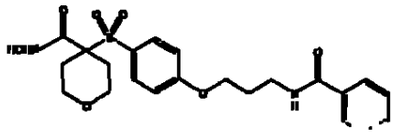
C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, haloarilo, C_1-C_6-alquilo sustituido con halógeno, C_1-C_6-alquilarilo, C_1-C_6-alquilarilo sustituido con halógeno, hidroxiarilo, y heteroarilo.

51. Un compuesto o sal del mismo de acuerdo con la cláusula 50 en el cual E^5 es fenilo optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, -$N(R^{11})(R^{12})$, -$C(O)(R^{13})$, -S-R^{11}, -$S(O)_2$-R^{11}, arilo, aril-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, haloarilo, C_1-C_6-alquilo sustituido con halógeno, C_1-C_6-alquilarilo, C_1-C_6-alquilarilo sustituido con halógeno, hidroxiarilo, y heteroarilo.

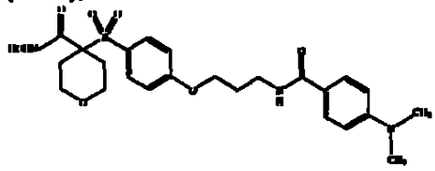
52. Un compuesto o sal del mismo de acuerdo con la cláusula 51 en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



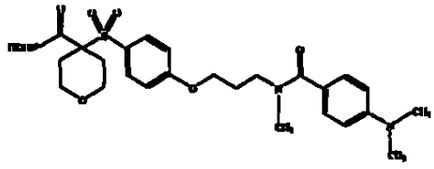
(52-1),



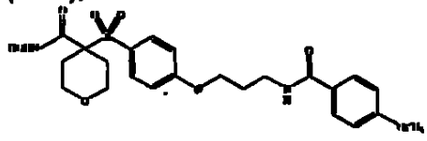
(52-2),



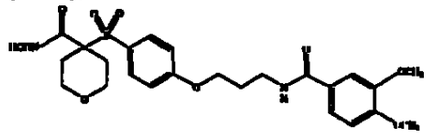
(52-3),



(52-4),

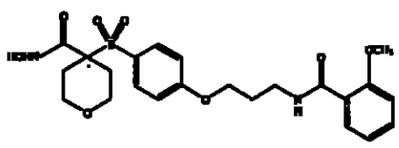


(52-5),

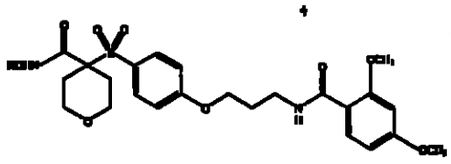


(52-6),

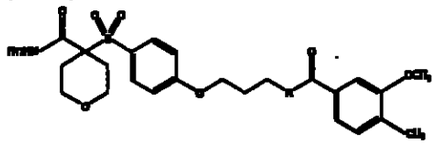
1193



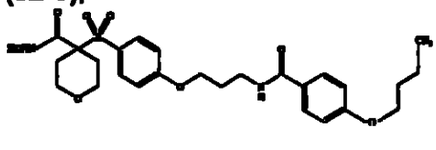
(52-7),



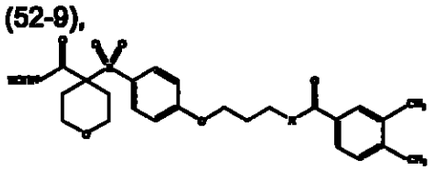
(52-8),



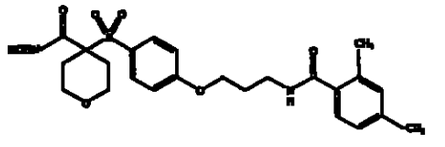
(52-9),



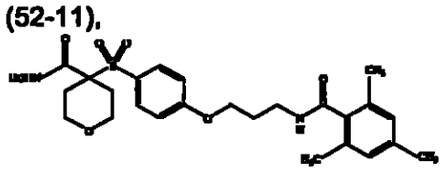
(52-10),



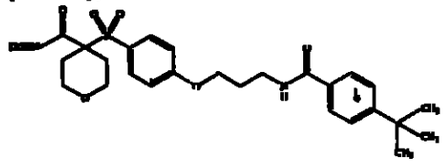
(52-11),



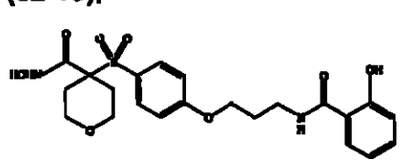
(52-12),



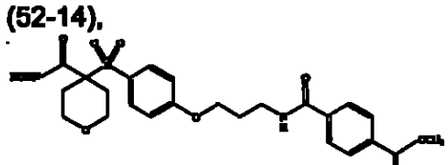
(52-13),



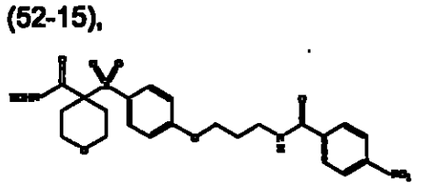
(52-14),



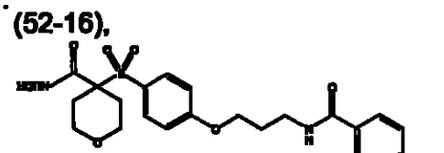
(52-15),



(52-16),



(52-17),

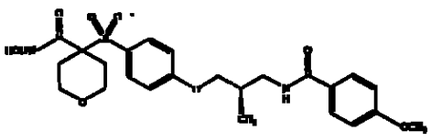


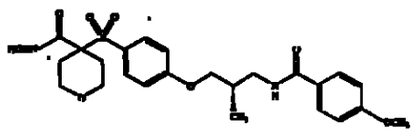
(52-18),

(52-19),

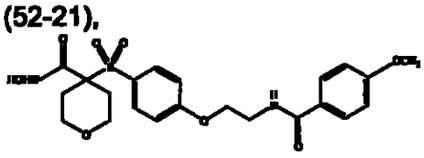
(52-20),

1194

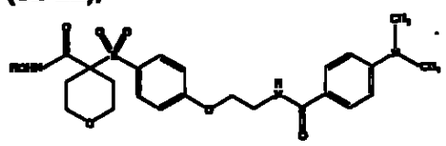




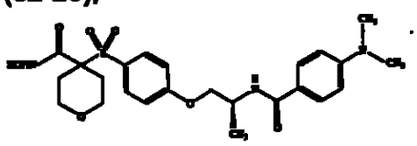
(52-21),



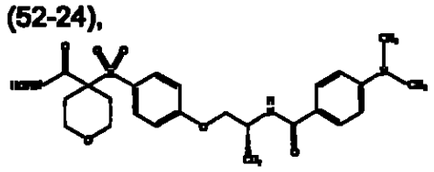
(52-22),



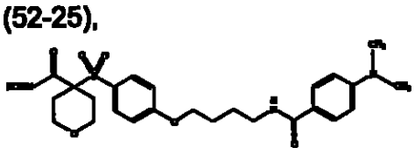
(52-23),



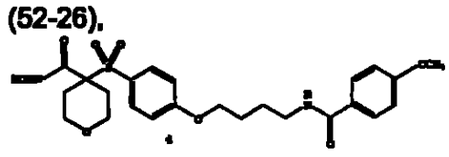
(52-24),



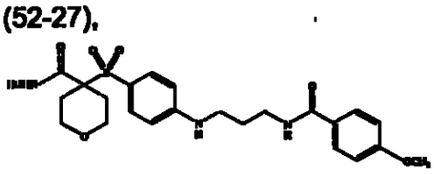
(52-25),



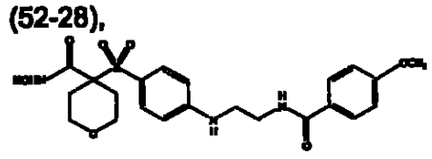
(52-26),



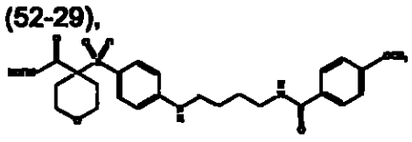
(52-27),



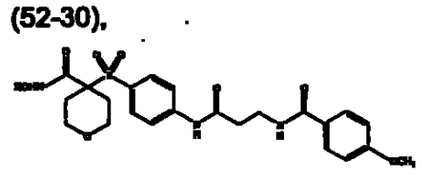
(52-28),



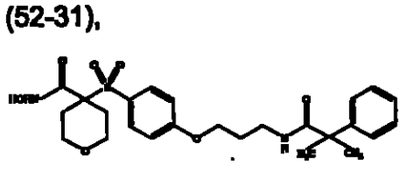
(52-29),



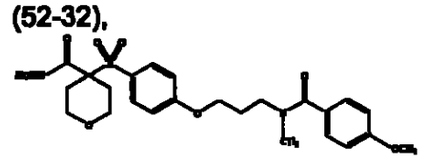
(52-30),



(52-31),

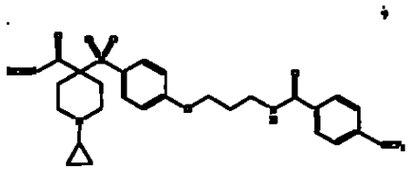


(52-32),

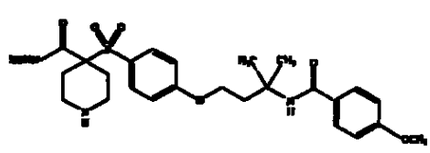


(52-33),

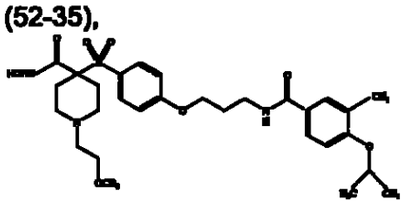
(52-34),



(52-35),

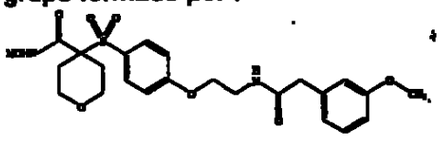


(52-36), y

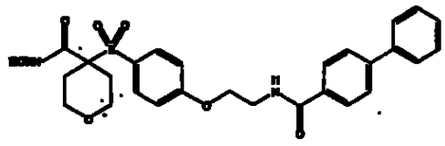


(52-37).

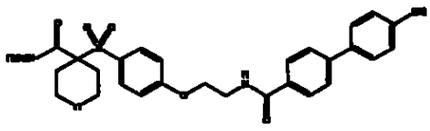
53. Un compuesto o sal del mismo de acuerdo con la cláusula 51 en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



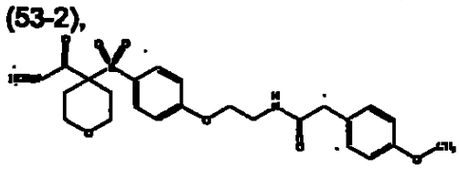
(53-1),



(53-2),

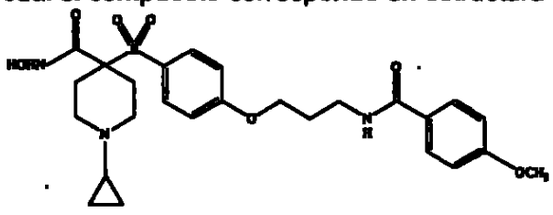


(53-3), y



(53-4).

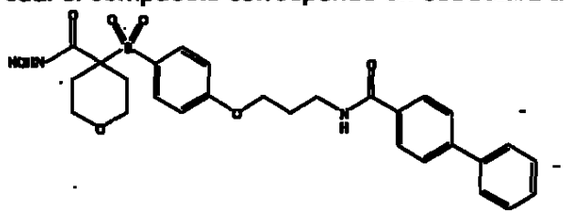
54. Un compuesto o sal del mismo de acuerdo con la cláusula 51 en el cual el compuesto corresponde en estructura a la siguiente fórmula:



(54-1).

1196

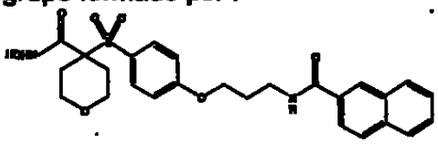
55. Un compuesto o sal del mismo de acuerdo con la cláusula 51 en el cual el compuesto corresponde en estructura a la siguiente fórmula:



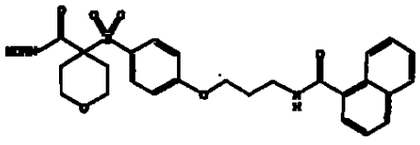
(55-1).

56. Un compuesto o sal del mismo de acuerdo con la cláusula 50 en el cual E^5 es naftalenilo optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, -$N(R^{11})(R^{12})$, -$C(O)(R^{13})$, -S-R^{11}, -$S(O)_2$-R^{11}, arilo, aril-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, haloarilo, C_1-C_6-alquilo sustituido con halógeno, C_1-C_6-alquilarilo, C_1-C_6-alquilarilo sustituido con halógeno, hidroxiarilo, y heteroarilo.

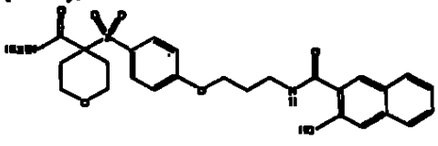
57. Un compuesto o sal del mismo de acuerdo con la cláusula 56 en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



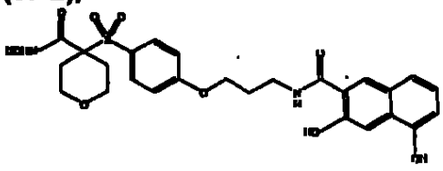
(57-1),



(57-2),

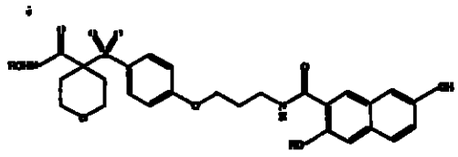


(57-3),

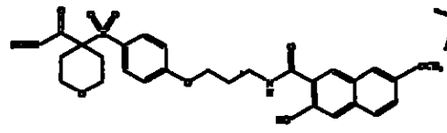


(57-4),

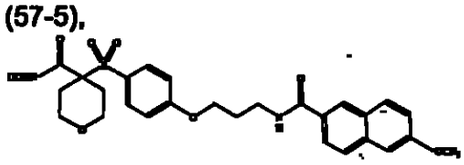
1197



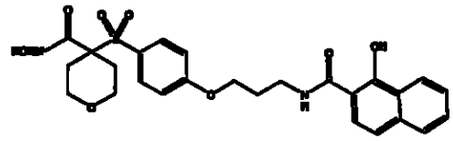
(57-5),



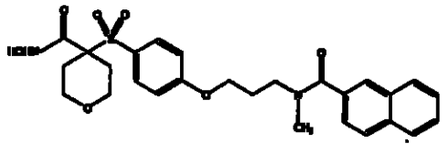
(57-6),



(57-7),



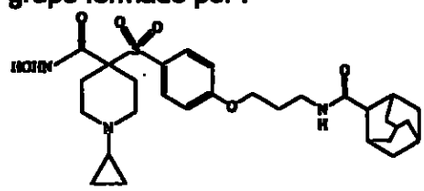
(57-8), y



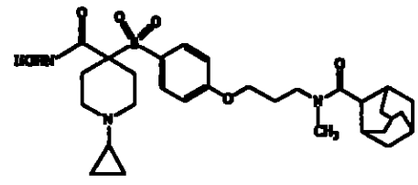
(57-9).

58. Un compuesto o sal del mismo de acuerdo con la cláusula 50 en el cual E_1^5 es cicloalquilo optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, -N(R^{11})(R^{12}), -C(O)(R^{13}), -S-R^{11}, -S(O)$_2$-R^{11}, arilo, aril-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, haloarilo, C_1-C_6-alquilo sustituido con halógeno, C_1-C_6-alquilarilo, C_1-C_6-alquilarilo sustituido con halógeno, hidroxiarilo, y heteroarilo.

59. Un compuesto o sal del mismo de acuerdo con la cláusula 58 en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



y

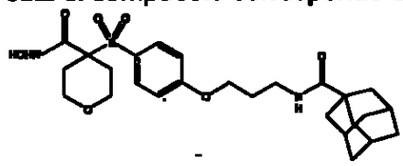


(59-1)

(59-2).

1198

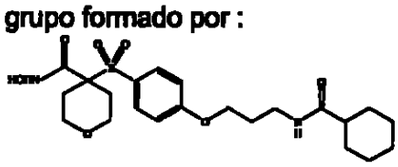
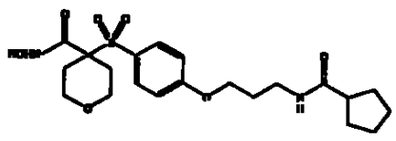
60. Un compuesto o sal del mismo de acuerdo con la cláusula 58 en el cual el compuesto corresponde en estructura a la siguiente fórmula:



(60-1).

61. Un compuesto o sal del mismo de acuerdo con la cláusula 58 en el cual E^5 es C_5-C_8-cicloalquilo optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_8-alquilo, C_1-C_8-alcoxi, C_1-C_8-alcoxi-C_1-C_8-alquilo, -$N(R^{11})(R^{12})$, -$C(O)(R^{13})$, -S-R^{11}, -$S(O)_2$-R^{11}, arilo, aril-C_1-C_8-alquilo, halo-C_1-C_8-alquilo, halo-C_1-C_8-alcoxi, C_1-C_8-alcoxi-C_1-C_8-alquilo sustituido con halógeno, haloarilo, C_1-C_8-alquilo sustituido con halógeno, C_1-C_8-alquilarilo, C_1-C_8-alquilarilo sustituido con halógeno, hidroxiarilo, y heteroarilo.

62. Un compuesto o sal del mismo de acuerdo con la cláusula 61 en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :

 y 

(62-1) (62-2).

63. Un compuesto o sal del mismo de acuerdo con la cláusula 49 en el cual E^5 es heterociclilo optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_8-alquilo, C_1-C_8-alcoxi, C_1-C_8-alcoxi-C_1-C_8-alquilo, -$N(R^{11})(R^{12})$, -$C(O)(R^{13})$, -S-R^{11}, -$S(O)_2$-R^{11}, arilo, aril-C_1-C_8-alquilo, halo-C_1-C_8-alquilo, halo-

1199

C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, haloarilo, C_1-C_6-alquilo sustituido con halógeno, C_1-C_6-alquilarilo, C_1-C_6-alquilarilo sustituido con halógeno, hidroxiarilo, y heteroarilo.

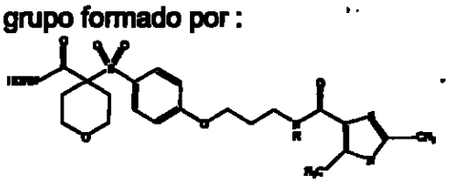
64. Un compuesto o sal del mismo de acuerdo con la cláusula 63 en el cual E^5 se selecciona del grupo formado por furanilo, tetrahidropiranilo, dihidrofuranilo, tetrahidrofuranilo, tiofenilo, dihidrotiofenilo, tetrahidrotiofenilo, pirrolilo, isopirrolilo, pirrolinilo, pirrolidinilo, imidazolilo, isoimidazolilo, imidazolinilo, imidazolidinilo, pirazolilo, pirazolinilo, pirazolidinilo, triazolilo, tetrazolilo, ditiolilo, oxatiolilo, oxazolilo, isoxazolilo, oxazolidinilo, isoxazolidinilo, tiazolilo, isotiazolilo, tiazolinilo, isotiazolinilo, tiazolidinilo, isotiazolidinilo,, tiodiazolilo, oxatiazolilo, oxadiazolilo, oxatriazolilo, dioxazolilo, oxatiazolilo, oxatiolilo, oxatiolanilo, piranilo, dihidropiranilo, piridinilo, piperidinilo, diazinilo, piperazinilo, triazinilo, oxazinilo, isoxazinilo, oxatiazinilo, oxadiazinilo, morfolinilo, azepinilo, oxepinilo, tiepinilo, diazepinilo, indolizinilo, pirindinilo, piranopirrolilo, 4H-quinolizinilo, purinilo, naftiridinilo, piridopiridinilo, pteridinilo, indolilo, isoindolilo, indoleninilo, isoindazolilo, benzazinilo, ftalazinilo, quinoxalinilo, quinazolinilo, benzodiazinilo, benzopiranilo, benzotiopiranilo, benzoxazolilo, indoxazinilo, antranililo, benzodioxolilo, benzodioxanilo, benzoxadiazolilo, benzofuranilo, isobenzofuranilo, benzotienilo, isobenzotienilo, benzotiazolilo, benzotiadiazolilo, bencimidazolilo, benzotriazolilo, benzoxazinilo, bencisoxazinilo, tetrahidroisoquinolinilo, carbazolilo, xantenilo, y acridinilo donde:

cualquier miembro de dicho grupo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-

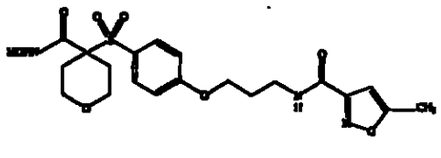
alquilo, -N(R^{11})(R^{12}), -C(O)(R^{13}), -S-R^{11}, -S(O)$_2$-R^{11}, arilo, aril-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, haloarilo, C_1-C_6-alquilo sustituido con halógeno, C_1-C_6-alquilarilo, C_1-C_6-alquilarilo sustituido con halógeno, hidroxiarilo, y heteroarilo.

65. Un compuesto o sal del mismo de acuerdo con la cláusula 64 en el cual E^5 se selecciona del grupo formado por piridinilo, pirrolilo, isopirrolilo, oxazolilo, isoxazolo, tiazolilo, furanilo, morfolinilo, tetrazolilo, imidazolilo, tienilo donde cualquier miembro de dicho grupo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, -N(R^{11})(R^{12}), -C(O)(R^{13}), -S-R^{11}, -S(O)$_2$-R^{11}, arilo, aril-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, haloarilo, C_1-C_6-alquilo sustituido con halógeno, C_1-C_6-alquilarilo, C_1-C_6-alquilarilo sustituido con halógeno, hidroxiarilo, y heteroarilo.

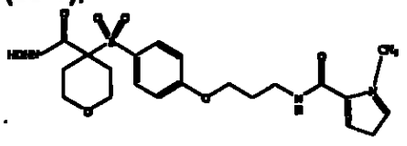
66. Un compuesto o sal del mismo de acuerdo con la cláusula 65 en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



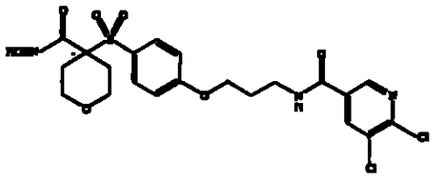
(66-1),



(66-2),

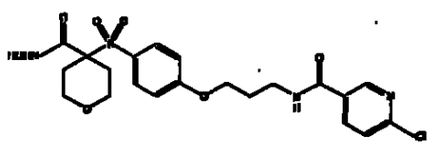


(66-3),

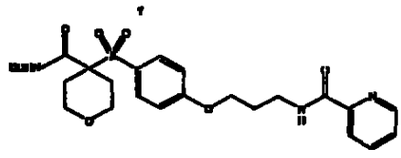


(66-4),

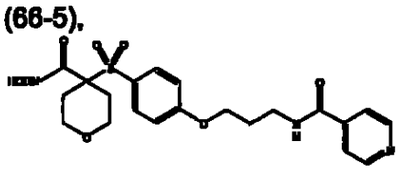
1201



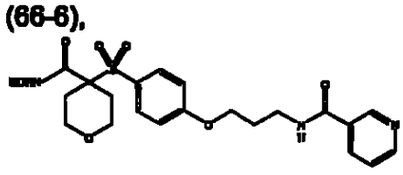
(66-5),



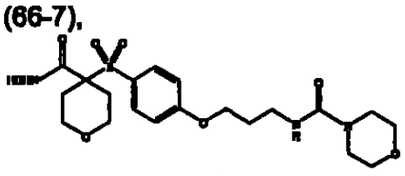
(66-6),



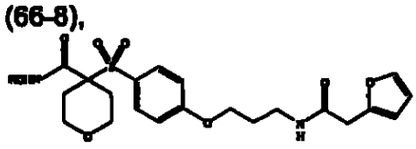
(66-7),



(66-8),

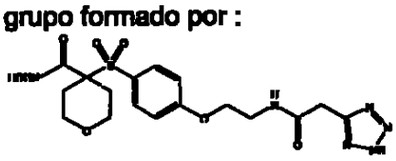


(66-9), y

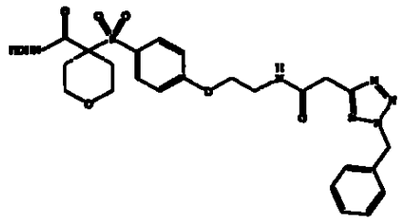


(66-10).

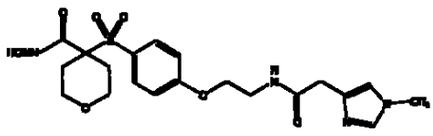
67. Un compuesto o sal del mismo de acuerdo con la cláusula 65 en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



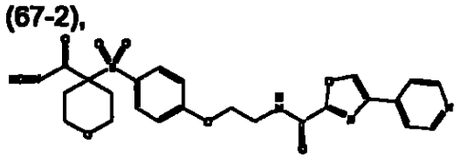
(67-1),



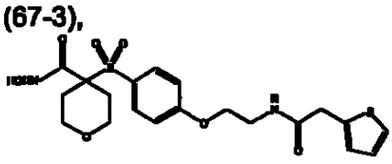
(67-2),



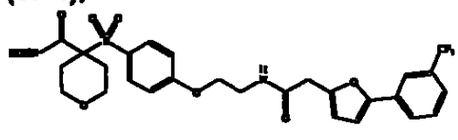
(67-3),



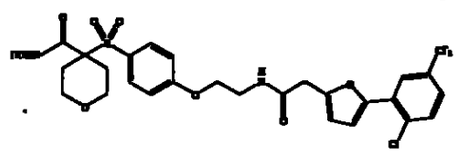
(67-4),



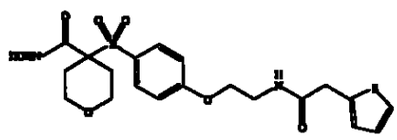
(67-5),



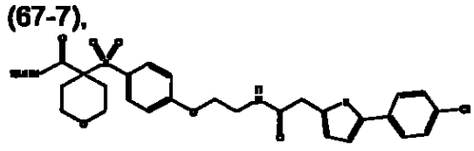
(67-6),



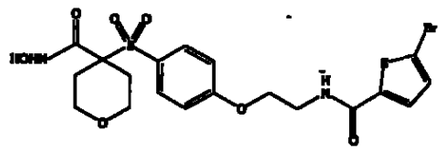
(67-7),



(67-8),



(67-9), y



(67-10).

68. Un compuesto o sal del mismo de acuerdo con la cláusula 63 en el cual E^5 es heterociclilo de 2 anillos fusionados optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, -CN, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, $-N(R^{11})(R^{12})$, $-C(O)(R^{13})$, $-S-R^{11}$, $-S(O)_2-R^{11}$, arilo, aril-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, haloarilo, C_1-C_6-alquilo sustituido con halógeno, C_1-C_6-alquilarilo, C_1-C_6-alquilarilo sustituido con halógeno, hidroxiarilo, y heteroarilo.

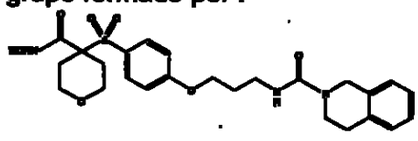
69. Un compuesto o sal del mismo de acuerdo con la cláusula 68 en el cual E^5 se selecciona del grupo formado por indolizinilo, pirindinilo, piranopirrolilo, 4H-quinolizinilo, purinilo, naftiridinilo, piridopiridinilo, pteridinilo, indolilo, isoindolilo, indoleninilo, isoindazolilo, benzazinilo, ftalazinilo, quinoxalinilo, quinazolinilo, benzodiazinilo, benzopiranilo, benzotiopiranilo, benzoxazolilo, indoxazinilo, antranililo, benzodioxolilo, benzodioxanilo, benzoxadiazolilo, benzofuranilo, isobenzofuranilo, benzotienilo, isobenzotienilo, benzotiazolilo, benzotiadiazolilo, bencimidazolilo, benzotriazolilo, benzoxazinilo, bencisoxazinilo, y tetrahidroisoquinolinilo donde:

1203

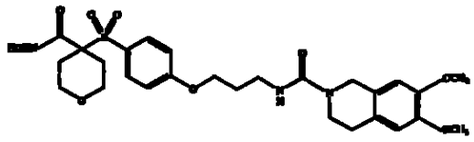
cualquier miembro de dicho grupo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, -CN, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, $-N(R^{11})(R^{12})$, $-C(O)(R^{13})$, $-S-R^{11}$, $-S(O)_2-R^{11}$, arilo, aril-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, haloarilo, C_1-C_6-alquilo sustituido con halógeno, hidroxiarilo, y heteroarilo.

70. Un compuesto o sal del mismo de acuerdo con la cláusula 69 en el cual E^5 se selecciona del grupo formado por benzazinilo, benzofuranilo, tetrahidroisoquinolinilo, indolilo, benzoxazolilo, benzotienilo, y benzotiazolilo donde cualquier miembro de dicho grupo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, -CN, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, $-N(R^{11})(R^{12})$, $-C(O)(R^{13})$, $-S-R^{11}$, $-S(O)_2-R^{11}$, arilo, aril-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, haloarilo, C_1-C_6-alquilo sustituido con halógeno, C_1-C_6-alquilarilo, C_1-C_6-alquilarilo sustituido con halógeno, hidroxiarilo, y heteroarilo.

71. Un compuesto o sal del mismo de acuerdo con la cláusula 70 en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :

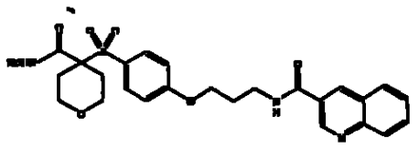


(71-1),

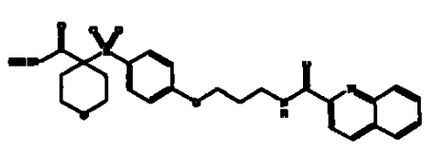


(71-2),

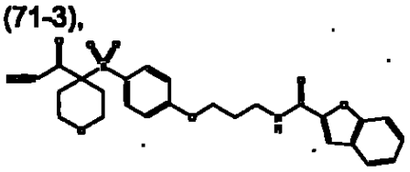
1204



(71-3),

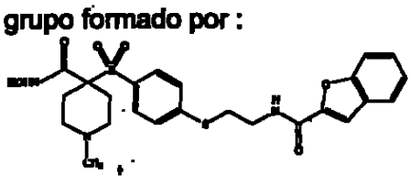


(71-4), y

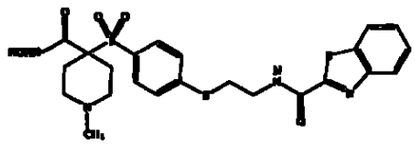


(71-5).

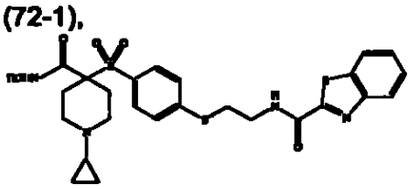
72. Un compuesto o sal del mismo de acuerdo con la cláusula 70 en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



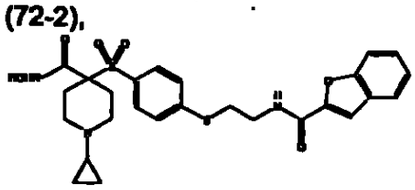
(72-1),



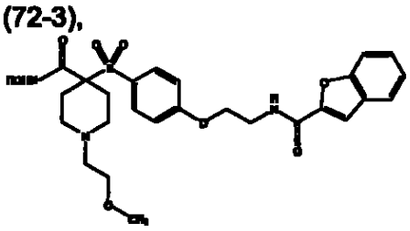
(72-2),



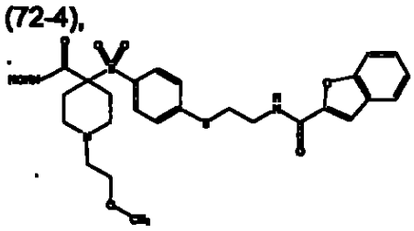
(72-3),



(72-4),

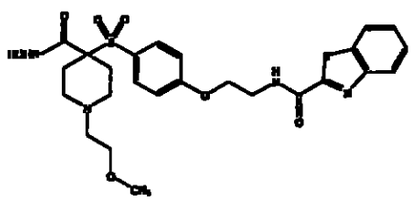


(72-5),

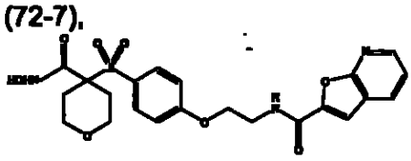


(72-6),

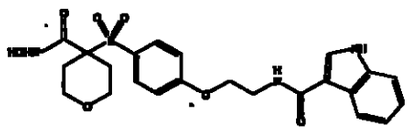
1205



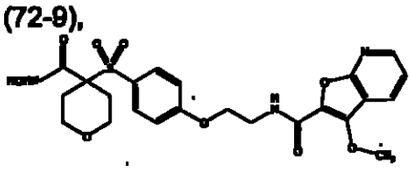
(72-7),



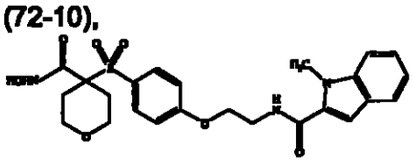
(72-8),



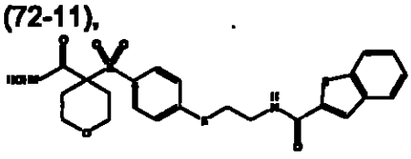
(72-9),



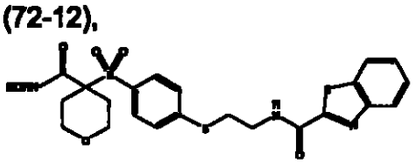
(72-10),



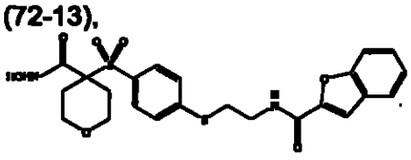
(72-11),



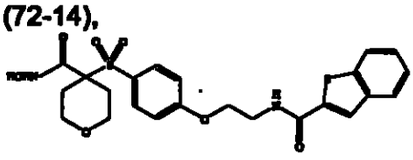
(72-12),



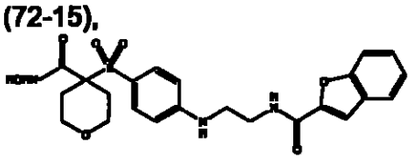
(72-13),



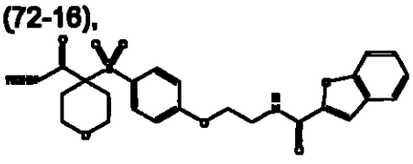
(72-14),



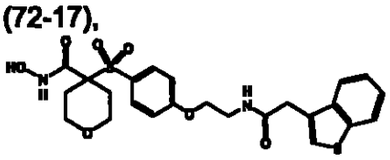
(72-15),



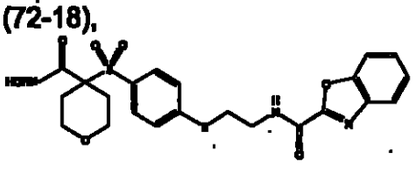
(72-16),



(72-17),



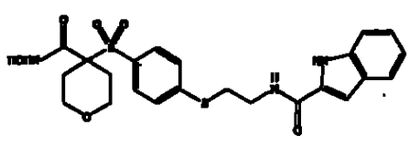
(72-18),



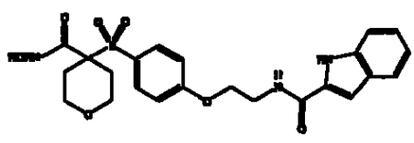
(72-19),

(72-20),

1206



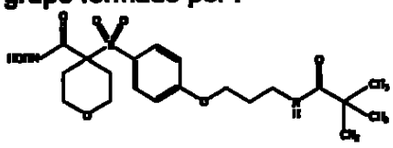
(72-21), y



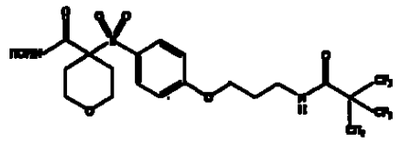
(72-22).

73. Un compuesto o sal del mismo de acuerdo con la cláusula 49 en el cual E^5 se selecciona del grupo formado por -OH, C_1-C_6-alquilo, C_2-C_6-alquenilo, C_2-C_6-alquinilo, C_1-C_6-alcoxi, o C_1-C_6-alcoxi-C_1-C_6-alquilo donde cualquier miembro (excepto -OH) de dicho grupo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, y -CN.

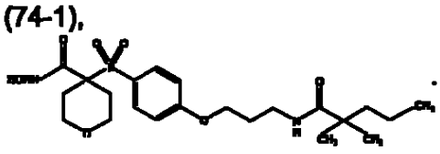
74. Un compuesto o sal del mismo de acuerdo con la cláusula 73 en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



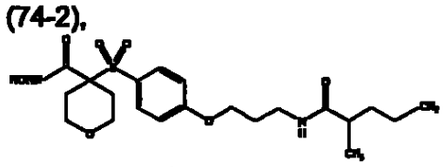
(74-1),



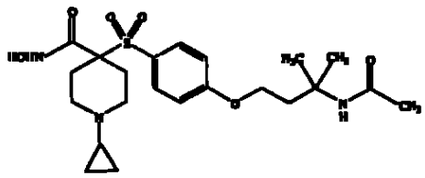
(74-2),



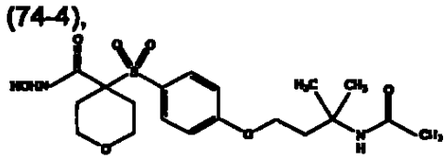
(74-3),



(74-4),



(74-5), y



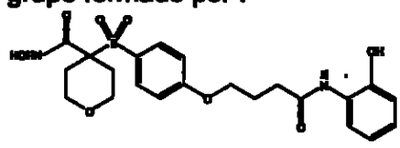
(74-6).

1207

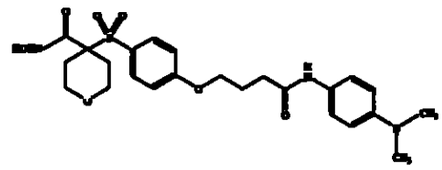
75. Un compuesto o sal del mismo de acuerdo con la cláusula 7 en el cual E^3 es -C(O)-N(R^4)-.

76. Un compuesto o sal del mismo de acuerdo con la cláusula 75 en el cual E^5 es fenilo optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, -N(R^{11})(R^{12}), -C(O)(R^{13}), -S-R^{11}, -S(O)$_2$-R^{11}, arilo, aril-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, haloarilo, C_1-C_6-alquilo sustituido con halógeno, C_1-C_6-alquilarilo, C_1-C_6-alquilarilo sustituido con halógeno, hidroxiarilo, y heteroarilo.

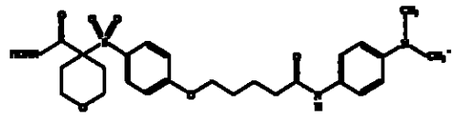
77. Un compuesto o sal del mismo de acuerdo con la cláusula 76 en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



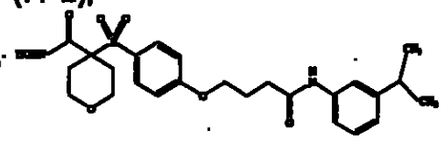
(77-1),



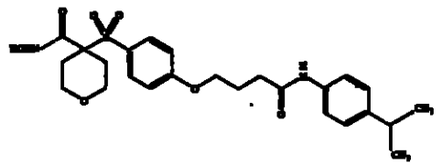
(77-2),



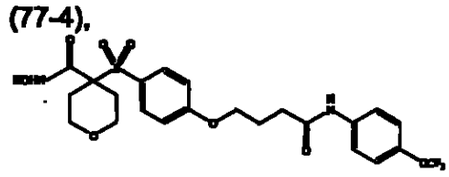
(77-3),



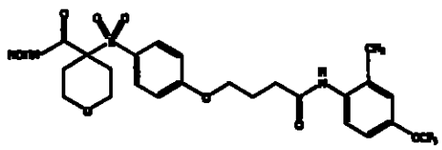
(77-4),



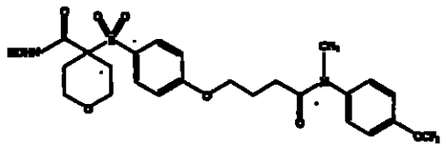
(77-5),



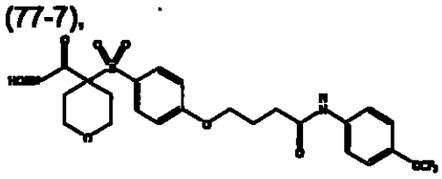
(77-6),



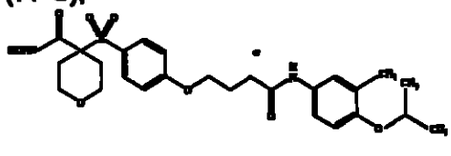
(77-7),



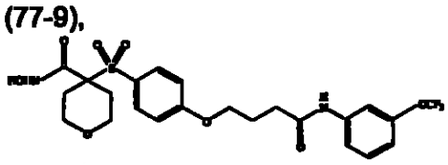
(77-8),



(77-9),

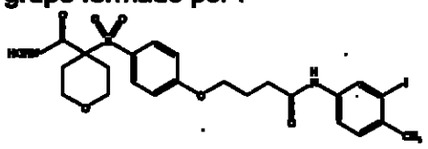


(77-10), y

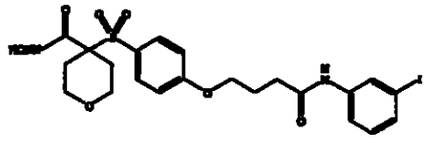


(77-11).

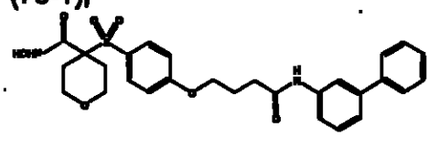
78. Un compuesto o sal del mismo de acuerdo con la cláusula 76 en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



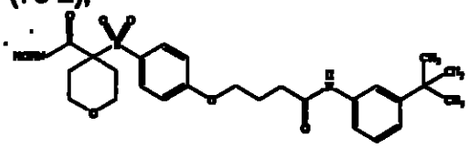
(78-1),



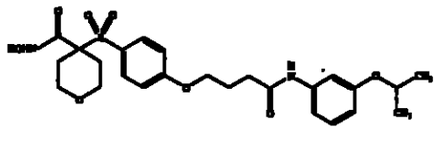
(78-2),



(78-3),



(78-4), y

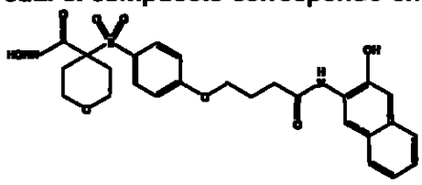


(78-5).

1209

79. Un compuesto o sal del mismo de acuerdo con la cláusula 75 en el cual E^5 es naftalenilo optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo; -$N(R^{11})(R^{12})$, -$C(O)(R^{13})$, -S-R^{11}, -$S(O)_2$-R^{11}, arilo, aril-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, haloarilo, C_1-C_6-alquilo sustituido con halógeno, C_1-C_6-alquilarilo, C_1-C_6-alquilarilo sustituido con halógeno, hidroxiarilo, y heteroarilo.

80. Un compuesto o sal del mismo de acuerdo con la cláusula 79 en el cual el compuesto corresponde en estructura a la siguiente fórmula:

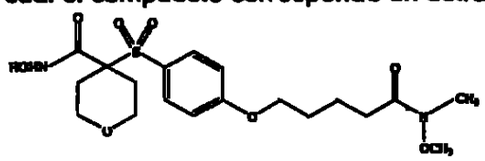


(80-1).

81. Un compuesto o sal del mismo de acuerdo con la cláusula 75 en el cual E^5 se selecciona del grupo formado por -OH, C_1-C_6-alquilo, C_2-C_6-alquenilo, C_2-C_6-alquinilo, C_1-C_6-alcoxi, o C_1-C_6-alcoxi-C_1-C_6-alquilo donde cualquier miembro (excepto -OH) de dicho grupo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, y -CN.

1210

82. Un compuesto o sal del mismo de acuerdo con la cláusula 81 en el cual el compuesto corresponde en estructura a la siguiente fórmula:

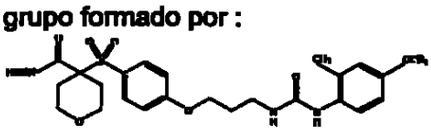


(82-1).

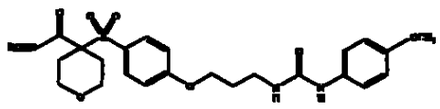
83. Un compuesto o sal del mismo de acuerdo con la cláusula 7 en el cual E^3 es $-N(R^4)-C(O)-N(R^5)-$.

84. Un compuesto o sal del mismo de acuerdo con la cláusula 83 en el cual E^5 es fenilo optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, -CN, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, $-N(R^{11})(R^{12})$, $-C(O)(R^{13})$, $-S-R^{11}$, $-S(O)_2-R^{11}$, arilo, aril-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, haloarilo, C_1-C_6-alquilo sustituido con halógeno, C_1-C_6-alquilarilo, C_1-C_6-alquilarilo sustituido con halógeno, hidroxiarilo, y heteroarilo.

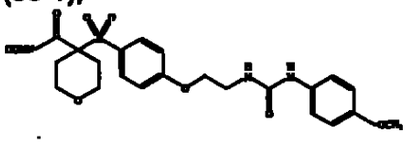
85. Un compuesto o sal del mismo de acuerdo con la cláusula 84 en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



(85-1),



(85-2), y

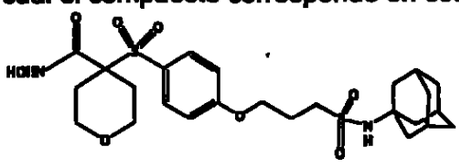


(85-3).

1211

86. Un compuesto o sal del mismo de acuerdo con la cláusula 7 en el cual E^3 es $-S(O)_2-N(R^4)-$.

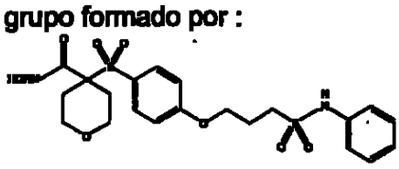
87. Un compuesto o sal del mismo de acuerdo con la cláusula 86 en el cual el compuesto corresponde en estructura a la siguiente fórmula:



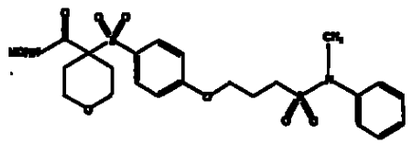
(87-3).

88. Un compuesto o sal del mismo de acuerdo con la cláusula 86 en el cual E^5 es fenilo optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, -CN, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, $-N(R^{11})(R^{12})$, $-C(O)(R^{13})$, $-S-R^{11}$, $-S(O)_2-R^{11}$, arilo, aril-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, haloarilo, C_1-C_6-alquilo sustituido con halógeno, C_1-C_6-alquilarilo, C_1-C_6-alquilarilo sustituido con halógeno, hidroxiarilo, y heteroarilo.

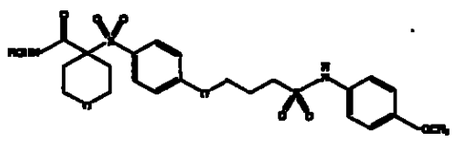
89. Un compuesto o sal del mismo de acuerdo con la cláusula 88 en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



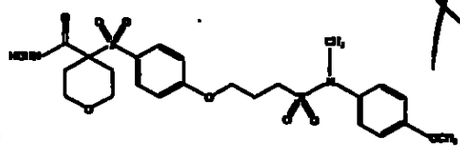
(89-1),



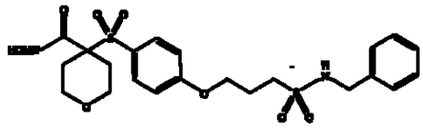
(89-2),



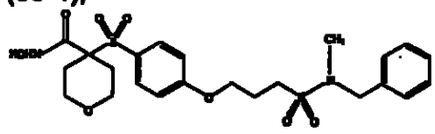
(89-3),



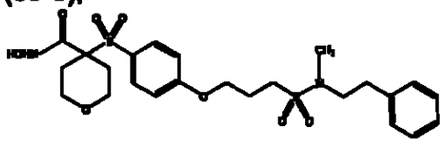
(89-4),



(89-5),



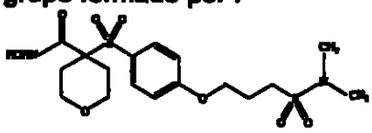
(89-6), y



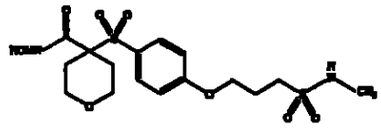
(89-7).

90. Un compuesto o sal del mismo de acuerdo con la cláusula 86 en el cual E^5 se selecciona del grupo formado por -H, -OH, C_1-C_6-alquilo, C_2-C_6-alquenilo, C_2-C_6-alquinilo, C_1-C_6-alcoxi, o C_1-C_6-alcoxi-C_1-C_6-alquilo donde cualquier miembro (excepto -H o -OH) de dicho grupo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, y -CN.

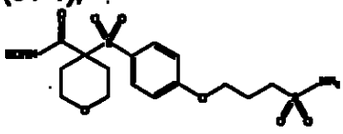
91. Un compuesto o sal del mismo de acuerdo con la cláusula 90 en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



(91-1),



(91-2), y



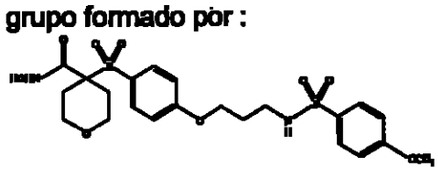
(91-3).

1213

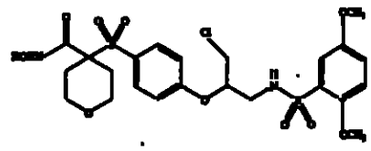
92. Un compuesto o sal del mismo de acuerdo con la cláusula 7 en el cual E^3 es $-N(R^4)-S(O)_2-$.

93. Un compuesto o sal del mismo de acuerdo con la cláusula 92 en el cual E^5 es fenilo optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, -CN, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, $-N(R^{11})(R^{12})$, $-C(O)(R^{13})$, $-S-R^{11}$, $-S(O)_2-R^{11}$, arilo, aril-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, haloarilo, C_1-C_6-alquilo sustituido con halógeno, C_1-C_6-alquilarilo, C_1-C_6-alquilarilo sustituido con halógeno, hidroxiarilo, y heteroarilo.

94. Un compuesto o sal del mismo de acuerdo con la cláusula 93 en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :

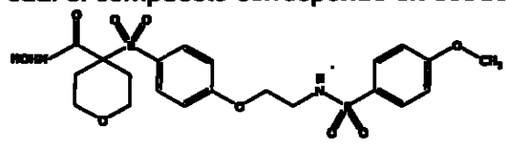


y



(94-1) (94-2).

95. Un compuesto o sal del mismo de acuerdo con la cláusula 93 en el cual el compuesto corresponde en estructura a la siguiente fórmula:

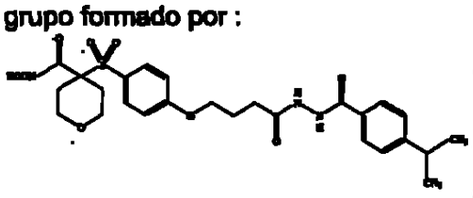


(95-1).

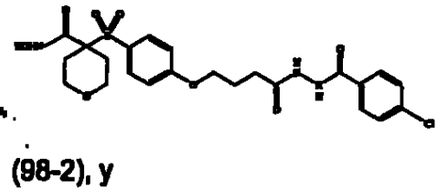
96. Un compuesto o sal del mismo de acuerdo con la cláusula 7 en el cual E^3 es $-C(O)-N(R^4)-N(R^5)-C(O)-$.

97. Un compuesto o sal del mismo de acuerdo con la cláusula 96 en el cual E^5 es fenilo optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, -$N(R^{11})(R^{12})$, -$C(O)(R^{13})$, -S-R^{11}, -$S(O)_2$-R^{11}, arilo, aril-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, haloarilo, C_1-C_6-alquilo sustituido con halógeno, C_1-C_6-alquilarilo, C_1-C_6-alquilarilo sustituido con halógeno, hidroxiarilo, y heteroarilo.

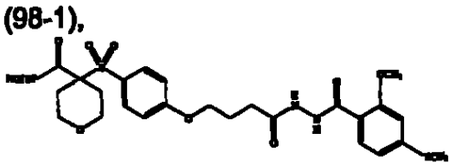
98. Un compuesto o sal del mismo de acuerdo con la cláusula 97 en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



(98-1),



(98-2), y



(98-3).

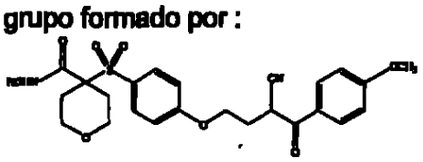
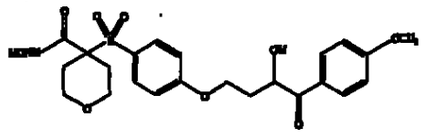
99. Un compuesto o sal del mismo de acuerdo con la cláusula 7 en el cual E^3 es -$C(R^4)(R^5)$-C(O)-.

100. Un compuesto o sal del mismo de acuerdo con la cláusula 99 en el cual E^5 es fenilo optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2,.-CN, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, -$N(R^{11})(R^{12})$, -$C(O)(R^{13})$, -S-R^{11}, -$S(O)_2$-R^{11}, arilo, aril-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-

1215

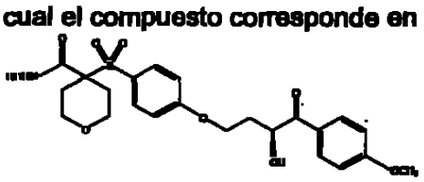
C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, haloarilo, C_1-C_6-alquilo sustituido con halógeno, C_1-C_6-alquilarilo, C_1-C_6-alquilarilo sustituido con halógeno, hidroxiarilo, y heteroarilo.

101. Un compuesto o sal del mismo de acuerdo con la cláusula 100 en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :

 y 

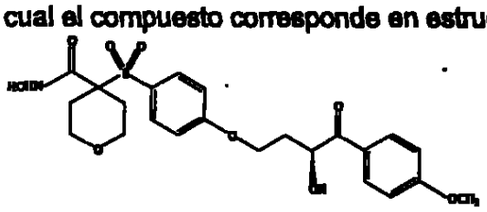
(101-1) (101-2).

102. Un compuesto o sal del mismo de acuerdo con la cláusula 100 en el cual el compuesto corresponde en estructura a la siguiente fórmula:



(102-1).

103. Un compuesto o sal del mismo de acuerdo con la cláusula 100 en el cual el compuesto corresponde en estructura a la siguiente fórmula:



(103-1).

104. Un compuesto o sal del mismo de acuerdo con la cláusula 7 en el cual E^3 es -O-C(O)-.

105. Un compuesto o sal del mismo de acuerdo con la cláusula 104 en el cual E^5 es heterociclilo es optativamente sustituido con uno o más sustituyentes

1216

independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, -$N(R^{11})(R^{12})$, -$C(O)(R^{13})$, -S-R^{11}, -$S(O)_2$-R^{11}, arilo, aril-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, haloarilo, C_1-C_6-alquilo sustituido con halógeno, C_1-C_6-alquilarilo, C_1-C_6-alquilarilo sustituido con halógeno, hidroxiarilo, y heteroarilo.

106. Un compuesto o sal del mismo de acuerdo con la cláusula 105 en el cual E^5 es heterociclilo de 2 anillos fusionados optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, -$N(R^{11})(R^{12})$, -$C(O)(R^{13})$, -S-R^{11}, -$S(O)_2$-R^{11}, arilo, aril-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, haloarilo, C_1-C_6-alquilo sustituido con halógeno, C_1-C_6-alquilarilo, C_1-C_6-alquilarilo sustituido con halógeno, hidroxiarilo, y heteroarilo.

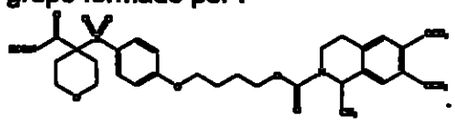
107. Un compuesto o sal del mismo de acuerdo con la cláusula 106 en el cual E^5 se selecciona del grupo formado por indolizinilo, pirindinilo, piranopirrolilo, 4H-quinolizinilo, purinilo, naftiridinilo, piridopiridinilo, pteridinilo, indolilo, isoindolilo, indoleninilo, isoindazolilo, benzazinilo, ftalazinilo, quinoxalinilo, quinazolinilo, benzodiazinilo, benzopiranilo, benzotiopiranilo, benzoxazolilo, indoxazinilo, antranililo, benzodioxolilo, benzodioxanilo, benzoxadiazolilo, benzofuranilo, isobenzofuranilo, benzotienilo, isobenzotienilo, benzotiazolilo, benzotiadiazolilo, bencimidazolilo, benzotriazolilo, benzoxazinilo, bencisoxazinilo, y tetrahidroisoquinolinilo donde:

cualquier miembro de dicho grupo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado

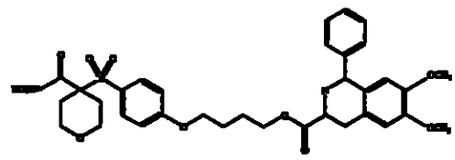
por halógeno, -OH, -NO_2, -CN, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, -$N(R^{11})(R^{12})$, -$C(O)(R^{13})$, -S-R^{11}, -$S(O)_2$-R^{11}, arilo, aril-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, haloarilo, C_1-C_6-alquilo sustituido con halógeno, C_1-C_6-alquilarilo, C_1-C_6-alquilarilo sustituido con halógeno, hidroxiarilo, y heteroarilo.

108. Un compuesto o sal del mismo de acuerdo con la cláusula 107 en el cual E^5 es tetrahidroisoquinolinilo optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, -$N(R^{11})(R^{12})$, -$C(O)(R^{13})$, -S-R^{11}, -$S(O)_2$-R^{11}, arilo, aril-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, haloarilo, C_1-C_6-alquilo sustituido con halógeno, C_1-C_6-alquilarilo, C_1-C_6-alquilarilo sustituido con halógeno, hidroxiarilo, y heteroarilo.

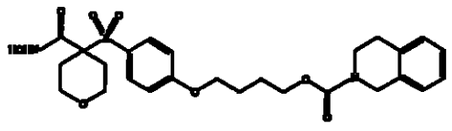
109. Un compuesto o sal del mismo de acuerdo con la cláusula 108 en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



(109-1),



(109-2), y



(109-3).

110. Un compuesto o sal del mismo de acuerdo con la cláusula 7 en el cual E^3 es -$N(R^4)$-.

1218

111. Un compuesto o sal del mismo de acuerdo con la cláusula 110 en el cual E^5 es heterociclilo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, -$N(R^{11})(R^{12})$, -$C(O)(R^{13})$, -S-R^{11}, -$S(O)_2$-R^{11}, arilo, aril-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, haloarilo, C_1-C_6-alquilo sustituido con halógeno, C_1-C_6-alquilarilo, C_1-C_6-alquilarilo sustituido con halógeno, hidroxiarilo, y heteroarilo.

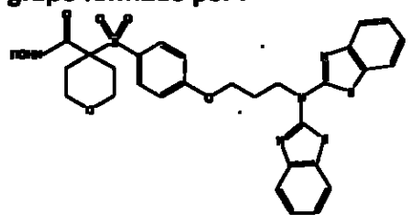
112. Un compuesto o sal del mismo de acuerdo con la cláusula 111 en el cual E^5 es heterociclilo de 2 anillos fusionados optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, -$N(R^{11})(R^{12})$, -$C(O)(R^{13})$, -S-R^{11}, -$S(O)_2$-R^{11}, arilo, aril-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, haloarilo, C_1-C_6-alquilo sustituido con halógeno, C_1-C_6-alquilarilo, C_1-C_6-alquilarilo sustituido con halógeno, hidroxiarilo, y heteroarilo.

113. Un compuesto o sal del mismo de acuerdo con la cláusula 112 en el cual E^5 se selecciona del grupo formado por indolizinilo, pirindinilo, piranopirrolilo, 4H-quinolizinilo, purinilo, naftiridinilo, piridopiridinilo, pteridinilo, indolilo, isoindolilo, indoleninilo, isoindazolilo, benzazinilo, ftalazinilo, quinoxalinilo, quinazolinilo, benzodiazinilo, benzopiranilo, benzotiopiranilo, benzoxazolilo, indoxazinilo, antranililo, benzodioxolilo, benzodioxanilo, benzoxadiazolilo, benzofuranilo, isobenzofuranilo, benzotienilo, isobenzotienilo, benzotiazolilo, benzotiadiazolilo, bencimidazolilo, benzotriazolilo, benzoxazinilo, bencisoxazinilo, y tetrahidroisoquinolinilo donde:

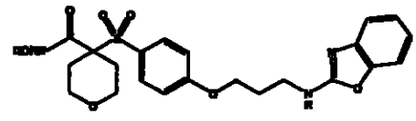
cualquier miembro de dicho grupo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, -CN, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, $-N(R^{11})(R^{12})$, $-C(O)(R^{13})$, $-S-R^{11}$, $-S(O)_2-R^{11}$, arilo, aril-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, haloarilo, C_1-C_6-alquilo sustituido con halógeno, C_1-C_6-alquilarilo, C_1-C_6-alquilarilo sustituido con halógeno, hidroxiarilo, y heteroarilo.

114. Un compuesto o sal del mismo de acuerdo con la cláusula 113 en el cual E^5 se selecciona del grupo formado por benzoxazolilo, benzotiazolilo, y bencimidazolilo donde cualquier miembro de dicho grupo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, -CN, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, $-N(R^{11})(R^{12})$, $-C(O)(R^{13})$, $-S-R^{11}$, $-S(O)_2-R^{11}$, arilo, aril-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, haloarilo, C_1-C_6-alquilo sustituido con halógeno, C_1-C_6-alquilarilo, C_1-C_6-alquilarilo sustituido con halógeno, hidroxiarilo, y heteroarilo.

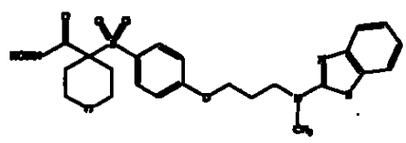
115. Un compuesto o sal del mismo de acuerdo con la cláusula 114 en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



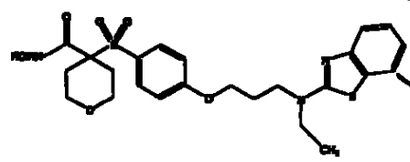
(115-1),



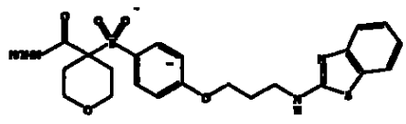
(115-2),



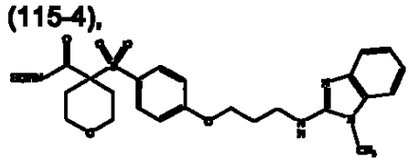
(115-3),



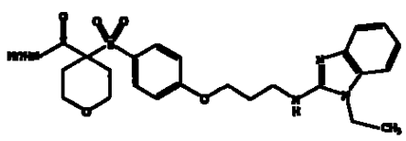
(115-4),



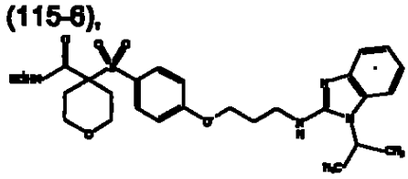
(115-5),



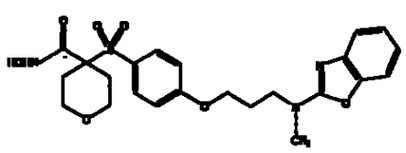
(115-6),



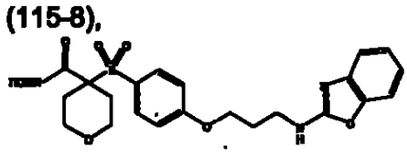
(115-7),



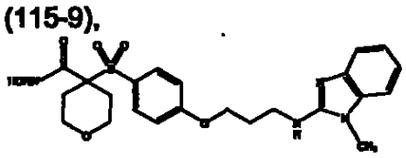
(115-8),



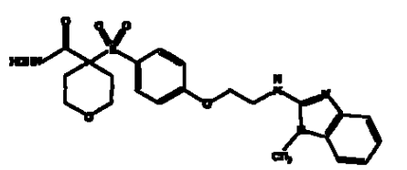
(115-9),



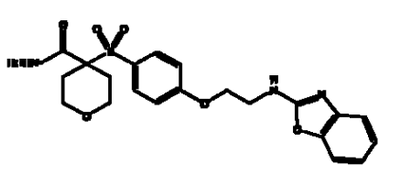
(115-10),



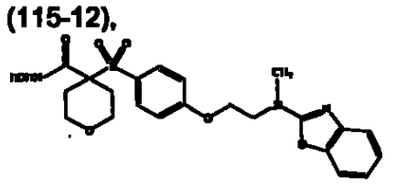
(115-11),



(115-12),



(115-13), y

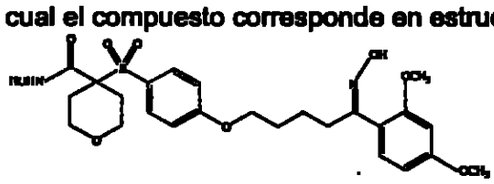


(115-14).

116. Un compuesto o sal del mismo de acuerdo con la cláusula 7 en el cual E^3 es $-C(NR^3)-$.

117. Un compuesto o sal del mismo de acuerdo con la cláusula 116 en el cual E^5 es fenilo optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, -N(R^{11})(R^{12}), -C(O)(R^{13}), -S-R^{11}, -S(O)$_2$-R^{11}, arilo, aril-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, haloarilo, C_1-C_6-alquilo sustituido con halógeno, C_1-C_6-alquilarilo, C_1-C_6-alquilarilo sustituido con halógeno, hidroxiarilo, y heteroarilo.

118. Un compuesto o sal del mismo de acuerdo con la cláusula 117 en el cual el compuesto corresponde en estructura a la siguiente fórmula:

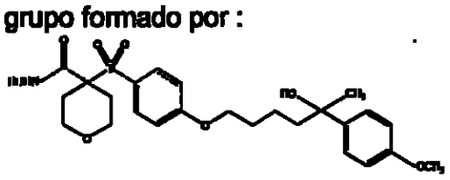


(118-1).

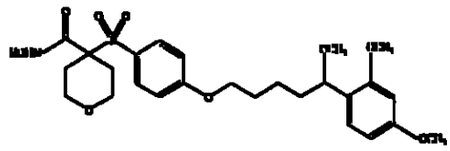
119. Un compuesto o sal del mismo de acuerdo con la cláusula 7 en el cual E^3 es -C(R^7)(R^8)-.

120. Un compuesto o sal del mismo de acuerdo con la cláusula 119 en el cual E^5 es fenilo optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, -N(R^{11})(R^{12}), -C(O)(R^{13}), -S-R^{11}, -S(O)$_2$-R^{11}, arilo, aril-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, haloarilo, C_1-C_6-alquilo sustituido con halógeno, C_1-C_6-alquilarilo, C_1-C_6-alquilarilo sustituido con halógeno, hidroxiarilo, y heteroarilo.

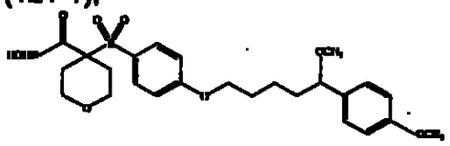
121. Un compuesto o sal del mismo de acuerdo con la cláusula 120 en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



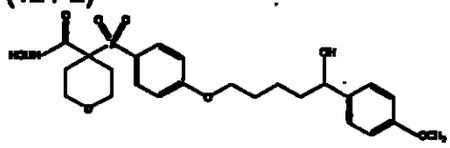
(121-1),



(121-2)



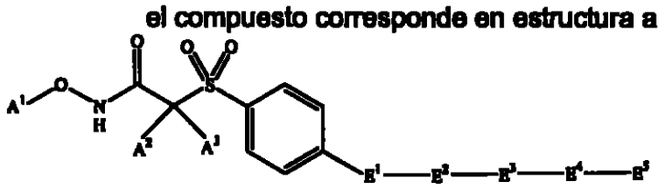
(121-3), y



(121-4).

122. Un compuesto o sal del mismo en el cual:

el compuesto corresponde en estructura a la Fórmula 122-1:



(122-1); y

A^1 se selecciona del grupo formado por -H, alquilcarbonilo, alcoxicarbonilo, carbociclilcarbonilo, carbociclilalquilcarbonilo, heterociclilcarbonilo, heterociclilalquilcarbonilo, carbocicliloxicarbonilo, carbociclilalcoxicarbonilo, aminoalquilcarbonilo, alquil(tiocarbonilo), alcoxi(tiocarbonilo), carbociclil(tiocarbonilo), carbociclilalquil(tiocarbonilo), heterociclil(tiocarbonilo), heterociclilalquil(tiocarbonilo), carbociclil(oxi(tiocarbonilo), carbociclilalcoxi(tiocarbonilo), y

aminoalquil(tiocarbonilo), donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido; y

A^2 y A^3, junto con el átomo de carbono al cual ambos están unidos, forman un heterociclilo optativamente sustituido que contiene entre 5 y 8 miembros en el anillo; y

E^1 se selecciona del grupo formado por -O-, $-S(O)_2-$, -S(O)-, $-N(R^1)-$, $-C(O)-N(R^1)-$, $-N(R^1)-C(O)-$, y $-C(R^1)(R^2)-$; y

E^2 se selecciona del grupo formado por alquilo, cicloalquilo, alquilcicloalquilo, cicloalquilalquilo, y alquilcicloalquilalquilo donde cualquier miembro de dicho grupo es optativamente sustituido; y

E^2 forma un enlace de al menos 2 átomos de carbono entre E^1 y E^3; y

E^3 se selecciona del grupo formado por carbociclilo y heterociclilo donde el carbociclilo o heterociclilo tiene 5 o 6 miembros en el anillo y es optativamente sustituido; y

E^4 se selecciona del grupo formado por un enlace, alquilo, alquenilo, -O-, y, $-N(R^3)-$, donde el alquilo o alquenilo es optativamente sustituido; y

E^5 se selecciona del grupo formado por carbociclilo y heterociclilo donde el carbociclilo o heterociclilo es optativamente sustituido; y

R^1 y R^2 se seleccionan independientemente del grupo formado por -H y alquilo en el cual el alquilo es optativamente sustituido; y

R^3 se selecciona del grupo formado por -H y alquilo en el cual el alquilo es optativamente sustituido; y

ni R^1 ni R^2 forman una estructura de anillo con E^2, E^3, E^4, o E^5.

123. Un compuesto o sal del mismo de acuerdo con la cláusula 122 en el cual:

A^1 se selecciona del grupo formado por -H, C_1-C_8-alquilcarbonilo, C_1-C_8-alcoxicarbonilo, carbociclilcarbonilo, carbociclil-C_1-C_8-alquilcarbonilo, heterociclilcarbonilo, heterociclil-C_1-C_8-alquilcarbonilo, carbociclíloxicarbonilo, carbociclil-C_1-C_8-alcoxicarbonilo, $N(R^4)(R^5)$-C_1-C_8-alquilcarbonilo, C_1-C_8-alquil(tiocarbonilo), C_1-C_8-alcoxi(tiocarbonilo), carbociclil(tiocarbonilo), carbociclil-C_1-C_8-alquil(tiocarbonilo), heterociclil(tiocarbonilo), heterociclil-C_1-C_8-alquil(tiocarbonilo), carbociclíloxi(tiocarbonilo), carbociclil-C_1-C_8-alcoxi(tiocarbonilo), y $N(R^4)(R^5)$-C_1-C_8-alquil(tiocarbonilo); y

E^2 se selecciona del grupo formado por C_2-C_{20}-alquilo, cicloalquilo, C_1-C_{10}-alquilcicloalquilo, cicloalquil-C_1-C_{10}-alquilo, C_1-C_{10}-alquilcicloalquil-C_1-C_{10}-alquilo donde cualquier miembro de dicho grupo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, C_1-C_8-alquilo, y halo-C_1-C_8-alquilo; y

E^3 se seleccioria del grupo formado por carbociclilo y heterociclilo en el cual el carbociclilo o heterociclilo:

tiene 5 o 6 miembros en el anillo, y

es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, ceto, C_1-C_8-alquilo, C_1-C_8-alcoxi, C_1-C_8-alcoxi-C_1-C_8-alquilo, carbociclilo, carbociclil-C_1-C_8-alquilo, heterociclilo, y heterociclil-C_1-C_8-alquilo en el cual

cualquiera de dichos sustituyentes (excepto halógeno, -OH, o ceto) es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, C_1-C_8-alquilo, C_1-C_8-

alcoxi, C_1-C_8-alcoxi-C_1-C_8-alquilo, C_1-C_8-alquiltio, halo-C_1-C_8-alquilo, halo-C_1-C_8-alcoxi, halo-C_1-C_8-alquiltio, y C_1-C_8-alcoxi-C_1-C_8-alquilo sustituido con halógeno ; y

E^4 se selecciona del grupo formado por un enlace, -O-, -N(R^3)-, C_1-C_{20}-alquilo, y C_2-C_{20}-alquenilo en el cual el C_1-C_{20}-alquilo o C_2-C_{20}-alquenilo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por:

halógeno, y

carbociclilo optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_8-alquilo, C_1-C_8-alcoxi, C_1-C_8-alcoxi-C_1-C_8-alquilo, carbociclilo, carbociclil-C_1-C_8-alquilo, halo-C_1-C_8-alquilo, halo-C_1-C_8-alcoxi, halocarbociclilo, carbociclil-C_1-C_8-alquilo sustituido con halógeno, y C_1-C_8-alcoxi-C_1-C_8-alquilo sustituido con halógeno ; y

E^5 se selecciona del grupo formado por carbociclilo y heterociclilo en el cual el carbociclilo o heterociclilo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, ceto, C_1-C_8-alquilo, C_2-C_8-alquenilo, C_2-C_8-alquinilo, C_1-C_8-alcoxi, C_1-C_8-alcoxi-C_1-C_8-alquilo, -N(R^6)(R^7), -C(O)(R^8), -S-R^6, -S(O)$_2$-R^6, carbociclilo, carbociclil-C_1-C_8-alquilo, halo-C_1-C_8-alquilo, halo-C_1-C_8-alcoxi, C_1-C_8-alcoxi-C_1-C_8-alquilo sustituido con halógeno , halocarbociclilo, y carbociclil-C_1-C_8-alquilo sustituido con halógeno; y

R^1 y R^2 se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, y halo-C_1-C_8-alquilo; y

R^3 se selecciona del grupo formado por -H, C_1-C_6-alquilo, y halo-C_1-C_6-alquilo; y

R^4 y R^5 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, C_1-C_6-alcoxicarbonilo, C_1-C_6-alquilcarbonilo, carbociclil-C_1-C_6-alquilo, y carbociclil-C_1-C_6-alcoxicarbonilo; y

R^6 y R^7 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, heterociclil-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo sustituido con halógeno, haloheterociclilo, y heterociclil-C_1-C_6-alquilo sustituido con halógeno; y

R^8 se selecciona del grupo formado por -H, C_1-C_6-alquilo, -O-R^9, -N(R^9)(R^{10}), carbociclil-C_1-C_6-alquilo, heterociclil-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, carbociclil-C_1-C_6-alquilo sustituido con halógeno, y heterociclil-C_1-C_6-alquilo sustituido con halógeno; y

R^9 y R^{10} se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, heterociclil-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo sustituido con halógeno, haloheterociclilo, y heterociclil-C_1-C_6-alquilo sustituido con halógeno.

124. Un compuesto o sal del mismo de acuerdo con la cláusula 123 en el cual A^1 es -H.

125. Un compuesto o sal del mismo de acuerdo con la cláusula 124 en el cual:

E^2 es C_2-C_6-alquilo optativamente sustituido con uno o más halógenos; y

1227

E^3 se selecciona del grupo formado por carbociclilo y heterociclilo donde el carbociclilo o heterociclilo:

tiene 5 o 6 miembros en el anillo, y

es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, ceto, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo donde:

cualquiera de dichos sustituyentes (excepto halógeno, -OH, o ceto) es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alquiltio, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, y halo-C_1-C_6-alquiltio; y

E^4 se selecciona del grupo formado por un enlace, -O-, -N(R^3)-, C_1-C_3-alquilo, y C_2-C_3-alquenilo donde el C_1-C_3-alquilo o C_2-C_3-alquenilo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por:

halógeno, y

carbociclilo optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, halocarbociclilo, y carbociclil-C_1-C_6-alquilo sustituido con halógeno; y

E^5 se selecciona del grupo formado por carbociclilo y heterociclilo donde el carbociclilo o heterociclilo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, -CN, ceto, C_1-C_6-alquilo, C_2-C_6-alquenilo, C_2-C_6-alquinilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, $-N(R^6)(R^7)$, $-C(O)(R^8)$, $-S-R^8$, $-S(O)_2-R^8$, carbociclilo, carbociclil-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, halocarbociclilo, y carbociclil-C_1-C_6-alquilo sustituido con halógeno; y

R^1 y R^2 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, y halo-C_1-C_6-alquilo; y

R^3 se selecciona del grupo formado por -H, C_1-C_6-alquilo, y halo-C_1-C_6-alquilo; y

R^6 y R^7 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido con uno o más halógenos; y

R^8 se selecciona del grupo formado por -H, C_1-C_6-alquilo, $-O-R^9$, $-N(R^9)(R^{10})$, carbociclil-C_1-C_6-alquilo, heterociclil-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, carbociclil-C_1-C_6-alquilo sustituido con halógeno, y heterociclil-C_1-C_6-alquilo sustituido con halógeno; y

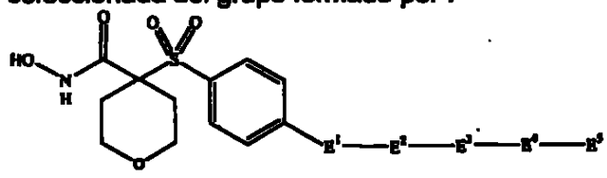
R^9 y R^{10} se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, heterociclil-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo sustituido con halógeno, haloheterociclilo, y heterociclil-C_1-C_6-alquilo sustituido con halógeno.

1229

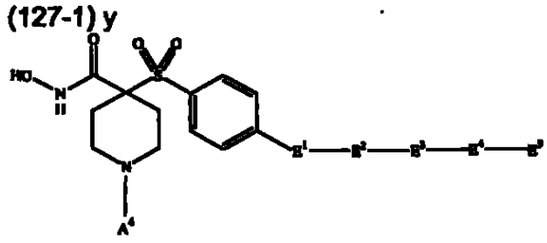
126. Un compuesto o sal del mismo de acuerdo con la cláusula 125 en el cual A^2 y A^3, junto con el átomo de carbono al cual están ambos unidos, forman un heterociclilo optativamente sustituido que contiene ya sea 5 o 6 miembros en el anillo.

127. Un compuesto o sal del mismo de acuerdo con la cláusula 126 en el cual:

el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



(127-1) y



(127-2); y

A^4 se selecciona del grupo formado por -H, alquilo, alquilcarbonilo, alquilcarbonilalquilo, alquilcarbonilalquilcarbonilo, alcoxicarbonilo, alcoxicarbonilalquilo, alcoxicarbonilalquilcarbonilo, alquilsulfonilo, alquiliminocarbonilo, alquenilo, alquinilo, alcoxialquilo, alquiltioalquilo, alquilsulfonilalquilo, alquilsufoxidoalquilo, alquiltioalquenilo, alquilsulfoxidoalquenilo, alquilsulfonilalquenilo, carbociclilo, carbociclilalquilo, carbociclilalcoxialquilo, carbociclilcarbonilo, carbociclilsulfonilo, carbociclliliminocarbonilo, carbociclioxicarbonilo, carbociliitioalquilo,

carbociliisulfoxidoalquilo, carbociliisulfonilalquilo, carbociliitioalquenilo, carbociliisulfoxidoalquenilo, carbociliisulfonilalquenilo, heterociclilo, heterocilialquilo, heterocilialcoxialquilo, heterociliicarbonilo, heterociliitioalquilo, heterociliisulfoxidoalquilo, heterociliisulfonilalquilo, heterociliitioalquenilo, heterociliisulfoxidoalquenilo, heterociliisulfonilalquenilo, heterociliisulfonilo, heterociliiminocarbonilo, heterociliialquilcarbonilo, heterociliicarbonilalquilcarbonilo, heterociliisulfonilo, heterociliicarbonilalquilo, aminoalquilcarbonilo, aminocarbonilo, aminocarbonilalquilcarbonilo, aminosulfonilo, aminosulfonilalquilo, aminoalquilo, aminocarbonilalquilo, y aminoalquilsulfonilo donde:

cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido.

128. Un compuesto o sal del mismo de acuerdo con la cláusula 127 en el cual:

A^4 se selecciona del grupo formado por -H, C_1-C_8-alquilo, C_1-C_8-alquilcarbonilo, C_1-C_8-alquilcarbonil-C_1-C_8-alquilo, C_1-C_8-alquilcarbonil-C_1-C_8-alquilcarbonilo, C_1-C_8-alcoxicarbonilo, C_1-C_8-alcoxicarbonil-C_1-C_8-alquilo, C_1-C_8-alcoxicarbonil-C_1-C_8-alquilcarbonilo, C_1-C_8-alquilsulfonilo, C_1-C_8-alquiliminocarbonilo, C_2-C_8-alquenilo, C_2-C_8-alquinilo, C_1-C_8-alcoxi-C_1-C_8-alquilo, C_1-C_8-alquiltio-C_1-C_8-alquilo, C_1-C_8-alquiltio-C_2-C_8-alquenilo, C_1-C_8-alquilsulfóxido-C_1-C_8-alquilo, C_1-C_8-alquilsulfóxido-C_2-C_8-alquenilo, C_1-C_8-alquilsulfonil-C_1-C_8-alquilo, C_1-C_8-alquilsulfonil-C_2-C_8-alquenilo, carbociclilo, carbociclil-C_1-C_8-alquilo, carbociclil-C_1-C_8-alcoxi-C_1-C_8-alquilo, carbociclilcarbonilo, carbociclilsulfonilo, carbocicliliminocarbonilo, carbociclioxicarbonilo, carbociclitio-C_1-C_8-alquilo, carbociclitio-C_2-C_8-alquenilo,

carbociclilsulfóxido-C_1-C_6-alquilo, carbociclilsulfóxido-C_2-C_6-alquenilo, carbociclilsulfonil-C_1-C_6-alquilo, carbociclilsulfonil-C_2-C_6-alquenilo, heterociclilo, heterociclil-C_1-C_6-alquilo, heterociclil-C_1-C_6-alcoxi-C_1-C_6-alquilo, heterociclilcarbonilo, heterociclilti o-C_1-C_6-alquilo, heterociclilsulfóxido-C_1-C_6-alquilo, heterociclilsulfonil-C_1-C_6-alquilo, heterociclilti o-C_2-C_6-alquenilo, heterociclilsulfóxido-C_2-C_6-alquenilo, heterociclilsulfonil-C_2-C_6-alquenilo, heterociclilsulfonilo, heterociclilimi nocarbonilo, heterociclil-C_1-C_6-alquilcarbonilo, heterociclilcarbonil-C_1-C_6-alquilcarbonilo, heterociclilsulfonilo, heterociclilcarbonil-C_1-C_6-alquilo, N(R^{11})(R^{12})-C_1-C_6-alquilcarbonilo, N(R^{11})(R^{12})-carbonilo, N(R^{11})(R^{12})-carbonil-C_1-C_6-alquilcarbonilo, N(R^{11})(R^{12})-sulfonilo, N(R^{11})(R^{12})-sulfonil-C_1-C_6-alquilo, N(R^{11})(R^{12})-C_1-C_6-alquilo, N(R^{11})(R^{12})-carbonil-C_1-C_6-alquilo, y N(R^{11})(R^{12})-C_1-C_6-alquilsulfonilo donde:

cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -CN, -C(O)-OH, -SH, $-SO_3H$, y NO_2; y

R^{11} y R^{12} se seleccionan independientemente del grupo formado por -H, -OH, C_1-C_6-alquilo, C_1-C_6-alquil-carbonilo, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_2-C_6-alquenilo, C_2-C_6-alquinilo, C_1-C_6-alquil-tio-C_1-C_6-alquilo, C_1-C_6-alquil-sulfóxido-C_1-C_6-alquilo, C_1-C_6-alquil-sulfonil-C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, carbociclilcarbonilo, carbociclil-C_1-C_6-alcoxi-C_1-C_6-alquilo, carbociclilti o-C_1-C_6-alquilo, carbociclilsulfóxido-C_1-C_6-alquilo, carbociclilsulfonil-C_1-C_6-alquilo, heterociclilo, heterociclil-C_1-C_6-alquilo, heterociclil-C_1-C_6-alcoxi-C_1-C_6-alquilo, heterociclilcarbonilo, heterociclilti o-C_1-C_6-alquilo, heterociclilsulfóxido-C_1-C_6-

alquilo, heterociclilsulfonil-C_1-C_6-alquilo, aminocarbonil-C_1-C_6-alquilo, C_1-C_6-alquiloxicarbonilamino-C_1-C_6-alquilo, y amino-C_1-C_6-alquilo donde:

cualquier miembro (excepto -H o -OH) de dicho grupo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -CN, -C(O)-OH, -SH, $-SO_3H$, y NO_2, y

el nitrógeno del amino-C_1-C_6-alquilo es optativamente sustituido con 1 o 2 sustituyentes seleccionados independientemente del grupo formado por C_1-C_6-alquilo, C_1-C_6-alquilcarbonilo, carbociclilo, y carbociclil-C_1-C_6-alquilo, y

no más de uno de R^{11} o R^{12} es -OH.

129. Un compuesto o sal del mismo de acuerdo con la cláusula 128 en el cual A^4 se selecciona del grupo formado por -H, C_1-C_6-alquilo, C_1-C_6-alcoxi-C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, C_1-C_6-alquilsulfonilo, C_3-C_6-alquenilo, C_3-C_6-alquinilo donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido con halógeno.

130. Un compuesto o sal del mismo de acuerdo con la cláusula 129 en el cual A^4 se selecciona del grupo formado por -H, C_1-C_4-alquilo, C_1-C_2-alcoxi-C_1-C_3-alquilo, C_3-C_6-cicloalquilo, C_3-C_6-cicloalquil-C_1-C_3-alquilo, fenilo, fenil-C_1-C_3-alquilo, C_1-C_2-alquilsulfonilo, C_3-C_4-alquenilo, C_3-C_4-alquinilo donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido con halógeno.

131. Un compuesto o sal del mismo de acuerdo con la cláusula 130 en el cual A^4 se selecciona del grupo formado por -H, etilo, metoxietilo, ciclopropilo, ciclopropilmetilo, bencilo, metilsulfonilo, C_3-alquenilo, y C_3-alquinilo donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido con halógeno.

1233

132. Un compuesto o sal del mismo de acuerdo con la cláusula 131 en el cual A^4 se selecciona del grupo formado por -H, etilo, metoxietilo, ciclopropilo, ciclopropilmetilo, y bencilo donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido con halógeno.

133. Un compuesto o sal del mismo de acuerdo con la cláusula 128 en el cual la sal comprende un ácido seleccionado del grupo formado por HCl y CF_3COOH.

134. Un compuesto o sal del mismo de acuerdo con la cláusula 128 en el cual E^2 es C_2-C_5-alquilo optativamente sustituido con uno o más halógenos.

135. Un compuesto o sal del mismo de acuerdo con la cláusula 134 en el cual E^2 es $-(CH_2)_m-$, y m es entre 2 y 5.

136. Un compuesto o sal del mismo de acuerdo con la cláusula 135 en el cual E^4 es un enlace.

137. Un compuesto o sal del mismo de acuerdo con la cláusula 128 en el cual E^3 es heterociclilo optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, ceto, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, heterociclil-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, y C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno donde:

cualquiera de dichos sustituyentes (excepto halógeno, -OH, o ceto) es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alquiltio, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, y halo-C_1-C_6-alquiltio.

1234

138. Un compuesto o sal del mismo de acuerdo con la cláusula 137 en el cual E^3 se selecciona del grupo formado por furanilo, tetrahidropiranilo, dihidrofuranilo, tetrahidrofuranilo, tiofenilo, dihidrotiofenilo, tetrahidrotiofenilo, pirrolilo, isopirrolilo, pirrolinilo, pirrolidinilo, imidazolilo, isoimidazolilo, imidazolinilo, imidazolidinilo, pirazolilo, pirazolinilo, pirazolidinilo, triazolilo, tetrazolilo, ditiolilo, oxatiolilo, oxazolilo, isoxazolilo, oxazolidinilo, isoxazolidinilo, tiazolilo, isotiazolilo, tiazolinilo, isotiazolinilo, tiazolidinilo, isotiazolidinilo, tiodiazolilo, oxatiazolilo, oxadiazolilo, oxatriazolilo, dioxazolilo, oxatiazolilo, oxatiolilo, oxatiolanilo, piranilo, dihidropiranilo, piridinilo, piperidinilo, diazinilo, piperazinilo, triazinilo, oxazinilo, isoxazinilo, oxatiazinilo, oxadiazinilo, morfolinilo, azepinilo, oxepinilo, tiepinilo, diazepinilo, indolizinilo, pirindinilo, piranopirrolilo, 4H-quinolizinilo, purinilo, naftiridinilo, piridopiridinilo, pteridinilo, indolilo, isoindolilo, indoleninilo, isoindazolilo, benzazinilo, ftalazinilo, quinoxalinilo, quinazolinilo, benzodiazinilo, benzopiranilo, benzotiopiranilo, benzoxazolilo, indoxazinilo, antranililo, benzodioxolilo, benzodioxanilo, benzoxadiazolilo, benzofuranilo, isobenzofuranilo, benzotienilo, isobenzotienilo, benzotiazolilo, benzotiadiazolilo, bencimidazolilo, benzotriazolilo, benzoxazinilo, bencisoxazinilo, tetrahidroisoquinolinilo, carbazolilo, xantenilo, y acridinilo donde

cualquier miembro de dicho grupo es optativamente sustituido (en la medida en que dicho miembro contenga uno o más hidrógenos sustituibles) con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, ceto, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, heterociclil-C_1-C_6-

1235

alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, y C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno donde:

cualquiera de dichos sustituyentes (excepto halógeno, -OH, o ceto) es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alquiltio, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, y halo-C_1-C_6-alquiltio.

139. Un compuesto o sal del mismo de acuerdo con la cláusula 137 en el cual E^3 contiene no más de un miembro heteroátomo en el anillo .

140. Un compuesto o sal del mismo de acuerdo con la cláusula 139 en el cual E^3 se selecciona del grupo formado por furanilo, tetrahidropiranilo, dihidrofuranilo, tetrahidrofuranilo, tiofenilo, dihidrotiofenilo, tetrahidrotiofenilo, pirrolinilo, pirrolilo, isopirrolilo, pirrolidinilo, piridinilo, piperidinilo, piranilo, dihidropiranilo, y tetrahidropiranilo donde:

cualquier miembro de dicho grupo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grup formado por halógeno, -OH, ceto, C_1-C_6-alquilo, C_1-C_6-alcoxi, y C_1-C_6-alcoxi-C_1-C_6-alquilo donde:

cualquiera de dichos sustituyentes (excepto halógeno, -OH, o ceto) es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno y -OH.

141. Un compuesto o sal del mismo de acuerdo con la cláusula 139 en el cual E^3 es piridinilo optativamente sustituido con uno o más sustituyentes

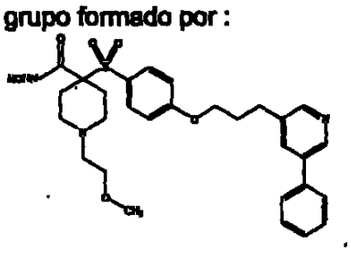
1236

independientemente seleccionados del grupo formado por halógeno, -OH, C_1-C_6-alquilo, C_1-C_6-alcoxi, y C_1-C_6-alcoxi-C_1-C_6-alquilo donde:

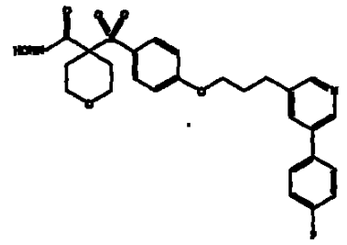
cualquiera de dichos sustituyentes (excepto halógeno o -OH) es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno y -OH.

142. Un compuesto o sal del mismo de acuerdo con la cláusula 141 en el cual E^5 es fenilo optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_6-alquilo, C_2-C_6-alquenilo, C_2-C_6-alquinilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, -$N(R^6)(R^7)$, -$C(O)(R^8)$, -S-R^8, -$S(O)_2$-R^8, fenilo, fenil-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, halofenilo, y fenil-C_1-C_6-alquilo sustituido con halógeno.

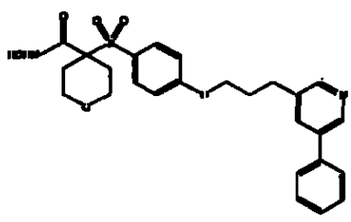
143. Un compuesto o sal del mismo de acuerdo con la cláusula 142 en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



(143-1),

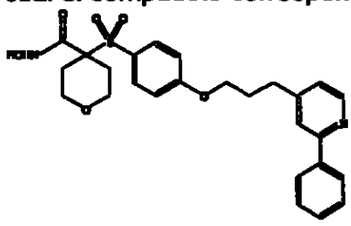


(143-2), y



(143-3).

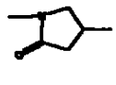
144. Un compuesto o sal del mismo de acuerdo con la cláusula 142 en el cual el compuesto corresponde en estructura a la siguiente fórmula:



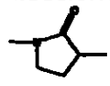
(144-1)..

145. Un compuesto o sal del mismo de acuerdo con la cláusula 139 en el cual:

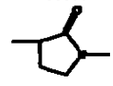
E^3 se selecciona del grupo formado por :



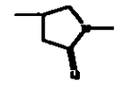
(145-1),



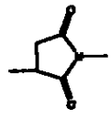
(145-2),



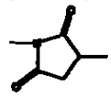
(145-3),



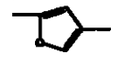
(145-4),



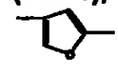
(145-5),



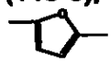
(145-6),



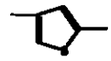
(145-7),



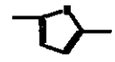
(145-8),



(145-9),



(145-10),

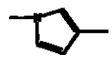
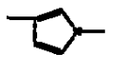
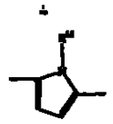
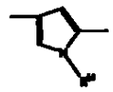
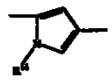


(145-11),



(145-12),

1238


(145-13),

(145-14),

(145-15),

(145-16), y

(145-17); y

cualquier miembro de dicho grupo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo donde:

cualquiera de dichos sustituyentes (excepto halógeno o -OH) es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alquiltio, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, y halo-C_1-C_6-alquiltio; y

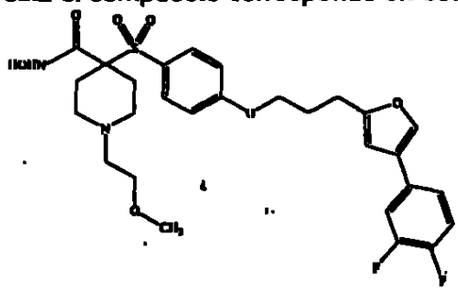
R^{14} se selecciona del grupo formado por halógeno, -OH, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo en el cual

cualquier miembro (excepto halógeno o -OH) de dicho grupo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alquiltio, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, y halo-C_1-C_6-alquiltio.

146. Un compuesto o sal del mismo de acuerdo con la cláusula 145 en el cual E^3 es furanilo optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, ceto, C_1-C_6-alquilo, C_1-C_6-alcoxi, y C_1-C_6-alcoxi-C_1-C_6-alquilo donde:

cualquiera de dichos sustituyentes (excepto halógeno, -OH, o ceto) es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno y -OH.

147. Un compuesto o sal del mismo de acuerdo con la cláusula 146 en el cual el compuesto corresponde en estructura a la siguiente fórmula:



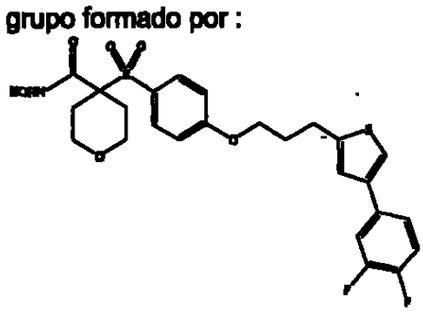
(147-1).

148. Un compuesto o sal del mismo de acuerdo con la cláusula 145 en el cual E^3 es tienilo optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, ceto, C_1-C_6-alquilo, C_1-C_6-alcoxi, y C_1-C_6-alcoxi-C_1-C_6-alquilo donde:

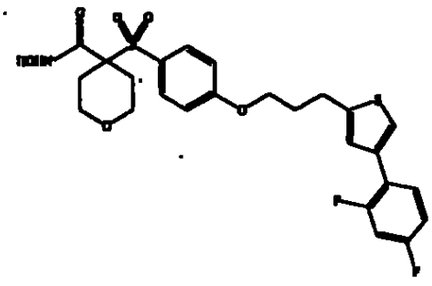
cualquiera de dichos sustituyentes (excepto halógeno, -OH, o ceto) es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno y -OH.

1240

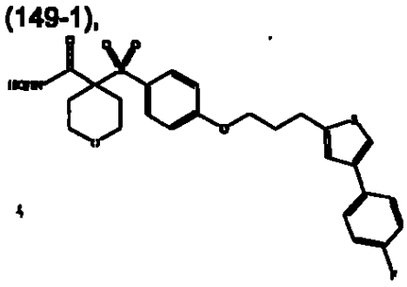
149. Un compuesto o sal del mismo de acuerdo con la cláusula 148 en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



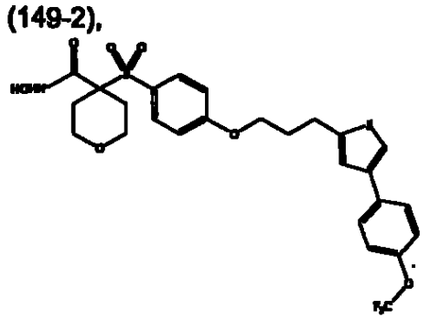
(149-1),



(149-2),

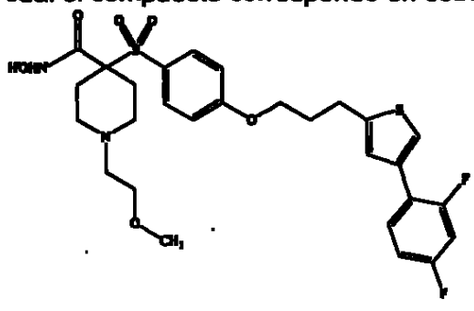


(149-3), y



(149-4).

150. Un compuesto o sal del mismo de acuerdo con la cláusula 148 en el cual el compuesto corresponde en estructura a la siguiente fórmula:



(150-1).

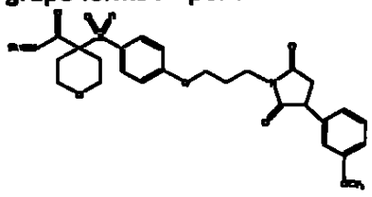
1241

151. Un compuesto o sal del mismo de acuerdo con la cláusula 145 en el cual E^3 es pirrolidinilo optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, ceto, C_1-C_6-alquilo, C_1-C_6-alcoxi, y C_1-C_6-alcoxi-C_1-C_6-alquilo donde:

cualquiera de dichos sustituyentes (excepto halógeno, -OH, o ceto) es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno y -OH.

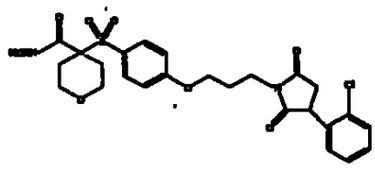
152. Un compuesto o sal del mismo de acuerdo con la cláusula 151 en el cual E^5 es fenilo optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_6-alquilo, C_2-C_6-alquenilo, C_2-C_6-alquinilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, -N(R^6)(R^7), -C(O)(R^8), -S-R^6, -S(O)$_2$-R^5, fenilo, fenil-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, halofenilo, y fenil-C_1-C_6-alquilo sustituido con halógeno.

153. Un compuesto o sal del mismo de acuerdo con la cláusula 152 en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



(153-1)

y



(153-2).

154. Un compuesto o sal del mismo de acuerdo con la cláusula 137 en el cual E^3 contiene nomás y no menos de dos miembros heteroátomos en el anillo.

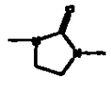
155. Un compuesto o sal del mismo de acuerdo con la cláusula 154 en el cual E^3 se selecciona del grupo formado por pirazolilo, pirazolinilo, pirazolidinilo, imidazolilo, isoimidazolilo, imidazolinilo, imidazolidinilo, ditiolilo, tiazolilo, isotiazolilo, tiazolinilo, isotiazolinilo, tiazolidinilo, isotiazolidinilo, oxatiolilo, oxatiolanilo, oxazolilo, isoxazolilo, oxazolidinilo, isoxazolidinilo, piridinilo, piperazinilo, pirimidinilo, piridazinilo, oxazinilo, y morfolinilo donde:

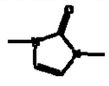
cualquier miembro de dicho grupo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, ceto, C_1-C_6-alquilo, C_1-C_6-alcoxi, y C_1-C_6-alcoxi-C_1-C_6-alquilo donde:

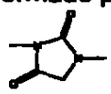
cualquiera de dichos sustituyentes (excepto halógeno, -OH, o ceto) es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno y -OH.

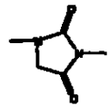
156. Un compuesto o sal del mismo de acuerdo con la cláusula 154 en el cual:

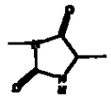
E^3 se selecciona del grupo formado por :

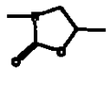

(156-1),

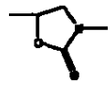

(156-2),

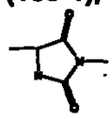

(156-3),

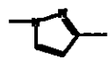
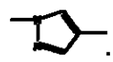

(156-4),


(156-5),

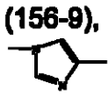
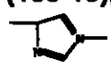
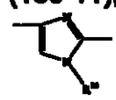
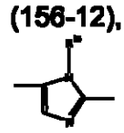
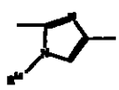

(156-6),

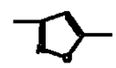
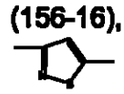
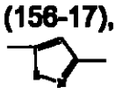
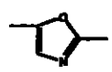
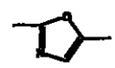
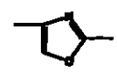
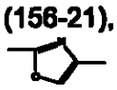
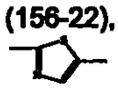
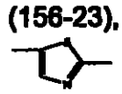
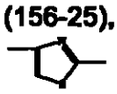

(156-7),


(156-8),


(156-9),

(156-10),

(156-11),

(156-12),

(156-13),

(156-14),

(156-15),

(156-16),

(156-17),

(156-18),

(156-19),

(156-20),

(156-21),

(156-22),

(156-23),

(156-24),

(156-25),

(156-26),

(156-27),
(156-28), y

(156-29); y

cualquier miembro de dicho grupo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo donde:

cualquiera de dichos sustituyentes (excepto halógeno o -OH) es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alquiltio, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, y halo-C_1-C_6-alquiltio; y

1244

R^{14} se selecciona del grupo formado por halógeno, -OH, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo donde:

cualquier miembro (excepto halógeno o -OH) de dicho grupo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alquiltio, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, y halo-C_1-C_6-alquiltio.

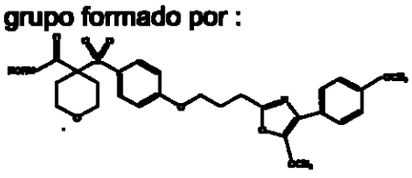
157. Un compuesto o sal del mismo de acuerdo con la cláusula 156 en el cual E^3 se selecciona del grupo formado por oxazolilo y isoxazolilo donde:

el oxazolilo o isoxazolilo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, C_1-C_6-alquilo, C_1-C_6-alcoxi, y C_1-C_6-alcoxi-C_1-C_6-alquilo donde:

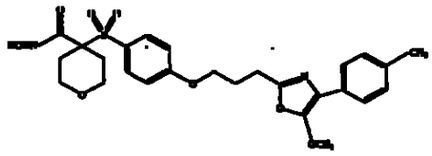
cualquiera de dichos sustituyentes (excepto halógeno o -OH) es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno y -OH.

158. Un compuesto o sal del mismo de acuerdo con la cláusula 157 en el cual E^5 es fenilo optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_6-alquilo, C_2-C_6-alquenilo, C_2-C_6-alquinilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, -$N(R^6)(R^7)$, -$C(O)(R^6)$, -S-R^6, -$S(O)_2$-R^6, fenilo, fenil-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, halofenilo, y fenil-C_1-C_6-alquilo sustituido con halógeno.

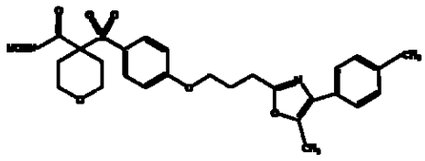
159. Un compuesto o sal del mismo de acuerdo con la cláusula 158 en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



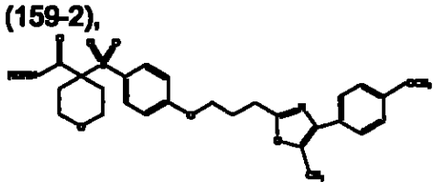
(159-1),



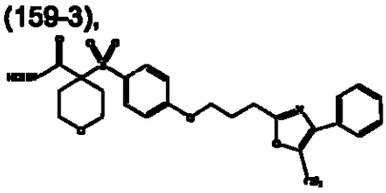
(159-2),



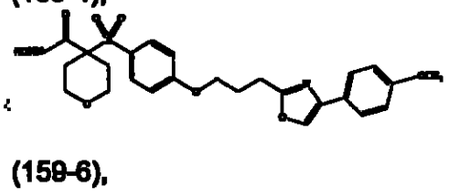
(159-3),



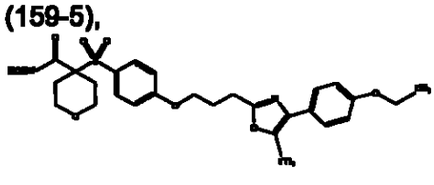
(159-4),



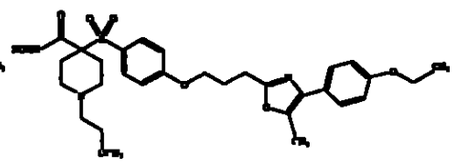
(159-5),



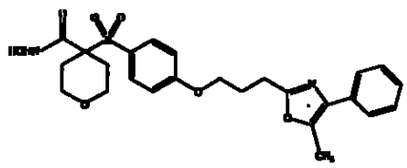
(159-6),



(159-7),



(159-8), y



(159-9).

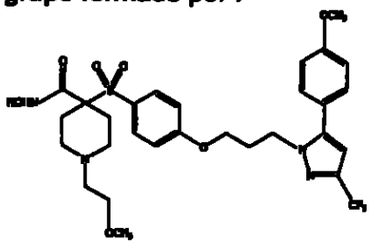
160. Un compuesto o sal del mismo de acuerdo con la cláusula 156 en el cual E^3 se selecciona del grupo formado por pirazolilo y isoimidazolilo donde:

el pirazolilo e isoimidazolilo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, C_1-C_6-alquilo, C_1-C_6-alcoxi, y C_1-C_6-alcoxi-C_1-C_6-alquilo donde:

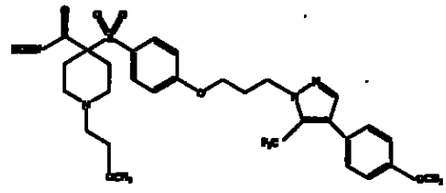
cualquiera de dichos sustituyentes (excepto halógeno o -OH) es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno y -OH.

161. Un compuesto o sal del mismo de acuerdo con la cláusula 160 en el cual E^5 es fenilo optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_6-alquilo, C_2-C_6-alquenilo, C_2-C_6-alquinilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, -$N(R^6)(R^7)$, -$C(O)(R^8)$, -S-R^8, -$S(O)_2$-R^8, fenilo, fenil-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, halofenilo, y fenil-C_1-C_6-alquilo sustituido con halógeno.

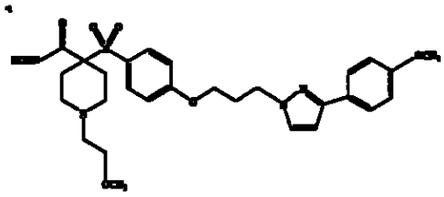
162. Un compuesto o sal del mismo de acuerdo con la cláusula 161 en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



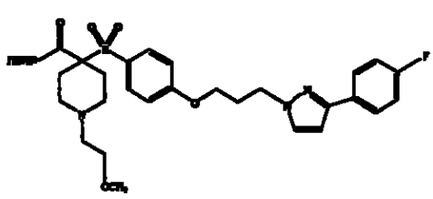
(162-1),



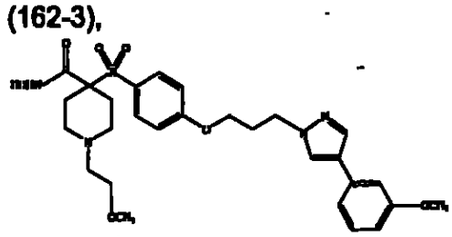
(162-2)



(162-3),



(162-4), y



(162-5).

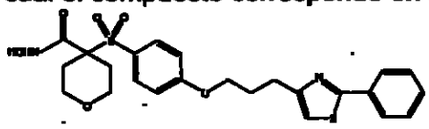
163. Un compuesto o sal del mismo de acuerdo con la cláusula 156 en el cual E^3 se selecciona del grupo formado por tiazolilo y isotiazolilo donde:

el tiazolilo y isotiazolilo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, C_1-C_6-alquilo, C_1-C_6-alcoxi, y C_1-C_6-alcoxi-C_1-C_6-alquilo donde:

cualquiera de dichos sustituyentes (excepto halógeno o -OH) es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno y -OH.

164. Un compuesto o sal del mismo de acuerdo con la cláusula 163 en el cual E^5 es fenilo optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_6-alquilo, C_2-C_6-alquenilo, C_2-C_6-alquinilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, -$N(R^6)(R^7)$, -$C(O)(R^6)$, -S-R^6, -$S(O)_2$-R^6, fenilo, fenil-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, halofenilo, y fenil-C_1-C_6-alquilo sustituido con halógeno.

165. Un compuesto o sal del mismo de acuerdo con la cláusula 164 en el cual el compuesto corresponde en estructura a la siguiente fórmula:



(165-1).

166. Un compuesto o sal del mismo de acuerdo con la cláusula 156 en el cual E^3 se selecciona del grupo formado por pirazolidinilo y imidazolidinilo donde:

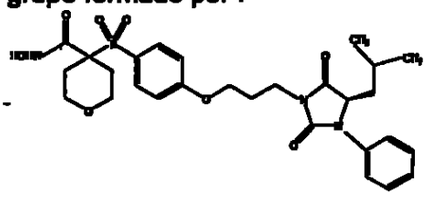
el pirazolidinilo y imidazolidinilo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, ceto, C_1-C_6-alquilo, C_1-C_6-alcoxi, y C_1-C_6-alcoxi-C_1-C_6-alquilo donde:

cualquiera de dichos sustituyentes (excepto halógeno, -OH, o ceto) es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno y -OH.

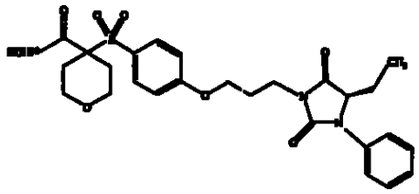
167. Un compuesto o sal del mismo de acuerdo con la cláusula 166 en el cual E^5 es fenilo optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_6-alquilo, C_2-C_6-alquenilo, C_2-C_6-alquinilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, -$N(R^6)(R^7)$, -$C(O)(R^8)$, -S-R^8, -$S(O)_2$-R^8, fenilo, fenil-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, halofenilo, y fenil-C_1-C_6-alquilo sustituido con halógeno.

1249

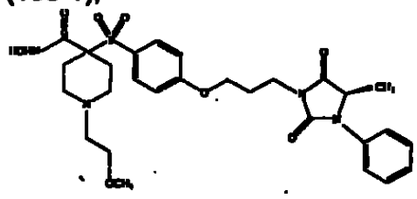
168. Un compuesto o sal del mismo de acuerdo con la cláusula 167 en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



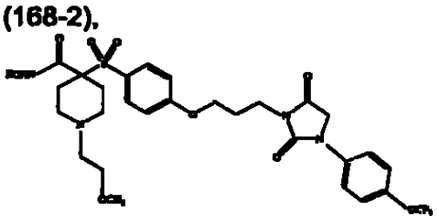
(168-1),



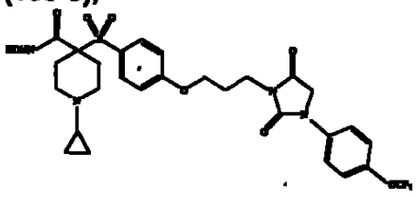
(168-2),



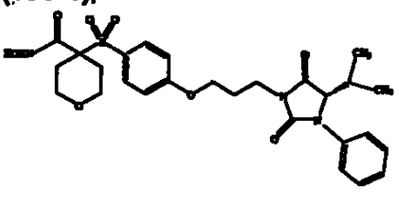
(168-3),



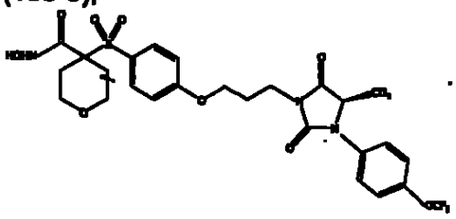
(168-4),



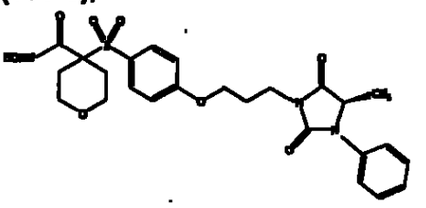
(168-5),



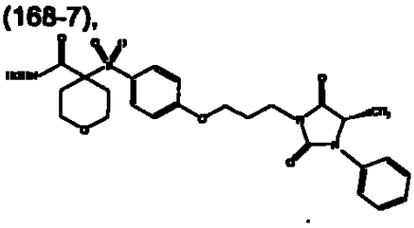
(168-6),



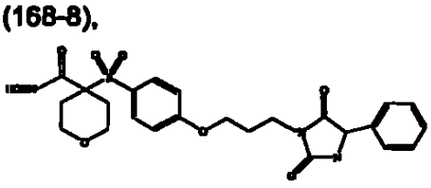
(168-7),



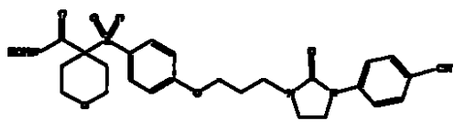
(168-8),



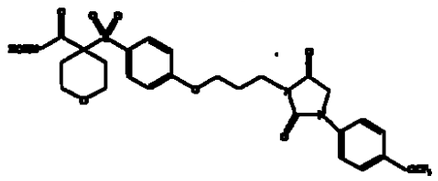
(168-9),



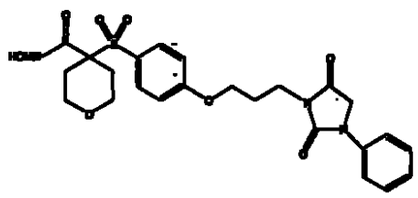
(168-10),



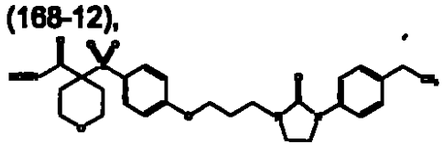
(168-11),



(168-12),



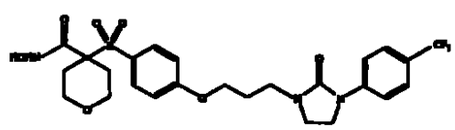
(168-13),



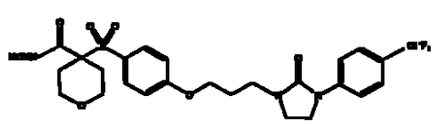
(168-14),



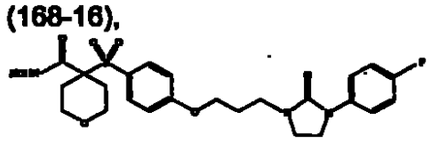
(168-15),



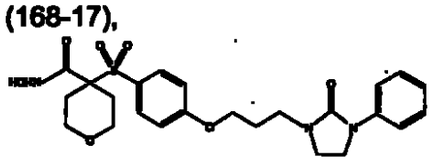
(168-16),



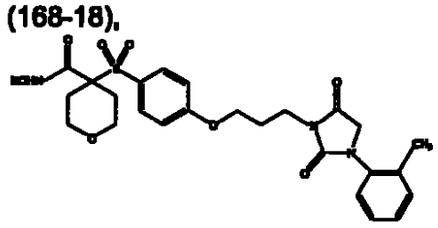
(168-17),



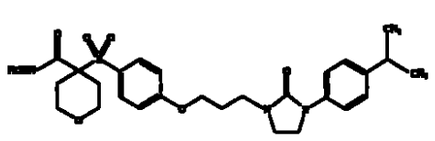
(168-18),



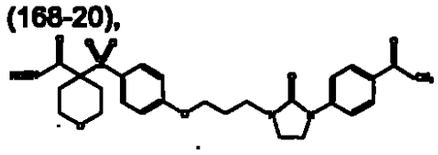
(168-19),



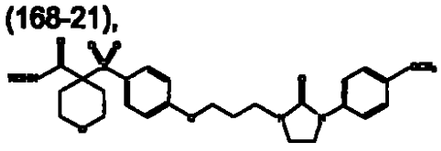
(168-20),



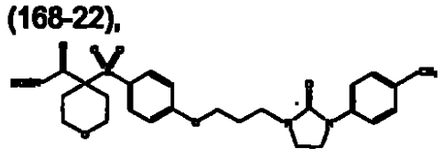
(168-21),



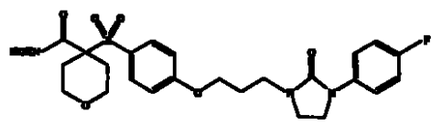
(168-22),



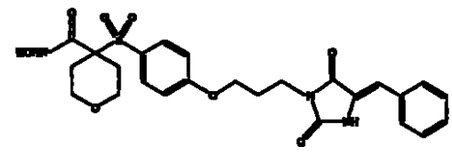
(168-23),



(168-24),



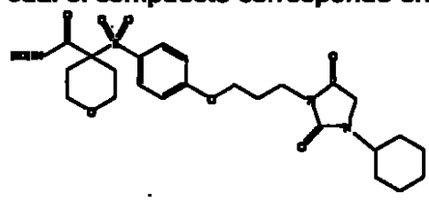
(168-25), y



(168-26).

169. Un compuesto o sal del mismo de acuerdo con la cláusula 166 en el cual E^5 es C_5-C_6-cicloalquilo optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_6-alquilo, C_2-C_6-alquenilo, C_2-C_6-alquinilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, -$N(R^6)(R^7)$, -$C(O)(R^8)$, -S-R^6, -$S(O)_2$-R^6, fenilo, fenil-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, halofenilo, y fenil-C_1-C_6-alquilo sustituido con halógeno.

170. Un compuesto o sal del mismo de acuerdo con la cláusula 169 en el cual el compuesto corresponde en estructura a la siguiente fórmula:



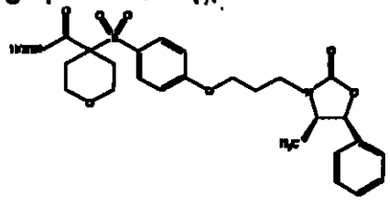
(170-1).

171. Un compuesto o sal del mismo de acuerdo con la cláusula 156 en el cual E^3 es oxazolidinilo optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, ceto, C_1-C_6-alquilo, C_1-C_6-alcoxi, y C_1-C_6-alcoxi-C_1-C_6-alquilo donde:

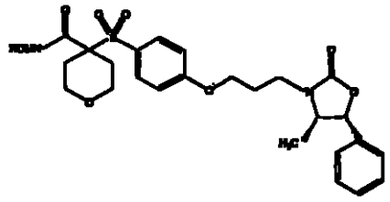
cualquiera de dichos sustituyentes (excepto halógeno, -OH, o ceto) es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno y -OH.

172. Un compuesto o sal del mismo de acuerdo con la cláusula 171 en el cual E^5 es fenilo optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_6-alquilo, C_2-C_6-alquenilo, C_2-C_6-alquinilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, -N(R^6)(R^7), -C(O)(R^6), -S-R^6, -S(O)$_2$-R^6, fenilo, fenil-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, halofenilo, y fenil-C_1-C_6-alquilo sustituido con halógeno.

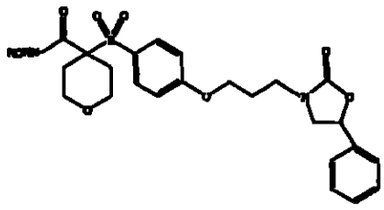
173. Un compuesto o sal del mismo de acuerdo con la cláusula 172 en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



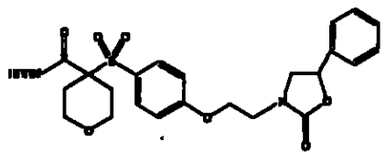
(173-1),



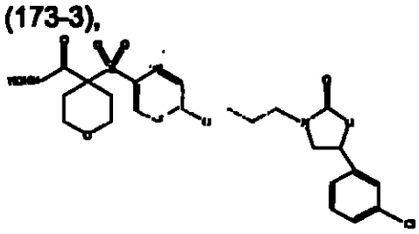
(173-2),



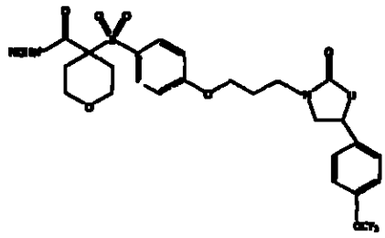
(173-3),



(173-4),



(173-5), y



(173-6).

174. Un compuesto o sal del mismo de acuerdo con la cláusula 137 en el cual E^3 contiene nomás y no menos de 3 heteroátomos.

175. Un compuesto o sal del mismo de acuerdo con la cláusula 174 en el cual E^3 se selecciona del grupo formado por oxadiazolilo, tiadiazolilo, y triazolilo donde:

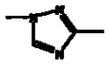
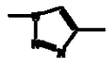
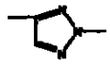
el triazolilo es optativamente sustituido con un sustituyente seleccionado del grupo formado por halógeno, -OH, C_1-C_6-alquilo, C_1-C_6-alcoxi, y C_1-C_6-alcoxi-C_1-C_6-alquilo,

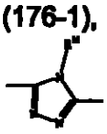
cualquiera de dichos sustituyentes (excepto halógeno o -OH) es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno y -OH.

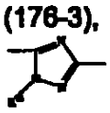
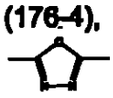
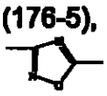
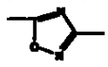
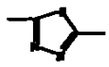
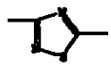
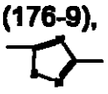
1254

176. Un compuesto o sal del mismo de acuerdo con la cláusula 174 en el cual:

E^3 se selecciona del grupo formado por :


(176-1),

(176-2),

(176-3),

(176-4),

(176-5),

(176-6),

(176-7),

(176-8),

(176-9),

(176-10),

(176-11),

(176-12), y

(176-13); y

cualquier miembro de dicho grupo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo donde:

cualquiera de dichos sustituyentes (excepto halógeno o -OH) es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alquiltio, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, y halo-C_1-C_6-alquiltio; y

1255

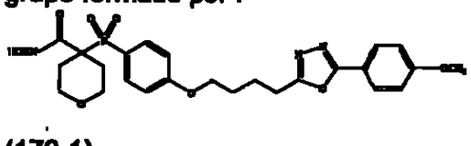
R^{14} se selecciona del grupo formado por halógeno, -OH, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo donde:

cualquier miembro (excepto halógeno o -OH) de dicho grupo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alquiltio, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, y halo-C_1-C_6-alquiltio.

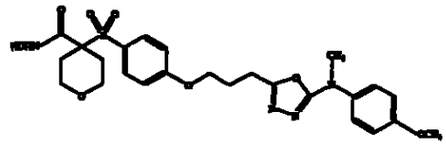
177. Un compuesto o sal del mismo de acuerdo con la cláusula 176 en el cual E^3 es oxadiazolilo.

178. Un compuesto o sal del mismo de acuerdo con la cláusula 177 en el cual E^5 es fenilo optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_6-alquilo, C_2-C_6-alquenilo, C_2-C_6-alquinilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, -N(R^6)(R^7), -C(O)(R^8), -S-R^8, -S(O)$_2$-R^8, fenilo, fenil-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, halofenilo, y fenil-C_1-C_6-alquilo sustituido con halógeno.

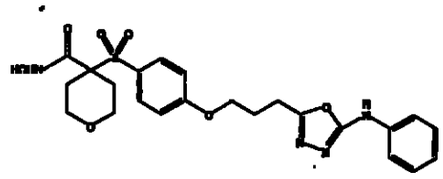
179. Un compuesto o sal del mismo de acuerdo con la cláusula 178 en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



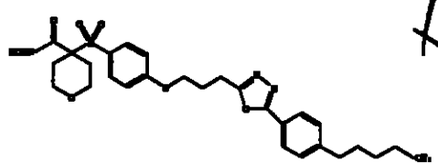
(179-1),



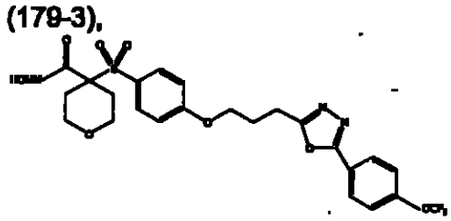
(179-2),



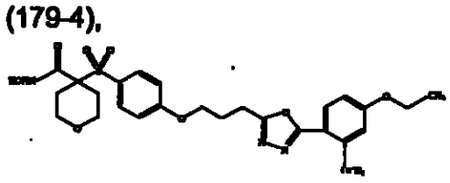
(179-3),



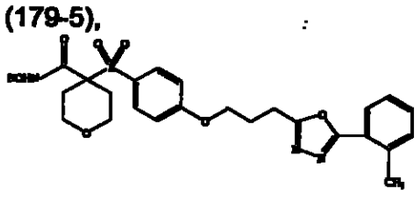
(179-4),



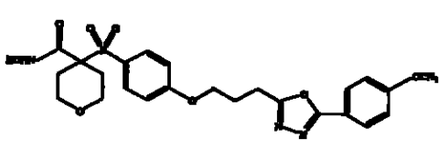
(179-5),



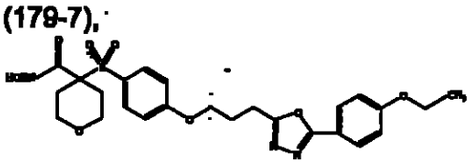
(179-6),



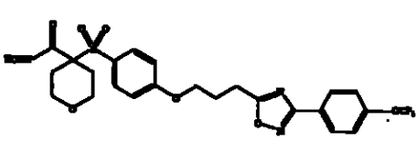
(179-7),



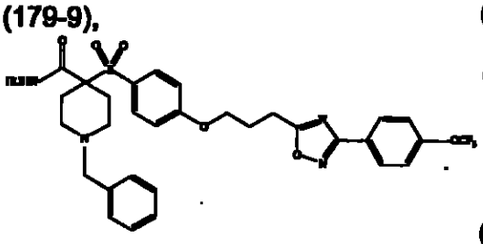
(179-8),



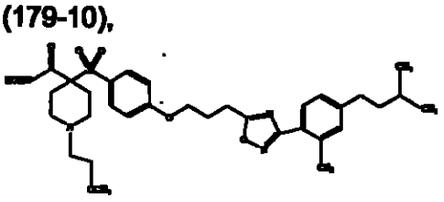
(179-9),



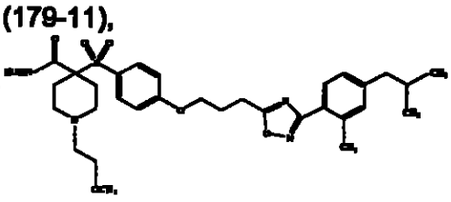
(179-10),



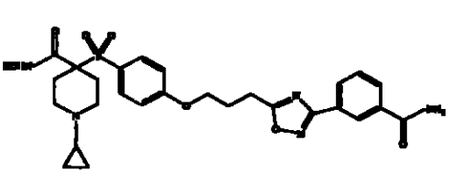
(179-11),



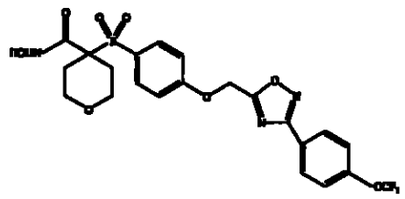
(179-12),



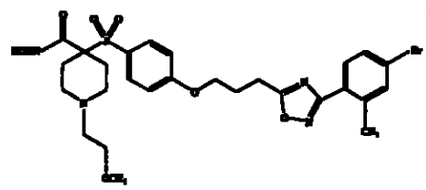
(179-13),



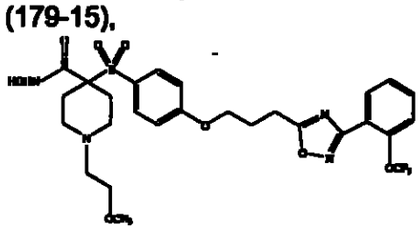
(179-14),



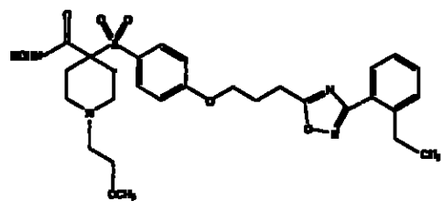
(179-15),



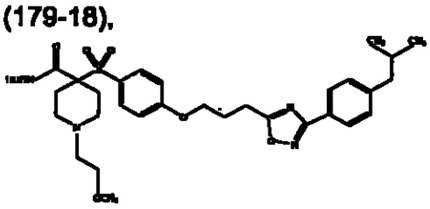
(179-16),



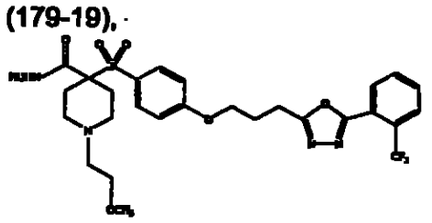
(179-18),



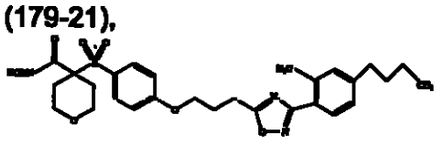
(179-19),



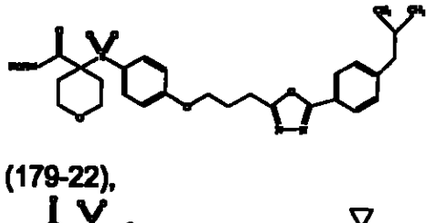
(179-20),



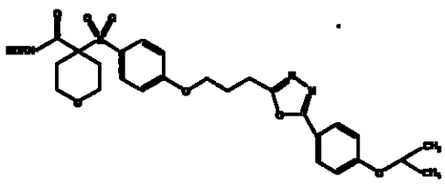
(179-21),



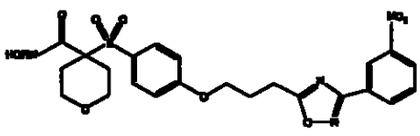
(179-23),



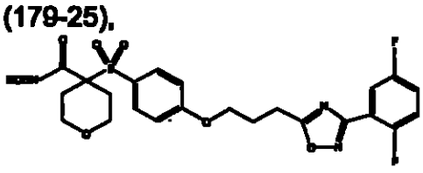
(179-22),



(179-24),



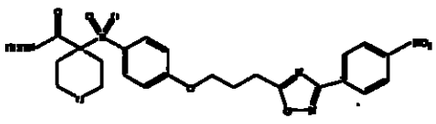
(179-25),



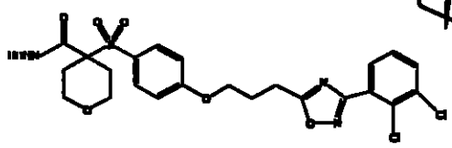
(179-26),

(179-27),

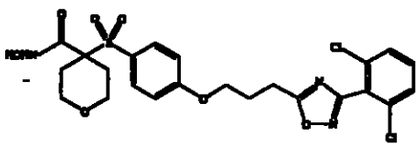
1258



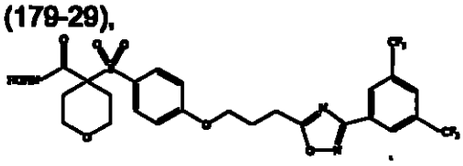
(179-28),



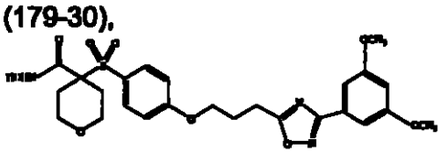
(179-29),



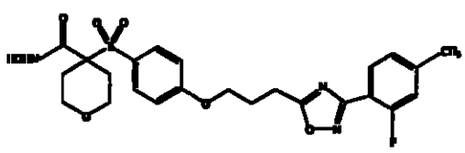
(179-30),



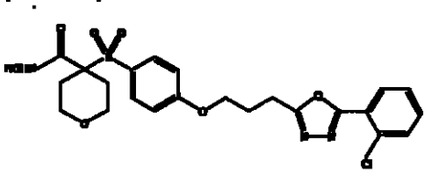
(179-31),



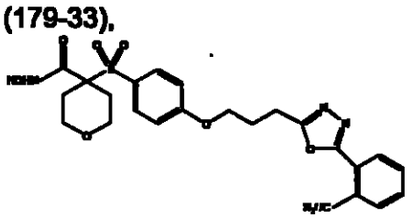
(179-32),



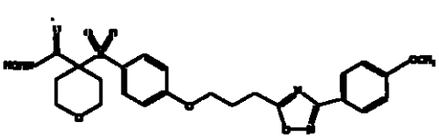
(179-33),



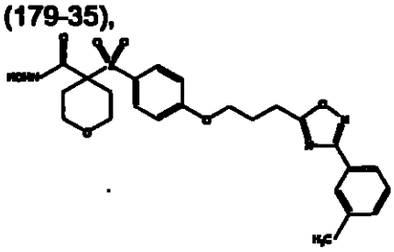
(179-34),



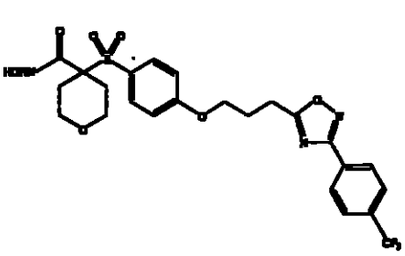
(179-35),



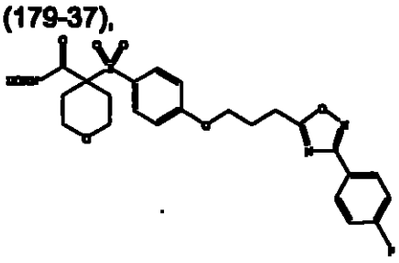
(179-36),



(179-37),

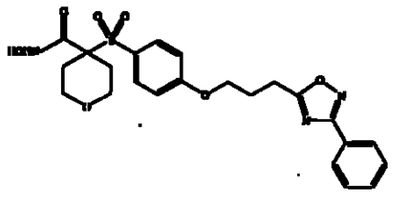


(179-38),

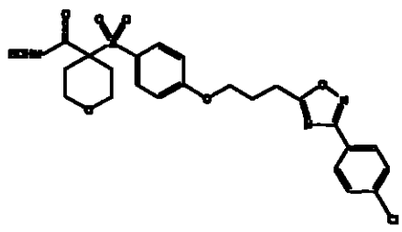


(179-39),

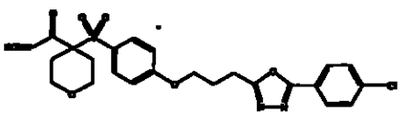
1259



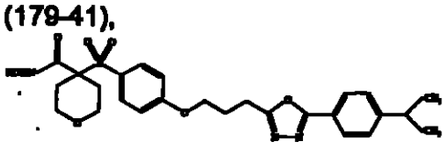
(179-40),



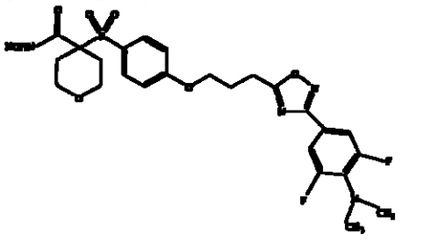
(179-41),



(179-42),



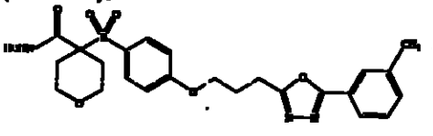
(179-43),



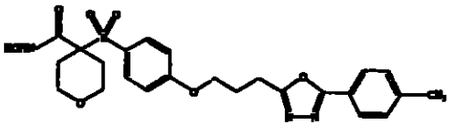
(179-44),



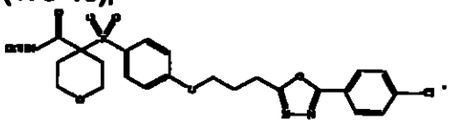
(179-45),



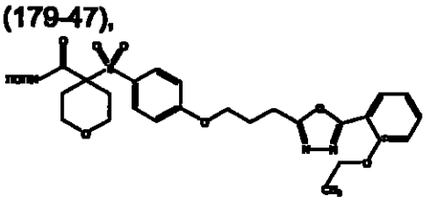
(179-46),



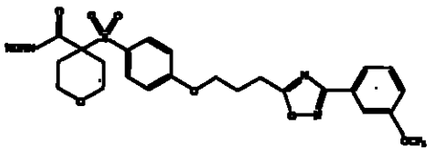
(179-47),



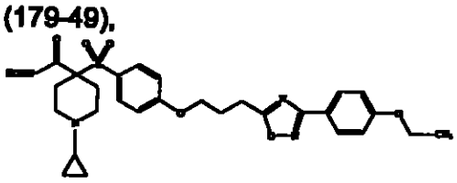
(179-48),



(179-49),

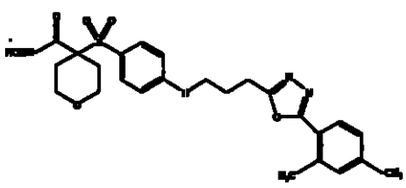


(179-50),

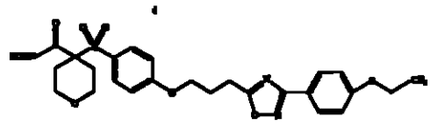


(179-51),

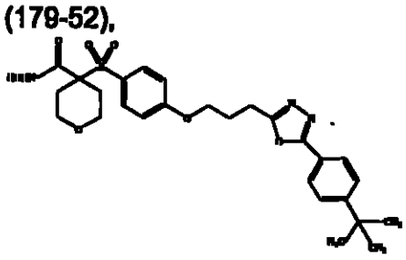
1260



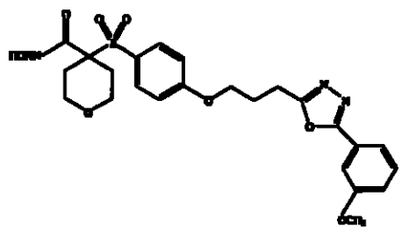
(179-52),



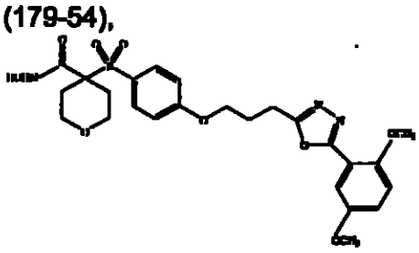
(179-53),



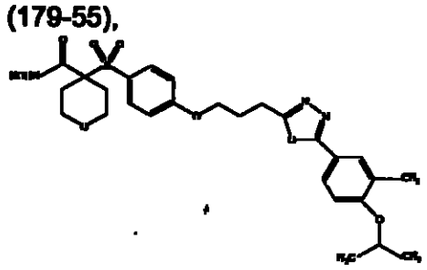
(179-54),



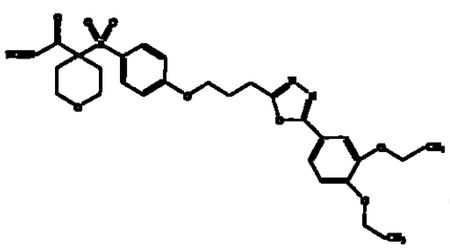
(179-55),



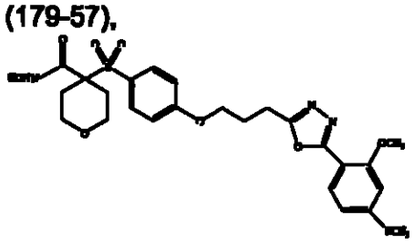
(179-56),



(179-57),



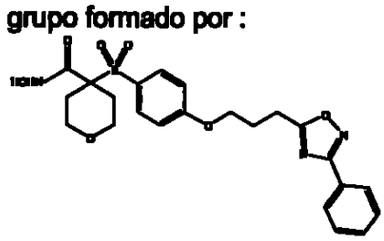
(179-58), y



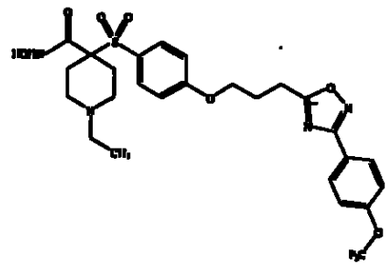
(179-59).

1261

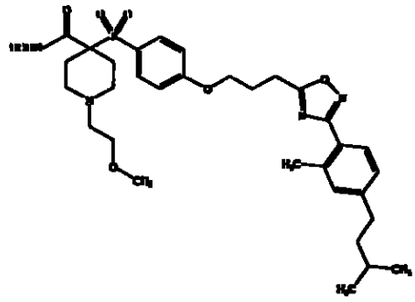
180. Un compuesto o sal del mismo de acuerdo con la cláusula 178 en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



(180-1),

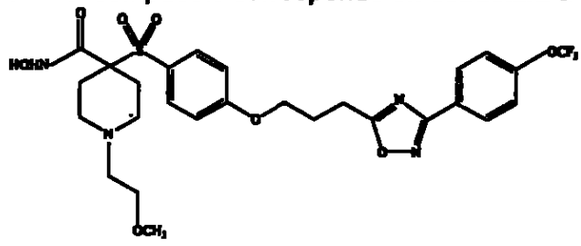


(180-2), y



(180-3).

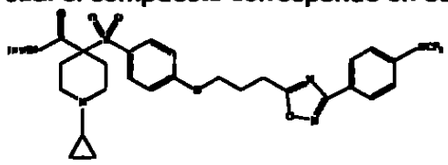
181. Un compuesto o sal del mismo de acuerdo con la cláusula 178 en el cual el compuesto corresponde en estructura a la siguiente fórmula:



181-1

1262

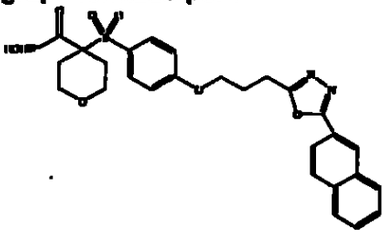
182. Un compuesto o sal del mismo de acuerdo con la cláusula 178 en el cual el compuesto corresponde en estructura a la siguiente fórmula:



(182-1).

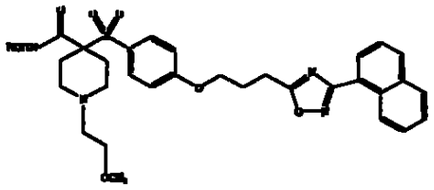
183. Un compuesto o sal del mismo de acuerdo con la cláusula 177 en el cual E^5 es naftalenilo optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_6-alquilo, C_2-C_6-alquenilo, C_2-C_6-alquinilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, -$N(R^6)(R^7)$, -$C(O)(R^8)$, -S-R^8, -$S(O)_2$-R^8, fenilo, fenil-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, halofenilo, y fenil-C_1-C_6-alquilo sustituido con halógeno.

184. Un compuesto o sal del mismo de acuerdo con la cláusula 183, en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



(¡Error! No se encuentra el origen de la referencia.-1)

Y



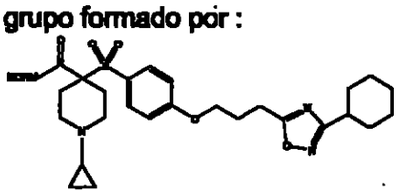
(¡Error! No se encuentra el origen de la referencia.-2).

185. Un compuesto o sal del mismo de acuerdo con la cláusula 177, en el cual E^5 es C_5-C_6-cicloalquilo optativamente sustituido con uno o más

1263

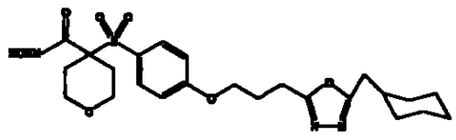
sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_6-alquilo, C_2-C_6-alquenilo, C_2-C_6-alquinilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, -$N(R^6)(R^7)$, -$C(O)(R^8)$, -S-R^6, -$S(O)_2$-R^6, fenilo, fenil-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, halofenilo, y fenil-C_1-C_6-alquilo sustituido con halógeno.

186. Un compuesto o sal del mismo de acuerdo con la cláusula 185, en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



(186-1)

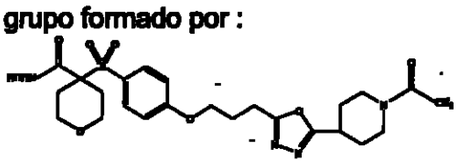
y



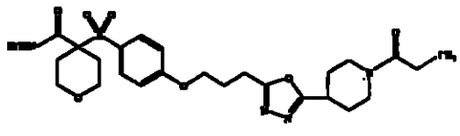
(186-2).

187. Un compuesto o sal del mismo de acuerdo con la cláusula 177, en el cual E^5 es heterociclilo optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, ceto, C_1-C_6-alquilo, C_2-C_6-alquenilo, C_2-C_6-alquinilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, -$N(R^6)(R^7)$, -$C(O)(R^8)$, -S-R^6, -$S(O)_2$-R^6, fenilo, fenil-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, halofenilo, y fenil-C_1-C_6-alquilo sustituido con halógeno.

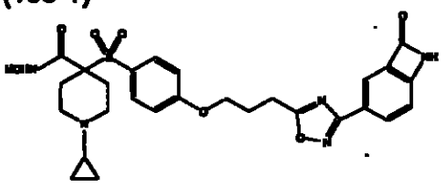
188. Un compuesto o sal del mismo de acuerdo con la cláusula 187, en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



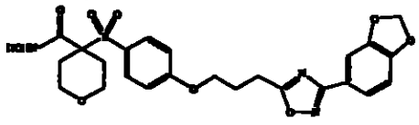
(188-1)



(188-2),

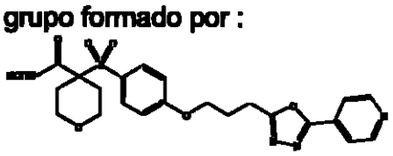


(188-3), y



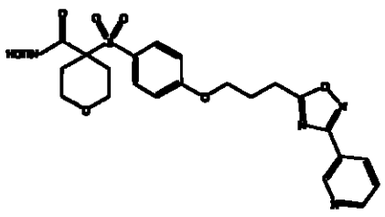
(188-4).

189. Un compuesto o sal del mismo de acuerdo con la cláusula 187, en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



(189-1)

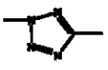
y



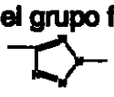
(189-2).

190. Un compuesto o sal del mismo de acuerdo con la cláusula 137, en el cual E^3 contiene al menos 4 miembros heteroátomos en el anillo.

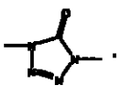
191. Un compuesto o sal del mismo de acuerdo con la cláusula 190, en el cual E^3 se selecciona del grupo formado por :



(191-1),



(191-2), y

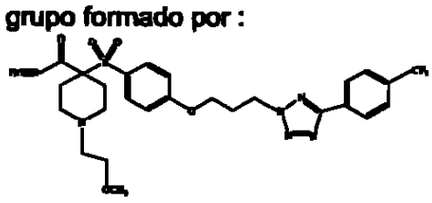


(191-3).

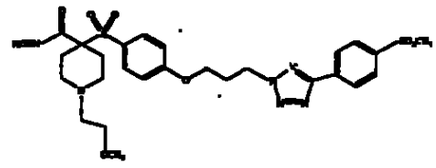
1265

192. Un compuesto o sal del mismo de acuerdo con la cláusula 191, en el cual E^5 es fenilo optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_6-alquilo, C_2-C_6-alquenilo, C_2-C_6-alquinilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, -$N(R^6)(R^7)$, -$C(O)(R^6)$, -S-R^6, -$S(O)_2$-R^6, fenilo, fenil-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, halofenilo, y fenil-C_1-C_6-alquilo sustituido con halógeno.

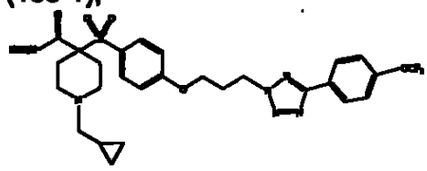
193. Un compuesto o sal del mismo de acuerdo con la cláusula 192, en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



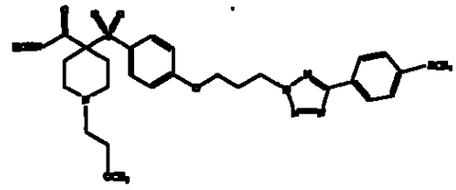
(193-1),



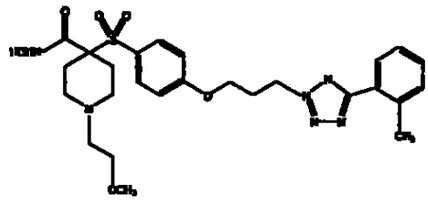
(193-2),



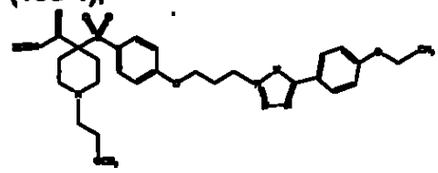
(193-3),



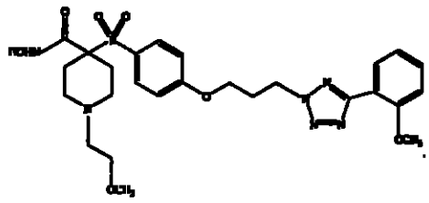
(193-4),



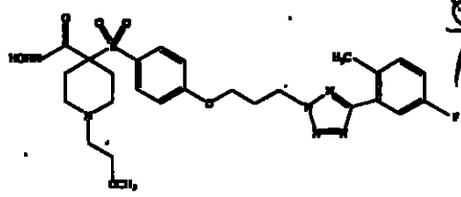
(193-5),



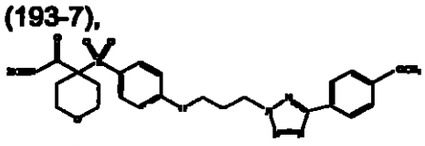
(193-6),



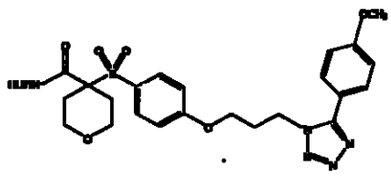
(193-7),



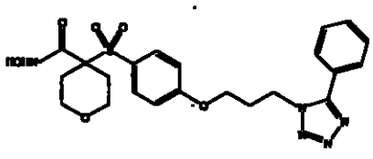
(193-8),



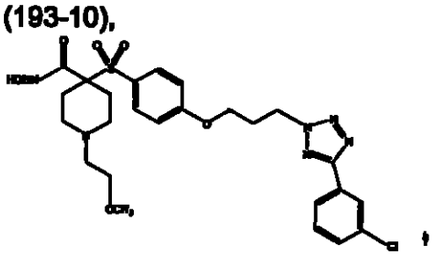
(193-9),



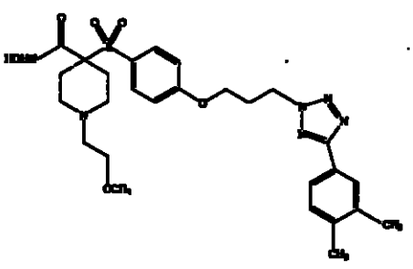
(193-10),



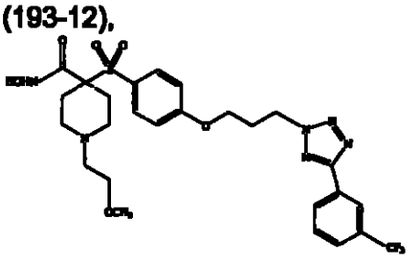
(193-11),



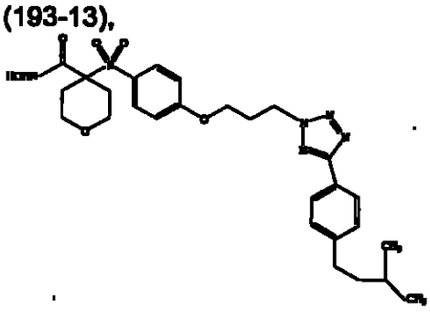
(193-12),



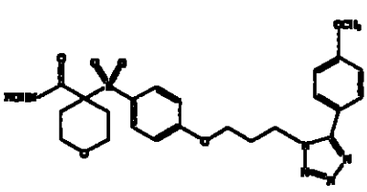
(193-13),



(193-14),

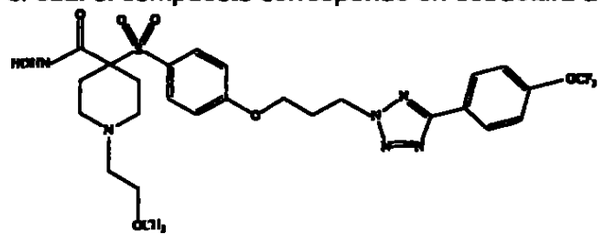


(193-15), y



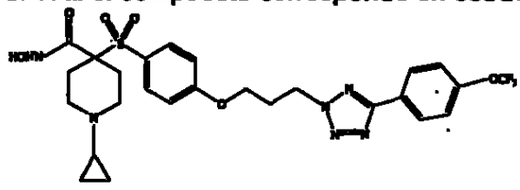
(193-16).

194. Un compuesto o sal del mismo de acuerdo con la cláusula 192, en el cual el compuesto corresponde en estructura a la siguiente fórmula:



(194-1).

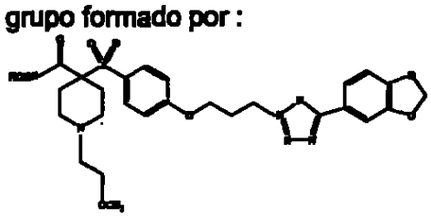
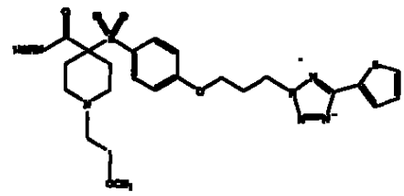
195. Un compuesto o sal del mismo de acuerdo con la cláusula 192, en el cual el compuesto corresponde en estructura a la siguiente fórmula:



(195-1).

196. Un compuesto o sal del mismo de acuerdo con la cláusula 191, en el cual E^5 es heterociclilo optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, ceto, C_1-C_6-alquilo, C_2-C_6-alquenilo, C_2-C_6-alquinilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, -$N(R^6)(R^7)$, -$C(O)(R^8)$, -S-R^6, -$S(O)_2$-R^6, fenilo, fenil-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, halofenilo, y fenil-C_1-C_6-alquilo sustituido con halógeno.

197. Un compuesto o sal del mismo de acuerdo con la cláusula 196, en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :

 y 

(197-1) (197-2).

198. Un compuesto o sal del mismo de acuerdo con la cláusula 128, en el cual E^3 es ciclopropilo, ciclobutilo, ciclopentilo, ciclopentenilo, ciclopentadienilo, ciclohexilo, ciclohexenilo, ciclohexadienilo, fenilo, naftalenilo, tetrahidronaftalenilo, indenilo, isoindenilo, indanilo, biciclodecanilo, antracenilo, fenantrenilo, benzonaftenilo, fluorenelio, decalinilo, y norpinanilo, donde:

cualquier miembro de dicho grupo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, ceto, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo, donde:

cualquiera de dichos sustituyentes (excepto halógeno, -OH, o ceto) es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alquiltio, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, y halo-C_1-C_6-alquiltio.

1269

199. Un compuesto o sal del mismo de acuerdo con la cláusula 198, en el cual E^3 es fenilo optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo, donde:

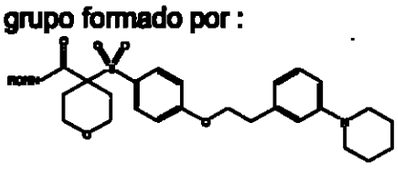
cualquiera de dichos sustituyentes (excepto halógeno o -OH) es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alquiltio, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, y halo-C_1-C_6-alquiltio.

200. Un compuesto o sal del mismo de acuerdo con la cláusula 199, en el cual E^5 se selecciona del grupo formado por piperidinilo, piperazinilo, imidazolilo, furanilo, tienilo, piridinilo, pirimidilo, benzodioxolilo, benzodioxanilo, benzofurilo, y benzotienilo, donde

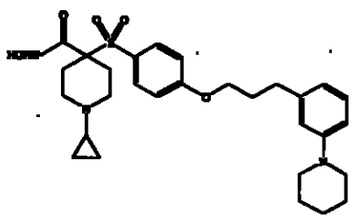
cualquier miembro de dicho grupo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, -CN, C_1-C_6-alquilo, C_2-C_6-alquenilo, C_2-C_6-alquinilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, $-N(R^6)(R^7)$, $-C(O)(R^6)$, $-S-R^6$, $-S(O)_2-R^6$, fenilo, fenil-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, halofenilo, y fenil-C_1-C_6-alquilo sustituido con halógeno.

1230

201. Un compuesto o sal del mismo de acuerdo con la cláusula 200, en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



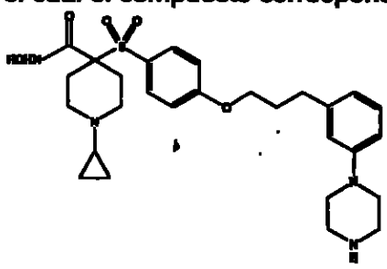
y



(201-1)

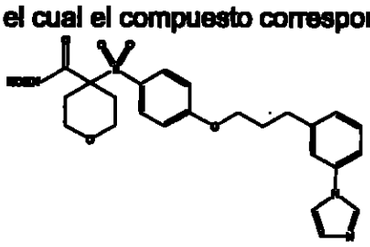
(201-2).

202. Un compuesto o sal del mismo de acuerdo con la cláusula 200, en el cual el compuesto corresponde en estructura a la siguiente fórmula:



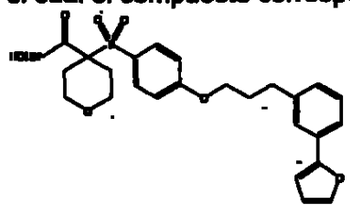
(202-1).

203. Un compuesto o sal del mismo de acuerdo con la cláusula 200, en el cual el compuesto corresponde en estructura a la siguiente fórmula:



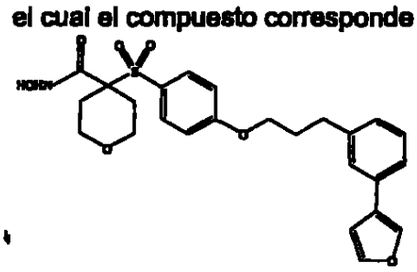
(203-1).

204. Un compuesto o sal del mismo de acuerdo con la cláusula 200, en el cual el compuesto corresponde en estructura a la siguiente fórmula:



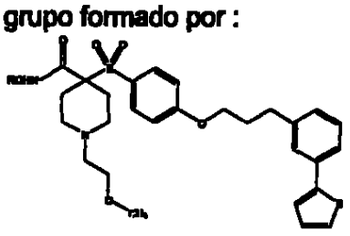
(204-1).

205. Un compuesto o sal del mismo de acuerdo con la cláusula 200, en el cual el compuesto corresponde en estructura a la siguiente fórmula:

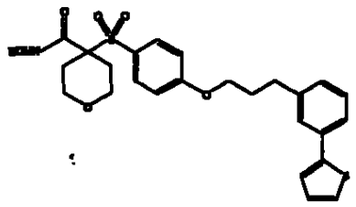


(205-1).

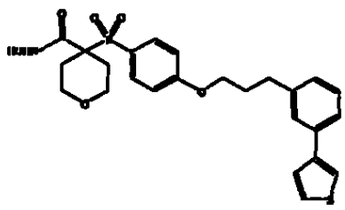
206. Un compuesto o sal del mismo de acuerdo con la cláusula 200, en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



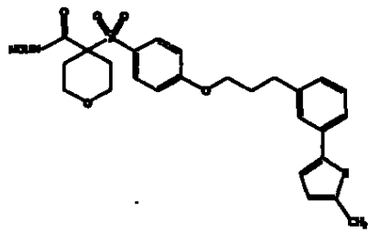
(206-1),



(206-2),

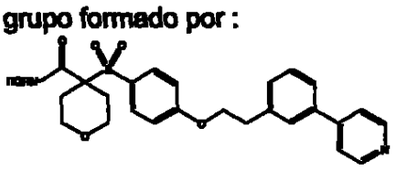


(206-3), y

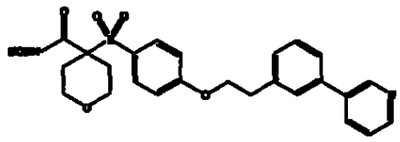


(206-4).

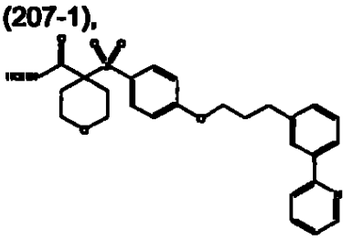
207. Un compuesto o sal del mismo de acuerdo con la cláusula 200, en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



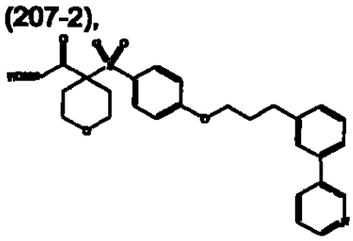
(207-1),



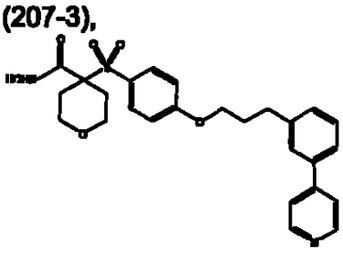
(207-2),



(207-3),



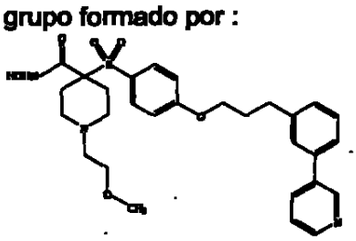
(207-4), y



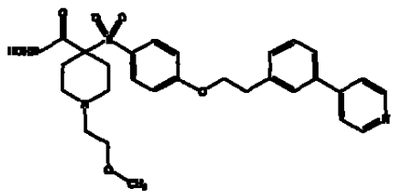
(207-5).

1273

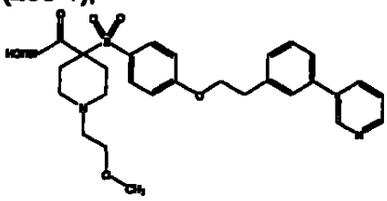
208. Un compuesto o sal del mismo de acuerdo con la cláusula 200, en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



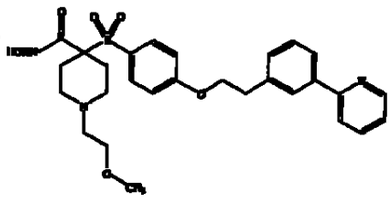
(208-1),



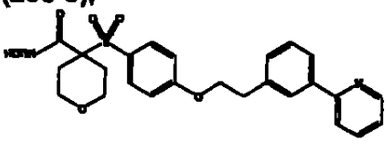
(208-2),



(208-3),

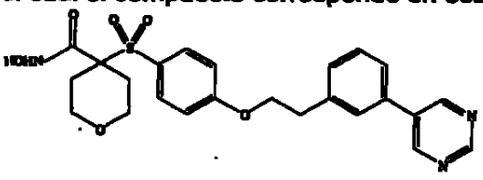


(208-4), y



(208-5).

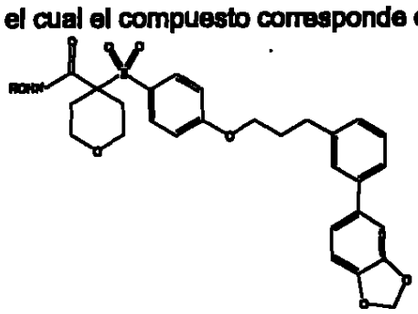
209. Un compuesto o sal del mismo de acuerdo con la cláusula 200, en el cual el compuesto corresponde en estructura a la siguiente fórmula:



(209-1).

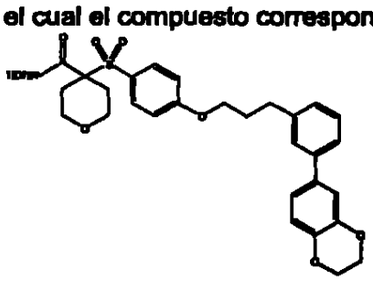
1274.

210. Un compuesto o sal del mismo de acuerdo con la cláusula 200, en el cual el compuesto corresponde en estructura a la siguiente fórmula:



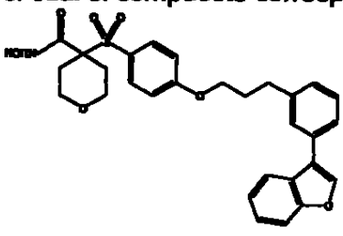
(210-1).

211. Un compuesto o sal del mismo de acuerdo con la cláusula 200, en el cual el compuesto corresponde en estructura a la siguiente fórmula:



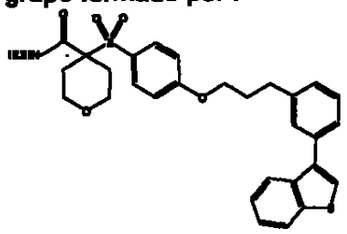
(211-1).

212. Un compuesto o sal del mismo de acuerdo con la cláusula 200, en el cual el compuesto corresponde en estructura a la siguiente fórmula: .

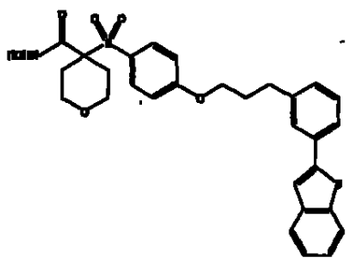


(212-1).

213. Un compuesto o sal del mismo de acuerdo con la cláusula 200, en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



y



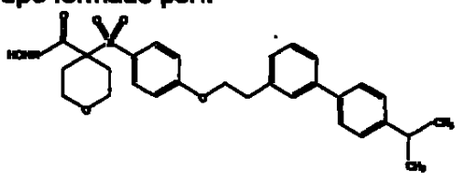
(213-1)

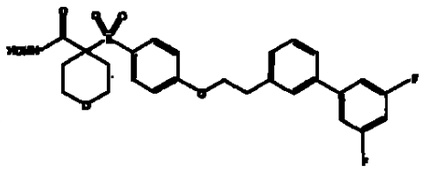
(213-1).

214. Un compuesto o sal del mismo de acuerdo con la cláusula 199, en el cual E^5 se selecciona del grupo formado por fenilo y naftalenilo, donde:

el fenilo y naftalenilo optativamente son sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_6-alquilo, C_2-C_6-alquenilo, C_2-C_6-alquinilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, -$N(R^6)(R^7)$, -$C(O)(R^6)$, -S-R^6, -$S(O)_2$-R^6, fenilo, fenil-C_1-C_6-alquilo, halo-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, halofenilo, y fenil-C_1-C_6-alquilo sustituido con halógeno.

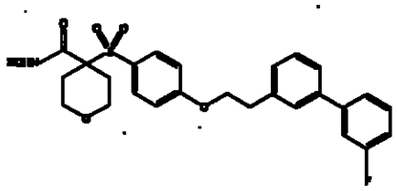
215. Un compuesto o sal del mismo de acuerdo con la cláusula 214, en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por.:

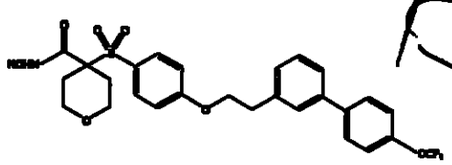




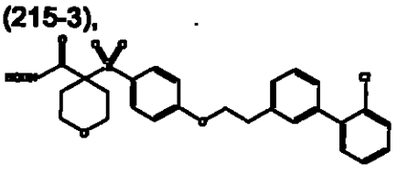
(215-1),

(215-2),

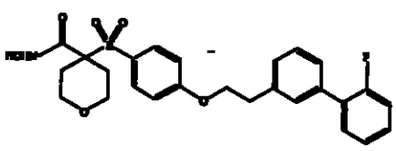




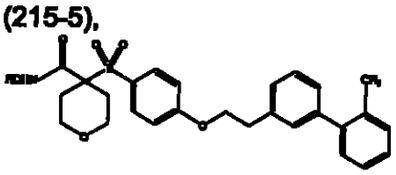
(215-3),



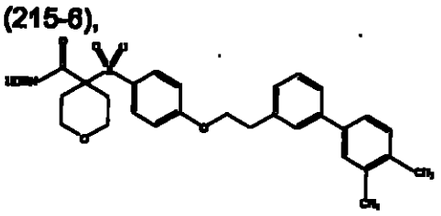
(215-4),



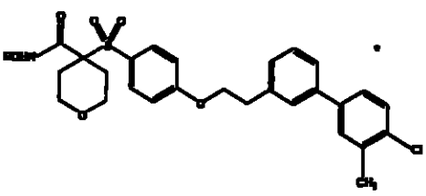
(215-5),



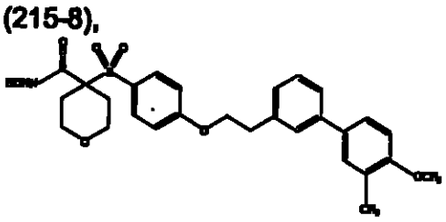
(215-6),



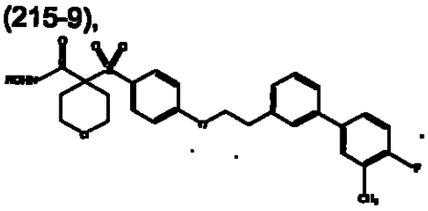
(215-7),



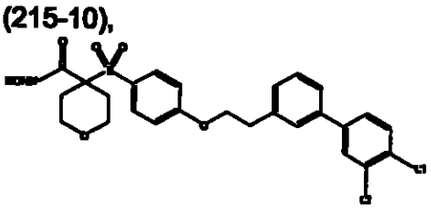
(215-8),



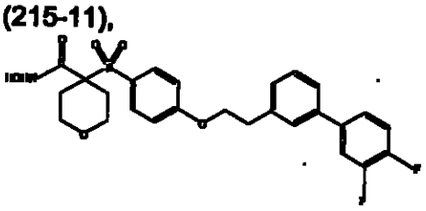
(215-9),



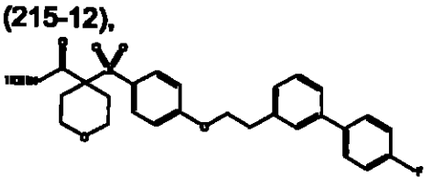
(215-10),



(215-11),

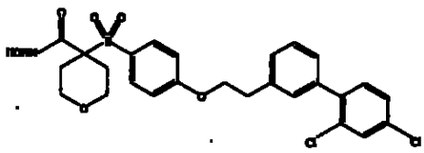


(215-12),

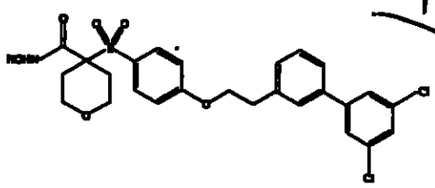


(215-13),

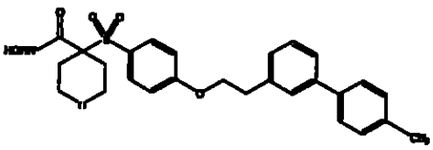
(215-14),



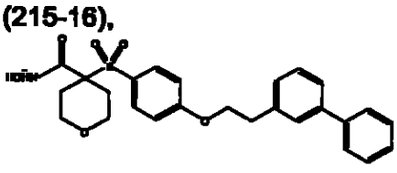
(215-15),



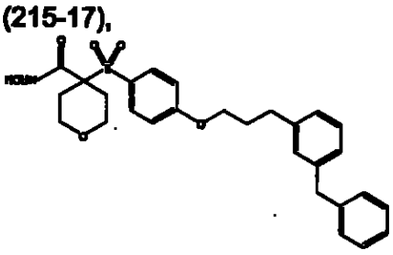
(215-16),



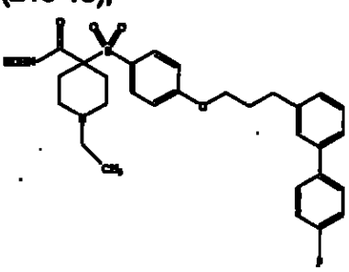
(215-17),



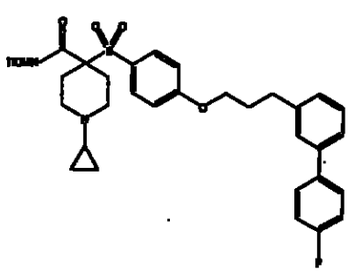
(215-18),



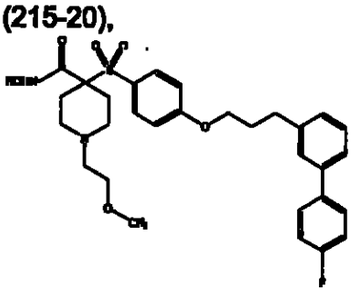
(215-19),



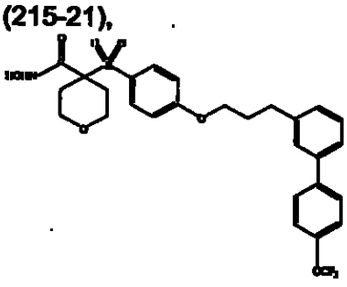
(215-20),



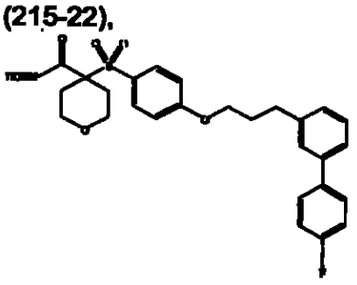
(215-21),



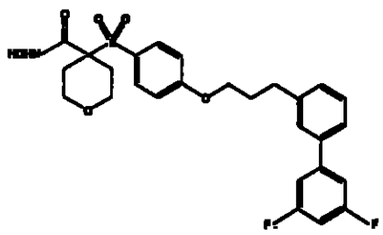
(215-22),



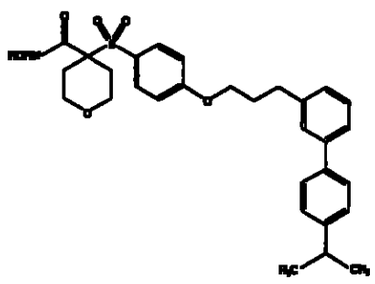
(215-23),



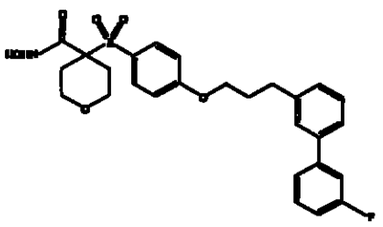
(215-24),



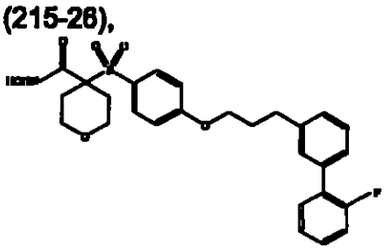
(215-25),



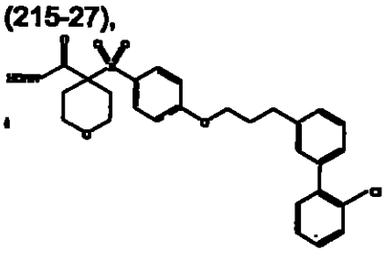
(215-26),



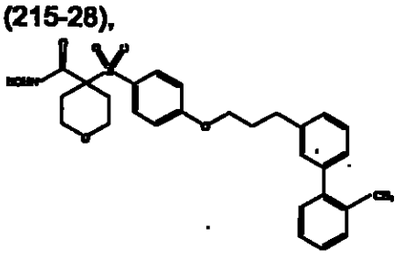
(215-27),



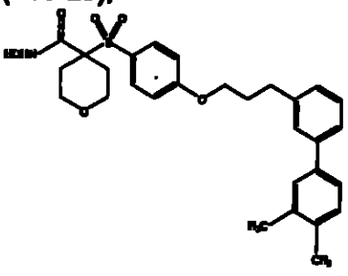
(215-28),



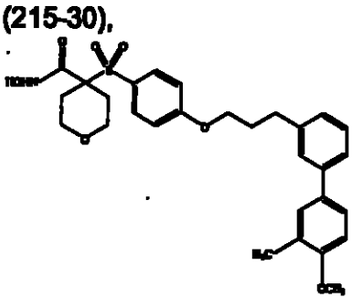
(215-29),



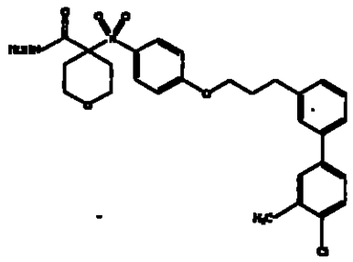
(215-30),



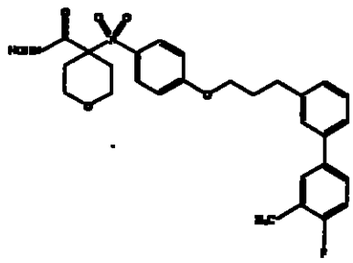
(215-31),



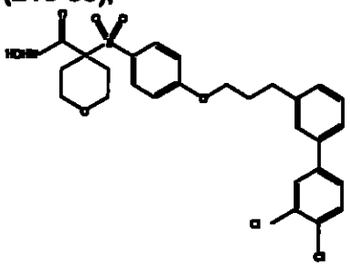
(215-32),



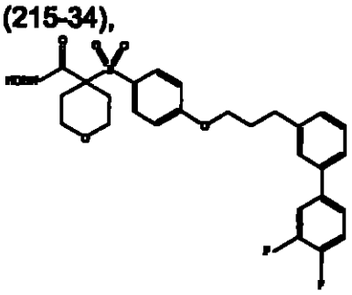
(215-33),



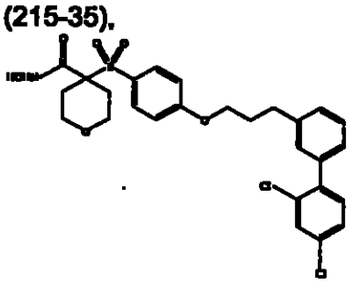
(215-34),



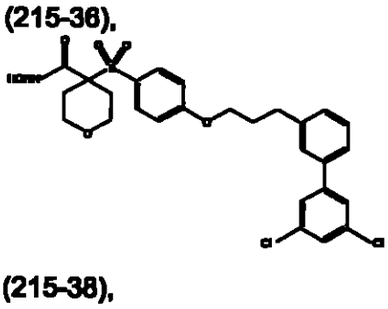
(215-35),



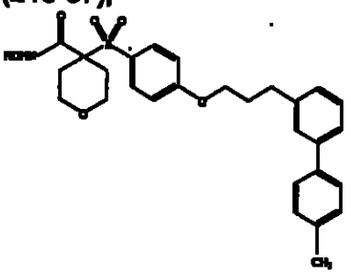
(215-36),



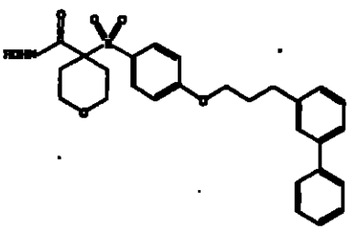
(215-37),



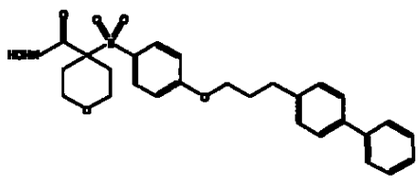
(215-38),



(215-39),

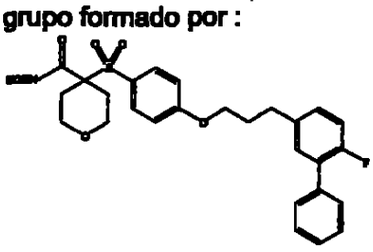


(215-40), y

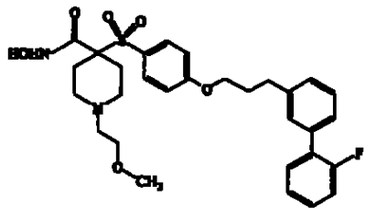


(215-41).

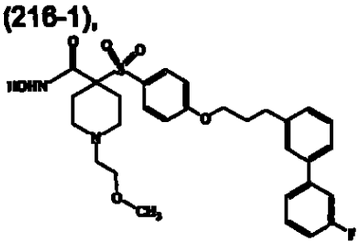
216. Un compuesto o sal del mismo de acuerdo con la cláusula 214, en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



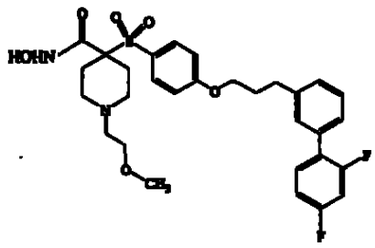
(216-1),



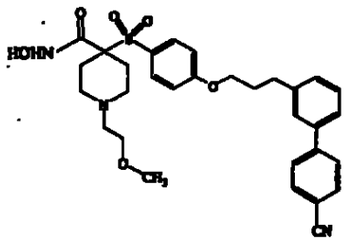
(216-2),



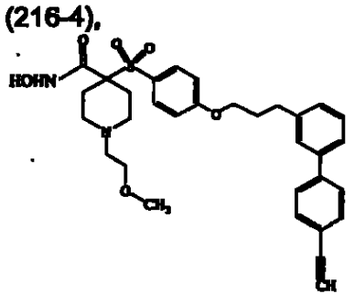
(216-3),



(216-4),

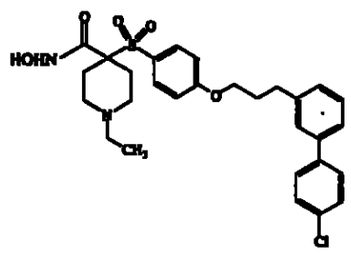


(216-5),

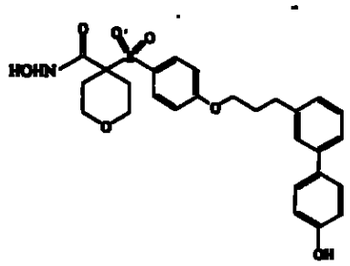


(216-6),

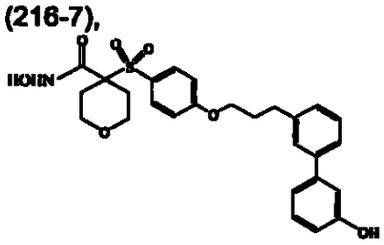
1281



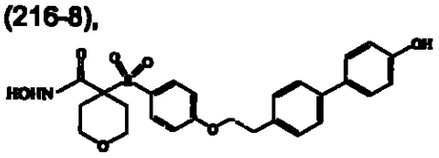
(216-7),



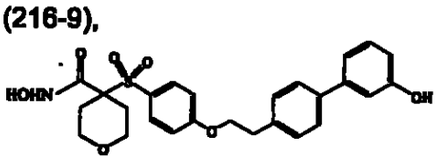
(216-8),



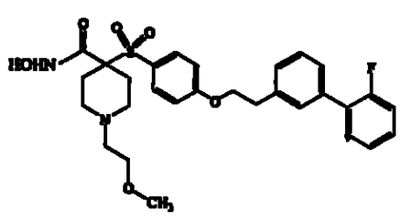
(216-9),



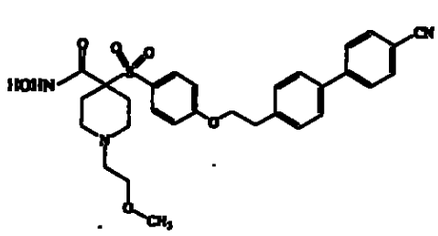
(216-10),



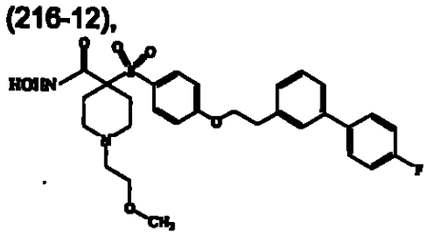
(216-11),



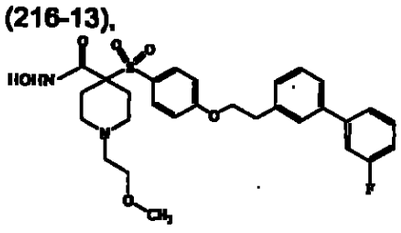
(216-12),



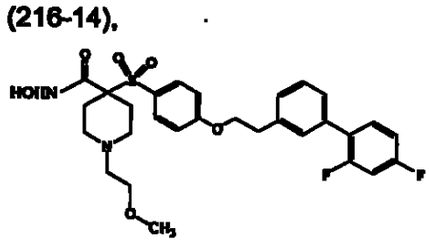
(216-13),



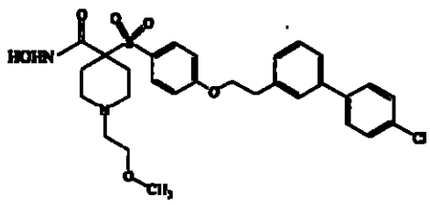
(216-14),



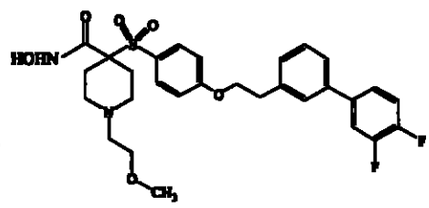
(216-15),



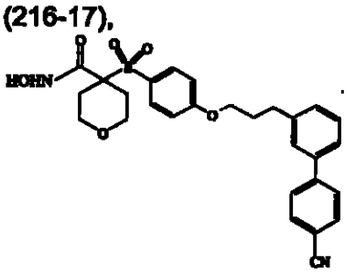
(216-16),



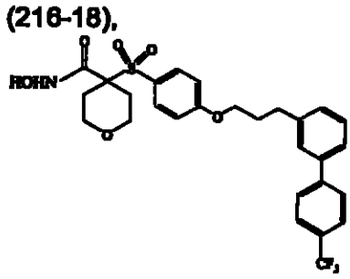
(216-17),



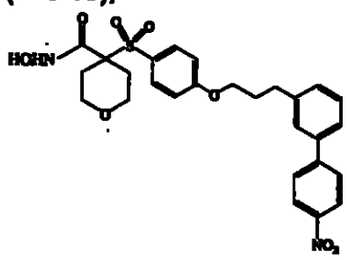
(216-18),



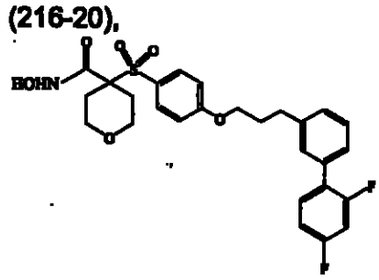
(216-19),



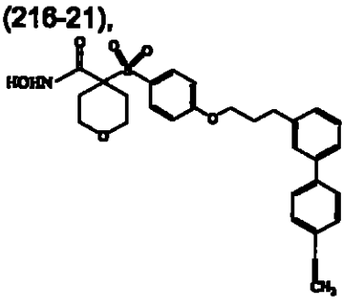
(216-20),



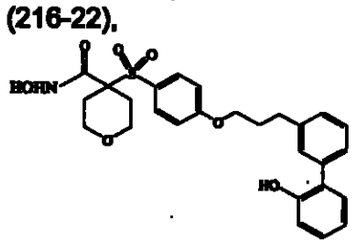
(216-21),



(216-22),

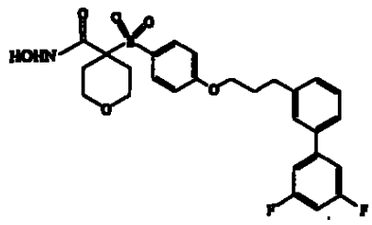


(216-23),



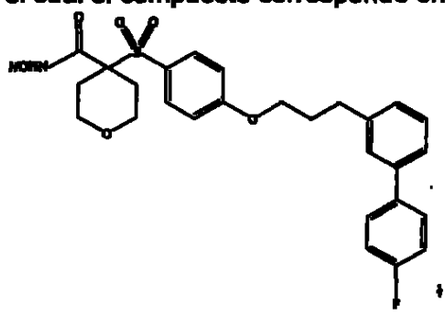
(216-24), y

1283



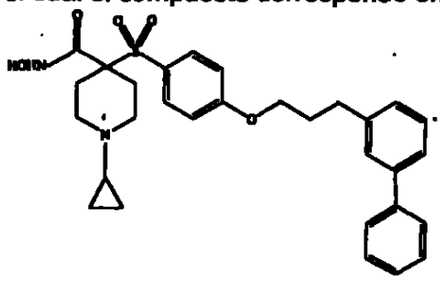
(216-25).

217. Un compuesto o sal del mismo de acuerdo con la cláusula 214, en el cual el compuesto corresponde en estructura a la siguiente fórmula:



(217-1).

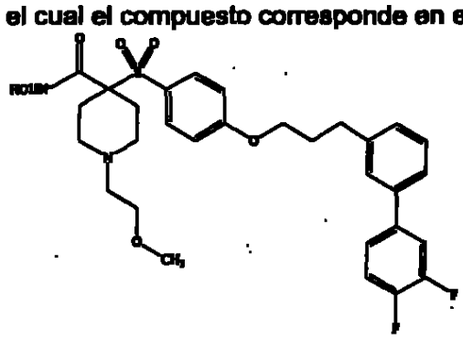
218. Un compuesto o sal del mismo de acuerdo con la cláusula 214, en el cual el compuesto corresponde en estructura a la siguiente fórmula:



(218-1).

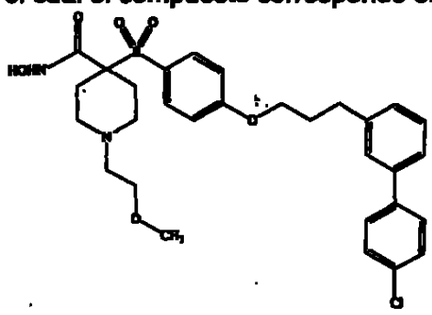
1284

219. Un compuesto o sal del mismo de acuerdo con la cláusula 214, en el cual el compuesto corresponde en estructura a la siguiente fórmula:



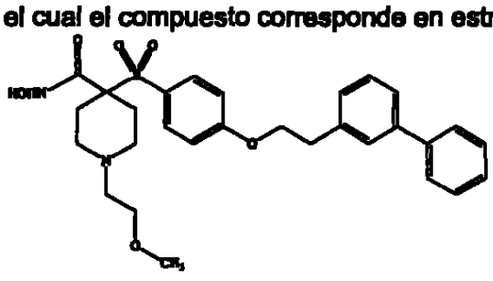
(219-1).

220. Un compuesto o sal del mismo de acuerdo con la cláusula 214, en el cual el compuesto corresponde en estructura a la siguiente fórmula:



(220-1).

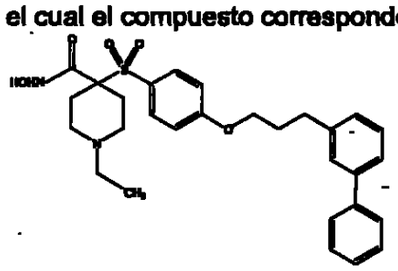
221. Un compuesto o sal del mismo de acuerdo con la cláusula 214, en el cual el compuesto corresponde en estructura a la siguiente fórmula:



(221-1).

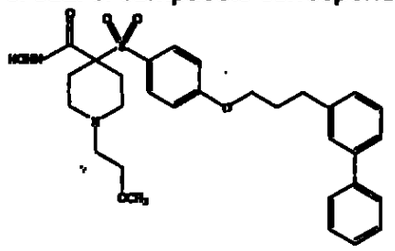
1285

222. Un compuesto o sal del mismo de acuerdo con la cláusula 214, en el cual el compuesto corresponde en estructura a la siguiente fórmula:



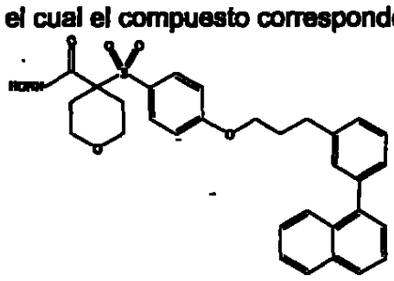
(222-1).

223. Un compuesto o sal del mismo de acuerdo con la cláusula 214, en el cual el compuesto corresponde en estructura a la siguiente fórmula:

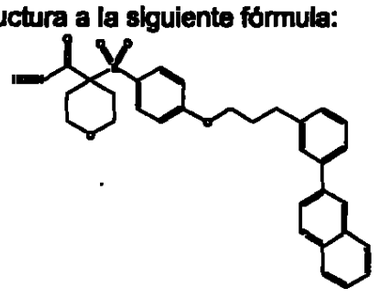


(223-1).

224. Un compuesto o sal del mismo de acuerdo con la cláusula 214, en el cual el compuesto corresponde en estructura a la siguiente fórmula:



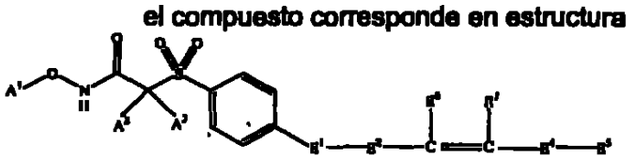
y



(224-1) (224-2).

225. Un compuesto o sal del mismo, en el cual:

el compuesto corresponde en estructura a la Fórmula 225-1



(225-1);

A^1 se selecciona del grupo formado por -H, alquilcarbonilo, alcoxicarbonilo, carbociclilcarbonilo, carbociclilalquilcarbonilo, heterociclilcarbonilo, heterociclilalquilcarbonilo, carbocicliloxicarbonilo, carbociclilalcoxicarbonilo, aminoalquilcarbonilo, alquil(tiocarbonilo), alcoxi(tiocarbonilo), carbociclil(tiocarbonilo), carbociclilalquil(tiocarbonilo), heterociclil(tiocarbonilo), heterociclilalquil(tiocarbonilo), carbocicliloxi(tiocarbonilo), carbociclilalcoxi(tiocarbonilo), y aminoalquil(tiocarbonilo), donde cualquier miembro (excepto -H) de dicho grupo es opcionalmente sustituido; y

A^2 y A^3, junto con el átomo de carbono al cual ambos están unidos, forman un heterociclilo opcionalmente sustituido que contiene entre 5 y 8 miembros en el anillo; y

E^1 se selecciona del grupo formado por -O-, $-S(O)_z-$, -S(O)-, $-N(R^1)-$, $-C(O)-N(R^1)-$, $-N(R^1)-C(O)-$, y $-C(R^1)(R^2)-$; y

E^2 se selecciona del grupo formado por alquilo, cicloalquilo, alquilcicloalquilo, cicloalquilalquilo, y alquilcicloalquilalquilo, donde cualquier miembro de dicho grupo es optativamente sustituido; y

E^4 se selecciona del grupo formado por un enlace y alquilo, donde el alquilo es optativamente sustituido; y

E^5 se selecciona del grupo formado por alquilo, alquenilo, alquinilo, alcoxi, alcoxialquilo, carbociclilo, y heterociclilo, donde cualquier miembro de dicho grupo es optativamente sustituido; y

E^6 se selecciona del grupo formado por -H, halógeno, y alquilo, donde el alquilo es optativamente sustituido;

E^7 se selecciona del grupo formado por -H, alquilo, alquenilo, alquinilo, $-S(O)_z-R^3$, $-NO_2$, $-C(O)-N(R^3)(R^4)$, $-(C)(OR^3)$, carbociclilo, carbociclilalquilo, alcoxicarbociclilo, -CN, -C=N-OH, y -C=NH, donde el alquilo, alquenilo, alquinilo, carbociclilo, carbociclilalquilo, o alcoxicarbociclilo es optativamente sustituido; y

R^1 y R^2 se seleccionan independientemente del grupo formado por -H y alquilo, donde el alquilo es optativamente sustituido; y

R^3 y R^4 se seleccionan independientemente del grupo formado por -H, alquilo, carbociclilo, carbociclilalquilo, heterociclilo, heterociclilalquilo, donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido; y

ni R^1 ni R^2 forman una estructura de anillo con E^2, E^4, E^5, E^6, o E^7.

226. Un compuesto o sal del mismo de acuerdo con la cláusula 225, donde:

A^1 se selecciona del grupo formado por -H, C_1-C_8-alquilcarbonilo, C_1-C_8-alcoxicarbonilo, carbociclilcarbonilo, carbociclil-C_1-C_8-alquilcarbonilo, heterociclilcarbonilo, heterociclil-C_1-C_8-alquilcarbonilo, carbociclilloxicarbonilo, carbociclil-C_1-C_8-alcoxicarbonilo, $N(R^5)(R^6)$-C_1-C_8-alquilcarbonilo, C_1-C_8-alquil(tiocarbonilo), C_1-C_8-alcoxi(tiocarbonilo), carbociclil(tiocarbonilo), carbociclil-C_1-C_8-alquil(tiocarbonilo), heterociclil(tiocarbonilo), heterociclil-C_1-C_8-alquil(tiocarbonilo), carbociclilloxi(tiocarbonilo), carbociclil-C_1-C_8-alcoxi(tiocarbonilo), y $N(R^5)(R^6)$-C_1-C_8-alquil(tiocarbonilo); y

E^2 se selecciona del grupo formado por C_1-C_{20}-alquilo, cicloalquilo, C_1-C_{10}-alquilcicloalquilo, cicloalquil-C_1-C_{10}-alquilo, y C_1-C_{10}-alquilcicloalquil-C_1-C_{10}-alquilo, donde cualquier miembro de dicho grupo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, C_1-C_8-alquilo, y halo-C_1-C_8-alquilo; y

E^4 se selecciona del grupo formado por un enlace, C_1-C_{20}-alquilo, y halo-C_1-C_{20}-alquilo; y

E^5 se selecciona del grupo formado por C_1-C_{20}-alquilo, C_2-C_{20}-alquenilo, C_2-C_{20}-alquinilo, C_1-C_{20}-alcoxi, C_1-C_{20}-alcoxi-C_1-C_{20}-alquilo, carbociclilo, y heterociclilo, donde:

el C_1-C_{20}-alquilo, C_2-C_{20}-alquenilo, C_2-C_{20}-alquinilo, C_1-C_{20}-alcoxi, o C_1-C_{20}-alcoxi-C_1-C_{20}-alquilo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, y -CN, y

el carbociclilo o heterociclilo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, -CN, ceto, C_1-C_8-alquilo, halo-C_1-C_8-alquilo, C_1-C_8-alcoxi, C_1-C_8-alcoxi-C_1-C_8-alquilo, halo-C_1-C_8-alcoxi, $-N(R^7)(R^8)$, $-C(O)(R^8)$, $-S-R^7$, $-S(O)_2-R^7$, carbociclilo, halocarbociclilo, carbociclil-C_1-C_8-alquilo, y C_1-C_8-alcoxi-C_1-C_8-alquilo sustituido con halógeno ; y

E^6 se selecciona del grupo formado por -H, halógeno, y C_1-C_8-alquilo, donde el C_1-C_8-alquilo es optativamente sustituido con uno o más halógenos;

E^7 se selecciona del grupo formado por -H, C_1-C_8-alquilo, C_1-C_8-alquenilo, C_1-C_8-alquinilo, $-S(O)_2-R^3$, $-NO_2$, $-C(O)-N(R^3)(R^4)$, $-(C)(OR^3)$, carbociclilo, carbociclil-C_1-C_8-alquilo, C_1-C_8-alcoxicarbociclilo, -CN, -C=N-OH, y -C=NH, donde el C_1-C_8-alquilo, C_1-C_8-alquenilo, C_1-C_8-alquinilo, carbociclilo, carbociclil-C_1-C_8-alquilo, o C_1-C_8-alcoxicarbociclilo es optativamente sustituido con uno o más halógenos; y

R^1 y R^2 se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, y halo-C_1-C_8-alquilo; y

R^3 y R^4 se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, carbociclilo, carbociclil-C_1-C_8-alquilo, heterociclilo, heterociclil-C_1-C_8-alquilo, donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido con uno o más halógenos; y

R^5 y R^6 se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, C_1-C_8-alcoxicarbonilo, C_1-C_8-alquilcarbonilo, carbociclil-C_1-C_8-alquilo, y carbociclil-C_1-C_8-alcoxicarbonilo; y

1290

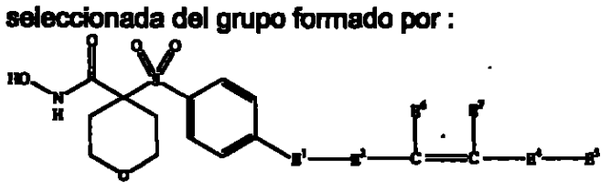
R^7 y R^8 se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, carbociclilo, carbociclil-C_1-C_8-alquilo, heterociclilo, y heterociclil-C_1-C_8-alquilo, donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido con uno o más halógenos; y

R^9 se selecciona del grupo formado por -H, C_1-C_8-alquilo, -O-R^{10}, -N(R^{10})(R^{11}), carbociclil-C_1-C_8-alquilo, y heterociclil-C_1-C_8-alquilo, en el cual el C_1-C_8-alquilo, carbociclil-C_1-C_8-alquilo, o heterociclil-C_1-C_8-alquilo es optativamente sustituido con uno o más halógenos; y

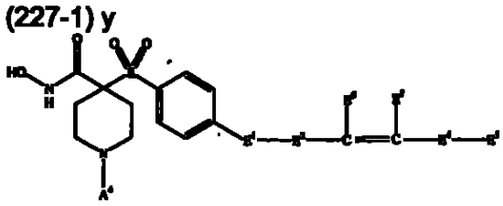
R^{10} y R^{11} se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, carbociclilo, carbociclil-C_1-C_8-alquilo, heterociclilo, y heterociclil-C_1-C_8-alquilo, donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido con uno o más halógenos.

227. Un compuesto o sal del mismo de acuerdo con la cláusula 226, en el cual:

el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



(227-1) y



(227-2); y

A^4 se selecciona del grupo formado por -H, alquilo, alquilcarbonilo, alquilcarbonilalquilo, alquilcarbonilalquilcarbonilo, alcoxicarbonilo,

alcoxicarbonilalquilo, alcoxicarbonilalquilcarbonilo, alquilsulfonilo, alquiliminocarbonilo, alquenilo, alquinilo, alcoxialquilo, alquiltioalquilo, alquilsulfonilalquilo, alquilsufoxidoalquilo, alquiltioalquenilo, alquilsulfoxidoalquenilo, alquilsulfonilalquenilo, carbociclilo, carbociclilalquilo, carbociclilalcoxialquilo, carbociclilcarbonilo, carbociclilsulfonilo, carbociclliminocarbonilo, carbociclloxicarbonilo, carbocililtioalquilo, carbociliisulfoxidoalquilo, carbocliisulfonilalquilo, carbociclitioalquenilo, carbociclilsulfoxidoalquenilo, carbociclilsulfonilalquenilo, heterociclilo, heterociclilalquilo, heterociclilalcoxialquilo, heterociclilcarbonilo, heterociclitioalquilo, heterociclilsulfoxidoalquilo, heterociclilsulfonilalquilo, heterociclitioalquenilo, heterociclilsulfoxidoalquenilo, heterociclilsulfonilalquenilo, heterociclilsulfonilo, heterociclliminocarbonilo, heterociclilalquilcarbonilo, heterociclilcarbonilalquilcarbonilo, heterociclilsulfonilo, heterociclilcarbonilalquilo, aminoalquilcarbonilo, aminocarbonilo, aminocarbonilalquilcarbonilo, aminosulfonilo, aminosulfonilalquilo, aminoalquilo, aminocarbonilalquilo, y aminoalquilsulfonilo, donde:

cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido.

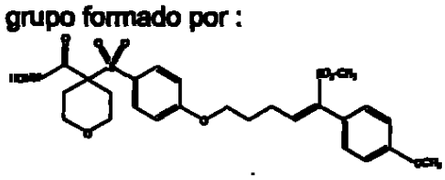
228. Un compuesto o sal del mismo de acuerdo con la cláusula 227, en el cual E^5 es fenilo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_6-alquilo, halo-C_1-C_6-alquilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, halo-C_1-C_6-alcoxi, -$N(R^7)(R^8)$, -$C(O)(R^9)$, -S-R^7, -$S(O)_2$-R^7, carbociclilo,

1292

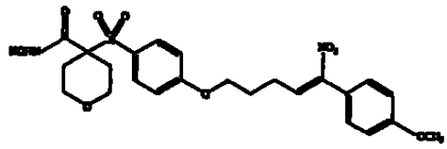
halocarbociclilo, carbociclil-C_1-C_6-alquilo, y C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno.

229. Un compuesto o sal del mismo de acuerdo con la cláusula 228, en el cual E^4 es un enlace.

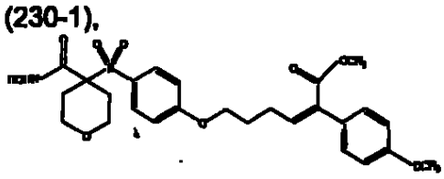
230. Un compuesto o sal del mismo de acuerdo con la cláusula 229, en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



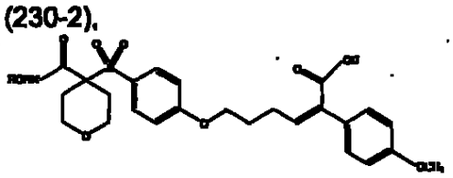
(230-1),



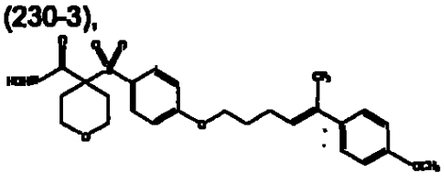
(230-2),



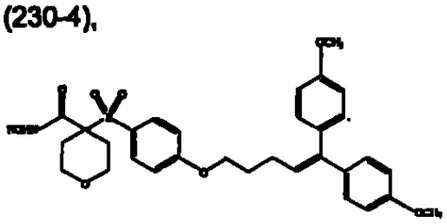
(230-3),



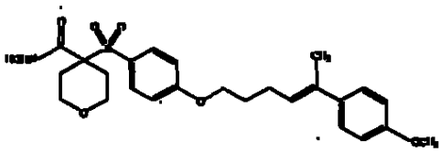
(230-4),



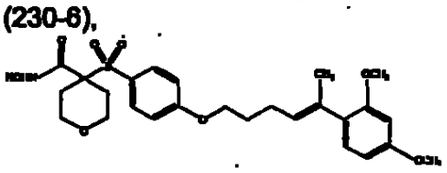
(230-5),



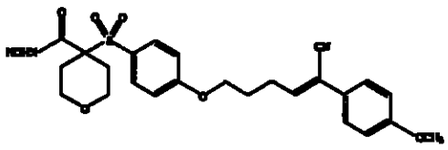
(230-6),



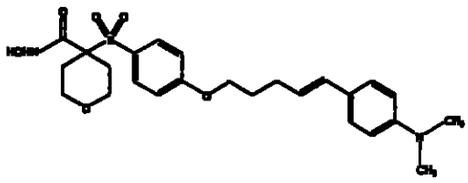
(230-7),



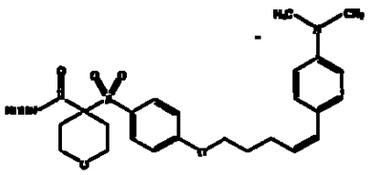
(230-8),



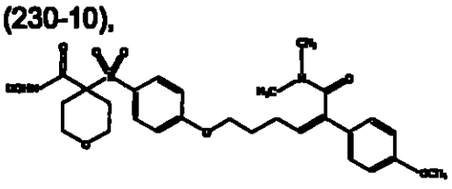
(230-9),



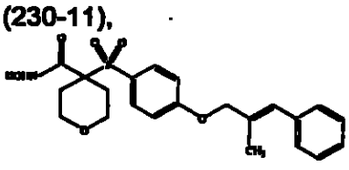
(230-10),



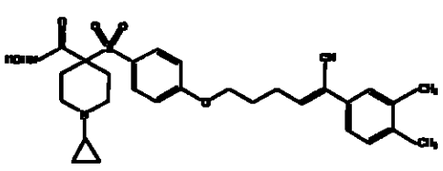
(230-11),



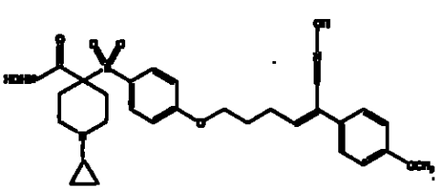
(230-12),



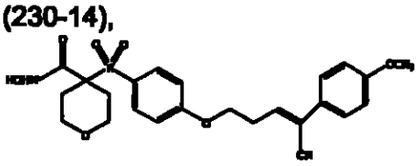
(230-13),



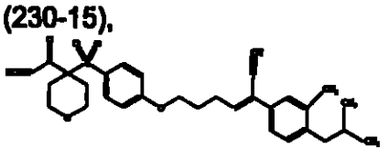
(230-14),



(230-15),

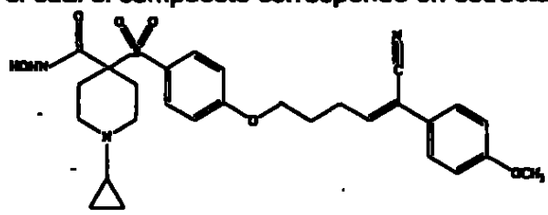


(230-16), y



(230-17).

231. Un compuesto o sal del mismo de acuerdo con la cláusula 229, en el cual el compuesto corresponde en estructura a la siguiente fórmula:



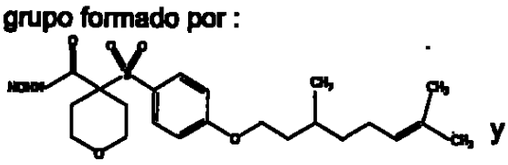
(231-1).

232. Un compuesto o sal del mismo de acuerdo con la cláusula 227, en el cual E^5 se selecciona del grupo formado por C_1-C_6-alquilo, C_2-C_6-alquenilo, C_2-C_6-alquinilo, C_1-C_6-alcoxi, y C_1-C_6-alcoxi-C_1-C_6-alquilo, donde:

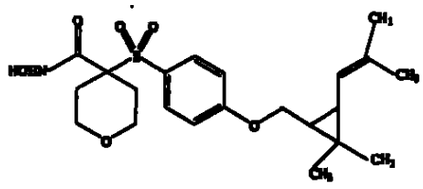
cualquier miembro de dicho grupo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, y -CN.

233. Un compuesto o sal del mismo de acuerdo con la cláusula 232, en el cual E^5 es C_1-C_6-alquilo.

234. Un compuesto o sal del mismo de acuerdo con la cláusula 233, en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



y



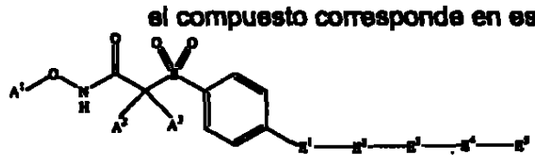
(234-1)

(234-2).

1295

235. Un compuesto o sal del mismo, en el cual:

el compuesto corresponde en estructura a la Fórmula 235-1:



(235-1);

A^1 se selecciona del grupo formado por -H, alquilcarbonilo, alcoxicarbonilo, carbociclilcarbonilo, carbociclilalquilcarbonilo, heterociclilcarbonilo, heterociclilalquilcarbonilo, carbocicliloxicarbonilo, carbociclilalcoxicarbonilo, aminoalquilcarbonilo, alquil(tiocarbonilo), alcoxi(tiocarbonilo), carbociclil(tiocarbonilo), carbociclilalquil(tiocarbonilo), heterociclil(tiocarbonilo), heterociclilalquil(tiocarbonilo), carbociclíloxi(tiocarbonilo), carbociclilalcoxi(tiocarbonilo), y aminoalquil(tiocarbonilo), donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido; y

A^2 y A^3, junto con el átomo de carbono al cual ambos están unidos, forman un heterociclilo optativamente sustituido que contiene entre 5 y 8 miembros en el anillo; y

E^1 se selecciona del grupo formado por -O-, $-S(O)_2-$, -S(O)-, $-N(R^3)-$, $-C(O)-N(R^3)-$, $-N(R^3)-C(O)-$, y $-C(R^1)(R^2)-$; y

E^2 se selecciona del grupo formado por un enlace, alquilo, cicloalquilo, alquilcicloalquilo, cicloalquilalquilo, y alquilcicloalquilalquilo, donde cualquier miembro (con la excepción de el enlace) de dicho grupo es optativamente sustituido; y

E^3 es carbonilpirrolidinilo, donde el carbonilpirrolidinilo es optativamente sustituido; y

1296

E^4 se selecciona del grupo formado por un enlace, alquilo, y alquenilo, donde el alquilo o alquenilo es optativamente sustituido; y

E^5 se selecciona del grupo formado por alquilo, alquenilo, alquinilo, alcoxi, alcoxialquilo, carbociclilo, y heterociclilo, donde cualquier miembro de dicho grupo es optativamente sustituido; y

R^1 y R^2 se seleccionan independientemente del grupo formado por -H y alquilo, donde el alquilo es optativamente sustituido; y

ni R^1 ni R^2 forman una estructura de anillo con E^2, E^3, E^4, o E^5.

236. Un compuesto o sal del mismo de acuerdo con la cláusula 235, en el cual:

A^1 se selecciona del grupo formado por -H, C_1-C_8-alquilcarbonilo, C_1-C_8-alcoxicarbonilo, carbociclilcarbonilo, carbociclil-C_1-C_8-alquilcarbonilo, heterociclilcarbonilo, heterociclil-C_1-C_8-alquilcarbonilo, carbociclíloxdcarbonilo, carbociclil-C_1-C_8-alcoxicarbonilo, $N(R^3)(R^4)$-C_1-C_8-alquilcarbonilo, C_1-C_8-alquil(tiocarbonilo), C_1-C_8-alcoxi(tiocarbonilo), carbociclil(tiocarbonilo), carbociclil-C_1-C_8-alquil(tiocarbonilo), heterociclil(tiocarbonilo), heterociclil-C_1-C_8-alquil(tiocarbonilo), carbociclíloxi(tiocarbonilo), carbociclil-C_1-C_8-alcoxi(tiocarbonilo), y $N(R^3)(R^4)$-C_1-C_8-alquil(tiocarbonilo); y

E^2 se selecciona del grupo formado por un enlace, C_1-C_{20}-alquilo, cicloalquilo, C_1-C_{10}-alquilcicloalquilo, cicloalquil-C_1-C_{10}-alquilo, y C_1-C_{10}-alquilcicloalquil-C_1-C_{10}-alquilo, donde cualquier miembro de dicho grupo (con la excepción de el enlace) es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, C_1-C_8-alquilo, y halo-C_1-C_8-alquilo; y

E^3 es carbonilpirrolidinilo, donde el carbonilpirrolidinilo es optativamente sustituido con uno o más halógenos; y

E^4 se selecciona del grupo formado por un enlace, C_1-C_{20}-alquilo, halo-C_1-C_{20}-alquilo, C_2-C_{20}-alquenilo, y halo-C_2-C_{20}-alquenilo; y

E^5 se selecciona del grupo formado por C_1-C_{20}-alquilo, C_2-C_{20}-alquenilo, C_2-C_{20}-alquinilo, C_1-C_{20}-alcoxi, C_1-C_{20}-alcoxi-C_1-C_{20}-alquilo, carbociclilo, y heterociclilo, donde:

el C_1-C_{20}-alquilo, C_2-C_{20}-alquenilo, C_2-C_{20}-alquinilo, C_1-C_{20}-alcoxi, o C_1-C_{20}-alcoxi-C_1-C_{20}-alquilo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, y -CN, y

el carbociclilo o heterociclilo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, ceto, C_1-C_8-alquilo, halo-C_1-C_8-alquilo, C_1-C_8-alcoxi, halo-C_1-C_8-alcoxi, C_1-C_8-alcoxi-C_1-C_8-alquilo, C_1-C_8-alcoxi-C_1-C_8-alquilo sustituido con halógeno , -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbociclilo, halocarbociclilo, carbociclil-C_1-C_8-alquilo, y carbociclil-C_1-C_8-alquilo sustituido con halógeno; y

R^1 y R^2 se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, y halo-C_1-C_8-alquilo; y

R^3 y R^4 se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, C_1-C_8-alcoxicarbonilo, C_1-C_8-alquilcarbonilo, carbociclil-C_1-C_8-alquilo, y carbociclil-C_1-C_8-alcoxicarbonilo; y

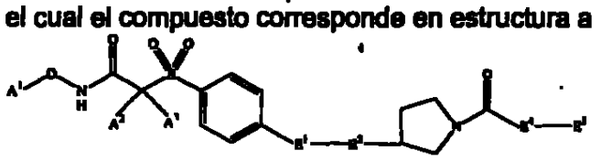
R^5 y R^6 se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, carbociclilo, carbociclil-C_1-C_8-alquilo, heterociclilo, y

heterociclil-C_1-C_8-alquilo, donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido con uno o más halógenos; y

R^7 se selecciona del grupo formado por -H, C_1-C_8-alquilo, -O-R^8, -N(R^8)(R^9), carbociclil-C_1-C_8-alquilo, y heterociclil-C_1-C_8-alquilo, en el cual el C_1-C_8-alquilo, carbociclil-C_1-C_8-alquilo, o heterociclil-C_1-C_8-alquilo es optativamente sustituido con uno o más halógenos; y

R^8 y R^9 se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, carbociclilo, carbociclil-C_1-C_8-alquilo, heterociclilo, y heterociclil-C_1-C_8-alquilo, donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido con uno o más halógenos.

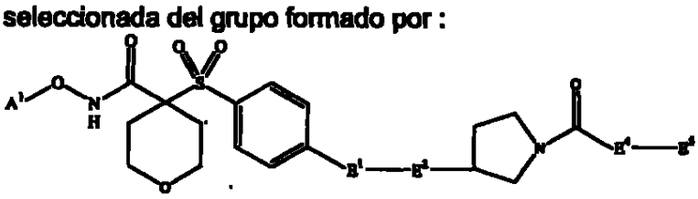
237. Un compuesto o sal del mismo de acuerdo con la cláusula 236, en el cual el compuesto corresponde en estructura a la Fórmula 237-1:



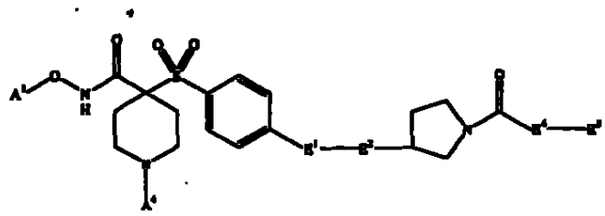
(237-1).

238. Un compuesto o sal del mismo de acuerdo con la cláusula 237, en el cual:

el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



(238-1) y



(238-2); y

A^4 se selecciona del grupo formado por -H, alquilo, alquilcarbonilo, alquilcarbonilalquilo, alquilcarbonilalquilcarbonilo, alcoxicarbonilo, alcoxicarbonilalquilo, alcoxicarbonilalquilcarbonilo, alquilsulfonilo, alquliminocarbonilo, alquenilo, alquinilo, alcoxialquilo, alquiltioalquilo, alquilsulfonilalquilo, alquilsufoxidoalquilo, alquiltioalquenilo, alquilsulfoxidoalquenilo, alquilsulfonilalquenilo, carbociclilo, carbociclilalquilo, carbociclilalcoxialquilo, carbociclilcarbonilo, carbociclilsulfonilo, carbociclilliminocarbonilo, carbociclioxicarbonilo, carbocililtioalquilo, carbociclilsulfoxidoalquilo, carbociclilsulfonilalquilo, carbociclitioalquenilo, carbociclilsulfoxidoalquenilo, carbociclilsulfonilalquenilo, heterociclilo, heterociclilalquilo, heterociclilalcoxialquilo, heterociclilcarbonilo, heterociclitioalquilo, heterociclilsulfoxidoalquilo, heterociclilsulfonilalquilo, heterociclitioalquenilo, heterociclilsulfoxidoalquenilo, heterociclilsulfonilalquenilo, heterociclilsulfonilo, heterociclilliminocarbonilo, heterociclilalquilcarbonilo, heterociclilcarbonilalquilcarbonilo, heterociclilsulfonilo, heterociclilcarbonilalquilo, aminoalquilcarbonilo, aminocarbonilo, aminocarbonilalquilcarbonilo, aminosulfonilo, aminosulfonilalquilo, aminoalquilo, aminocarbonilalquilo, y aminoalquilsulfonilo, donde:

cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido.

239. Un compuesto o sal del mismo de acuerdo con la cláusula 238, en el cual E^5 se selecciona del grupo formado por carbociclilo y heterociclilo, donde:

el carbociclilo o heterociclilo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, -CN, ceto, C_1-C_6-alquilo, halo-C_1-C_6-alquilo, C_1-C_6-alcoxi, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbociclilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo, y carbociclil-C_1-C_6-alquilo sustituido con halógeno.

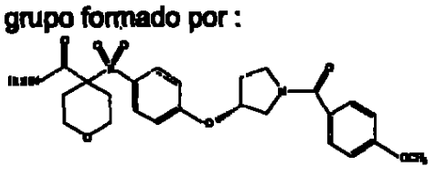
240. Un compuesto o sal del mismo de acuerdo con la cláusula 239, en el cual E^5 es carbociclilo optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, -CN, ceto, C_1-C_6-alquilo, halo-C_1-C_6-alquilo, C_1-C_6-alcoxi, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbociclilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo, y carbociclil-C_1-C_6-alquilo sustituido con halógeno.

241. Un compuesto o sal del mismo de acuerdo con la cláusula 240, en el cual E^5 es fenilo optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, -CN, C_1-C_6-alquilo, halo-C_1-C_6-alquilo, C_1-C_6-alcoxi, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbociclilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo, y carbociclil-C_1-C_6-alquilo sustituido con halógeno.

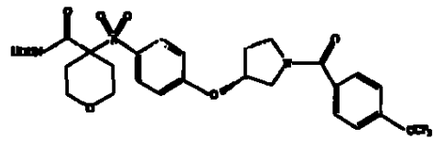
1301

242. Un compuesto o sal del mismo de acuerdo con la cláusula 241, en el cual E^4 es un enlace.

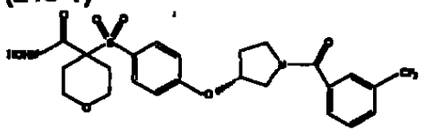
243. Un compuesto o sal del mismo de acuerdo con la cláusula 242, en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



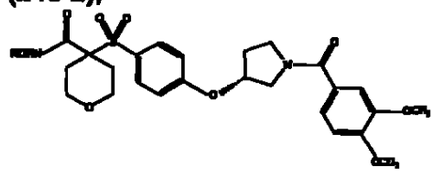
(243-1)



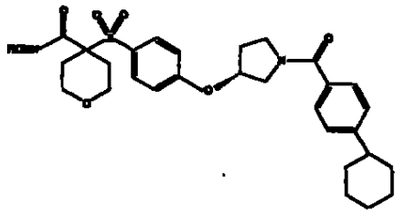
(243-2),



(243-3),



(243-4), y



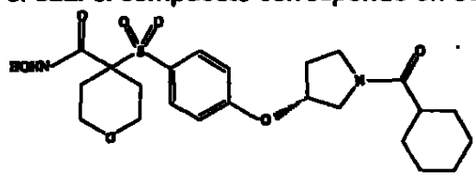
(243-5).

244. Un compuesto o sal del mismo de acuerdo con la cláusula 240, en el cual E^5 es C_5-C_8-cicloalquilo optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, ceto, C_1-C_8-alquilo, halo-C_1-C_8-alquilo, C_1-C_8-alcoxi, halo-C_1-C_8-alcoxi, C_1-C_8-alcoxi-C_1-C_8-alquilo, C_1-C_8-alcoxi-C_1-C_8-alquilo sustituido con halógeno, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^8, -$S(O)_2$-R^8, carbociclilo,

halocarbociclilo, carbociclil-C_1-C_6-alquilo, y carbociclil-C_1-C_6-alquilo sustituido con halógeno.

245. Un compuesto o sal del mismo de acuerdo con la cláusula 244, en el cual E^4 es un enlace.

246. Un compuesto o sal del mismo de acuerdo con la cláusula 245, en el cual el compuesto corresponde en estructura a la siguiente fórmula:



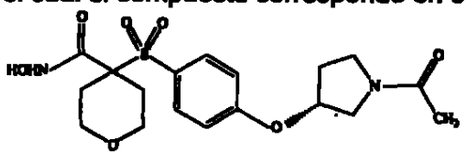
(246-1).

247. Un compuesto o sal del mismo de acuerdo con la cláusula 238, en el cual E^5 se selecciona del grupo formado por C_1-C_6-alquilo, C_2-C_6-alquenilo, C_2-C_6-alquinilo, C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, donde:

el C_1-C_6-alquilo, C_2-C_6-alquenilo, C_2-C_6-alquinilo, C_1-C_6-alcoxi, o C_1-C_6-alcoxi-C_1-C_6-alquilo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, y -CN.

248. Un compuesto o sal del mismo de acuerdo con la cláusula 247, en el cual E^4 es un enlace, y E^5 es C_1-C_6-alquilo.

249. Un compuesto o sal del mismo de acuerdo con la cláusula 248, en el cual el compuesto corresponde en estructura a la siguiente fórmula:

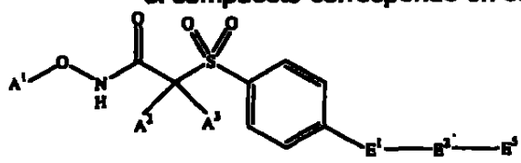


(249-1)

1303

250. Un compuesto o sal del mismo, en el cual

el compuesto corresponde en estructura a la Fórmula 250-1:



(250-1); y

A^1 se selecciona del grupo formado por -H, alquilcarbonilo, alcoxicarbonilo, carbociclilcarbonilo, carbociclilalquilcarbonilo, heterociclilcarbonilo, heterociclilalquilcarbonilo, carbocicliloxicarbonilo, carbociclilalcoxicarbonilo, aminoalquilcarbonilo, alquil(tiocarbonilo), alcoxi(tiocarbonilo), carbociclil(tiocarbonilo), carbociclilalquil(tiocarbonilo), heterociclil(tiocarbonilo), heterociclilalquil(tiocarbonilo), carbociclil(tiocarbonilo), carbociclilalcoxi(tiocarbonilo), y aminoalquil(tiocarbonilo), donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido; y

A^2 y A^3, junto con el átomo de carbono al cual ambos están unidos, forman un heterociclilo optativamente sustituido que contiene entre 5 y 8 miembros en el anillo; y

E^1 se selecciona del grupo formado por -O-, $-S(O)_2-$, -S(O)-, $-N(R^1)-$, $-C(O)-N(R^1)-$, $-N(R^1)-C(O)-$, y $-C(R^1)(R^2)-$; y

E^2 se selecciona del grupo formado por alquilo, cicloalquilo, alquilcicloalquilo, cicloalquilalquilo, y alquilcicloalquilalquilo, donde cualquier miembro de dicho grupo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, alquilo, y haloalquilo; y

1304

E^5 se selecciona del grupo formado por alquilo, alquenilo, alquinilo, cicloalquilo, ciclopentenilo, ciclopentadienilo, ciclohexenilo, y ciclohexadienilo, donde

el alquilo , alquenilo, o alquinilo (a) contiene al menos 4 átomos de carbono, y (b) es optativamente sustituido con uno o más sustituyentes seleccionados del grupo formado por -OH, $-NO_2$, -CN, y halógeno, y

el cicloalquilo, ciclopentenilo, ciclopentadienilo, ciclohexenilo, o ciclohexadienilo es optativamente sustituido; y

R^1 y R^2 se seleccionan independientemente del grupo formado por -H y alquilo, donde el alquilo es optativamente sustituido; y

ni R^1 ni R^2 forman una estructura de anillo con E^5.

251. Un compuesto o sal del mismo de acuerdo con la cláusula 250, en el cual

A^1 se selecciona del grupo formado por -H, C_1-C_8-alquilcarbonilo, C_1-C_8-alcoxicarbonilo, carbociclilcarbonilo, carbociclil-C_1-C_8-alquilcarbonilo, heterociclilcarbonilo, heterociclil-C_1-C_8-alquilcarbonilo, carbociclíloxicarbonilo, carbociclil-C_1-C_8-alcoxicarbonilo, $N(R^3)(R^4)$-C_1-C_8-alquilcarbonilo, C_1-C_8-alquil(tiocarbonilo), C_1-C_8-alcoxi(tiocarbonilo), carbociclil(tiocarbonilo), carbociclil-C_1-C_8-alquil(tiocarbonilo), heterociclil(tiocarbonilo), heterociclil-C_1-C_8-alquil(tiocarbonilo), carbociclíloxi(tiocarbonilo), carbociclil-C_1-C_8-alcoxi(tiocarbonilo), y $N(R^3)(R^4)$-C_1-C_8-alquil(tiocarbonilo); y

E^2 se selecciona del grupo formado por C_1-C_{20}-alquilo, cicloalquilo, C_1-C_{10}-alquilcicloalquilo, cicloalquil-C_1-C_{10}-alquilo, y C_1-C_{10}-alquilcicloalquil-C_1-C_{10}-alquilo, donde cualquier miembro de dicho grupo es optativamente

1305

sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, C_1-C_8-alquilo, y halo-C_1-C_8-alquilo; y

E^5 se selecciona del grupo formado por C_4-C_{20}-alquilo, C_4-C_{20}-alquenilo, y C_4-C_{20}-alquinilo, cicloalquilo, ciclopentenilo, ciclopentadienilo, ciclohexenilo, y ciclohexadienilo, donde

el C_4-C_{20}-alquilo, C_4-C_{20}-alquenilo, o C_4-C_{20}-alquinilo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por -OH, -NO_2, -CN, y halógeno, y

el cicloalquilo, ciclopentenilo, ciclopentadienilo, ciclohexenilo, o ciclohexadienilo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, ceto, C_1-C_8-alquilo, halo-C_1-C_8-alquilo, C_1-C_8-alcoxi, halo-C_1-C_8-alcoxi, C_1-C_8-alcoxi-C_1-C_8-alquilo, C_1-C_8-alcoxi-C_1-C_8-alquilo sustituido con halógeno , -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbociclilo, halocarbociclilo, carbociclil-C_1-C_8-alquilo, y carbociclil-C_1-C_8-alquilo sustituido con halógeno; y

R^1 y R^2 se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, y halo-C_1-C_8-alquilo; y

R^3 y R^4 se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, C_1-C_8-alcoxicarbonilo, C_1-C_8-alquilcarbonilo, carbociclil-C_1-C_8-alquilo, y carbociclil-C_1-C_8-alcoxicarbonilo; y

R^5 y R^6 se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, carbociclilo, carbociclil-C_1-C_8-alquilo, heterociclilo, y heterociclil-C_1-C_8-alquilo, donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido con uno o más halógenos; y

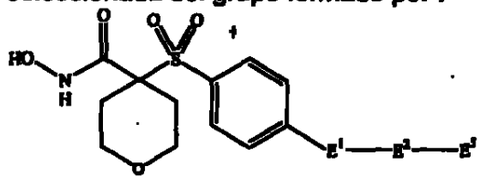
1306

R^7 se selecciona del grupo formado por -H, C_1-C_8-alquilo, -O-R^8, -N(R^8)(R^9), carbociclil-C_1-C_8-alquilo, y heterociclil-C_1-C_8-alquilo, en el cual el C_1-C_8-alquilo, carbociclil-C_1-C_8-alquilo, o heterociclil-C_1-C_8-alquilo es optativamente sustituido con uno o más halógenos; y

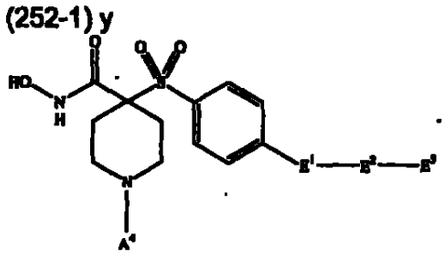
R^8 y R^9 se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, carbociclilo, carbociclil-C_1-C_8-alquilo, heterociclilo, y heterociclil-C_1-C_8-alquilo, donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido con uno o más halógenos.

252. Un compuesto o sal del mismo de acuerdo con la cláusula 251, en el cual

el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



(252-1) y



(252-2); y

A^4 se selecciona del grupo formado por -H, alquilo, alquilcarbonilo, alquilcarbonilalquilo, alquilcarbonilalquilcarbonilo, alcoxicarbonilo, alcoxicarbonilalquilo, alcoxicarbonilalquilcarbonilo, alquilsulfonilo, alquiliminocarbonilo, alquenilo, alquinilo, alcoxialquilo, alquiltioalquilo,

1307

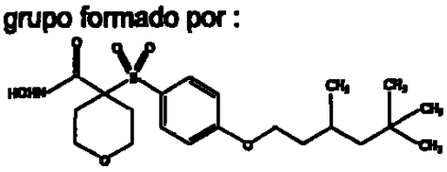
alquilsulfonilalquilo, alquilsufoxidoalquilo, alquiltioalquenilo, alquilsulfoxidoalquenilo, alquilsulfonilalquenilo, carbociclilo, carbociclilalquilo, carbociclilalcoxialquilo, carbociclilcarbonilo, carbociclilsulfonilo, carbociclliminocarbonilo, carbociclioxicarbonilo, carbociliitioalquilo, carbocliilsulfoxidoalquilo, carbocliilsulfonilalquilo, carbociclitioalquenilo, carbociclilsulfoxidoalquenilo, carbociclilsulfonilalquenilo, heterociclilo, heterociclilalquilo, heterociclilalcoxialquilo, heterociclilcarbonilo, heterociclitioalquilo, heterociclilsulfoxidoalquilo, heterociclilsulfonilalquilo, heterociclitioalquenilo; heterociclilsulfoxidoalquenilo, heterociclilsulfonilalquenilo, heterociclilsulfonilo, heterociclliminocarbonilo, heterociclilalquilcarbonilo, heterociclilcarbonilalquilcarbonilo, heterociclilsulfonilo, heterociclilcarbonilalquilo, aminoalquilcarbonilo, aminocarbonilo, aminocarbonilalquilcarbonilo, aminosulfonilo, aminosulfonilalquilo, aminoalquilo, aminocarbonilalquilo, y aminoalquilsulfonilo, donde

cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido.

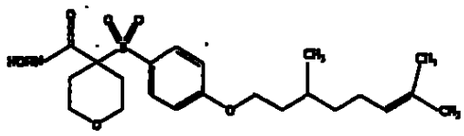
253. Un compuesto o sal del mismo de acuerdo con la cláusula 252, en el cual E^5 se selecciona del grupo formado por C_4-C_8-alquilo, C_4-C_8-alquenilo, y C_4-C_8-alquinilo, donde

el C_4-C_8-alquilo, C_4-C_8-alquenilo, o C_4-C_8-alquinilo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por -OH, -NO_2, -CN, y halógeno.

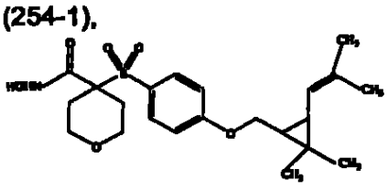
254. Un compuesto o sal del mismo de acuerdo con la cláusula 253, en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



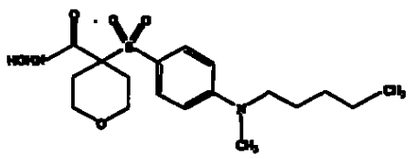
(254-1),



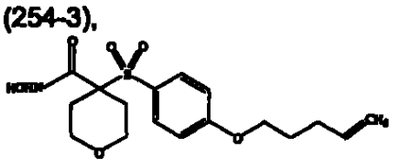
(254-2),



(254-3),

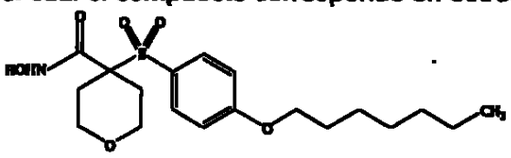


(254-4), y



(254-5).

255. Un compuesto o sal del mismo de acuerdo con la cláusula 253, en el cual el compuesto corresponde en estructura a la siguiente fórmula:



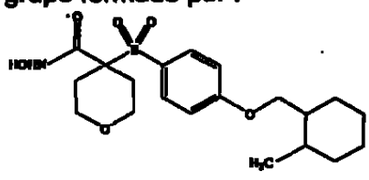
(255-1).

256. Un compuesto o sal del mismo de acuerdo con la cláusula 252, en el cual E^5 es C_3-C_8-cicloalquilo opcionalmente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, ceto, C_1-C_8-alquilo, halo-C_1-C_8-alquilo, C_1-C_8-alcoxi, halo-C_1-C_8-alcoxi, C_1-C_8-alcoxi-C_1-C_8-alquilo, C_1-C_8-alcoxi-C_1-C_8-alquilo

1309

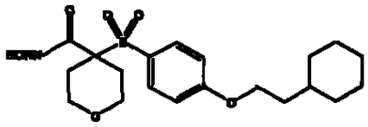
sustituido con halógeno, -N(R^5)(R^6), -C(O)(R^7), -S-R^5, -S(O)$_2$-R^5, carbociclilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo, y carbociclil-C_1-C_6-alquilo sustituido con halógeno.

257. Un compuesto o sal del mismo de acuerdo con la cláusula 256, en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



(257-1)

y



(257-2).

258. Un compuesto o sal del mismo de acuerdo con la cláusula 252, en el cual E^5 se selecciona del grupo formado por ciclopentenilo, ciclopentadienilo, ciclohexenilo, y ciclohexadienilo, donde

cualquier miembro de dicho grupo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO$_2$, -CN, ceto, C_1-C_6-alquilo, halo-C_1-C_6-alquilo, C_1-C_6-alcoxi, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, -N(R^5)(R^6), -C(O)(R^7), -S-R^5, -S(O)$_2$-R^5, carbociclilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo, y carbociclil-C_1-C_6-alquilo sustituido con halógeno.

1310

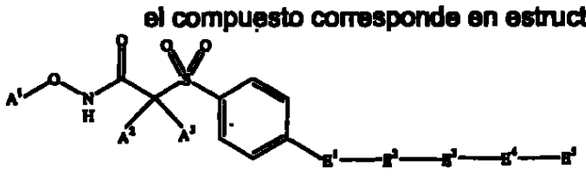
259. Un compuesto o sal del mismo de acuerdo con la cláusula 258, en el cual el compuesto corresponde en estructura a la siguiente fórmula:



(259-1).

260. Un compuesto o sal del mismo, en el cual

el compuesto corresponde en estructura a la Fórmula 260-1:



(260-1); y

A^1 se selecciona del grupo formado por -H, alquilcarbonilo, alcoxicarbonilo, carbociclilcarbonilo, carbociclilalquilcarbonilo, heterociclilcarbonilo, heterociclilalquilcarbonilo, carbocicliloxicarbonilo, carbociclilalcoxicarbonilo, aminoalquilcarbonilo, alquil(tiocarbonilo), alcoxi(tiocarbonilo), carbociclil(tiocarbonilo), carbociclilalquil(tiocarbonilo), heterociclil(tiocarbonilo), heterociclilalquil(tiocarbonilo), carbocicliloxi(tiocarbonilo), carbociclilalcoxi(tiocarbonilo), y aminoalquil(tiocarbonilo), donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido; y

A^2 y A^3, junto con el átomo de carbono al cual ambos están unidos, forman un heterociclilo optativamente sustituido que contiene entre 5 y 8 miembros en el anillo; y

E^1 se selecciona del grupo formado por -O-, $-S(O)_2-$, -S(O)-, $-N(R^1)-$, $-C(O)-N(R^1)-$, $-N(R^1)-C(O)-$, y $-C(R^1)(R^2)-$; y

1311

E^2 se selecciona del grupo formado por alquilo, cicloalquilo, alquilcicloalquilo, cicloalquilalquilo, y alquilcicloalquilalquilo, donde cualquier miembro de dicho grupo es optativamente sustituido; y

E^3 es carbonilpiperidinilo, donde el carbonilpiperidinilo es optativamente sustituido; y

E^4 se selecciona del grupo formado por un enlace, alquilo, y alquenilo, donde el alquilo o alquenilo es optativamente sustituido; y

E^5 se selecciona del grupo formado por alquilo, alquenilo, alquinilo, alcoxi, alcoxialquilo, carbociclilo, y heterociclilo, donde cualquier miembro de dicho grupo es optativamente sustituido; y

R^1 y R^2 se seleccionan independientemente del grupo formado por -H y alquilo, donde el alquilo es optativamente sustituido; y

ni R^1 ni R^2 forman una estructura de anillo con E^2, E^3, E^4, o E^5.

261. Un compuesto o sal del mismo de acuerdo con la cláusula 260, en el cual

A^1 se selecciona del grupo formado por -H, C_1-C_8-alquilcarbonilo, C_1-C_8-alcoxicarbonilo, carbociclilcarbonilo, carbociclil-C_1-C_8-alquilcarbonilo, heterociclilcarbonilo, heterociclil-C_1-C_8-alquilcarbonilo, carbocicliloxicarbonilo, carbociclil-C_1-C_8-alcoxicarbonilo, $N(R^3)(R^4)$-C_1-C_8-alquilcarbonilo, C_1-C_8-alquil(tiocarbonilo), C_1-C_8-alcoxi(tiocarbonilo), carbociclil(tiocarbonilo), carbociclil-C_1-C_8-alquil(tiocarbonilo), heterociclil(tiocarbonilo), heterociclil-C_1-C_8-alquil(tiocarbonilo), carbocicliloxi(tiocarbonilo), carbociclil-C_1-C_8-alcoxi(tiocarbonilo), y $N(R^3)(R^4)$-C_1-C_8-alquil(tiocarbonilo); y

E^2 se selecciona del grupo formado por C_1-C_{20}-alquilo, cicloalquilo, C_1-C_{10}-alquilcicloalquilo, cicloalquil-C_1-C_{10}-alquilo, y C_1-C_{10}-alquilcicloalquil-C_1-

1312

C_{10}-alquilo, donde cualquier miembro de dicho grupo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, C_1-C_6-alquilo, y halo-C_1-C_6-alquilo; y

E^3 es carbonilpiperidinilo, donde el carbonilpiperidinilo es optativamente sustituido con uno o más halógenos; y

E^4 se selecciona del grupo formado por un enlace, C_1-C_{20}-alquilo, halo-C_1-C_{20}-alquilo, C_2-C_{20}-alquenilo, y halo-C_2-C_{20}-alquenilo; y

E^5 se selecciona del grupo formado por C_1-C_{20}-alquilo, C_2-C_{20}-alquenilo, C_2-C_{20}-alquinilo, C_1-C_{20}-alcoxi, C_1-C_{20}-alcoxi-C_1-C_{20}-alquilo, carbociclilo, y heterociclilo, donde

el C_1-C_{20}-alquilo, C_2-C_{20}-alquenilo, C_2-C_{20}-alquinilo, C_1-C_{20}-alcoxi, o C_1-C_{20}-alcoxi-C_1-C_{20}-alquilo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, y -CN, y

el carbociclilo o heterociclilo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, -CN, ceto, C_1-C_6-alquilo, halo-C_1-C_6-alquilo, C_1-C_6-alcoxi, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno , $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbociclilo, halocarbociclilo, y carbociclil-C_1-C_6-alquilo; y

R^1 y R^2 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, y halo-C_1-C_6-alquilo; y

R^3 y R^4 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, C_1-C_6-alcoxicarbonilo, C_1-C_6-alquilcarbonilo, carbociclil-C_1-C_6-alquilo, y carbociclil-C_1-C_6-alcoxicarbonilo; y

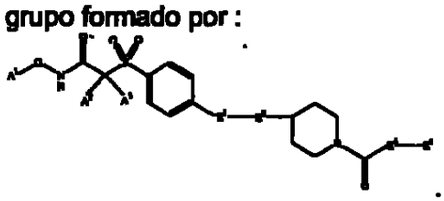
1313

R^5 y R^6 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo, donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido con uno o más halógenos; y

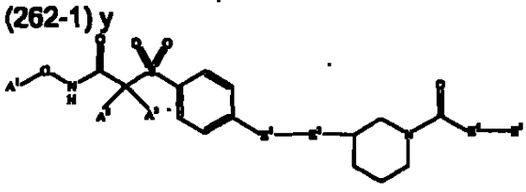
R^7 se selecciona del grupo formado por -H, C_1-C_6-alquilo, -O-R^8, -N(R^8)(R^9), carbociclil-C_1-C_6-alquilo, y heterociclil-C_1-C_6-alquilo, donde el C_1-C_6-alquilo, carbociclil-C_1-C_6-alquilo, o heterociclil-C_1-C_6-alquilo es optativamente sustituido con uno o más halógenos; y

R^8 y R^9 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo, donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido con uno o más halógenos.

262. Un compuesto o sal del mismo de acuerdo con la cláusula 261, en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



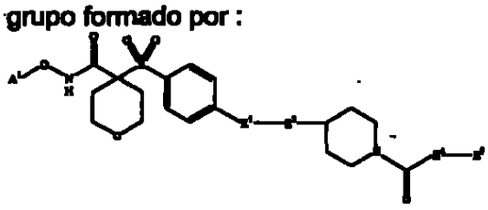
(262-1) y



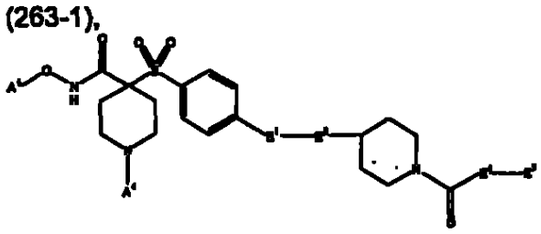
(262-2).

1314

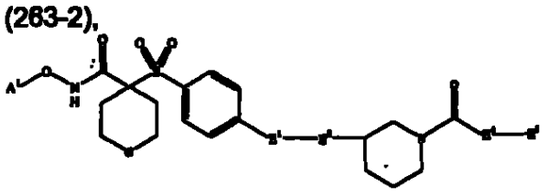
263. Un compuesto o sal del mismo de acuerdo con la cláusula 262, en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



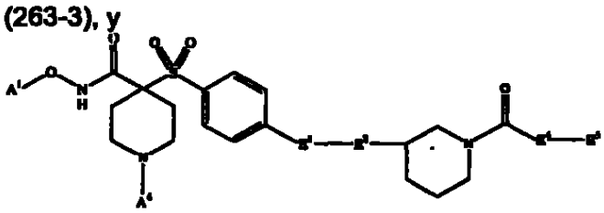
(263-1),



(263-2),



(263-3), y



(263-4); y

A^4 se selecciona del grupo formado por -H, alquilo, alquilcarbonilo, alquilcarbonilalquilo, alquilcarbonilalquilcarbonilo, alcoxicarbonilo, alcoxicarbonilalquilo, alcoxicarbonilalquilcarbonilo, alquilsulfonilo, alquiliminocarbonilo, alquenilo, alquinilo, alcoxialquilo, alquiltioalquilo, alquilsulfonilalquilo, alquilsufoxidoalquilo, alquiltioalquenilo,

1315

alquilsulfoxidoalquenilo, alquilsulfonilalquenilo, carbociclilo, carbociclilalquilo, carbociclilalcoxialquilo, carbociclilcarbonilo, carbociclilsulfonilo, carbociclliminocarbonilo, carbociclioxicarbonilo, carbociliitioalquilo, carbociclilsulfoxidoalquilo, carbociclilsulfonilalquilo, carbociclitioalquenilo, carbociclilsulfoxidoalquenilo, carbociclilsulfonilalquenilo, heterociclilo, heterociclilalquilo, heterociclilalcoxialquilo, heterociclilcarbonilo, heterociclitioalquilo, heterociclilsulfoxidoalquilo, heterociclilsulfonilalquilo, heterociclitioalquenilo, heterociclilsulfoxidoalquenilo, heterociclilsulfonilalquenilo, heterociclilsulfonilo, heterociclliminocarbonilo, heterociclilalquilcarbonilo, heterociclilcarbonilalquilcarbonilo, heterociclilsulfonilo, heterociclilcarbonilalquilo, aminoalquilcarbonilo, aminocarbonilo, aminocarbonilalquilcarbonilo, aminosulfonilo, aminosulfonilalquilo, aminoalquilo, aminocarbonilalquilo, y aminoalquilsulfonilo, donde

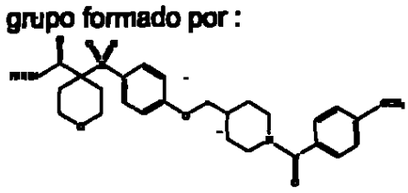
cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido.

264. Un compuesto o sal del mismo de acuerdo con la cláusula 263, en el cual E^5 es fenilo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_6-alquilo, halo-C_1-C_6-alquilo, C_1-C_6-alcoxi, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbociclilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo, y carbociclil-C_1-C_6-alquilo sustituido con halógeno.

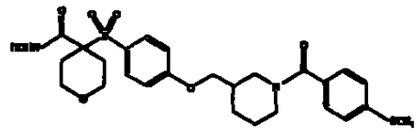
265. Un compuesto o sal del mismo de acuerdo con la cláusula 264, en el cual E^4 es un enlace.

1316

266. Un compuesto o sal del mismo de acuerdo con la cláusula 265, en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



y



(266-1)

(266-2).

267. Un compuesto o sal del mismo, en el cual

el compuesto corresponde en estructura a la Fórmula 267-1:



(267-1); y

A^1 se selecciona del grupo formado por -H, alquilcarbonilo, alcoxicarbonilo, carbociclilcarbonilo, carbociclilalquilcarbonilo, heterociclilcarbonilo, heterociclilalquilcarbonilo, carbocicliloxicarbonilo, carbociclilalcoxicarbonilo, aminoalquilcarbonilo, alquil(tiocarbonilo), alcoxi(tiocarbonilo), carbociclil(tiocarbonilo), carbociclilalquil(tiocarbonilo), heterociclil(tiocarbonilo), heterociclilalquil(tiocarbonilo), carbociclíloxi(tiocarbonilo), carbociclilalcoxi(tiocarbonilo), y aminoalquil(tiocarbonilo), donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido; y

1317

A^2 y A^3, junto con el átomo de carbono al cual ambos están unidos, forman un heterociclilo optativamente sustituido que contiene entre 5 y 8 miembros en el anillo; y

E^1 se selecciona del grupo formado por -O-, $-S(O)_2-$, -S(O)-, $-N(R^1)-$, $-C(O)-N(R^1)-$, $-N(R^1)-C(O)-$, y $-C(R^1)(R^2)-$; y

E^2 se selecciona del grupo formado por alquilo, cicloalquilo, alquilcicloalquilo, cicloalquilalquilo, y alquilcicloalquilalquilo, donde cualquier miembro de dicho grupo es optativamente sustituido; y

E^2 forma un enlace de al menos 3 átomos de carbono entre E^1 y E^5; y

E^5 se selecciona del grupo formado por heterociclilo optativamente sustituido, carbociclilo de anillos fusionados optativamente sustituido, y carbociclilo de anillo único sustituido; y

R^1 y R^2 se seleccionan independientemente del grupo formado por -H y alquilo, donde el alquilo es optativamente sustituido; y

ni R^1 ni R^2 forman una estructura de anillo con E^5.

268. Un compuesto o sal del mismo de acuerdo con la cláusula 267, en el cual

A^1 se selecciona del grupo formado por -H, C_1-C_8-alquilcarbonilo, C_1-C_8-alcoxicarbonilo, carbociclilcarbonilo, carbociclil-C_1-C_8-alquilcarbonilo, heterociclilcarbonilo, heterociclil-C_1-C_8-alquilcarbonilo, carbocicliloxicarbonilo, carbociclil-C_1-C_8-alcoxicarbonilo, $N(R^3)(R^4)$-C_1-C_8-alquilcarbonilo, C_1-C_8-alquil(tiocarbonilo), C_1-C_8-alcoxi(tiocarbonilo), carbociclil(tiocarbonilo), carbociclil-C_1-C_8-alquil(tiocarbonilo), heterociclil(tiocarbonilo), heterociclil-C_1-

1318

C_8-alquil(tiocarbonilo), carbocicliloxi(tiocarbonilo), carbociclil-C_1-C_8-alcoxi(tiocarbonilo), y $N(R^3)(R^4)$-C_1-C_8-alquil(tiocarbonilo); y

E^2 se selecciona del grupo formado por C_3-C_{20}-alquilo, cicloalquilo, C_1-C_{10}-alquil-cicloalquilo, cicloalquil-C_1-C_{10}-alquilo, y C_1-C_{10}-alquil-cicloalquil-C_1-C_{10}-alquilo, donde el Cualquier miembro de dicho grupo es optativamente sustituido con uno o más halógenos; y

E^5 se selecciona del grupo formado por carbociclilo de un solo anillo, carbociclilo de anillos fusionados, y heterociclilo, donde

el carbociclilo de un solo anillo:

es sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, -CN, ceto, C_1-C_8-alquilo, halo-C_1-C_8-alquilo, C_1-C_8-alcoxi, halo-C_1-C_8-alcoxi, C_1-C_8-alcoxi-C_1-C_8-alquilo, C_1-C_8-alcoxi-C_1-C_8-alquilo sustituido con halógeno , $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbociclilo, halocarbociclilo, carbociclil-C_1-C_8-alquilo, carbociclil-C_1-C_8-alquilo sustituido con halógeno, es optativamente sustituido en el mismo átomo con dos sustituyentes seleccionados independientemente del grupo formado por alquilo y haloalquilo, donde los dos sustituyentes juntos forman C_5-C_6-cicloalquilo o halo-C_5-C_6-cicloalquilo, y

el heterociclilo o carbociclilo de anillos fusionados:

es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, -CN, ceto, C_1-C_8-alquilo, halo-C_1-C_8-alquilo, C_1-C_8-alcoxi, halo-C_1-C_8-alcoxi, C_1-C_8-alcoxi-C_1-C_8-alquilo, C_1-C_8-alcoxi-C_1-C_8-alquilo sustituido con halógeno , $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbociclilo, halocarbociclilo, y carbociclil-C_1-C_8-alquilo, es optativamente sustituido en el mismo átomo con

1319

dos sustituyentes seleccionados independientemente del grupo formado por alquilo y haloalquilo, donde los dos sustituyentes juntos forman C_5-C_8-cicloalquilo o halo-C_5-C_8-cicloalquilo; y

R^1 y R^2 se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, y halo-C_1-C_8-alquilo; y

R^3 y R^4 se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, C_1-C_8-alcoxicarbonilo, C_1-C_8-alquilcarbonilo, carbociclil-C_1-C_8-alquilo, y carbociclil-C_1-C_8-alcoxicarbonilo; y

R^5 y R^6 se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, carbociclilo, carbociclil-C_1-C_8-alquilo, heterociclilo, y heterociclil-C_1-C_8-alquilo, donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido con uno o más halógenos; y

R^7 se selecciona del grupo formado por -H, C_1-C_8-alquilo, -O-R^8, -N(R^8)(R^9), carbociclil-C_1-C_8-alquilo, y heterociclil-C_1-C_8-alquilo, donde el C_1-C_8-alquilo, carbociclil-C_1-C_8-alquilo, o heterociclil-C_1-C_8-alquilo es optativamente sustituido con uno o más halógenos; y

R^8 y R^9 se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, carbociclilo, carbociclil-C_1-C_8-alquilo, heterociclilo, y heterociclil-C_1-C_8-alquilo, donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido con uno o más halógenos.

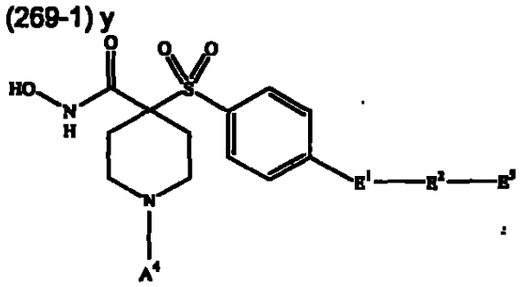
1320

269. Un compuesto o sal del mismo de acuerdo con la cláusula 268, en el cual

el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



(269-1) y



(269-2); y

A^4 se selecciona del grupo formado por -H, alquilo, alquilcarbonilo, alquilcarbonilalquilo, alquilcarbonilalquilcarbonilo, alcoxicarbonilo, alcoxicarbonilalquilo, alcoxicarbonilalquilcarbonilo, alquilsulfonilo, alquiliminocarbonilo, alquenilo, alquinilo, alcoxialquilo, alquiltioalquilo, alquilsulfonilalquilo, alquilsufoxidoalquilo, alquiltioalquenilo, alquilsulfoxidoalquenilo, alquilsulfonilalquenilo, carbociclilo, carbociclilalquilo, carbociclilalcoxialquilo, carbociclilcarbonilo, carbociclilsulfonilo, carbociclliliminocarbonilo, carbociclioxicarbonilo, carbocliltioalquilo, carbociclilsulfoxidoalquilo, carbocliisulfonilalquilo, carbociclitioalquenilo, carbociclilsulfoxidoalquenilo, carbociclilsulfonilalquenilo, heterociclilo, heterociclilalquilo, heterociclilalcoxialquilo, heterociclilcarbonilo,

1324

heterocicliltioalquilo, heterociclilsulfoxidoalquilo, heterociclilsulfonilalquilo, heterociclitioalquenilo, heterociclilsulfoxidoalquenilo, heterociclilsulfonilalquenilo, heterociclilsulfonilo, heterociclliminocarbonilo, heterociclilalquilcarbonilo, heterociclilcarbonilalquilcarbonilo, heterociclilsulfonilo, heterociclilcarbonilalquilo, aminoalquilcarbonilo, aminocarbonilo, aminocarbonilalquilcarbonilo, aminosulfonilo, aminosulfonilalquilo, aminoalquilo, aminocarbonilalquilo, y aminoalquilsulfonilo, donde

cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido.

270. Un compuesto o sal del mismo de acuerdo con la cláusula 269, en el cual E^5 es carbociclilo de un solo anillo, el cual:

es sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, -CN, ceto, C_1-C_6-alquilo, halo-C_1-C_6-alquilo, C_1-C_6-alcoxi, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbociclilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo, y carbociclil-C_1-C_6-alquilo sustituido con halógeno; y

es optativamente sustituido en el mismo átomo con dos sustituyentes seleccionados independientemente del grupo formado por alquilo y haloalquilo, donde los dos sustituyentes juntos forman C_5-C_6-cicloalquilo o halo-C_5-C_6-cicloalquilo.

271. Un compuesto o sal del mismo de acuerdo con la cláusula 270, en el cual E^5 es carbociclilo de anillo único sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -

1322

NO_2, -CN, ceto, C_1-C_6-alquilo, halo-C_1-C_6-alquilo, C_1-C_6-alcoxi, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbociclilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo, y carbociclil-C_1-C_6-alquilo sustituido con halógeno.

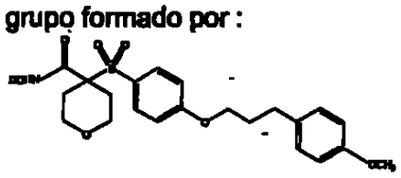
272. Un compuesto o sal del mismo de acuerdo con la cláusula 271, en el cual E^5 se selecciona del grupo formado por ciclopropilo, ciclobutilo, ciclopentilo, ciclopentenilo, ciclopentadienilo, ciclohexilo, ciclohexenilo, ciclohexadienilo, y fenilo, donde un miembro de dicho grupo:

es sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, ceto, C_1-C_6-alquilo, halo-C_1-C_6-alquilo, C_1-C_6-alcoxi, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbociclilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo, y carbociclil-C_1-C_6-alquilo sustituido con halógeno.

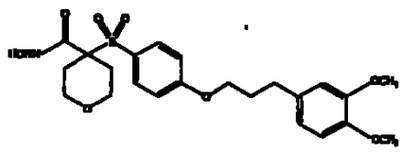
273. Un compuesto o sal del mismo de acuerdo con la cláusula 272, en el cual E^5 es fenilo sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_6-alquilo, halo-C_1-C_6-alquilo, C_1-C_6-alcoxi, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbociclilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo, y carbociclil-C_1-C_6-alquilo sustituido con halógeno.

1323 274

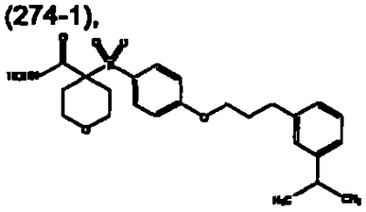
274. Un compuesto o sal del mismo de acuerdo con la cláusula 273, en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



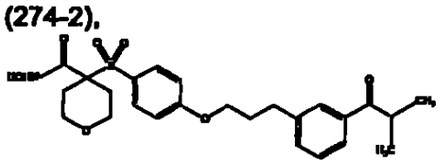
(274-1),



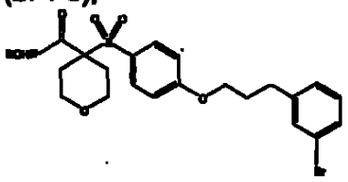
(274-2),



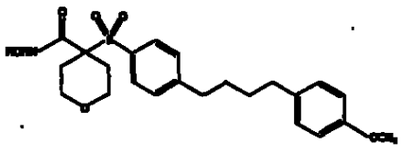
(274-3),



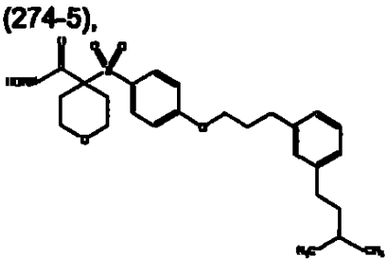
(274-4),



(274-5),



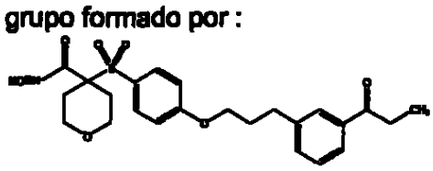
(274-6), y



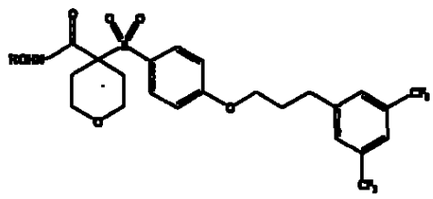
(274-7).

1324

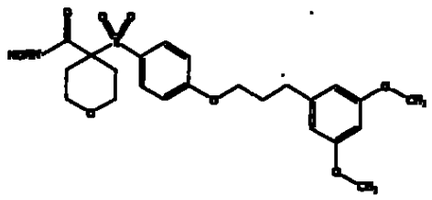
275. Un compuesto o sal del mismo de acuerdo con la cláusula 273, en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



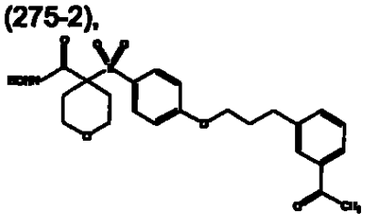
(275-1),



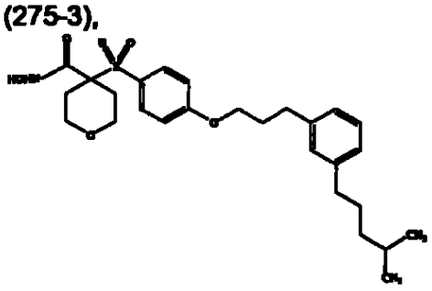
(275-2),



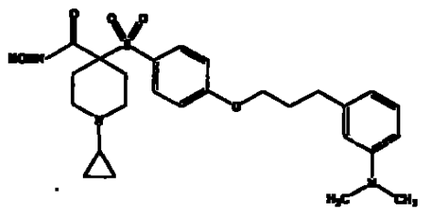
(275-3),



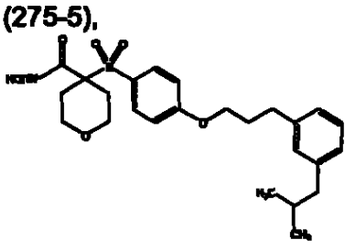
(275-4),



(275-5),



(275-6), y



(275-7).

276. Un compuesto o sal del mismo de acuerdo con la cláusula 269, en el cual E^5 es carbociclilo de anillos fusionados, el cual:

es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, ceto, C_1-C_6-alquilo, halo-C_1-C_6-alquilo, C_1-C_6-alcoxi, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbociclilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo, y carbociclil-C_1-C_6-alquilo sustituido con halógeno; y

es optativamente sustituido en el mismo átomo con dos sustituyentes seleccionados independientemente del grupo formado por alquilo y haloalquilo, donde los dos sustituyentes juntos forman C_5-C_6-cicloalquilo o halo-C_5-C_6-cicloalquilo.

277. Un compuesto o sal del mismo de acuerdo con la cláusula 276, en el cual E^5 es carbociclilo de anillos fusionados optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, ceto, C_1-C_6-alquilo, halo-C_1-C_6-alquilo, C_1-C_6-alcoxi, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbociclilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo, y carbociclil-C_1-C_6-alquilo sustituido con halógeno.

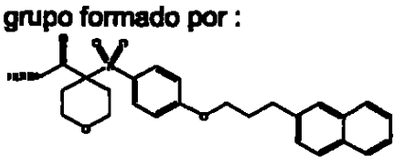
1326

278. Un compuesto o sal del mismo de acuerdo con la cláusula 277, en el cual E^5 se selecciona del grupo formado por naftalenilo, tetrahidronaftalenilo, indenilo, isoindenilo, indanilo, biciclodecanilo, antracenilo, fenantreno, benzonaftenilo, fluoreneilo, decalinilo, y norpinanilo, donde un miembro de dicho grupo:

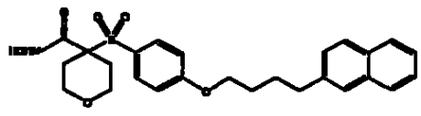
es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, ceto, C_1-C_6-alquilo, halo-C_1-C_6-alquilo, C_1-C_6-alcoxi, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbociclilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo, y carbociclil-C_1-C_6-alquilo sustituido con halógeno.

279. Un compuesto o sal del mismo de acuerdo con la cláusula 278, en el cual E^5 es naftalenilo optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_6-alquilo, halo-C_1-C_6-alquilo, C_1-C_6-alcoxi, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbociclilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo, y carbociclil-C_1-C_6-alquilo sustituido con halógeno.

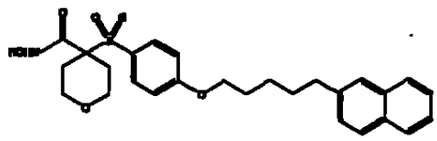
280. Un compuesto o sal del mismo de acuerdo con la cláusula 279, en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



(280-1),



(280-2), y



(280-3).

281. Un compuesto o sal del mismo de acuerdo con la cláusula 269, en el cual E^5 es heterociclilo, el cual:

es optativamente sustituido en el mismo átomo con dos sustituyentes seleccionados independientemente del grupo formado por alquilo y haloalquilo, donde los dos sustituyentes juntos forman C_3-C_6-cicloalquilo o halo-C_3-C_6-cicloalquilo; y

es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, ceto, C_1-C_6-alquilo, halo-C_1-C_6-alquilo, C_1-C_6-alcoxi, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbociclilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo, y carbociclil-C_1-C_6-alquilo sustituido con halógeno.

282. Un compuesto o sal del mismo de acuerdo con la cláusula 281, en el cual E^5 es heterociclilo, el cual:

es sustituido en el mismo átomo con dos sustituyentes seleccionados independientemente del grupo formado por alquilo y haloalquilo, donde los dos sustituyentes juntos forman C_3-C_6-cicloalquilo o halo-C_3-C_6-cicloalquilo; y

es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, ceto, C_1-C_6-alquilo, halo-C_1-C_6-alquilo, C_1-C_6-alcoxi, halo-C_1-C_6-

alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, -N(R^5)(R^6), -C(O)(R^7), -S-R^5, -S(O)$_2$-R^5, carbociclilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo, y carbociclil-C_1-C_6-alquilo sustituido con halógeno.

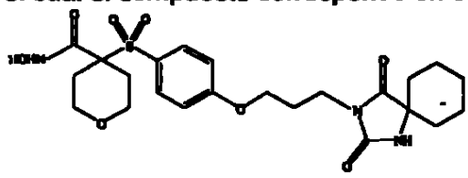
283. Un compuesto o sal del mismo de acuerdo con la cláusula 282, en el cual E^5 se selecciona del grupo formado por dihidrofuranilo, tetrahidrofuranilo, dihidrotiofenilo, tetrahidrotiofenilo, pirrolinilo, pirrolidinilo, imidazolinilo, imidazolidinilo, pirazolinilo, pirazolidinilo, ditiolilo, oxatiolilo, tiazolinilo, isotiazolinilo, tiazolidinilo, isotiazolidinilo, oxatiolanilo, piranilo, dihidropiranilo, piperidinilo, piperazinilo, y morfolinilo, donde un miembro de dicho grupo:

es sustituido en el mismo átomo con dos sustituyentes seleccionados independientemente del grupo formado por alquilo y haloalquilo, donde los dos sustituyentes juntos forman C_5-C_6-cicloalquilo o halo-C_5-C_6-cicloalquilo; y

es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, ceto, C_1-C_6-alquilo, halo-C_1-C_6-alquilo, C_1-C_6-alcoxi, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, . C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, -N(R^5)(R^6), -C(O)(R^7), -S-R^5, -S(O)$_2$-R^5, carbociclilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo, y carbociclil-C_1-C_6-alquilo sustituido con halógeno.

1329

284. Un compuesto o sal del mismo de acuerdo con la cláusula 283, en el cual el compuesto corresponde en estructura a la siguiente fórmula:



(284-1).

285. Un compuesto o sal del mismo de acuerdo con la cláusula 281, en el cual E^5 es heterociclilo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, ceto, C_1-C_6-alquilo, halo-C_1-C_6-alquilo, C_1-C_6-alcoxi, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbociclilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo, y carbociclil-C_1-C_6-alquilo sustituido con halógeno.

286. Un compuesto o sal del mismo de acuerdo con la cláusula 285, en el cual E^5 se selecciona del grupo formado por furanilo, tetrahidropiranilo, dihidrofuranilo, tetrahidrofuranilo, tiofenilo, dihidrotiofenilo, tetrahidrotiofenilo, pirrolilo, isopirrolilo, pirrolinilo, pirrolidinilo, imidazolilo, isoimidazolilo, imidazolinilo, imidazolidinilo, pirazolilo, pirazolinilo, pirazolidinilo, triazolilo, tetrazolilo, ditiolilo, oxatiolilo, oxazolilo, isoxazolilo, oxazolidinilo, isoxazolidinilo, tiazolilo, isotiazolilo, tiazolinilo, isotiazolinilo, tiazolidinilo, isotiazolidinilo, tiodiazolilo, oxatiazolilo, oxadiazolilo, oxatriazolilo, dioxazolilo, oxatiazolilo, oxatiolilo, oxatiolanilo, piranilo, dihidropiranilo, piridinilo, piperidinilo, diazinilo, piperazinilo, triazinilo, oxazinilo, isoxazinilo, oxatiazinilo, oxadiazinilo,

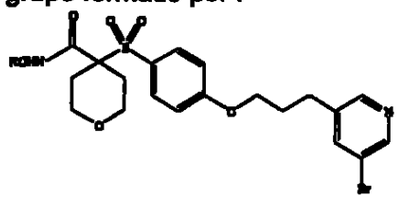
1330

morfolinilo, azepinilo, oxepinilo, tiepinilo, y diazepinilo, donde un miembro de dicho grupo:

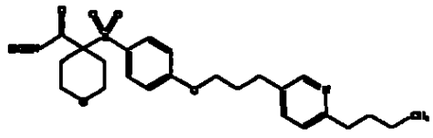
es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, ceto, C_1-C_6-alquilo, halo-C_1-C_6-alquilo, C_1-C_6-alcoxi, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbociclilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo, y carbociclil-C_1-C_6-alquilo sustituido con halógeno.

287. Un compuesto o sal del mismo de acuerdo con la cláusula 286, en el cual E^5 es piridinilo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, ceto, C_1-C_6-alquilo, halo-C_1-C_6-alquilo, C_1-C_6-alcoxi, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^6, -$S(O)_2$-R^5, carbociclilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo, y carbociclil-C_1-C_6-alquilo sustituido con halógeno.

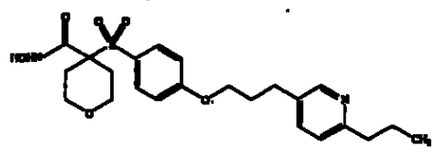
288. Un compuesto o sal del mismo de acuerdo con la cláusula 287, en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



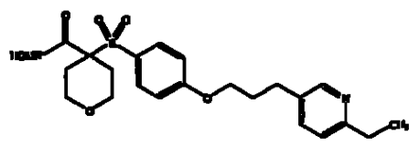
(288-1),



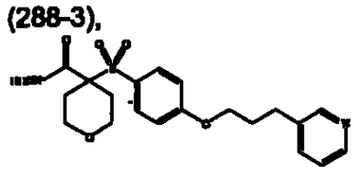
(288-2),



(288-3),



(288-4), y



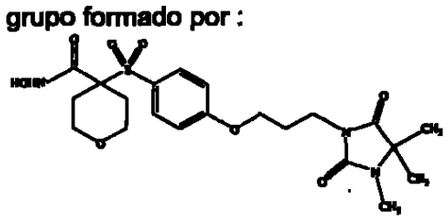
(288-5).

289. Un compuesto o sal del mismo de acuerdo con la cláusula 286, en el cual E^5 se selecciona del grupo formado por imidazolilo, imidazolinilo, imidazolidinilo, pirazolilo, pirazolinilo, y pirazolidinilo, donde un miembro de dicho grupo:

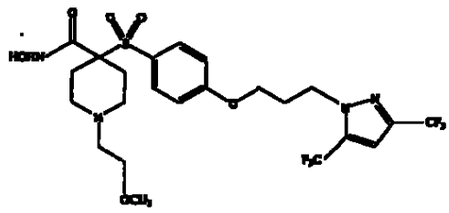
es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, ceto, C_1-C_6-alquilo, halo-C_1-C_6-alquilo, C_1-C_6-alcoxi, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbociclilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo, y carbociclil-C_1-C_6-alquilo sustituido con halógeno.

1332

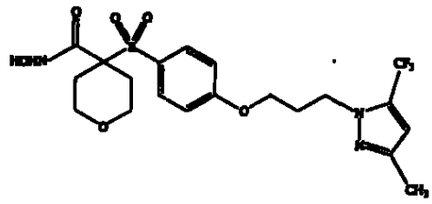
290. Un compuesto o sal del mismo de acuerdo con la cláusula 289, en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



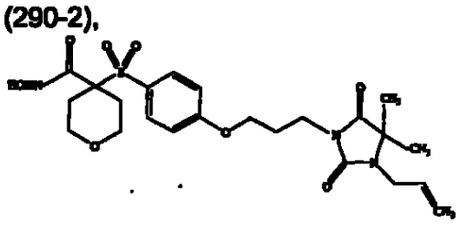
(290-1)



(290-2),



(290-3), y



(290-4).

291. Un compuesto o sal del mismo de acuerdo con la cláusula 285, en el cual E^5 es heterociclilo de anillo fusionado optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, -CN, ceto, C_1-C_6-alquilo, halo-C_1-C_6-alquilo, C_1-C_6-alcoxi, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbociclilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo, y carbociclil-C_1-C_6-alquilo sustituido con halógeno.

292. Un compuesto o sal del mismo de acuerdo con la cláusula 291, en el cual E^5 se selecciona del grupo formado por indolizinilo, pirindinilo, piranopirrolilo, 4H-quinolizinilo, purinilo, naftiridinilo, piridopiridinilo, pteridinilo, indolilo, isoindolilo, indoleninilo, isoindazolilo, benzazinilo, ftalazinilo,

1333

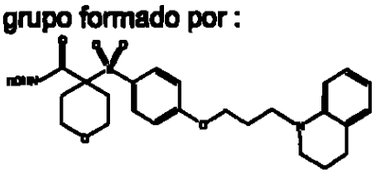
quinoxalinilo, quinazolinilo, benzodiazinilo, benzopiranilo, benzotiopiranilo, benzoxazolilo, indoxazinilo, antranililo, benzodioxolilo, benzodioxanilo, benzoxadiazolilo, benzofuranilo, isobenzofuranilo, benzotienilo, isobenzotienilo, benzotiazolilo, benzotiadiazolilo, bencimidazolilo, benzotriazolilo, benzoxazinilo, bencisoxazinilo, tetrahidroisoquinolinilo, carbazolilo, xantenilo, y acridinilo, donde un miembro de dicho grupo:

es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, ceto, C_1-C_6-alquilo, halo-C_1-C_6-alquilo, C_1-C_6-alcoxi, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbociclilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo, y carbociclil-C_1-C_6-alquilo sustituido con halógeno.

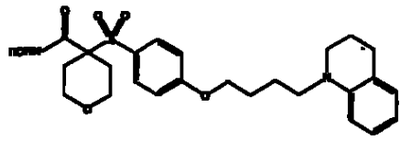
293. Un compuesto o sal del mismo de acuerdo con la cláusula 292, en el cual E^5 es tetrahidroisoquinolinilo, el cual,

es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, ceto, C_1-C_6-alquilo, halo-C_1-C_6-alquilo, C_1-C_6-alcoxi, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbociclilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo, y carbociclil-C_1-C_6-alquilo sustituido con halógeno.

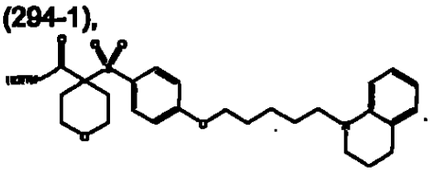
294. Un compuesto o sal del mismo de acuerdo con la cláusula 293, en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



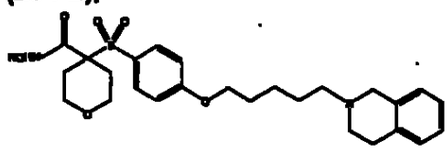
(294-1),



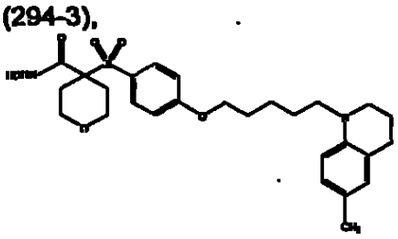
(294-2),



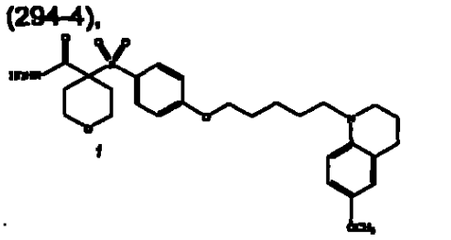
(294-3),



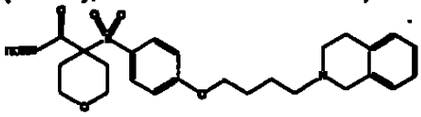
(294-4),



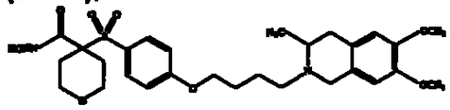
(294-5),



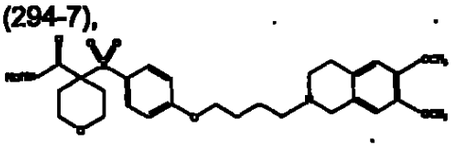
(294-6),



(294-7),



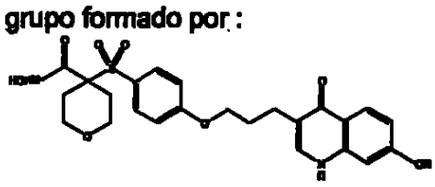
(294-8), y



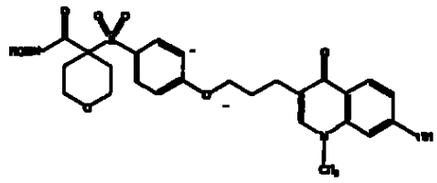
(294-9).

1335

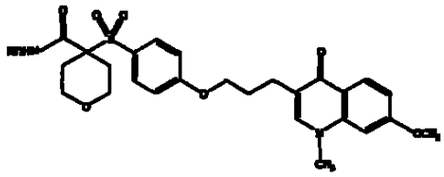
295. Un compuesto o sal del mismo de acuerdo con la cláusula 291, en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



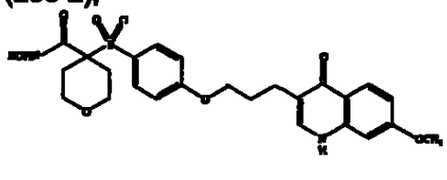
(295-1),



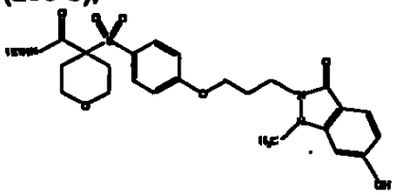
(295-2),



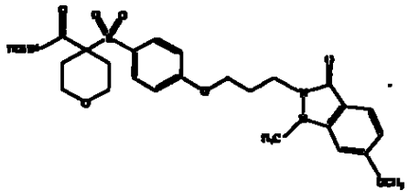
(295-3),



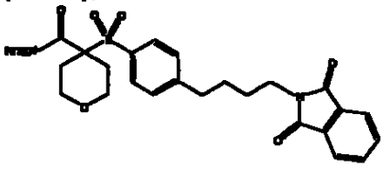
(295-4),



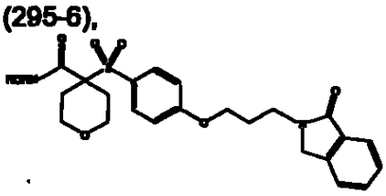
(295-5),



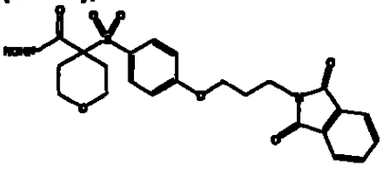
(295-6),



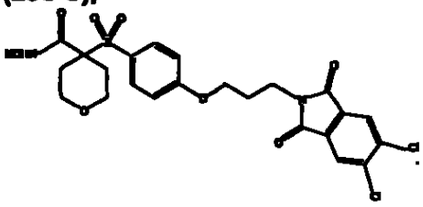
(295-7),



(295-8),

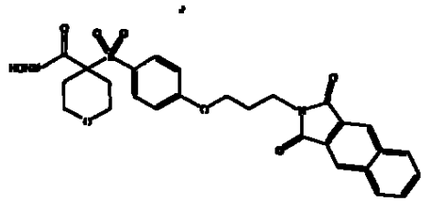


(295-9),

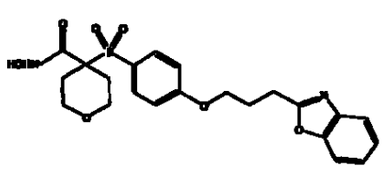


(295-10),

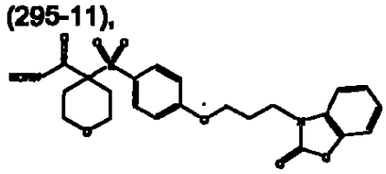
1336



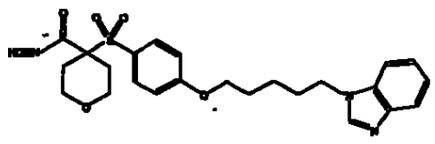
(295-11),



(295-12),



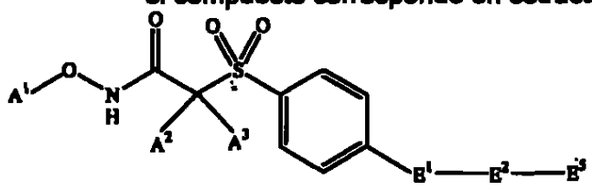
(295-13), y



(295-14).

296. Un compuesto o sal del mismo, en el cual

el compuesto corresponde en estructura a la Fórmula 296-1:



(296-1); y

A^1 se selecciona del grupo formado por -H, alquilcarbonilo, alcoxicarbonilo, carbociclilcarbonilo, carbociclilalquilcarbonilo, heterociclilcarbonilo, heterociclilalquilcarbonilo, carbocicliloxicarbonilo, carbociclilalcoxicarbonilo, aminoalquilcarbonilo, alquil(tiocarbonilo), alcoxi(tiocarbonilo), carbociclil(tiocarbonilo), carbociclilalquil(tiocarbonilo), heterociclil(tiocarbonilo), heterociclilalquil(tiocarbonilo), carbocicliloxi(tiocarbonilo), carbociclilalcoxi(tiocarbonilo), y aminoalquil(tiocarbonilo), donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido; y

1337

A^2 y A^3, junto con el átomo de carbono al cual ambos están unidos, forman un heterociclilo optativamente sustituido que contiene entre 5 y 8 miembros en el anillo; y

E^1 se selecciona del grupo formado por -O-, $-S(O)_2-$, -S(O)-, $-N(R^1)-$, $-C(O)-N(R^1)-$, $-N(R^1)-C(O)-$, y $-C(R^1)(R^2)-$; y

R^1 y R^2 se seleccionan independientemente del grupo formado por -H y alquilo, donde el alquilo es optativamente sustituido; y

E^2 se selecciona del grupo formado por alquilo, cicloalquilo, alquilcicloalquilo, cicloalquilalquilo, y alquilcicloalquilalquilo, donde cualquier miembro de dicho grupo es optativamente sustituido; y

E^2 forma un enlace de al menos 4 átomos de carbono entre E^1 y E^5; y

E^5 se selecciona del grupo formado por -OH y carbociclilo optativamente sustituido; y

ni R^1 ni R^2 forman una estructura de anillo con E^5.

297. Un compuesto o sal del mismo de acuerdo con la cláusula 296, en el cual

A^1 se selecciona del grupo formado por -H, C_1-C_8-alquilcarbonilo, C_1-C_8-alcoxicarbonilo, carbociclilcarbonilo, carbociclil-C_1-C_8-alquilcarbonilo, heterociclilcarbonilo, heterociclil-C_1-C_8-alquilcarbonilo, carbocicliloxicarbonilo, carbociclil-C_1-C_8-alcoxicarbonilo, $N(R^3)(R^4)$-C_1-C_8-alquilcarbonilo, C_1-C_8-alquil(tiocarbonilo), C_1-C_8-alcoxi(tiocarbonilo), carbociclil(tiocarbonilo), carbociclil-C_1-C_8-alquil(tiocarbonilo), heterociclil(tiocarbonilo), heterociclil-C_1-C_8-alquil(tiocarbonilo), carbocicliloxi(tiocarbonilo), carbociclil-C_1-C_8-alcoxi(tiocarbonilo), y $N(R^3)(R^4)$-C_1-C_8-alquil(tiocarbonilo); y

1338

E^2 se selecciona del grupo formado por C_4-C_{20}-alquilo, cicloalquilo, C_1-C_{10}-alquil-cicloalquilo, cicloalquil-C_1-C_{10}-alquilo, y C_1-C_{10}-alquil-cicloalquil-C_1-C_{10}-alquilo, donde el Cualquier miembro de dicho grupo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, C_1-C_6-alquilo, y halo-C_1-C_6-alquilo; y

E^5 se selecciona del grupo formado por -OH y carbociclilo, donde el carbociclilo:

es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, ceto, C_1-C_6-alquilo, halo-C_1-C_6-alquilo, C_1-C_6-alcoxi, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno , -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbociclilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo, y carbociclil-C_1-C_6-alquilo sustituido con halógeno, y

es optativamente sustituido con dos grupos C_1-C_6-alquilo o halo-C_1-C_6-alquilo en el mismo átomo que forman un C_3-C_6-cicloalquilo o C_3-C_6-halocicloalquilo, y

R^1 y R^2 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, y halo-C_1-C_6-alquilo; y

R^3 y R^4 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, C_1-C_6-alcoxicarbonilo, C_1-C_6-alquilcarbonilo, carbociclil-C_1-C_6-alquilo, y carbociclil-C_1-C_6-alcoxicarbonilo; y

R^5 y R^6 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo, donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido con uno o más halógenos; y

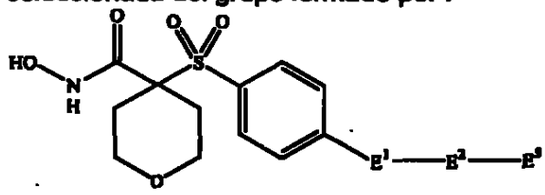
1339

R^7 se selecciona del grupo formado por -H, C_1-C_8-alquilo, -O-R^8, $N(R^8)(R^9)$, carbociclil-C_1-C_8-alquilo, y heterociclil-C_1-C_8-alquilo, donde el C_1-C_8-alquilo, carbociclil-C_1-C_8-alquilo, o heterociclil-C_1-C_8-alquilo es optativamente sustituido con uno o más halógenos; y

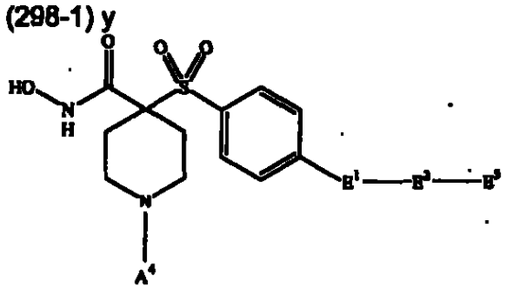
R^8 y R^9 se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, carbociclilo, carbociclil-C_1-C_8-alquilo, heterociclilo, y heterociclil-C_1-C_8-alquilo, donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido con uno o más halógenos.

298. Un compuesto o sal del mismo de acuerdo con la cláusula 297, en el cual

el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



(298-1) y



(298-2); y

A^4 se selecciona del grupo formado por -H, alquilo, alquilcarbonilo, alquilcarbonilalquilo, alquilcarbonilalquilcarbonilo, alcoxicarbonilo, alcoxicarbonilalquilo, alcoxicarbonilalquilcarbonilo, alquilsulfonilo,

1340

alquiliminocarbonilo, alquenilo, alquinilo, alcoxialquilo, alquiltioalquilo, alquilsulfonilalquilo, alquilsufoxidoalquilo, alquiltioalquenilo, alquilsulfoxidoalquenilo, alquilsulfonilalquenilo, carbociclilo, carbociclilalquilo, carbociclilalcoxialquilo, carbociclilcarbonilo, carbociclilsulfonilo, carbociclliminocarbonilo, carbocicliloxicarbonilo, carbocililtioalquilo, carbociclilsulfoxidoalquilo, carbociclilsulfonilalquilo, carbociclliltioalquenilo, carbociclilsulfoxidoalquenilo, carbociclilsulfonilalquenilo, heterociclilo, heterociclilalquilo, heterociclilalcoxialquilo, heterociclilcarbonilo, heterocicliltioalquilo, heterociclilsulfoxidoalquilo, heterociclilsulfonilalquilo, heterocicliltioalquenilo, heterociclilsulfoxidoalquenilo, heterociclilsulfonilalquenilo, heterociclilsulfonilo, heterociclliminocarbonilo, heterociclilalquilcarbonilo, heterociclilcarbonilalquilcarbonilo, heterociclilsulfonilo, heterociclilcarbonilalquilo, aminoalquilcarbonilo, aminocarbonilo, aminocarbonilalquilcarbonilo, aminosulfonilo, aminosulfonilalquilo, aminoalquilo, aminocarbonilalquilo, y aminoalquilsulfonilo, donde

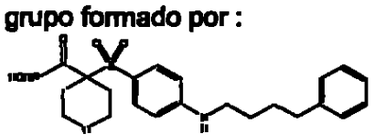
cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido.

299. Un compuesto o sal del mismo de acuerdo con la cláusula 298, en el cual E^5 es fenilo optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, ceto, C_1-C_6-alquilo, halo-C_1-C_6-alquilo, C_1-C_6-alcoxi, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbociclilo, halocarbociclilo,

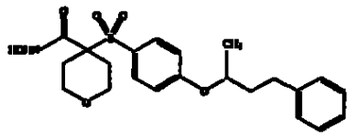
1341

carbociclil-C_1-C_6-alquilo, y carbociclil-C_1-C_6-alquilo sustituido con halógeno.

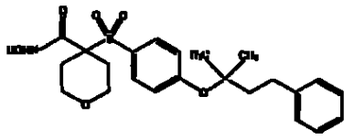
300. Un compuesto o sal del mismo de acuerdo con la cláusula 299, en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



(300-1),



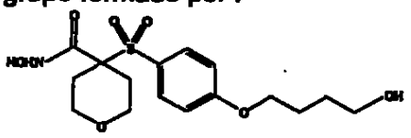
(300-2), y



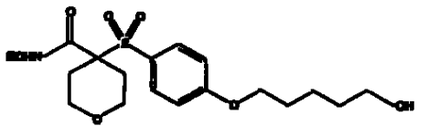
(300-3).

301. Un compuesto o sal del mismo de acuerdo con la cláusula 298, en el cual E^5 es -OH.

302. Un compuesto o sal del mismo de acuerdo con la cláusula 301, en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



y



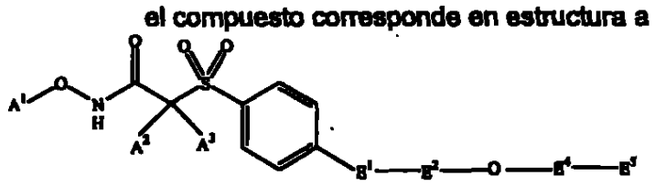
(302-1)

(302-2).

1342

303. Un compuesto o sal del mismo, en el cual

el compuesto corresponde en estructura a la Fórmula 303-1:



(303-1); y

A^1 se selecciona del grupo formado por -H, alquilcarbonilo, alcoxicarbonilo, carbociclilcarbonilo, carbociclilalquilcarbonilo, heterociclilcarbonilo, heterociclilalquilcarbonilo, carbocicliloxicarbonilo, carbociclilalcoxicarbonilo, aminoalquilcarbonilo, alquil(tiocarbonilo), alcoxi(tiocarbonilo), carbociclil(tiocarbonilo), carbociclilalquil(tiocarbonilo), heterociclil(tiocarbonilo), heterociclilalquil(tiocarbonilo), carbocicliloxi(tiocarbonilo), carbociclilalcoxi(tiocarbonilo), y aminoalquil(tiocarbonilo), donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido; y

A^2 y A^3, junto con el átomo de carbono al cual ambos están unidos, forman un heterociclilo optativamente sustituido que contiene entre 5 y 8 miembros en el anillo; y

E^1 se selecciona del grupo formado por $-S(O)_2-$, -S(O)-, $-N(R^1)-$, $-C(O)-N(R^1)-$, $-N(R^1)-C(O)-$, y $-C(R^1)(R^2)-$; y

E^2 se selecciona del grupo formado por alquilo, cicloalquilo, alquilcicloalquilo, cicloalquilalquilo, y alquilcicloalquilalquilo, donde cualquier miembro de dicho grupo es optativamente sustituido; y

E^4 se selecciona del grupo formado por un enlace, alquilo, y alquenilo, donde el alquilo o alquenilo es optativamente sustituido; y

1343

E^5 se selecciona del grupo formado por alquilo, alquenilo, alquinilo, alcoxi, alcoxialquilo, carbociclilo, y heterociclilo, donde cualquier miembro de dicho grupo es optativamente sustituido; y

R^1 y R^2 se seleccionan independientemente del grupo formado por -H y alquilo, donde el alquilo es optativamente sustituido; y

ni R^1 ni R^2 forman una estructura de anillo con E^2, E^4, o E^5

304. Un compuesto o sal del mismo de acuerdo con la cláusula 303, en el cual

A^1 se selecciona del grupo formado por -H, C_1-C_8-alquilcarbonilo, C_1-C_8-alcoxicarbonilo, carbociclilcarbonilo, carbociclil-C_1-C_8-alquilcarbonilo, heterociclilcarbonilo, heterociclil-C_1-C_8-alquilcarbonilo, carbocicliloxicarbonilo, carbociclil-C_1-C_8-alcoxicarbonilo, $N(R^3)(R^4)$-C_1-C_8-alquilcarbonilo, C_1-C_8-alquil(tiocarbonilo), C_1-C_8-alcoxi(tiocarbonilo), carbociclil(tiocarbonilo), carbociclil-C_1-C_8-alquil(tiocarbonilo), heterociclil(tiocarbonilo), heterociclil-C_1-C_8-alquil(tiocarbonilo), carbociclíloxi(tiocarbonilo), carbociclil-C_1-C_8-alcoxi(tiocarbonilo), y $N(R^3)(R^4)$-C_1-C_8-alquil(tiocarbonilo); y

E^2 se selecciona del grupo formado por C_1-C_{20}-alquilo, cicloalquilo, C_1-C_{10}-alquilcicloalquilo, cicloalquil-C_1-C_{10}-alquilo, y C_1-C_{10}-alquilcicloalquil-C_1-C_{10}-alquilo, donde cualquier miembro de dicho grupo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, C_1-C_8-alquilo, C_1-C_8-halo-alquilo; y

E^4 se selecciona del grupo formado por un enlace, C_1-C_{20}-alquilo, halo-C_1-C_{20}-alquilo, C_2-C_{20}-alquenilo, y halo-C_2-C_{20}-alquenilo; y

1344

E^5 se selecciona del grupo formado por C_1-C_{20}-alquilo, C_2-C_{20}-alquenilo, C_2-C_{20}-alquinilo, C_1-C_{20}-alcoxi, C_1-C_{20}-alcoxi-C_1-C_{20}-alquilo, carbociclilo, y heterociclilo, donde

el C_1-C_{20}-alquilo, C_2-C_{20}-alquenilo, C_2-C_{20}-alquinilo, C_1-C_{20}-alcoxi, o C_1-C_{20}-alcoxi-C_1-C_{20}-alquilo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, y -CN, y

el carbociclilo o heterociclilo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, ceto, C_1-C_8-alquilo, halo-C_1-C_8-alquilo, C_1-C_8-alcoxi, halo-C_1-C_8-alcoxi, C_1-C_8-alcoxi-C_1-C_8-alquilo, C_1-C_8-alcoxi-C_1-C_8-alquilo sustituido con halógeno , -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbociclilo, halocarbociclilo, carbociclil-C_1-C_8-alquilo, y carbociclil-C_1-C_8-alquilo sustituido con halógeno; y

R^1 y R^2 se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, y halo-C_1-C_8-alquilo; y

R^3 y R^4 se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, C_1-C_8-alcoxicarbonilo, C_1-C_8-alquilcarbonilo, carbociclil-C_1-C_8-alquilo, y carbociclil-C_1-C_8-alcoxicarbonilo; y

R^5 y R^6 se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, carbociclilo, carbociclil-C_1-C_8-alquilo, heterociclilo, y heterociclil-C_1-C_8-alquilo, donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido con uno o más halógenos; y

R^7 se selecciona del grupo formado por -H, C_1-C_8-alquilo, -O-R^5, -$N(R^5)(R^9)$, carbociclil-C_1-C_8-alquilo, y heterociclil-C_1-C_8-alquilo, donde el C_1-C_8-

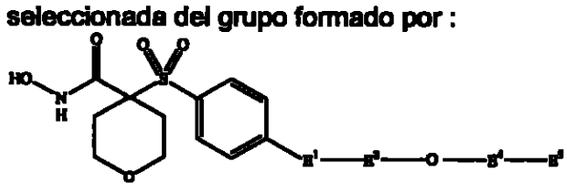
1345

alquilo, carbociclil-C_1-C_8-alquilo, o heterociclil-C_1-C_8-alquilo es optativamente sustituido con uno o más halógenos; y

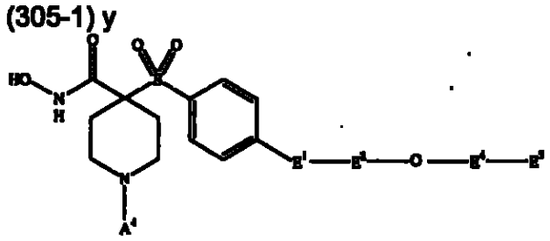
R^8 y R^9 se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, carbociclilo, carbociclil-C_1-C_8-alquilo, heterociclilo, y heterociclil-C_1-C_8-alquilo, donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido con uno o más halógenos.

305. Un compuesto o sal del mismo de acuerdo con la cláusula 304, en el cual

el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



(305-1) y



(305-2); y

A^4 se selecciona del grupo formado por -H, alquilo, alquilcarbonilo, alquilcarbonilalquilo, alquilcarbonilalquilcarbonilo, alcoxicarbonilo, alcoxicarbonilalquilo, alcoxicarbonilalquilcarbonilo, alquilsulfonilo, alquiliminocarbonilo, alquenilo, alquinilo, alcoxialquilo, alquiltioalquilo, alquilsulfonilalquilo, alquilsufoxidoalquilo, alquiltioalquenilo, alquilsulfoxidoalquenilo, alquilsulfonilalquenilo, carbociclilo, carbociclilalquilo, carbociclilalcoxialquilo, carbociclilcarbonilo, carbociclilsulfonilo,

1346

carbociclliminocarbonilo, carbociclloxicarbonilo, carbocicliltioalquilo, carbocicliisulfoxidoalquilo, carbocicliisulfonilalquilo, carbocicliltioalquenilo, carbocicliisulfoxidoalquenilo, carbocicliisulfonilalquenilo, heterociclilo, heterociclilalquilo, heterociclilalcoxialquilo, heterociclilcarbonilo, heterocicliltioalquilo, heterociclilsulfoxidoalquilo, heterociclilsulfonilalquilo, heterocicliltioalquenilo, heterociclilsulfoxidoalquenilo, heterociclilsulfonilalquenilo, heterociclilsulfonilo, heterociclliminocarbonilo, heterociclilalquilcarbonilo, heterociclilcarbonilalquilcarbonilo, heterociclilsulfonilo, heterociclilcarbonilalquilo, aminoalquilcarbonilo, aminocarbonilo, aminocarbonilalquilcarbonilo, aminosulfonilo, aminosulfonilalquilo, aminoalquilo, aminocarbonilalquilo, y aminoalquilsulfonilo, donde

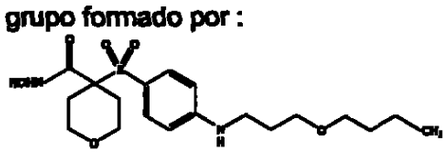
cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido.

306. Un compuesto o sal del mismo de acuerdo con la cláusula 305, en el cual E^5 se selecciona del grupo formado por C_1-C_8-alquilo, C_2-C_8-alquenilo, C_2-C_8-alquinilo, C_1-C_8-alcoxi, y C_1-C_8-alcoxi-C_1-C_8-alquilo, donde

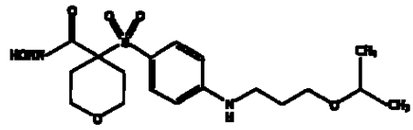
el C_1-C_8-alquilo, C_2-C_8-alquenilo, C_2-C_8-alquinilo, C_1-C_8-alcoxi, o C_1-C_8-alcoxi-C_1-C_8-alquilo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, y -CN.

1347

307. Un compuesto o sal del mismo de acuerdo con la cláusula 306, en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



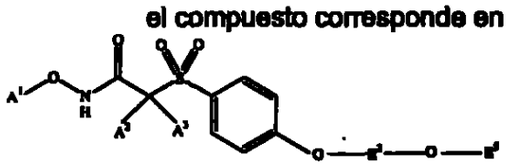
y



(307-1) (307-2).

308. Un compuesto o sal del mismo, en el cual

el compuesto corresponde en estructura a la Fórmula 308-1:



(308-1); y

A^1 se selecciona del grupo formado por -H, alquilcarbonilo, alcoxicarbonilo, carbociclilcarbonilo, carbociclilalquilcarbonilo, heterociclilcarbonilo, heterociclilalquilcarbonilo, carbocicliloxicarbonilo, carbociclilalcoxicarbonilo, aminoalquilcarbonilo, alquil(tiocarbonilo), alcoxi(tiocarbonilo), carbociclil(tiocarbonilo), carbociclilalquil(tiocarbonilo), heterociclil(tiocarbonilo), heterociclilalquil(tiocarbonilo), carbocicliloxi(tiocarbonilo), carbociclilalcoxi(tiocarbonilo), y aminoalquil(tiocarbonilo), donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido; y

A^2 y A^3, junto con el átomo de carbono al cual ambos están unidos, forman un heterociclilo optativamente sustituido que contiene entre 5 y 8 miembros en el anillo; y

E^2 se selecciona del grupo formado por alquilo, cicloalquilo, alquilcicloalquilo, cicloalquilalquilo, y alquilcicloalquilalquilo, donde cualquier miembro de dicho grupo es optativamente sustituido; y

E^2 comprende al menos 3 átomos de carbono; y

E^5 se selecciona del grupo formado por -H, alquilo, alquenilo, alquinilo, alcoxialquilo, carbociclilo, carbociclilalcoxialquilo, heterociclilo, heterociclilalquilo, y heterociclilalcoxialquilo, donde

el alquilo , alquenilo, alquinilo, o alcoxialquilo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, y -CN, y

el carbociclilo, carbociclilalcoxialquilo, heterociclilo, heterociclilalquilo, o heterociclilalcoxialquilo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, -CN, alquilo, haloalquilo, alcoxi, haloalcoxi, alcoxialquilo, alcoxialquilo sustituido con halógeno, $-N(R^3)(R^4)$, $-C(O)(R^5)$, $-S-R^3$, $-S(O)_2-R^3$, carbociclilo, halocarbociclilo, carbociclilalquilo, y carbociclilalquilo sustituido con halógeno; y

R^1 y R^2 se seleccionan independientemente del grupo formado por -H, alquilo, carbociclilo, carbociclilalquilo, heterociclilo, y heterociclilalquilo, donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido con uno o más halógenos; y

R^3 se selecciona del grupo formado por -H, alquilo, $-O-R^4$, $-N(R^4)(R^5)$, carbociclilalquilo, y heterociclilalquilo, donde el alquilo , carbociclilalquilo, o heterociclilalquilo es optativamente sustituido con uno o más halógenos; y

1349

R^4 y R^5 se seleccionan independientemente del grupo formado por -H, alquilo, carbociclilo, carbociclilalquilo, heterociclilo, y heterociclilalquilo, donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido con uno o más halógenos.

309. Un compuesto o sal del mismo de acuerdo con la cláusula 308, en el cual

A^1 se selecciona del grupo formado por -H, C_1-C_8-alquilcarbonilo, C_1-C_8-alcoxicarbonilo, carbociclilcarbonilo, carbociclil-C_1-C_8-alquilcarbonilo, heterociclilcarbonilo, heterociclil-C_1-C_8-alquilcarbonilo, carbociclioxicarbonilo, carbociclil-C_1-C_8-alcoxicarbonilo, $N(R^8)(R^7)$-C_1-C_8-alquilcarbonilo, C_1-C_8-alquil(tiocarbonilo), C_1-C_8-alcoxi(tiocarbonilo), carbociclil(tiocarbonilo), carbociclil-C_1-C_8-alquil(tiocarbonilo), heterociclil(tiocarbonilo), heterociclil-C_1-C_8-alquil(tiocarbonilo), carbociclioxi(tiocarbonilo), carbociclil-C_1-C_8-alcoxi(tiocarbonilo), y $N(R^6)(R^7)$-C_1-C_8-alquil(tiocarbonilo); y

E^2 se selecciona del grupo formado por C_3-C_{20}-alquilo, cicloalquilo, C_1-C_{10}-alquilcicloalquilo, cicloalquil-C_1-C_{10}-alquilo, y C_1-C_{10}-alquilcicloalquil-C_1-C_{10}-alquilo, donde cualquier miembro de dicho grupo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, C_1-C_8-alquilo, y halo-C_1-C_8-alquilo; y

E^5 se selecciona del grupo formado por -H, C_1-C_{20}-alquilo, C_2-C_{20}-alquenilo, C_2-C_{20}-alquinilo, C_1-C_{20}-alcoxi-C_1-C_{20}-alquilo, carbociclilo, carbociclil-C_1-C_{10}-alcoxi-C_1-C_{10}-alquilo, heterociclilo, heterociclil-C_1-C_{10}-alquilo, y heterociclil-C_1-C_{10}-alcoxi-C_1-C_{10}-alquilo, donde

el C_1-C_{20}-alquilo, C_2-C_{20}-alquenilo, C_2-C_{20}-alquinilo, o C_1-C_{20}-alcoxi-C_1-C_{20}-alquilo es optativamente sustituido con uno o más sustituyentes

1350

independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, y -CN, y

el carbociclilo, carbociclil-C_1-C_{10}-alcoxi-C_1-C_{10}-alquilo, heterociclilo, heterociclil-C_1-C_{10}-alquilo, o heterociclil-C_1-C_{10}-alcoxi-C_1-C_{10}-alquilo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, ceto, C_1-C_8-alquilo, halo-C_1-C_8-alquilo, C_1-C_8-alcoxi, halo-C_1-C_8-alcoxi, C_1-C_8-alcoxi-C_1-C_8-alquilo, C_1-C_8-alcoxi-C_1-C_8-alquilo sustituido con halógeno , -$N(R^3)(R^4)$, -$C(O)(R^5)$, -S-R^3, -$S(O)_2$-R^3, carbociclilo, halocarbociclilo, carbociclil-C_1-C_8-alquilo, y carbociclil-C_1-C_8-alquilo sustituido con halógeno; y

R^1 y R^2 se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, carbociclilo, carbociclil-C_1-C_8-alquilo, heterociclilo, y heterociclil-C_1-C_8-alquilo, donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido con uno o más halógenos; y

R^3 se selecciona del grupo formado por -H, C_1-C_8-alquilo, -O-R^4, -$N(R^4)(R^5)$, carbociclil-C_1-C_8-alquilo, y heterociclil-C_1-C_8-alquilo, donde el C_1-C_8-alquilo, carbociclil-C_1-C_8-alquilo, o heterociclil-C_1-C_8-alquilo es optativamente sustituido con uno o más halógenos; y

R^4 y R^5 se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, carbociclilo, carbociclil-C_1-C_8-alquilo, heterociclilo, y heterociclil-C_1-C_8-alquilo, donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido con uno o más halógenos; y

R^6 y R^7 se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, C_1-C_8-alcoxicarbonilo, C_1-C_8-alquilcarbonilo, carbociclil-C_1-C_8-alquilo, y carbociclil-C_1-C_8-alcoxicarbonilo.

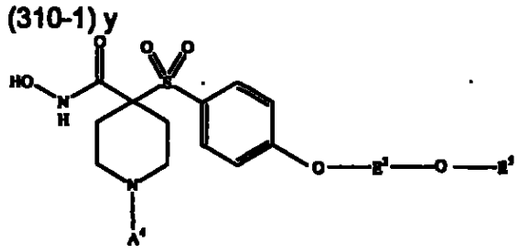
1351

310. Un compuesto o sal del mismo de acuerdo con la cláusula 309, en el cual

el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



(310-1) y



(310-2); y

A^4 se selecciona del grupo formado por -H, alquilo, alquilcarbonilo, alquilcarbonilalquilo, alquilcarbonilalquilcarbonilo, alcoxicarbonilo, alcoxicarbonilalquilo, alcoxicarbonilalquilcarbonilo, alquilsulfonilo, alquiliminocarbonilo, alquenilo, alquinilo, alcoxialquilo, alquiltioalquilo, alquilsulfonilalquilo, alquilsufoxidoalquilo, alquiltioalquenilo, alquilsulfoxidoalquenilo, alquilsulfonilalquenilo, carbociclilo, carbociclilalquilo, carbociclilalcoxialquilo, carbociclilcarbonilo, carbociclilsulfonilo, carbociclíliminocarbonilo, carbociclíloxicarbonilo, carbociliitioalquilo, carbocililsulfoxidoalquilo, carbocililsulfonilalquilo, carbociclíltioalquenilo, carbociclilsulfoxidoalquenilo, carbociclilsulfonilalquenilo, heterociclilo, heterociclilalquilo, heterociclilalcoxialquilo, heterociclilcarbonilo, heterociclíltioalquilo, heterociclilsulfoxidoalquilo, heterociclilsulfonilalquilo, heterociclíltioalquenilo, heterociclilsulfoxidoalquenilo,

1352

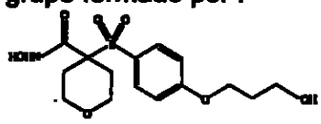
heterociclilsulfonilalquenilo, heterociclilsulfonilo, heterociclliminocarbonilo, heterociclilalquilcarbonilo, heterociclilcarbonilalquilcarbonilo, heterociclilsulfonilo, heterociclilcarbonilalquilo, aminoalquilcarbonilo, aminocarbonilo, aminocarbonilalquilcarbonilo, aminosulfonilo, aminosulfonilalquilo, aminoalquilo, aminocarbonilalquilo, y aminoalquilsulfonilo, donde

cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido.

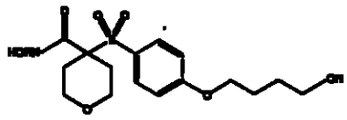
311. Un compuesto o sal del mismo de acuerdo con la cláusula 310, en el cual E^5 se selecciona del grupo formado por -H, C_1-C_8-alquilo, C_2-C_8-alquenilo, C_2-C_8-alquinilo, y C_1-C_8-alcoxi-C_1-C_8-alquilo, donde

el C_1-C_8-alquilo, C_2-C_8-alquenilo, C_2-C_8-alquinilo, o C_1-C_8-alcoxi-C_1-C_8-alquilo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, y -CN.

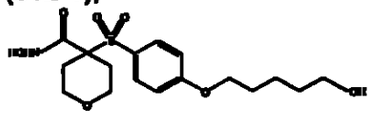
312. Un compuesto o sal del mismo de acuerdo con la cláusula 311, en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



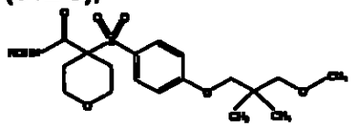
(312-1),



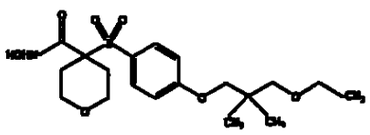
(312-2),



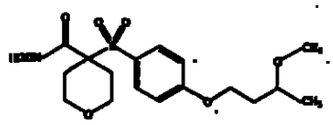
(312-3),



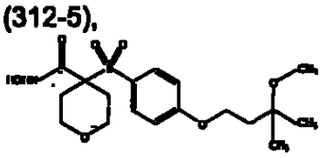
(312-4),



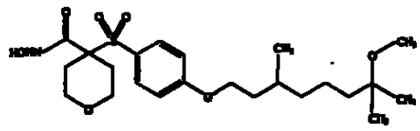
(312-5),



(312-6),



(312-7), y.



(312-8).

313. Un compuesto o sal del mismo de acuerdo con la cláusula 310, en el cual E^5 se selecciona del grupo formado por carbociclilo, carbociclil-C_1-C_6-alcoxi-C_1-C_6-alquilo, heterociclilo, heterociclil-C_1-C_6-alquilo, y heterociclil-C_1-C_6-alcoxi-C_1-C_6-alquilo, donde

el carbociclilo, carbociclil-C_1-C_6-alcoxi-C_1-C_6-alquilo, heterociclilo, heterociclil-C_1-C_6-alquilo, o heterociclil-C_1-C_6-alcoxi-C_1-C_6-alquilo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, ceto, C_1-C_6-alquilo, halo-C_1-C_6-alquilo, C_1-C_6-alcoxi, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, -$N(R^3)(R^4)$, -$C(O)(R^5)$, -S-R^3, -$S(O)_2$-R^3, carbociclilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo, y carbociclil-C_1-C_6-alquilo sustituido con halógeno.

314. Un compuesto o sal del mismo de acuerdo con la cláusula 313, en el cual E^5 es carbociclilo optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_6-alquilo, halo-C_1-C_6-alquilo, C_1-C_6-alcoxi, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, -

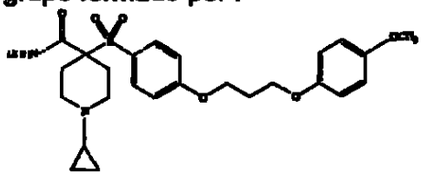
1354

$N(R^3)(R^4)$, $-C(O)(R^5)$, $-S-R^3$, $-S(O)_2-R^3$, carbociclilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo, y carbociclil-C_1-C_6-alquilo sustituido con halógeno.

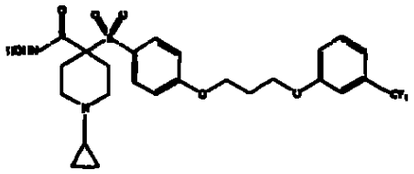
315. Un compuesto o sal del mismo de acuerdo con la cláusula 314, en el cual E^2 es C_3-C_5-alquilo optativamente sustituido con uno o más halógenos.

316. Un compuesto o sal del mismo de acuerdo con la cláusula 315, en el cual E^5 es fenilo optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, -CN, C_1-C_6-alquilo, halo-C_1-C_6-alquilo, C_1-C_6-alcoxi, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, $-N(R^3)(R^4)$, $-C(O)(R^5)$, $-S-R^3$, $-S(O)_2-R^3$, carbociclilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo, y carbociclil-C_1-C_6-alquilo sustituido con halógeno.

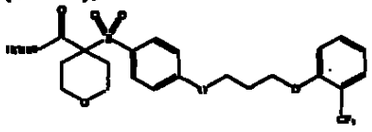
317. Un compuesto o sal del mismo de acuerdo con la cláusula 316, en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



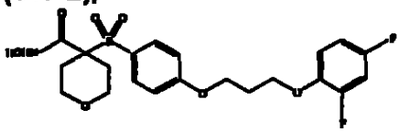
(317-1),



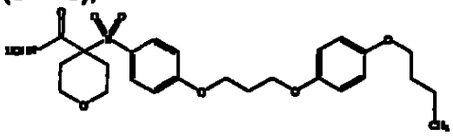
(317-2),



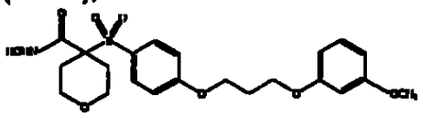
(317-3),



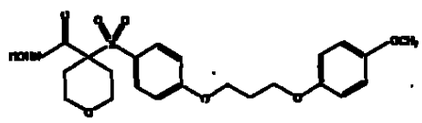
(317-4),



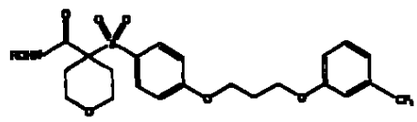
(317-5),



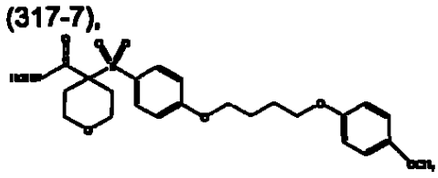
(317-6),



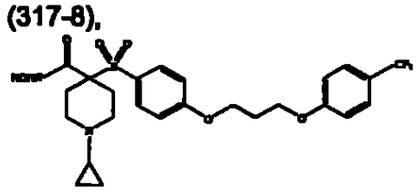
(317-7),



(317-8),



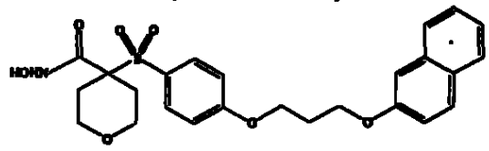
(317-9), y



(317-10).

318. Un compuesto o sal del mismo de acuerdo con la cláusula 315, en el cual E^5 es naftalenilo optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_6-alquilo, halo-C_1-C_6-alquilo, C_1-C_6-alcoxi, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, -$N(R^3)(R^4)$, -$C(O)(R^5)$, -S-R^3, -$S(O)_2$-R^3, carbociclilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo, y carbociclil-C_1-C_6-alquilo sustituido con halógeno.

319. Un compuesto o sal del mismo de acuerdo con la cláusula 318, en el cual el compuesto corresponde en estructura a la siguiente fórmula:



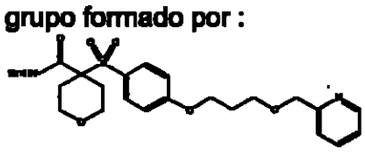
(319-1).

320. Un compuesto o sal del mismo de acuerdo con la cláusula 310, en el cual E^5 se selecciona del grupo formado por heterociclilo y heterociclil-C_1-C_6-alquilo, donde

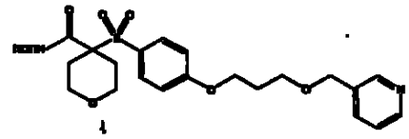
1356

el heterociclilo y heterociclil-C_1-C_6-alquilo optativamente son sustituidos con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, ceto, C_1-C_6-alquilo, halo-C_1-C_6-alquilo, C_1-C_6-alcoxi, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, -$N(R^3)(R^4)$, -$C(O)(R^5)$, -S-R^3, -$S(O)_2$-R^3, carbociclilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo, y carbociclil-C_1-C_6-alquilo sustituido con halógeno.

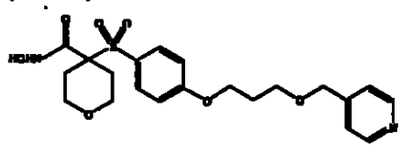
321. Un compuesto o sal del mismo de acuerdo con la cláusula 320, en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



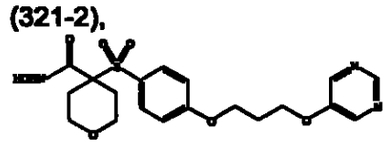
(321-1),



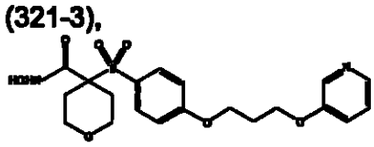
(321-2),



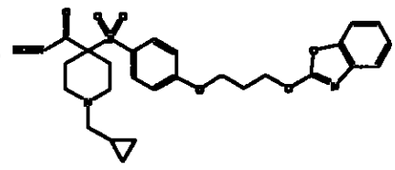
(321-3),



(321-4),



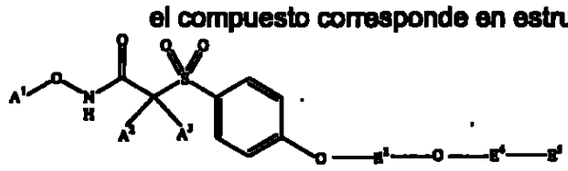
(321-5), y



(321-6).

322. Un compuesto o sal del mismo, en el cual

el compuesto corresponde en estructura a la Fórmula 322-1:



(322-1); y

A^1 se selecciona del grupo formado por -H, alquilcarbonilo, alcoxicarbonilo, carbociclilcarbonilo, carbociclilalquilcarbonilo, heterociclilcarbonilo, heterociclilalquilcarbonilo, carbociclíloxicarbonilo, carbociclilalcoxicarbonilo, aminoalquilcarbonilo, alquil(tiocarbonilo), alcoxi(tiocarbonilo), carbociclil(tiocarbonilo), carbociclilalquil(tiocarbonilo), heterociclil(tiocarbonilo), heterociclilalquil(tiocarbonilo), carbociclíloxi(tiocarbonilo), carbociclilalcoxi(tiocarbonilo), y aminoalquil(tiocarbonilo), donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido; y

A^2 y A^3, junto con el átomo de carbono al cual ambos están unidos, forman un heterociclilo optativamente sustituido que contiene entre 5 y 8 miembros en el anillo; y

E^2 se selecciona del grupo formado por alquilo, cicloalquilo, alquilcicloalquilo, cicloalquilalquilo, y alquilcicloalquilalquilo, donde cualquier miembro de dicho grupo es optativamente sustituido; y

E^4 se selecciona del grupo formado por un enlace, alquilo, y alquenilo, donde el alquilo o alquenilo es optativamente sustituido; y

E^5 se selecciona del grupo formado por :

optativamente-sustituido alquenilo, y

optativamente-sustituido alquinilo, y

optativamente sustituido alcoxi, y

optativamente sustituido alcoxialquilo, y

carbociclilo de anillo único sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por -OH, $-NO_2$, -CN, $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbociclilo, halocarbociclilo, carbociclilalquilo, carbociclilalquilo sustituido con halógeno, heterociclilo, haloheterociclilo, heterociclilalquilo, y heterociclilalquilo sustituido con halógeno, y

carbociclilo de anillo único con sustituciones múltiples, y

carbociclilo de anillos fusionados optativamente sustituido, y

heterociclilo optativamente sustituido; y

R^1 y R^2 se seleccionan independientemente del grupo formado por -H, alquilo, carbociclilo, carbociclilalquilo, heterociclilo, y heterociclilalquilo, donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido con uno o más halógenos; y

R^3 se selecciona del grupo formado por -H, alquilo, $-O-R^4$, $-N(R^4)(R^5)$, carbociclilalquilo, y heterociclilalquilo, donde el alquilo , carbociclilalquilo, o heterociclilalquilo es optativamente sustituido con uno o más halógenos; y

R^4 y R^5 se seleccionan independientemente del grupo formado por -H, alquilo, carbociclilo, carbociclilalquilo, heterociclilo, y heterociclilalquilo, donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido con uno o más halógenos; y

un átomo en E^2 optativamente está unido a un átomo en E^6 para formar un anillo.

1359

323. Un compuesto o sal del mismo de acuerdo con la cláusula 322, en el cual

A^1 se selecciona del grupo formado por -H, C_1-C_8-alquilcarbonilo, C_1-C_8-alcoxicarbonilo, carbociclilcarbonilo, carbociclil-C_1-C_8-alquilcarbonilo, heterociclilcarbonilo, heterociclil-C_1-C_8-alquilcarbonilo, carbocicliloxicarbonilo, carbociclil-C_1-C_8-alcoxicarbonilo, $N(R^6)(R^7)$-C_1-C_8-alquilcarbonilo, C_1-C_8-alquil(tiocarbonilo), C_1-C_8-alcoxi(tiocarbonilo), carbociclil(tiocarbonilo), carbociclil-C_1-C_8-alquil(tiocarbonilo), heterociclil(tiocarbonilo), heterociclil-C_1-C_8-alquil(tiocarbonilo), carbociclíloxi(tiocarbonilo), carbociclil-C_1-C_8-alcoxi(tiocarbonilo), y $N(R^6)(R^7)$-C_1-C_8-alquil(tiocarbonilo); y

E^2 se selecciona del grupo formado por C_1-C_{20}-alquilo, cicloalquilo, C_1-C_{10}-alquilcicloalquilo, cicloalquil-C_1-C_{10}-alquilo, y C_1-C_{10}-alquilcicloalquil-C_1-C_{10}-alquilo, donde cualquier miembro de dicho grupo es optativamente sustituido con uno o más sustituyentes seleccionados del grupo formado por halógeno, C_1-C_6-alquilo, halo-C_1-C_6-alquilo; y

E^4 se selecciona del grupo formado por un enlace, C_1-C_{20}-alquilo, halo-C_1-C_{20}-alquilo, C_2-C_{20}-alquenilo, y halo-C_2-C_{20}-alquenilo; y

E^5 se selecciona del grupo formado por C_2-C_{20}-alquenilo, C_2-C_{20}-alquinilo, C_1-C_{20}-alcoxi, C_1-C_{20}-alcoxi-C_1-C_{20}-alquilo, heterociclilo, carbociclilo de un solo anillo, y carbociclilo de anillos fusionados, donde

el C_2-C_{20}-alquenilo, C_2-C_{20}-alquinilo, C_1-C_{20}-alcoxi, o C_1-C_{20}-alcoxi-C_1-C_{20}-alquilo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, y -CN, y

el heterociclilo o carbociclilo de anillos fusionados es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_8-alquilo, halo-C_1-C_8-alquilo, C_1-C_8-alcoxi, halo-C_1-C_8-alcoxi, C_1-C_8-alcoxi-C_1-C_8-alquilo, C_1-C_8-alcoxi-C_1-C_8-alquilo sustituido con halógeno , -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbociclilo, halocarbociclilo, carbociclil-C_1-C_8-alquilo, carbociclil-C_1-C_8-alquilo sustituido con halógeno, heterociclilo, haloheterociclilo, heterociclil-C_1-C_8-alquilo, y heterociclil-C_1-C_8-alquilo sustituido con halógeno, y

el carbociclilo de anillo único es ya sea :

sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por -OH, -NO_2, -CN, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbociclilo, halocarbociclilo, carbociclil-C_1-C_8-alquilo, carbociclil-C_1-C_8-alquilo sustituido con halógeno, heterociclilo, haloheterociclilo, heterociclil-C_1-C_8-alquilo, y heterociclil-C_1-C_8-alquilo sustituido con halógeno, o

sustituido con 2 ó más sustituyentes seleccionados independientemente del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_8-alquilo, halo-C_1-C_8-alquilo, C_1-C_8-alcoxi, halo-C_1-C_8-alcoxi, C_1-C_8-alcoxi-C_1-C_8-alquilo, C_1-C_8-alcoxi-C_1-C_8-alquilo sustituido con halógeno , -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbociclilo, halocarbociclilo, carbociclil-C_1-C_8-alquilo, carbociclil-C_1-C_8-alquilo sustituido con halógeno, heterociclilo, haloheterociclilo, heterociclil-C_1-C_8-alquilo, y heterociclil-C_1-C_8-alquilo sustituido con halógeno; y

R^1 y R^2 se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, carbociclilo, carbociclil-C_1-C_8-alquilo, heterociclilo, y heterociclil-C_1-C_8-alquilo, donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido con uno o más halógenos; y

1361

R^3 se selecciona del grupo formado por -H, C_1-C_8-alquilo, -O-R^4, -N(R^4)(R^5), carbociclil-C_1-C_8-alquilo, y heterociclil-C_1-C_8-alquilo, donde el C_1-C_8-alquilo, carbociclil-C_1-C_8-alquilo, o heterociclil-C_1-C_8-alquilo es optativamente sustituido con uno o más halógenos; y

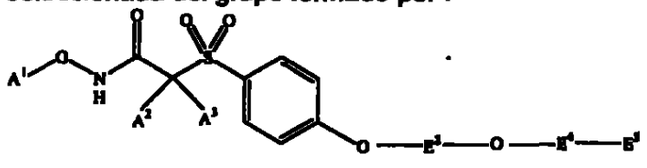
R^4 y R^5 se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, carbociclilo, carbociclil-C_1-C_8-alquilo, heterociclilo, y heterociclil-C_1-C_8-alquilo, donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido con uno o más halógenos; y

R^6 y R^7 se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, C_1-C_8-alcoxicarbonilo, C_1-C_8-alquilcarbonilo, carbociclil-C_1-C_8-alquilo, y carbociclil-C_1-C_8-alcoxicarbonilo; y

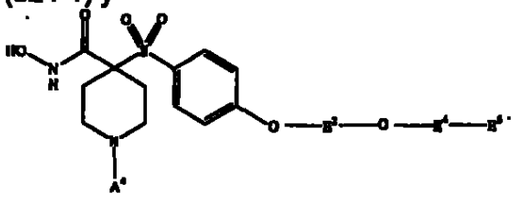
un átomo en E^2 optativamente está unido a un átomo en E^5 para formar un anillo.

324. Un compuesto o sal del mismo de acuerdo con la cláusula 323, en el cual

el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



(324-1) y



(324-2); y

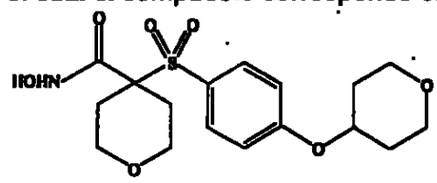
A^4 se selecciona del grupo formado por -H, alquilo, alquilcarbonilo, alquilcarbonilalquilo, alquilcarbonilalquilcarbonilo, alcoxicarbonilo, alcoxicarbonilalquilo, alcoxicarbonilalquilcarbonilo, alquilsulfonilo, alquiliminocarbonilo, alquenilo, alquinilo, alcoxialquilo, alquiltioalquilo, alquilsulfonilalquilo, alquilsufoxidoalquilo, alquiltioalquenilo, alquilsulfoxidoalquenilo, alquilsulfonilalquenilo, carbociclilo, carbociclilalquilo, carbociclilalcoxialquilo, carbociclilcarbonilo, carbociclilsulfonilo, carbocicliliminocarbonilo, carbociclioxicarbonilo, carbociliitioalquilo, carbocililsulfoxidoalquilo, carbocililsulfonilalquilo, carbociclitioalquenilo, carbociclilsulfoxidoalquenilo, carbociclilsulfonilalquenilo, heterociclilo, heterociclilalquilo, heterociclilalcoxialquilo, heterociclilcarbonilo, heterociclitioalquilo, heterociclilsulfoxidoalquilo, heterociclilsulfonilalquilo, heterociclitioalquenilo, heterociclilsulfoxidoalquenilo, heterociclilsulfonilalquenilo, heterociclilsulfonilo, heterociclilcarbonilalquilcarbonilo, heterociclilalquilcarbonilo, heterociclicarbonilalquilcarbonilo, heterociclilsulfonilo, heterociclilcarbonilalquilo, aminoalquilcarbonilo, aminocarbonilo, aminocarbonilalquilcarbonilo, aminosulfonilo, aminosulfonilalquilo, aminoalquilo, aminocarbonilalquilo, y aminoalquilsulfonilo, donde

cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido.

325. Un compuesto o sal del mismo de acuerdo con la cláusula 324, en el cual un átomo de E^2 está unido a un átomo de E^5 para formar un anillo.

1363

326. Un compuesto o sal del mismo de acuerdo con la cláusula 325, en el cual el compuesto corresponde en estructura a la siguiente fórmula:



(326-1).

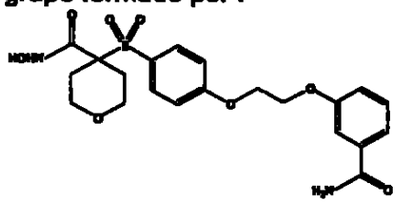
327. Un compuesto o sal del mismo de acuerdo con la cláusula 324, en el cual

E^5 es fenilo sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por -OH, $-NO_2$, -CN, $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbociclilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo, carbociclil-C_1-C_6-alquilo sustituido con halógeno, heterociclilo, haloheterociclilo, heterociclil-C_1-C_6-alquilo, y heterociclil-C_1-C_6-alquilo sustituido con halógeno; y

E^2 no está unido a un átomo de E^5 para formar un anillo.

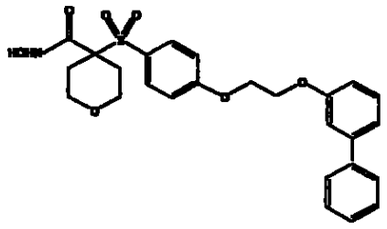
328. Un compuesto o sal del mismo de acuerdo con la cláusula 327, en el cual E^4 es un enlace.

329. Un compuesto o sal del mismo de acuerdo con la cláusula 328, en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



(329-1)

y



(329-2).

1364

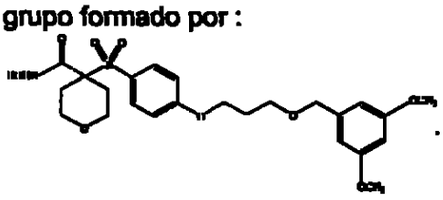
330. Un compuesto o sal del mismo de acuerdo con la cláusula 324, en el cual

E^5 es fenilo sustituido con 2 ó más sustituyentes seleccionados independientemente del grupo formado por halógeno, -OH, $-NO_2$, -CN, C_1-C_6-alquilo, halo-C_1-C_6-alquilo, C_1-C_6-alcoxi, halo-C_1-C_6-alcoxi, $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbociclilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo, carbociclil-C_1-C_6-alquilo sustituido con halógeno, heterociclilo, haloheterociclilo, heterociclil-C_1-C_6-alquilo, y heterociclil-C_1-C_6-alquilo sustituido con halógeno; y

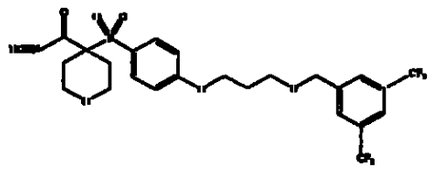
E^2 no está unido a un átomo de E^5 para formar un anillo.

331. Un compuesto o sal del mismo de acuerdo con la cláusula 330, en el cual E^4 es metilo.

332. Un compuesto o sal del mismo de acuerdo con la cláusula 331, en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



y



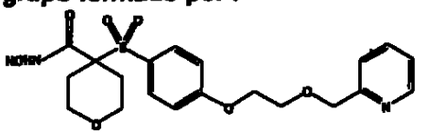
(332-1) (332-2).

333. Un compuesto o sal del mismo de acuerdo con la cláusula 324, en el cual E^5 es heterociclilo optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, -CN, C_1-C_6-alquilo, halo-C_1-C_6-alquilo, C_1-C_6-alcoxi, halo-C_1-C_6-alcoxi, C_1-

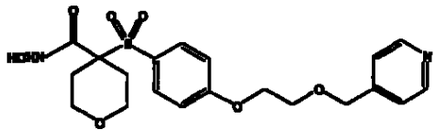
1365

C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbociclilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo, carbociclil-C_1-C_6-alquilo sustituido con halógeno, heterociclilo, haloheterociclilo, heterociclil-C_1-C_6-alquilo, y heterociclil-C_1-C_6-alquilo sustituido con halógeno.

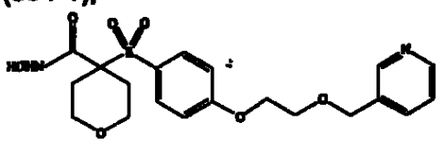
334. Un compuesto o sal del mismo de acuerdo con la cláusula 333, en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



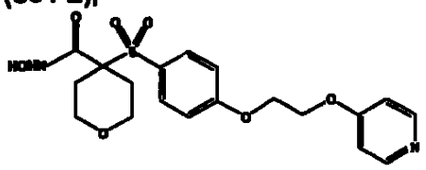
(334-1),



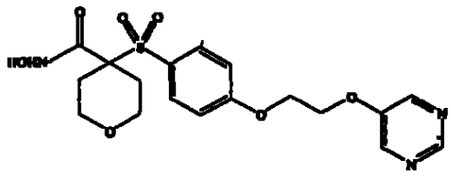
(334-2),



(334-3),



(334-4), y

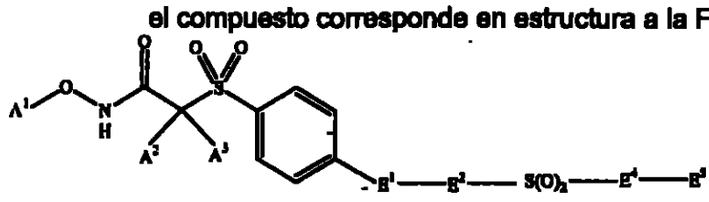


(334-5).

1366

335. Un compuesto o sal del mismo, en el cual

el compuesto corresponde en estructura a la Fórmula 335-1:



(335-1); y

A^1 se selecciona del grupo formado por -H, alquilcarbonilo, alcoxicarbonilo, carbociclilcarbonilo, carbociclilalquilcarbonilo, heterociclilcarbonilo, heterociclilalquilcarbonilo, carbocicliloxicarbonilo, carbociclilalcoxicarbonilo, aminoalquilcarbonilo, alquil(tiocarbonilo), alcoxi(tiocarbonilo), carbociclil(tiocarbonilo), carbociclilalquil(tiocarbonilo), heterociclil(tiocarbonilo), heterociclilalquil(tiocarbonilo), carbociclil oxi(tiocarbonilo), carbociclilalcoxi(tiocarbonilo), y aminoalquil(tiocarbonilo), donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido; y

A^2 y A^3, junto con el átomo de carbono al cual ambos están unidos, forman un heterociclilo optativamente sustituido que contiene entre 5 y 8 miembros en el anillo; y

E^1 se selecciona del grupo formado por $-S(O)_2-$, -S(O)-, $-N(R^1)-$, $-C(O)-N(R^1)-$, $-N(R^1)-C(O)-$, y $-C(R^1)(R^2)-$; y

E^2 se selecciona del grupo formado por alquilo, cicloalquilo, alquilcicloalquilo, cicloalquilalquilo, y alquilcicloalquilalquilo, donde cualquier miembro de dicho grupo es optativamente sustituido; y

E^4 se selecciona del grupo formado por un enlace, alquilo, y alquenilo, donde el alquilo o alquenilo es optativamente sustituido; y

E^5 se selecciona del grupo formado por alquilo, alquenilo, alquinilo, alcoxi, alcoxialquilo, carbociclilo, y heterociclilo, donde cualquier miembro de dicho grupo es optativamente sustituido; y

R^1 y R^2 se seleccionan independientemente del grupo formado por -H y alquilo, donde el alquilo es optativamente sustituido; y

ni R^1 ni R^2 forman una estructura de anillo con E^2, E^4, o E^5

336. Un compuesto o sal del mismo de acuerdo con la cláusula 335, en el cual

A^1 se selecciona del grupo formado por -H, C_1-C_8-alquilcarbonilo, C_1-C_8-alcoxicarbonilo, carbociclilcarbonilo, carbociclil-C_1-C_8-alquilcarbonilo, heterociclilcarbonilo, heterociclil-C_1-C_8-alquilcarbonilo, carbocicliloxicarbonilo, carbociclil-C_1-C_8-alcoxicarbonilo, $N(R^3)(R^4)$-C_1-C_8-alquilcarbonilo, C_1-C_8-alquil(tiocarbonilo), C_1-C_8-alcoxi(tiocarbonilo), carbociclil(tiocarbonilo), carbociclil-C_1-C_8-alquil(tiocarbonilo), heterociclil(tiocarbonilo), heterociclil-C_1-C_8-alquil(tiocarbonilo), carbociclil(oxi(tiocarbonilo), carbociclil-C_1-C_8-alcoxi(tiocarbonilo), y $N(R^3)(R^4)$-C_1-C_8-alquil(tiocarbonilo); y

E^2 se selecciona del grupo formado por C_1-C_{20}-alquilo, cicloalquilo, C_1-C_{10}-alquilcicloalquilo, cicloalquil-C_1-C_{10}-alquilo, y C_1-C_{10}-alquilcicloalquil-C_1-C_{10}-alquilo, donde cualquier miembro de dicho grupo es optativamente sustituido con uno o más sustituyentes seleccionados del grupo formado por halógeno, C_1-C_8-alquilo, y halo-C_1-C_8-alquilo; y

E^4 se selecciona del grupo formado por un enlace, C_1-C_{20}-alquilo, halo-C_1-C_{20}-alquilo, C_2-C_{20}-alquenilo, y halo-C_2-C_{20}-alquenilo; y

1368

E^5 se selecciona del grupo formado por C_1-C_{20}-alquilo, C_2-C_{20}-alquenilo, C_2-C_{20}-alquinilo, C_1-C_{20}-alcoxi, C_1-C_{20}-alcoxi-C_1-C_{20}-alquilo, carbociclilo, y heterociclilo, donde

el C_1-C_{20}-alquilo, C_2-C_{20}-alquenilo, C_2-C_{20}-alquinilo, C_1-C_{20}-alcoxi, o C_1-C_{20}-alcoxi-C_1-C_{20}-alquilo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, y -CN, y

el carbociclilo o heterociclilo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_8-alquilo, halo-C_1-C_8-alquilo, C_1-C_8-alcoxi, halo-C_1-C_8-alcoxi, -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbociclilo, halocarbociclilo, carbociclil-C_1-C_8-alquilo, y carbociclil-C_1-C_8-alquilo sustituido con halógeno; y

R^1 y R^2 se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, y halo-C_1-C_8-alquilo; y

R^3 y R^4 se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, C_1-C_8-alcoxicarbonilo, C_1-C_8-alquilcarbonilo, carbociclil-C_1-C_8-alquilo, y carbociclil-C_1-C_8-alcoxicarbonilo; y

R^5 y R^6 se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, carbociclilo, carbociclil-C_1-C_8-alquilo, heterociclilo, y heterociclil-C_1-C_8-alquilo, donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido con uno o más halógenos; y

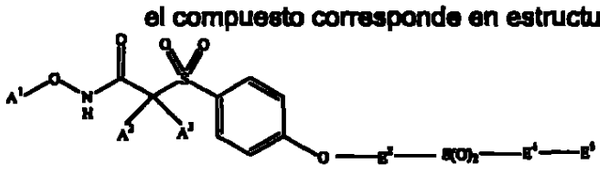
R^7 se selecciona del grupo formado por -H, C_1-C_8-alquilo, -O-R^8, -$N(R^8)(R^9)$, carbociclil-C_1-C_8-alquilo, y heterociclil-C_1-C_8-alquilo, donde el C_1-C_8-

alquilo, carbociclil-C_1-C_8-alquilo, o heterociclil-C_1-C_8-alquilo es optativamente sustituido con uno o más halógenos; y

R^8 y R^9 se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, carbociclilo, carbociclil-C_1-C_8-alquilo, heterociclilo, y heterociclil-C_1-C_8-alquilo, donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido con uno o más halógenos.

337. Un compuesto o sal del mismo, en el cual

el compuesto corresponde en estructura a la Fórmula 337-1:



(337-1); y

A^1 se selecciona del grupo formado por -H, alquilcarbonilo, alcoxicarbonilo, carbociclilcarbonilo, carbociclilalquilcarbonilo, heterociclilcarbonilo, heterociclilalquilcarbonilo, carbociclioxicarbonilo, carbociclilalcoxicarbonilo, aminoalquilcarbonilo, alquil(tiocarbonilo), alcoxi(tiocarbonilo), carbociclil(tiocarbonilo), carbociclilalquil(tiocarbonilo), heterociclil(tiocarbonilo), heterociclilalquil(tiocarbonilo), carbociclioxi(tiocarbonilo), carbociclilalcoxi(tiocarbonilo), y aminoalquil(tiocarbonilo), donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido; y

A^2 y A^3, junto con el átomo de carbono al cual ambos están unidos, forman un heterociclilo optativamente sustituido que contiene entre 5 y 8 miembros en el anillo; y

1370

E^2 se selecciona del grupo formado por alquilo, cicloalquilo, alquilcicloalquilo, cicloalquilalquilo, y alquilcicloalquilalquilo, donde cualquier miembro de dicho grupo es optativamente sustituido; y

E^4 se selecciona del grupo formado por alquilo y alquenilo, donde el alquilo o alquenilo es optativamente sustituido; y

E^5 se selecciona del grupo formado por -H, alquilo, alquenilo, alquinilo, alcoxi, carbociclilo, y heterociclilo, donde cualquier miembro de dicho grupo es optativamente sustituido.

338. Un compuesto o sal del mismo de acuerdo con la cláusula 337, en el cual

A^1 se selecciona del grupo formado por -H, C_1-C_8-alquilcarbonilo, C_1-C_8-alcoxicarbonilo, carbociclilcarbonilo, carbociclil-C_1-C_8-alquilcarbonilo, heterociclilcarbonilo, heterociclil-C_1-C_8-alquilcarbonilo, carbocicliloxicarbonilo, carbociclil-C_1-C_8-alcoxicarbonilo, $N(R^1)(R^2)$-C_1-C_8-alquilcarbonilo, C_1-C_8-alquil(tiocarbonilo), C_1-C_8-alcoxi(tiocarbonilo), carbociclil(tiocarbonilo), carbociclil-C_1-C_8-alquil(tiocarbonilo), heterociclil(tiocarbonilo), heterociclil-C_1-C_8-alquil(tiocarbonilo), carbocicliloxi(tiocarbonilo), carbociclil-C_1-C_8-alcoxi(tiocarbonilo), y $N(R^1)(R^2)$-C_1-C_8-alquil(tiocarbonilo); y

E^2 se selecciona del grupo formado por C_1-C_{20}-alquilo, cicloalquilo, C_1-C_{10}-alquilcicloalquilo, cicloalquil-C_1-C_{10}-alquilo, y C_1-C_{10}-alquilcicloalquil-C_1-C_{10}-alquilo, donde cualquier miembro de dicho grupo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, C_1-C_6-alquilo, y halo-C_1-C_6-alquilo; y

E^4 se selecciona del grupo formado por C_1-C_{20}-alquilo, halo-C_1-C_{20}-alquilo, C_2-C_{20}-alquenilo, y halo-C_2-C_{20}-alquenilo; y

1371

E^5 se selecciona del grupo formado por -H, C_1-C_{20}-alquilo, C_2-C_{20}-alquenilo, C_2-C_{20}-alquinilo, C_1-C_{20}-alcoxi, carbociclilo, y heterociclilo, donde

el C_1-C_{20}-alquilo, C_2-C_{20}-alquenilo, C_2-C_{20}-alquinilo, o C_1-C_{20}-alcoxi es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, y -CN, y

el carbociclilo o heterociclilo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, -CN, C_1-C_8-alquilo, halo-C_1-C_8-alquilo, C_1-C_8-alcoxi, halo-C_1-C_8-alcoxi, $-N(R^3)(R^4)$, $-C(O)(R^5)$, $-S-R^3$, $-S(O)_2-R^3$, carbociclilo, halocarbociclilo, carbociclil-C_1-C_8-alquilo, y carbociclil-C_1-C_8-alquilo sustituido con halógeno; y

R^1 y R^2 se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, C_1-C_8-alcoxicarbonilo, C_1-C_8-alquilcarbonilo, carbociclil-C_1-C_8-alquilo, y carbociclil-C_1-C_8-alcoxicarbonilo; y

R^3 y R^4 se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, carbociclilo, carbociclil-C_1-C_8-alquilo, heterociclilo, y heterociclil-C_1-C_8-alquilo, donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido con uno o más halógenos; y

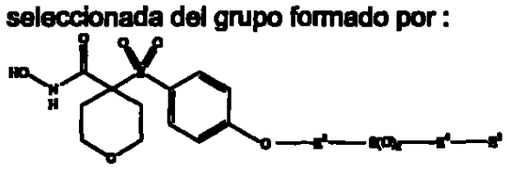
R^5 se selecciona del grupo formado por -H, C_1-C_8-alquilo, $-O-R^6$, $-N(R^6)(R^7)$, carbociclil-C_1-C_8-alquilo, y heterociclil-C_1-C_8-alquilo, donde el C_1-C_8-alquilo, carbociclil-C_1-C_8-alquilo, o heterociclil-C_1-C_8-alquilo es optativamente sustituido con uno o más halógenos; y

R^6 y R^7 se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, carbociclilo, carbociclil-C_1-C_8-alquilo, heterociclilo, y

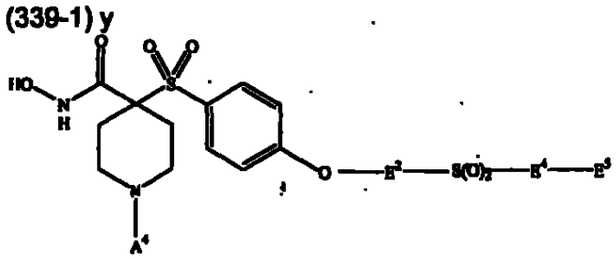
heterociclil-C_1-C_8-alquilo, donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido con uno o más halógenos.

339. Un compuesto o sal del mismo de acuerdo con la cláusula 338, en el cual

el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



(339-1) y



(339-2); y

A^4 se selecciona del grupo formado por -H, alquilo, alquilcarbonilo, alquilcarbonilalquilo, alquilcarbonilalquilcarbonilo, alcoxicarbonilo, alcoxicarbonilalquilo, alcoxicarbonilalquilcarbonilo, alquilsulfonilo, alquiliminocarbonilo, alquenilo, alquinilo, alcoxialquilo, alquiltioalquilo, alquilsulfonilalquilo, alquilsufoxidoalquilo, alquiltioalquenilo, alquilsulfoxidoalquenilo, alquilsulfonilalquenilo, carbociclilo, carbociclilalquilo, carbociclilalcoxialquilo, carbociclilcarbonilo, carbociclilsulfonilo, carbociclliliminocarbonilo, carbociclioxicarbonilo, carbociliitioalquilo, carbocililsulfoxidoalquilo, carbocliilsulfonilalquilo, carbociclitioalquenilo, carbociclilsulfoxidoalquenilo, carbociclilsulfonilalquenilo, heterociclilo, heterociclilalquilo, heterociclilalcoxialquilo, heterociclilcarbonilo,

1373

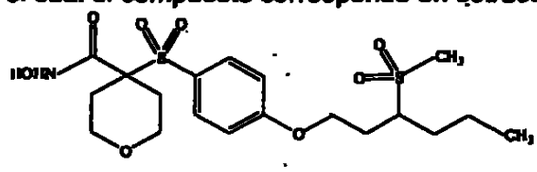
heterocicliltioalquilo, heterociclilsulfoxidoalquilo, heterociclilsulfonilalquilo, heterociclitioalquenilo, heterociclilsulfoxidoalquenilo, heterociclilsulfonilalquenilo, heterociclilsulfonilo, heterociclliminocarbonilo, heterociclilalquilcarbonilo, heterociclilcarbonilalquilcarbonilo, heterociclilsulfonilo, heterociclilcarbonilalquilo, aminoalquilcarbonilo, aminocarbonilo, aminocarbonilalquilcarbonilo, aminosulfonilo, aminosulfonilalquilo, aminoalquilo, aminocarbonilalquilo, y aminoalquilsulfonilo, donde

cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido.

340. Un compuesto o sal del mismo de acuerdo con la cláusula 339, en el cual E^5 se selecciona del grupo formado por -H, C_1-C_6-alquilo, C_2-C_6-alquenilo, C_2-C_6-alquinilo, y C_1-C_6-alcoxi, en el cual

el C_1-C_6-alquilo, C_2-C_6-alquenilo, C_2-C_6-alquinilo, o C_1-C_6-alcoxi es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, y -CN.

341. Un compuesto o sal del mismo de acuerdo con la cláusula 340, en el cual el compuesto corresponde en estructura a la siguiente fórmula:



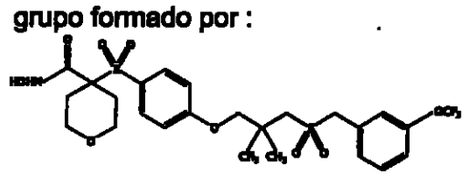
(341-1).

342. Un compuesto o sal del mismo de acuerdo con la cláusula 339, en el cual E^5 es fenilo optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -

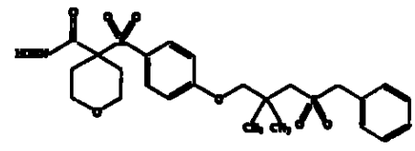
1374

NO_2, -CN, C_1-C_6-alquilo, halo-C_1-C_6-alquilo, C_1-C_6-alcoxi, halo-C_1-C_6-alcoxi, -$N(R^3)(R^4)$, -$C(O)(R^5)$, -S-R^3, -$S(O)_2$-R^3, carbociclilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo, y carbociclil-C_1-C_6-alquilo sustituido con halógeno.

343. Un compuesto o sal del mismo de acuerdo con la cláusula 342, en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



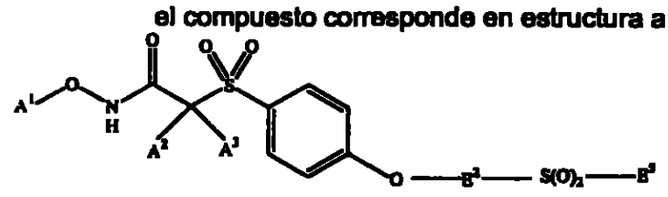
y



(343-1) (343-2).

344. Un compuesto o sal del mismo, en el cual

el compuesto corresponde en estructura a la Fórmula 344-1:



(344-1); y

A^1 se selecciona del grupo formado por -H, alquilcarbonilo, alcoxicarbonilo, carbociclilcarbonilo, carbociclilalquilcarbonilo, heterociclilcarbonilo, heterociclilalquilcarbonilo, carbocicliloxicarbonilo, carbociclilalcoxicarbonilo, aminoalquilcarbonilo, alquil(tiocarbonilo), alcoxi(tiocarbonilo), carbociclil(tiocarbonilo), carbociclilalquil(tiocarbonilo), heterociclil(tiocarbonilo), heterociclilalquil(tiocarbonilo), carbociclíloxi(tiocarbonilo), carbociclilalcoxi(tiocarbonilo), y aminoalquil(tiocarbonilo), donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido; y

1375

A^2 y A^3, junto con el átomo de carbono al cual ambos están unidos, forman un heterociclilo optativamente sustituido que contiene entre 5 y 8 miembros en el anillo; y

E^2 se selecciona del grupo formado por alquilo, cicloalquilo, alquilcicloalquilo, cicloalquilalquilo, y alquilcicloalquilalquilo, donde cualquier miembro de dicho grupo es optativamente sustituido; y

E^2 contiene menos de 5 átomos de carbono; y

E^5 se selecciona del grupo formado por alquilo, alquenilo, alquinilo, alcoxialquilo, carbociclilo, y heterociclilo, donde cualquier miembro de dicho grupo es optativamente sustituido.

345. Un compuesto o sal del mismo de acuerdo con la cláusula 344, en el cual

A^1 se selecciona del grupo formado por -H, C_1-C_8-alquilcarbonilo, C_1-C_8-alcoxicarbonilo, carbociclilcarbonilo, carbociclil-C_1-C_8-alquilcarbonilo, heterociclilcarbonilo, heterociclil-C_1-C_8-alquilcarbonilo, carbocicliloxicarbonilo, carbociclil-C_1-C_8-alcoxicarbonilo, $N(R^1)(R^2)$-C_1-C_8-alquilcarbonilo, C_1-C_8-alquil(tiocarbonilo); C_1-C_8-alcoxi(tiocarbonilo), carbociclil(tiocarbonilo), carbociclil-C_1-C_8-alquil(tiocarbonilo), heterociclil(tiocarbonilo), heterociclil-C_1-C_8-alquil(tiocarbonilo), carbocicliloxi(tiocarbonilo), carbociclil-C_1-C_8-alcoxi(tiocarbonilo), y $N(R^1)(R^2)$-C_1-C_8-alquil(tiocarbonilo); y

E^5 se selecciona del grupo formado por C_1-C_{20}-alquilo, C_2-C_{20}-alquenilo, C_2-C_{20}-alquinilo, C_1-C_{20}-alcoxi-C_1-C_{20}-alquilo, carbociclilo, y heterociclilo, donde

el C_1-C_{20}-alquilo, C_2-C_{20}-alquenilo, C_2-C_{20}-alquinilo, o C_1-C_{20}-alcoxi-C_1-C_{20}-alquilo es optativamente sustituido con uno o más sustituyentes

1376

independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, y -CN, y

el carbociclilo o heterociclilo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, ceto, C_1-C_8-alquilo, halo-C_1-C_8-alquilo, C_1-C_8-alcoxi, halo-C_1-C_8-alcoxi, C_1-C_8-alcoxi-C_1-C_8-alquilo, C_1-C_8-alcoxi-C_1-C_8-alquilo sustituido con halógeno , -$N(R^3)(R^4)$, -$C(O)(R^5)$, -S-R^3, -$S(O)_2$-R^3, carbociclilo, halocarbociclilo, carbociclil-C_1-C_8-alquilo, carbociclil-C_1-C_8-alquilo sustituido con halógeno, C_1-C_8-alquilcarbocicliloxi, y C_1-C_8-alquilcarbociclilo sustituido con halógeno; y

R^1 y R^2 se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, C_1-C_8-alcoxicarbonilo, C_1-C_8-alquilcarbonilo, carbociclil-C_1-C_8-alquilo, y carbociclil-C_1-C_8-alcoxicarbonilo; y

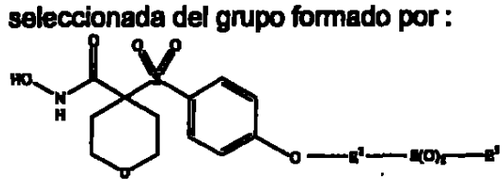
R^3 y R^4 se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, carbociclilo, carbociclil-C_1-C_8-alquilo, heterociclilo, y heterociclil-C_1-C_8-alquilo, donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido con uno o más halógenos; y

R^5 se selecciona del grupo formado por -H, C_1-C_8-alquilo, -O-R^6, -$N(R^6)(R^7)$, carbociclil-C_1-C_8-alquilo, y heterociclil-C_1-C_8-alquilo, donde el C_1-C_8-alquilo, carbociclil-C_1-C_8-alquilo, o heterociclil-C_1-C_8-alquilo es optativamente sustituido con uno o más halógenos; y

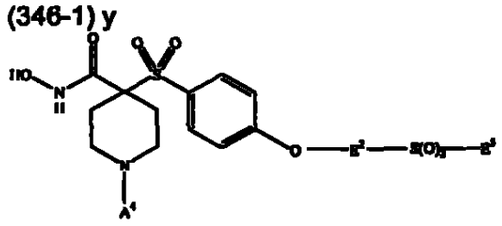
R^6 y R^7 se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, carbociclilo, carbociclil-C_1-C_8-alquilo, heterociclilo, y heterociclil-C_1-C_8-alquilo, donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido con uno o más halógenos.

346. Un compuesto o sal del mismo de acuerdo con la cláusula 345, en el cual

el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



(346-1) y



(346-2); y

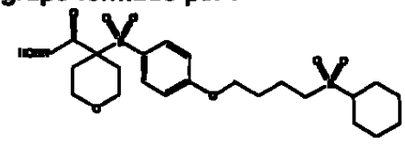
A^4 se selecciona del grupo formado por -H, alquilo, alquilcarbonilo, alquilcarbonilalquilo, alquilcarbonilalquilcarbonilo, alcoxicarbonilo, alcoxicarbonilalquilo, alcoxicarbonilalquilcarbonilo, alquilsulfonilo, alquiliminocarbonilo, alquenilo, alquinilo, alcoxialquilo, alquiltioalquilo, alquilsulfonilalquilo, alquilsufoxidoalquilo, alquiltioalquenilo, alquilsulfoxidoalquenilo, alquilsulfonilalquenilo, carbociclilo, carbociclilalquilo, carbociclilalcoxialquilo, carbociclilcarbonilo, carbociclilsulfonilo, carbociclliminocarbonilo, carbocicliloxicarbonilo, carbocililtioalquilo, carbocililsulfoxidoalquilo, carbocililsulfonilalquilo, carbociclitioalquenilo, carbociclilsulfoxidoalquenilo, carbociclilsulfonilalquenilo, heterociclilo, heterociclilalquilo, heterociclilalcoxialquilo, heterociclilcarbonilo, heterocicliltioalquilo, heterociclilsulfoxidoalquilo, heterociclilsulfonilalquilo, heterocicliltioalquenilo, heterociclilsulfoxidoalquenilo,

heterociclilsulfonilalquenilo, heterociclilsulfonilo, heterociclilliminocarbonilo, heterociclilalquilcarbonilo, heterociclilcarbonilalquilcarbonilo, heterociclilsulfonilo, heterociclilcarbonilalquilo, aminoalquilcarbonilo, aminocarbonilo, aminocarbonilalquilcarbonilo, aminosulfonilo, aminosulfonilalquilo, aminoalquilo, aminocarbonilalquilo, y aminoalquilsulfonilo, donde

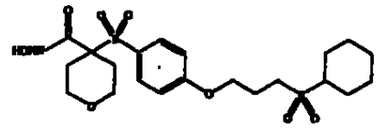
cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido.

347. Un compuesto o sal del mismo de acuerdo con la cláusula 346, en el cual E^5 es C_3-C_6-cicloalquilo optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, ceto, C_1-C_6-alquilo, halo-C_1-C_6-alquilo, C_1-C_6-alcoxi, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, -$N(R^3)(R^4)$, -$C(O)(R^5)$, -S-R^3, -$S(O)_2$-R^3, carbociclilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo, carbociclil-C_1-C_6-alquilo sustituido con halógeno, C_1-C_6-alquilcarbocicliloxi, y halógeno-sustituido C_1-C_6-alquilcarbocicliloxi.

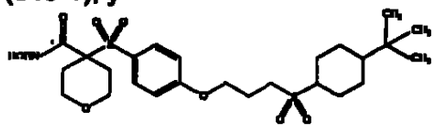
348. Un compuesto o sal del mismo de acuerdo con la cláusula 347, en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



(348-1),



(348-2), y

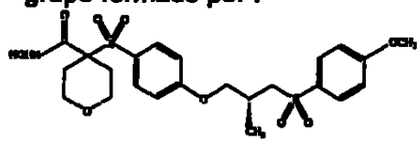


1379

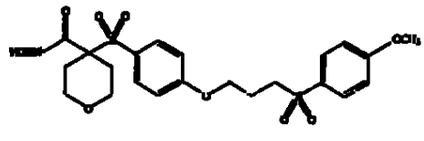
(348-3).

349. Un compuesto o sal del mismo de acuerdo con la cláusula 346, en el cual E^5 es fenilo optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_6-alquilo, halo-C_1-C_6-alquilo, C_1-C_6-alcoxi, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, -$N(R^3)(R^4)$, -$C(O)(R^5)$, -S-R^3, -$S(O)_z$-R^3, carbociclilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo, carbociclil-C_1-C_6-alquilo sustituido con halógeno, C_1-C_6-alquilcarbocicliloxi, y halógeno-sustituido C_1-C_6-alquilcarbocicliloxi.

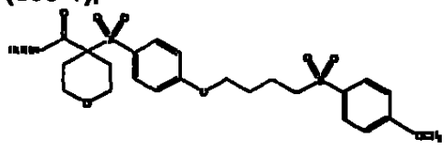
350. Un compuesto o sal del mismo de acuerdo con la cláusula 349, en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



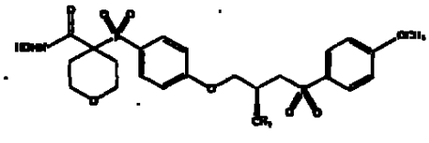
(350-1),



(350-2),



(350-3), y



(350-4).

351. Un compuesto o sal del mismo de acuerdo con la cláusula 346, en el cual E^5 se selecciona del grupo formado por furanilo, tetrahidropiranilo, dihidrofuranilo, tetrahidrofuranilo, tiofenilo, dihidrotiofenilo, tetrahidrotiofenilo, pirrolilo, isopirrolilo, pirrolinilo, pirrolidinilo, imidazolilo, isoimidazolilo,

1380

imidazolinilo, imidazolidinilo, pirazolilo, pirazolinilo, pirazolidinilo, triazolilo, tetrazolilo, ditiolilo, oxatiolilo, oxazolilo, isoxazolilo, oxazolidinilo, isoxazolidinilo, tiazolilo, isotiazolilo, tiazolinilo, isotiazolinilo, tiazolidinilo, isotiazolidinilo, tiodiazolilo, oxatiazolilo, oxadiazolilo, oxatriazolilo, dioxazolilo, oxatiazolilo, oxatiolilo, oxatiolanilo, piranilo, dihidropiranilo, piridinilo, piperidinilo, diazinilo, piperazinilo, triazinilo, oxazinilo, isoxazinilo, oxatiazinilo, oxadiazinilo, morfolinilo, azepinilo, oxepinilo, tiepinilo, diazepinilo, indolizinilo, pirindinilo, piranopirrolilo, 4H-quinolizinilo, purinilo, naftiridinilo, piridopiridinilo, pteridinilo, indolilo, isoindolilo, indoleninilo, isoindazolilo, benzazinilo, ftalazinilo, quinoxalinilo, quinazolinilo, benzodiazinilo, benzopiranilo, benzotiopiranilo, benzoxazolilo, indoxazinilo, antranililo, benzodioxolilo, benzodioxanilo, benzoxadiazolilo, benzofuranilo, isobenzofuranilo, benzotienilo, isobenzotienilo, benzotiazolilo, benzotiadiazolilo, bencimidazolilo, benzotriazolilo, benzoxazinilo, bencisoxazinilo, tetrahidroisoquinolinilo, carbazolilo, xantenilo, y acridinilo, donde un miembro de dicho grupo:

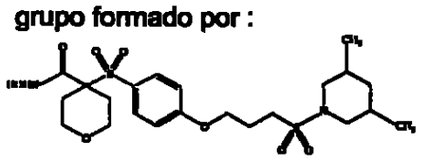
es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, ceto, C_1-C_6-alquilo, halo-C_1-C_6-alquilo, C_1-C_6-alcoxi, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, -$N(R^3)(R^4)$, -$C(O)(R^5)$, -S-R^3, -$S(O)_2$-R^3, carbociclilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo, carbociclil-C_1-C_6-alquilo sustituido con halógeno, C_1-C_6-alquilcarbocicliloxi, y halógeno-sustituido C_1-C_6-alquilcarbocicliloxi.

352. Un compuesto o sal del mismo de acuerdo con la cláusula 351, en el cual E^5 se selecciona del grupo formado por piperidinilo, morfolinilo, y tetrahidroisoquinolinilo, donde un miembro de dicho grupo:

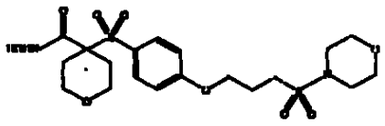
1381

es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, ceto, C_1-C_6-alquilo, halo-C_1-C_6-alquilo, C_1-C_6-alcoxi, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, -$N(R^3)(R^4)$, -$C(O)(R^5)$, -S-R^3, -$S(O)_2$-R^3, carbociclilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo, carbociclil-C_1-C_6-alquilo sustituido con halógeno, C_1-C_6-alquilcarbociciloxi, y halógeno-sustituido C_1-C_6-alquilcarbociciloxi.

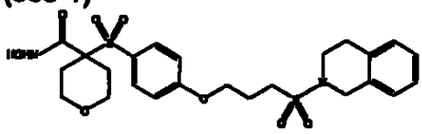
353. Un compuesto o sal del mismo de acuerdo con la cláusula 352, en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



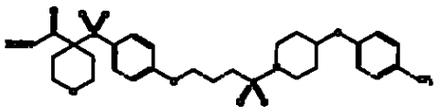
(353-1)



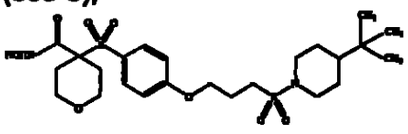
(353-2),



(353-3),



(353-4), y

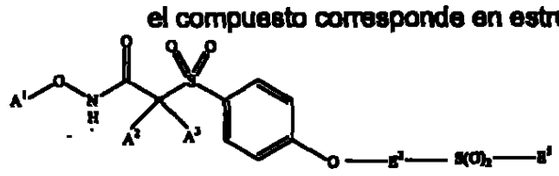


(353-5).

1382 XY

354. Un compuesto o sal del mismo, en el cual

el compuesto corresponde en estructura a la Fórmula 354-1:



(354-1); y

A^1 se selecciona del grupo formado por -H, alquilcarbonilo, alcoxicarbonilo, carbociclilcarbonilo, carbociclilalquilcarbonilo, heterociclilcarbonilo, heterociclilalquilcarbonilo, carbocicliloxicarbonilo, carbociclilalcoxicarbonilo, aminoalquilcarbonilo, alquil(tiocarbonilo), alcoxi(tiocarbonilo), carbociclil(tiocarbonilo), carbociclilalquil(tiocarbonilo), heterociclil(tiocarbonilo), heterociclilalquil(tiocarbonilo), carbociclioxi(tiocarbonilo), carbociclilalcoxi(tiocarbonilo), y aminoalquil(tiocarbonilo), donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido; y

A^2 y A^3, junto con el átomo de carbono al cual ambos están unidos, forman un heterociclilo optativamente sustituido que contiene entre 5 y 8 miembros en el anillo; y

E^2 se selecciona del grupo formado por alquilo, cicloalquilo, alquilcicloalquilo, cicloalquilalquilo, y alquilcicloalquilalquilo, donde cualquier miembro de dicho grupo es optativamente sustituido; y

E^5 se selecciona del grupo formado por alquilo, alquenilo, alquinilo, alcoxialquilo, carbociclilo saturado, carbociclilo parcialmente saturado, y heterociclilo, donde cualquier miembro de dicho grupo es optativamente sustituido.

1383

355. Un compuesto o sal del mismo de acuerdo con la cláusula 354, en el cual

A^1 se selecciona del grupo formado por -H, C_1-C_8-alquilcarbonilo, C_1-C_8-alcoxicarbonilo, carbociclilcarbonilo, carbociclil-C_1-C_8-alquilcarbonilo, heterociclilcarbonilo, heterociclil-C_1-C_8-alquilcarbonilo, carbociclíloxicarbonilo, carbociclil-C_1-C_8-alcoxicarbonilo, $N(R^1)(R^2)$-C_1-C_8-alquilcarbonilo, C_1-C_8-alquil(tiocarbonilo), C_1-C_8-alcoxi(tiocarbonilo), carbociclil(tiocarbonilo), carbociclil-C_1-C_8-alquil(tiocarbonilo), heterociclil(tiocarbonilo), heterociclil-C_1-C_8-alquil(tiocarbonilo), carbociclíloxi(tiocarbonilo), carbociclil-C_1-C_8-alcoxi(tiocarbonilo), y $N(R^1)(R^2)$-C_1-C_8-alquil(tiocarbonilo); y

E^2 se selecciona del grupo formado por C_1-C_{20}-alquilo, cicloalquilo, C_1-C_{10}-alquilcicloalquilo, cicloalquil-C_1-C_{10}-alquilo, y C_1-C_{10}-alquilcicloalquil-C_1-C_{10}-alquilo, donde cualquier miembro de dicho grupo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, C_1-C_6-alquilo, halo-C_1-C_6-alquilo; y

E^5 se selecciona del grupo formado por C_1-C_{20}-alquilo, C_2-C_{20}-alquenilo, C_2-C_{20}-alquinilo, C_1-C_{20}-alcoxi-C_1-C_{20}-alquilo, carbociclilo saturado, carbociclilo parcialmente saturado, y heterociclilo, donde

el C_1-C_{20}-alquilo, C_2-C_{20}-alquenilo, C_2-C_{20}-alquinilo, o C_1-C_{20}-alcoxi-C_1-C_{20}-alquilo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, y -CN, y

el carbociclilo saturado, carbociclilo parcialmente saturado, o heterociclilo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -

1384

NO_2, -CN, C_1-C_8-alquilo, halo-C_1-C_8-alquilo, C_1-C_8-alcoxi, halo-C_1-C_8-alcoxi, C_1-C_8-alcoxi-C_1-C_8-alquilo, C_1-C_8-alcoxi-C_1-C_8-alquilo sustituido con halógeno , -$N(R^3)(R^4)$, -$C(O)(R^5)$, -S-R^3, -$S(O)_2$-R^3, carbociclilo, halocarbociclilo, carbociclil-C_1-C_8-alquilo, carbociclil-C_1-C_8-alquilo sustituido con halógeno, C_1-C_8-alquilcarbocicliloxi, y C_1-C_8-alquilcarbociclilo sustituido con halógeno; y

R^1 y R^2 se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, C_1-C_8-alcoxicarbonilo, C_1-C_8-alquilcarbonilo, carbociclil-C_1-C_8-alquilo, y carbociclil-C_1-C_8-alcoxicarbonilo; y

R^3 y R^4 se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, carbociclilo, carbociclil-C_1-C_8-alquilo, heterociclilo, y heterociclil-C_1-C_8-alquilo, donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido con uno o más halógenos; y

R^5 se selecciona del grupo formado por -H, C_1-C_8-alquilo, -O-R^6, -$N(R^6)(R^7)$, carbociclil-C_1-C_8-alquilo, y heterociclil-C_1-C_8-alquilo, donde el C_1-C_8-alquilo, carbociclil-C_1-C_8-alquilo, o heterociclil-C_1-C_8-alquilo es optativamente sustituido con uno o más halógenos; y

R^6 y R^7 se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, carbociclilo, carbociclil-C_1-C_8-alquilo, heterociclilo, y heterociclil-C_1-C_8-alquilo, donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido con uno o más halógenos.

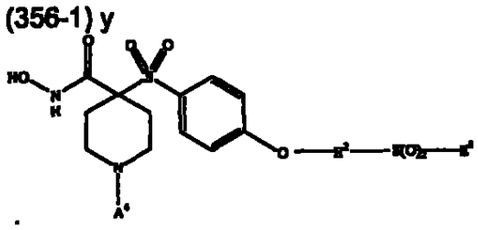
1385

356. Un compuesto o sal del mismo de acuerdo con la cláusula 355, en el cual

el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



(356-1) y



(356-2); y

A^4 se selecciona del grupo formado por -H, alquilo, alquilcarbonilo, alquilcarbonilalquilo, alquilcarbonilalquilcarbonilo, alcoxicarbonilo, alcoxicarbonilalquilo, alcoxicarbonilalquilcarbonilo, alquilsulfonilo, alquiliminocarbonilo, alquenilo, alquinilo, alcoxialquilo, alquiltioalquilo, alquilsulfonilalquilo, alquilsufoxidoalquilo, alquiltioalquenilo, alquilsulfoxidoalquenilo, alquilsulfonilalquenilo, carbociclilo, carbociclilalquilo, carbociclilalcoxialquilo, carbociclilcarbonilo, carbociclilsulfonilo, carbociclilliminocarbonilo, carbociclioxicarbonilo, carbociliitioalquilo, carbocililsulfoxidoalquilo, carbocililsulfonilalquilo, carbociclitioalquenilo, carbociclilsulfoxidoalquenilo, carbociclilsulfonilalquenilo, heterociclilo, heterociclilalquilo, heterociclilalcoxialquilo, heterociclilcarbonilo, heterociclitioalquilo, heterociclilsulfoxidoalquilo, heterociclilsulfonilalquilo, heterociclitioalquenilo, heterociclilsulfoxidoalquenilo,

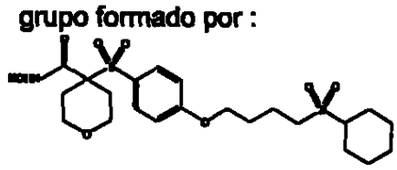
1386

heterociclilsulfonilalquenilo, heterociclilsulfonilo, heterociclliliminocarbonilo, heterociclilalquilcarbonilo, heterociclilcarbonilalquilcarbonilo, heterociclilsulfonilo, heterociclilcarbonilalquilo, aminoalquilcarbonilo, aminocarbonilo, aminocarbonilalquilcarbonilo, aminosulfonilo, aminosulfonilalquilo, aminoalquilo, aminocarbonilalquilo, y aminoalquilsulfonilo, donde

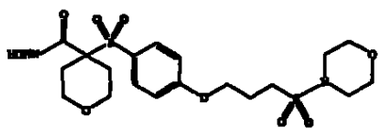
cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido.

357. Un compuesto o sal del mismo de acuerdo con la cláusula 356, en el cual E^5 es heterociclilo optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_6-alquilo, halo-C_1-C_6-alquilo, C_1-C_6-alcoxi, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, -$N(R^3)(R^4)$, -$C(O)(R^5)$, -S-R^3, -$S(O)_2$-R^3, carbociclilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo, carbociclil-C_1-C_6-alquilo sustituido con halógeno, C_1-C_6-alquilcarbocicliloxi, y halógeno-sustituido C_1-C_6-alquilcarbocicliloxi.

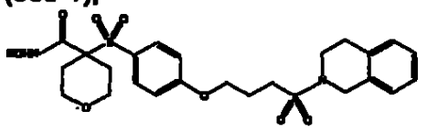
358. Un compuesto o sal del mismo de acuerdo con la cláusula 357, en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



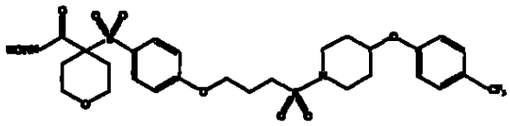
(358-1),



(358-2),

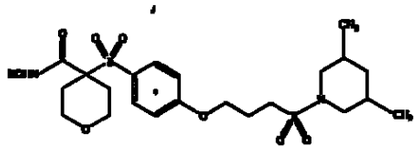


(358-3),

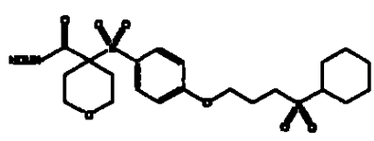


(358-4),

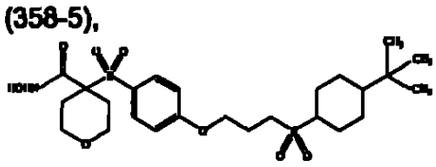
1387



(358-5),



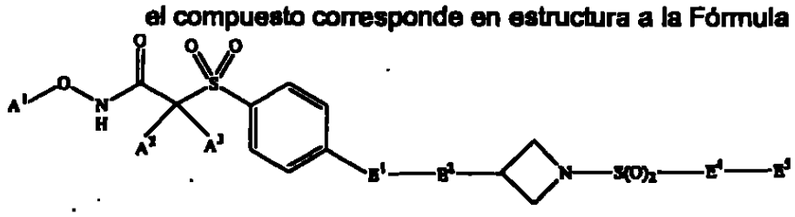
(358-6), y



(358-7).

359. Un compuesto o sal del mismo, en el cual

el compuesto corresponde en estructura a la Fórmula 359-1:



(359-1); y

A^1 se selecciona del grupo formado por -H, alquilcarbonilo, alcoxicarbonilo, carbociclilcarbonilo, carbociclilalquilcarbonilo, heterociclilcarbonilo, heterociclilalquilcarbonilo, carbocicliloxicarbonilo, carbociclilalcoxicarbonilo, aminoalquilcarbonilo, alquil(tiocarbonilo), alcoxi(tiocarbonilo), carbociclil(tiocarbonilo), carbociclilalquil(tiocarbonilo), heterociclil(tiocarbonilo), heterociclilalquil(tiocarbonilo), carbociclilloxi(tiocarbonilo), carbociclilalcoxi(tiocarbonilo), y aminoalquil(tiocarbonilo), donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido; y

1368

A^2 y A^3, junto con el átomo de carbono al cual ambos están unidos, forman un heterociclilo optativamente sustituido que contiene entre 5 y 8 miembros en el anillo; y

E^1 se selecciona del grupo formado por $-S(O)_2-$, -S(O)-, $-N(R^1)-$, $-C(O)-N(R^1)-$, $-N(R^1)-C(O)-$, y $-C(R^1)(R^2)-$; y

E^2 se selecciona del grupo formado por alquilo, cicloalquilo, alquilcicloalquilo, cicloalquilalquilo, y alquilcicloalquilalquilo, donde cualquier miembro de dicho grupo es optativamente sustituido; y

E^4 se selecciona del grupo formado por un enlace, alquilo, y alquenilo, donde el alquilo o alquenilo es optativamente sustituido; y

E^5 se selecciona del grupo formado por alquilo, alquenilo, alquinilo, alcoxi, alcoxialquilo, carbociclilo, y heterociclilo, donde cualquier miembro de dicho grupo es optativamente sustituido; y

R^1 y R^2 se seleccionan independientemente del grupo formado por -H y alquilo, donde el alquilo es optativamente sustituido; y

ni R^1 ni R^2 forman una estructura de anillo con E^2, E^4, o E^5.

360. Un compuesto o sal del mismo de acuerdo con la cláusula 359, en el cual

A^1 se selecciona del grupo formado por -H, C_1-C_8-alquilcarbonilo, C_1-C_8-alcoxicarbonilo, carbociclilcarbonilo, carbociclil-C_1-C_8-alquilcarbonilo, heterociclilcarbonilo, heterociclil-C_1-C_8-alquilcarbonilo, carbocicliloxicarbonilo, carbociclil-C_1-C_8-alcoxicarbonilo, . $N(R^3)(R^4)$-C_1-C_8-alquilcarbonilo, C_1-C_8-alquil(tiocarbonilo), C_1-C_8-alcoxi(tiocarbonilo), carbociclil(tiocarbonilo), carbociclil-C_1-C_8-alquil(tiocarbonilo), heterociclil(tiocarbonilo), heterociclil-C_1-

1389

C_8-alquil(tiocarbonilo), carbocicliloxi(tiocarbonilo), carbociclil-C_1-C_8-alcoxi(tiocarbonilo), y $N(R^3)(R^4)$-C_1-C_8-alquil(tiocarbonilo); y

E^2 se selecciona del grupo formado por C_1-C_{20}-alquilo, cicloalquilo, C_1-C_{10}-alquilcicloalquilo, cicloalquil-C_1-C_{10}-alquilo, y C_1-C_{10}-alquilcicloalquil-C_1-C_{10}-alquilo,. donde cualquier miembro de dicho grupo es optativamente sustituido con uno o más halógenos; y

E^4 se selecciona del grupo formado por un enlace, C_1-C_{20}-alquilo, halo-C_1-C_{20}-alquilo, C_2-C_{20}-alquenilo, y halo-C_2-C_{20}-alquenilo; y

E^5 se selecciona del grupo formado por C_1-C_{20}-alquilo, C_2-C_{20}-alquenilo, C_2-C_{20}-alquinilo, C_1-C_{20}-alcoxi, C_1-C_{20}-alcoxi-C_1-C_{20}-alquilo, carbociclilo, y heterociclilo, donde

el C_1-C_{20}-alquilo, C_2-C_{20}-alquenilo, C_2-C_{20}-alquinilo, C_1-C_{20}-alcoxi, o C_1-C_{20}-alcoxi-C_1-C_{20}-alquilo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, y -CN, y

el carbociclilo o heterociclilo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, $-NO_2$, -CN, C_1-C_8-alquilo, halo-C_1-C_8-alquilo, C_1-C_8-alcoxi, halo-C_1-C_8-alcoxi, C_1-C_8-alcoxi-C_1-C_8-alquilo, C_1-C_8-alcoxi-C_1-C_8-alquilo sustituido con halógeno , $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbociclilo, halocarbociclilo, carbociclil-C_1-C_8-alquilo, y carbociclil-C_1-C_8-alquilo sustituido con halógeno; y

R^1 y R^2 se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, y halo-C_1-C_8-alquilo; y

1390

R^3 y R^4 se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, C_1-C_8-alcoxicarbonilo, C_1-C_8-alquilcarbonilo, carbociclil-C_1-C_8-alquilo, y carbociclil-C_1-C_8-alcoxicarbonilo; y

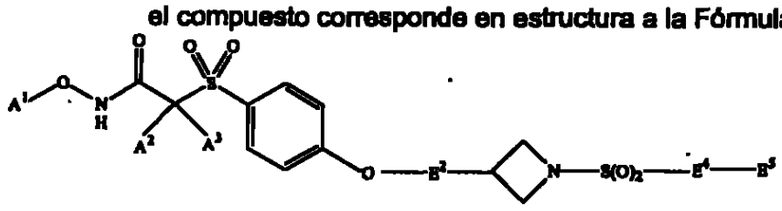
R^5 y R^6 se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, carbociclilo, carbociclil-C_1-C_8-alquilo, heterociclilo, y heterociclil-C_1-C_8-alquilo, donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido con uno o más halógenos; y

R^7 se selecciona del grupo formado por -H, C_1-C_8-alquilo, -O-R^8, -N(R^8)(R^9), carbociclil-C_1-C_8-alquilo, y heterociclil-C_1-C_8-alquilo, donde el C_1-C_8-alquilo, carbociclil-C_1-C_8-alquilo, o heterociclil-C_1-C_8-alquilo es optativamente sustituido con uno o más halógenos; y

R^8 y R^9 se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, carbociclilo, carbociclil-C_1-C_8-alquilo, heterociclilo, y heterociclil-C_1-C_8-alquilo, donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido con uno o más halógenos.

361. Un compuesto o sal del mismo, en el cual

el compuesto corresponde en estructura a la Fórmula 361-1:



(361-1); y

A^1 se selecciona del grupo formado por -H, alquilcarbonilo, alcoxicarbonilo, carbociclilcarbonilo, carbociclilalquilcarbonilo, heterociclilcarbonilo, heterociclilalquilcarbonilo, carbocicliloxicarbonilo, carbociclilalcoxicarbonilo, aminoalquilcarbonilo, alquil(tiocarbonilo),

alcoxi(tiocarbonilo), carbociclil(tiocarbonilo), carbociclilalquil(tiocarbonilo), heterociclil(tiocarbonilo), heterociclilalquil(tiocarbonilo), carbocicliloxi(tiocarbonilo), carbociclilalcoxi(tiocarbonilo), y aminoalquil(tiocarbonilo), donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido; y

A^2 y A^3, junto con el átomo de carbono al cual ambos están unidos, forman un heterociclilo optativamente sustituido que contiene entre 5 y 8 miembros en el anillo; y

E^2 se selecciona del grupo formado por un enlace, alquilo, cicloalquilo, alquilcicloalquilo, cicloalquilalquilo, y alquilcicloalquilalquilo, donde cualquier miembro de dicho grupo es optativamente sustituido; y

E^4 se selecciona del grupo formado por un enlace, alquilo, y alquenilo, donde el alquilo o alquenilo es optativamente sustituido; y

E^5 se selecciona del grupo formado por carbociclilo sustituido y heterociclilo optativamente sustituido, en el cual

el carbociclilo es sustituido con:

2 ó más sustituyentes seleccionados independientemente del grupo formado por halógeno, -OH, $-NO_2$, -CN, alquilo, haloalquilo, alcoxi, haloalcoxi, alcoxialquilo, alcoxialquilo sustituido con halógeno, $-N(R^3)(R^4)$, $-C(O)(R^5)$, $-S-R^3$, $-S(O)_2-R^3$, carbociclilo, halocarbociclilo, carbociclilalquilo, y carbociclilalquilo sustituido con halógeno, o

un sustituyente seleccionado del grupo formado por halógeno, -OH, $-NO_2$, -CN, $-C(O)-O-R^3$, $-S-R^3$, $-S(O)_2-R^3$, carbociclilo, halocarbociclilo, carbociclilalquilo, y carbociclilalquilo sustituido con halógeno, y

1392

el heterociclilo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, alquilo, haloalquilo, alcoxi, haloalcoxi, alcoxialquilo, alcoxialquilo sustituido con halógeno, -$N(R^3)(R^4)$, -$C(O)(R^5)$, -S-R^3, -$S(O)_2$-R^3, carbociclilo, halocarbociclilo, carbociclilalquilo, y carbociclilalquilo sustituido con halógeno; y

R^3 y R^4 se seleccionan independientemente del grupo formado por -H, alquilo, carbociclilo, carbociclilalquilo, heterociclilo, y heterociclilalquilo, donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido con uno o más halógenos; y

R^5 se selecciona del grupo formado por -H, alquilo, -O-R^6, -$N(R^6)(R^7)$, carbociclilalquilo, y heterociclilalquilo, donde el alquilo , carbociclilalquilo, o heterociclilalquilo es optativamente sustituido con uno o más halógenos; y

R^6 y R^7 se seleccionan independientemente del grupo formado por -H, alquilo, carbociclilo, carbociclilalquilo, heterociclilo, y heterociclilalquilo, donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido con uno o más halógenos.

362. Un compuesto o sal del mismo de acuerdo con la cláusula 361, en el cual

A^1 se selecciona del grupo formado por -H, C_1-C_8-alquilcarbonilo, C_1-C_8-alcoxicarbonilo, carbociclilcarbonilo, carbociclil-C_1-C_8-alquilcarbonilo, heterociclilcarbonilo, heterociclil-C_1-C_8-alquilcarbonilo, carbocicliloxicarbonilo, carbociclil-C_1-C_8-alcoxicarbonilo, $N(R^8)(R^9)$-C_1-C_8-alquilcarbonilo, C_1-C_8-alquil(tiocarbonilo), C_1-C_8-alcoxi(tiocarbonilo), carbociclil(tiocarbonilo), carbociclil-C_1-C_8-alquil(tiocarbonilo), heterociclil(tiocarbonilo), heterociclil-C_1-

1393

C_8-alquil(tiocarbonilo), carbocicliloxi(tiocarbonilo), carbociclil-C_1-C_8-alcoxi(tiocarbonilo), y N(R^6)(R^9)-C_1-C_8-alquil(tiocarbonilo); y

E^2 se selecciona del grupo formado por un enlace, C_1-C_{20}-alquilo, cicloalquilo, C_1-C_{10}-alquilcicloalquilo, cicloalquil-C_1-C_{10}-alquilo, y C_1-C_{10}-alquilcicloalquil-C_1-C_{10}-alquilo, donde cualquier miembro de dicho grupo es optativamente sustituido con uno o más halógenos; y

E^4 se selecciona del grupo formado por un enlace, C_1-C_{20}-alquilo, halo-C_1-C_{20}-alquilo, C_2-C_{20}-alquenilo, y halo-C_2-C_{20}-alquenilo; y

E^5 se selecciona del grupo formado por carbociclilo sustituido y heterociclilo optativamente sustituido, en el cual

el carbociclilo es sustituido con:

2 ó más sustituyentes seleccionados independientemente del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_8-alquilo, halo-C_1-C_8-alquilo, C_1-C_8-alcoxi, halo-C_1-C_8-alcoxi, C_1-C_8-alcoxi-C_1-C_8-alquilo, C_1-C_8-alcoxi-C_1-C_8-alquilo sustituido con halógeno , -N(R^3)(R^4), -C(O)(R^5), -S-R^3, -S(O)$_2$-R^3, carbociclilo, halocarbociclilo, carbociclil-C_1-C_8-alquilo, y carbociclil-C_1-C_8-alquilo sustituido con halógeno, o

un sustituyente seleccionado del grupo formado por halógeno, -OH, -NO_2, -CN, -C(O)-O-R^3, -S-R^3, -S(O)$_2$-R^3, carbociclilo, halocarbociclilo, carbociclil-C_1-C_8-alquilo, y carbociclil-C_1-C_8-alquilo sustituido con halógeno, y

el heterociclilo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_8-alquilo, halo-C_1-C_8-alquilo, C_1-C_8-alcoxi, halo-C_1-C_8-alcoxi, C_1-C_8-alcoxi-C_1-C_8-alquilo, halógeno-sustituido C_1-C_8-alcoxi-C_1-C_8-alquilo, -

1394

$N(R^3)(R^4)$, $-C(O)(R^5)$, $-S-R^3$, $-S(O)_2-R^3$, carbociclilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo, y carbociclil-C_1-C_6-alquilo sustituido con halógeno; y

R^3 y R^4 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo, donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido con uno o más halógenos; y

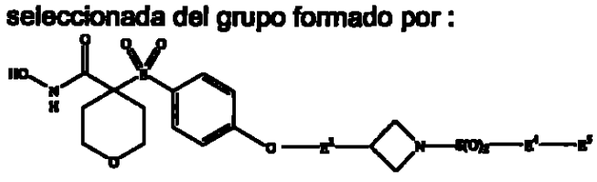
R^5 se selecciona del grupo formado por -H, C_1-C_6-alquilo, $-O-R^8$, $-N(R^6)(R^7)$, carbociclil-C_1-C_6-alquilo, y heterociclil-C_1-C_6-alquilo, donde el C_1-C_6-alquilo, carbociclil-C_1-C_6-alquilo, o heterociclil-C_1-C_6-alquilo es optativamente sustituido con uno o más halógenos; y

R^6 y R^7 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo, donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido con uno o más halógenos; y

R^8 y R^9 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, C_1-C_6-alcoxicarbonilo, C_1-C_6-alquilcarbonilo, carbociclil-C_1-C_6-alquilo, y carbociclil-C_1-C_6-alcoxicarbonilo.

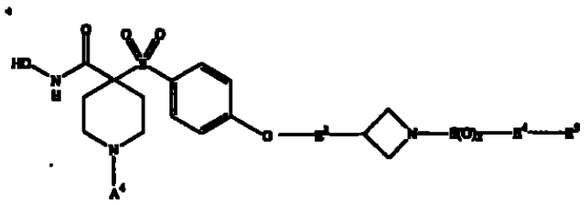
363. Un compuesto o sal del mismo de acuerdo con la cláusula 362, en el cual

el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



(363-1) y

1395



(363-2); y

A^4 se selecciona del grupo formado por -H, alquilo, alquilcarbonilo, alquilcarbonilalquilo, alquilcarbonilalquilcarbonilo, alcoxicarbonilo, alcoxicarbonilalquilo, alcoxicarbonilalquilcarbonilo, alquilsulfonilo, alquliminocarbonilo, alquenilo, alquinilo, alcoxialquilo, alquiltioalquilo, alquilsulfonilalquilo, alquilsufoxidoalquilo, alquiltioalquenilo, alquilsulfoxidoalquenilo, alquilsulfonilalquenilo, carbociclilo, carbociclilalquilo, carbociclilalcoxialquilo, carbociclilcarbonilo, carbociclilsulfonilo, carbociclliminocarbonilo, carbociclioxicarbonilo, carbocilitioalquilo, carbociclilsulfoxidoalquilo, carbociclilsulfonilalquilo, carbociclitioalquenilo, carbociclilsulfoxidoalquenilo, carbociclilsulfonilalquenilo, heterociclilo, heterociclilalquilo, heterociclilalcoxialquilo, heterociclilcarbonilo, heterocicliltioalquilo, heterociclilsulfoxidoalquilo, heterociclilsulfonilalquilo, heterocicliltioalquenilo, heterociclilsulfoxidoalquenilo, heterociclilsulfonilalquenilo, heterociclilsulfonilo, heterocicliliminocarbonilo, heterociclilalquilcarbonilo, heterociclilcarbonilalquilcarbonilo, heterociclilsulfonilo, heterociclilcarbonilalquilo, aminoalquilcarbonilo, aminocarbonilo, aminocarbonilalquilcarbonilo, aminosulfonilo, aminosulfonilalquilo, aminoalquilo, aminocarbonilalquilo, y aminoalquilsulfonilo, donde

cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido.

1396

364. Un compuesto o sal del mismo de acuerdo con la cláusula 363, en el cual E^5 es fenilo sustituido con:

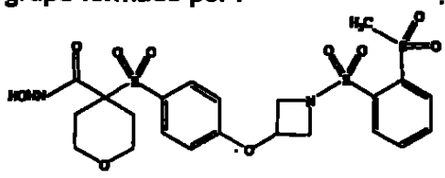
2 ó más sustituyentes seleccionados independientemente del grupo formado por halógeno, -OH, $-NO_2$, -CN, C_1-C_6-alquilo, halo-C_1-C_6-alquilo, C_1-C_6-alcoxi, halo-C_1-C_6-alcoxi, C_1-C_6-alcoxi-C_1-C_6-alquilo, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno, $-N(R^3)(R^4)$, $-C(O)(R^5)$, $-S-R^3$, $-S(O)_2-R^3$, carbociclilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo, y carbociclil-C_1-C_6-alquilo sustituido con halógeno, o

un sustituyente seleccionado del grupo formado por halógeno, -OH, $-NO_2$, -CN, $-C(O)-O-R^3$, $-S-R^3$, $-S(O)_2-R^3$, carbociclilo, halocarbociclilo, carbociclil-C_1-C_6-alquilo, y carbociclil-C_1-C_6-alquilo sustituido con halógeno.

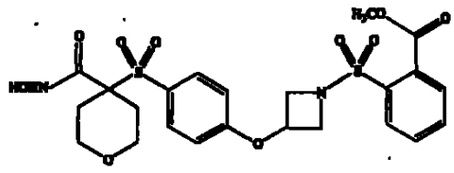
365. Un compuesto o sal del mismo de acuerdo con la cláusula 364, en el cual E^2 es un enlace.

366. Un compuesto o sal del mismo de acuerdo con la cláusula 365, en el cual E^4 es un enlace.

367. Un compuesto o sal del mismo de acuerdo con la cláusula 366, en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por .

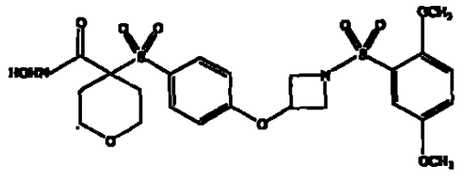


(367-1),



(367-2), y

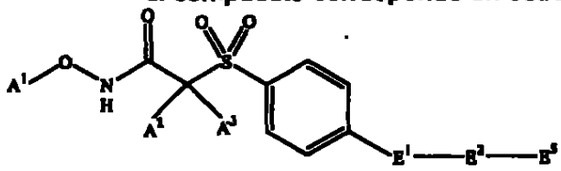
1397



(367-3).

368. Un compuesto o sal del mismo, en el cual

el compuesto corresponde en estructura a la Fórmula 368-1:



(368-1); y

A^1 se selecciona del grupo formado por -H, alquilcarbonilo, alcoxicarbonilo, carbociclilcarbonilo, carbociclilalquilcarbonilo, heterociclilcarbonilo, heterociclilalquilcarbonilo, carbocicliloxicarbonilo, carbociclilalcoxicarbonilo, aminoalquilcarbonilo, alquil(tiocarbonilo), alcoxi(tiocarbonilo), carbociclil(tiocarbonilo), carbociclilalquil(tiocarbonilo), heterociclil(tiocarbonilo), heterociclilalquil(tiocarbonilo), carbocicliloxi(tiocarbonilo), carbociclilalcoxi(tiocarbonilo), y aminoalquil(tiocarbonilo), donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido; y

A^2 y A^3, junto con el átomo de carbono al cual ambos están unidos, forman un heterociclilo optativamente sustituido que contiene entre 5 y 8 miembros en el anillo; y

E^1 se selecciona del grupo formado por -O-, $-S(O)_2-$, -S(O)-, -S-, $-N(R^1)-$, $-C(O)-N(R^1)-$, $-N(R^1)-C(O)-$, y $-C(R^1)(R^2)-$; y

1398

E^2 se selecciona del grupo formado por alquilo, cicloalquilo, alquilcicloalquilo, cicloalquilalquilo, y alquilcicloalquilalquilo, donde cualquier miembro de dicho grupo es optativamente sustituido; y

E^5 es sustituido heterociclilo; y

R^1 y R^2 se seleccionan independientemente del grupo formado por -H y alquilo, donde el alquilo es optativamente sustituido; y

ni R^1 ni R^2 forman una estructura de anillo con E^5.

369. Un compuesto o sal del mismo de acuerdo con la cláusula 368 , en el cual

A^1 se selecciona del grupo formado por -H, C_1-C_8-alquilcarbonilo, C_1-C_8-alcoxicarbonilo, carbociclilcarbonilo, carbociclil-C_1-C_8-alquilcarbonilo, heterociclilcarbonilo, heterociclil-C_1-C_8-alquilcarbonilo, carbocicliloxicarbonilo, carbociclil-C_1-C_8-alcoxicarbonilo, $N(R^3)(R^4)$-C_1-C_8-alquilcarbonilo, C_1-C_8-alquil(tiocarbonilo), C_1-C_8-alcoxi(tiocarbonilo), carbociclil(tiocarbonilo), carbociclil-C_1-C_8-alquil(tiocarbonilo), heterociclil(tiocarbonilo), heterociclil-C_1-C_8-alquil(tiocarbonilo), carbociclioxi(tiocarbonilo), carbociclil-C_1-C_8-alcoxi(tiocarbonilo), y $N(R^3)(R^4)$-C_1-C_8-alquil(tiocarbonilo); y

E^2 se selecciona del grupo formado por C_1-C_{20}-alquilo, cicloalquilo, C_1-C_{10}-alquil-cicloalquilo, cicloalquil-C_1-C_{10}-alquilo, y C_1-C_{10}-alquil-cicloalquil-C_1-C_{10}-alquilo, donde el Cualquier miembro de dicho grupo es optativamente sustituido con uno o más halógenos; y

E^5 es heterociclilo que es:

sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, ceto, C_1-C_8-alquilo, halo-C_1-C_8-alquilo, C_1-C_8-alcoxi, halo-C_1-C_8-alcoxi, C_1-C_8-alcoxi-C_1-C_8-

1399

alquilo, C_1-C_6-alcoxi-C_1-C_6-alquilo sustituido con halógeno , -$N(R^5)(R^6)$, -$C(O)(R^7)$, -S-R^5, -$S(O)_2$-R^5, carbociclilo, halocarbociclilo, y carbociclil-C_1-C_6-alquilo, y/o

sustituido en el mismo átomo con dos sustituyentes seleccionados independientemente del grupo formado por alquilo y haloalquilo, donde los dos sustituyentes juntos forman C_3-C_6-cicloalquilo o halo-C_3-C_6-cicloalquilo; y

R^1 y R^2 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, y halo-C_1-C_6-alquilo; y

R^3 y R^4 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, C_1-C_6-alcoxicarbonilo, C_1-C_6-alquilcarbonilo, carbociclil-C_1-C_6-alquilo, y carbociclil-C_1-C_6-alcoxicarbonilo; y

R^5 y R^6 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo, donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido con uno o más halógenos; y

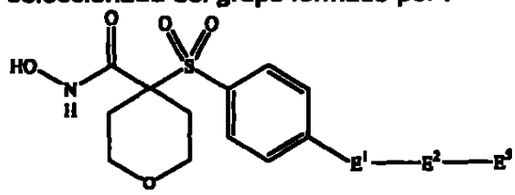
R^7 se selecciona del grupo formado por -H, C_1-C_6-alquilo, -O-R^8, -$N(R^8)(R^9)$, carbociclil-C_1-C_6-alquilo, y heterociclil-C_1-C_6-alquilo, donde el C_1-C_6-alquilo, carbociclil-C_1-C_6-alquilo, o heterociclil-C_1-C_6-alquilo es optativamente sustituido con uno o más halógenos; y

R^8 y R^9 se seleccionan independientemente del grupo formado por -H, C_1-C_6-alquilo, carbociclilo, carbociclil-C_1-C_6-alquilo, heterociclilo, y heterociclil-C_1-C_6-alquilo, donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido con uno o más halógenos.

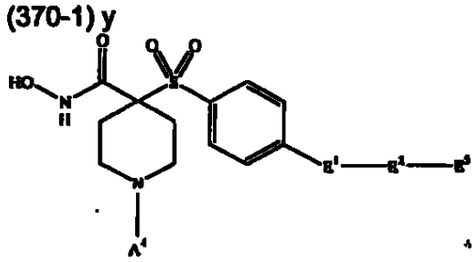
1400

370. Un compuesto o sal del mismo de acuerdo con la cláusula 369, en el cual

el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



(370-1) y



(370-2); y

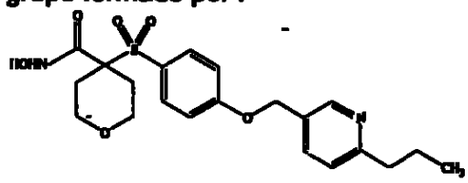
A^4 se selecciona del grupo formado por -H, alquilo, alquilcarbonilo, alquilcarbonilalquilo, alquilcarbonilalquilcarbonilo, alcoxicarbonilo, alcoxicarbonilalquilo, alcoxicarbonilalquilcarbonilo, alquilsulfonilo, alquiliminocarbonilo, alquenilo, alquinilo, alcoxialquilo, alquiltioalquilo, alquilsulfonilalquilo, alquilsufoxidoalquilo, alquiltioalquenilo, alquilsulfoxidoalquenilo, alquilsulfonilalquenilo, carbociclilo, carbociclilalquilo, carbociclilalcoxialquilo, carbociclilcarbonilo, carbociclilsulfonilo, carbociclioliminocarbonilo, carbociclioxicarbonilo, carbociliitioalquilo, carbocililsulfoxidoalquilo, carbocililsulfonilalquilo, carbociclitioalquenilo, carbocicilsulfoxidoalquenilo, carbociclilsulfonilalquenilo, heterociclilo, heterociclilalquilo, heterociclilalcoxialquilo, heterociclilcarbonilo, heterocicliltioalquilo, heterociclilsulfoxidoalquilo, heterociclilsulfonilalquilo,

1401

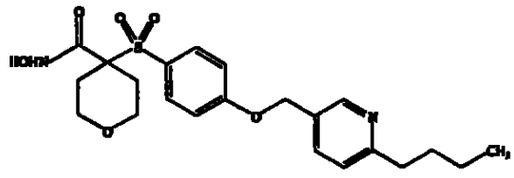
heterocicliltioalquenilo, heterociclilsulfoxidoalquenilo, heterociclilsulfonilalquenilo, heterociclilsulfonilo, heterociclliliminocarbonilo, heterociclilalquilcarbonilo, heterociclilcarbonilalquilcarbonilo, heterociclilsulfonilo, heterociclilcarbonilalquilo, aminoalquilcarbonilo, aminocarbonilo, aminocarbonilalquilcarbonilo, aminosulfonilo, aminosulfonilalquilo, aminoalquilo, aminocarbonilalquilo, y aminoalquilsulfonilo, donde

cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido.

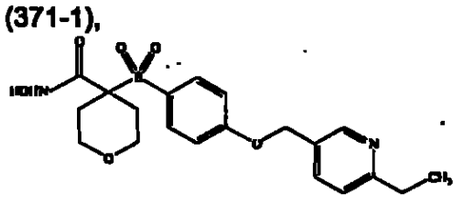
371. Un compuesto o sal del mismo de acuerdo con la cláusula 370, en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por .



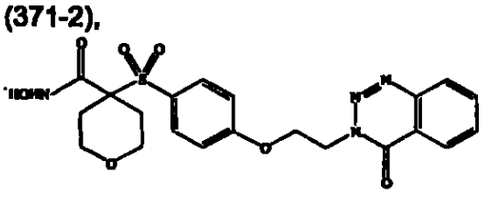
(371-1),



(371-2),



(371-3), y

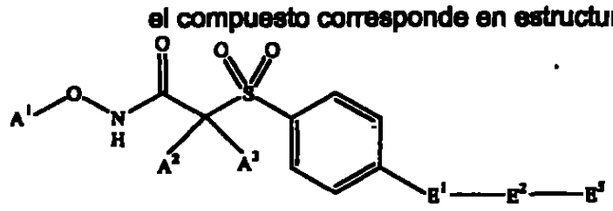


(371-4).

1402
1374

372. Un compuesto o sal del mismo, en el cual

el compuesto corresponde en estructura a la Fórmula 372-1:



(372-1); y

A^1 se selecciona del grupo formado por -H, alquilcarbonilo, alcoxicarbonilo, carbociclilcarbonilo, carbociclilalquilcarbonilo, heterociclilcarbonilo, heterociclilalquilcarbonilo, carbocicliloxicarbonilo, carbociclilalcoxicarbonilo, aminoalquilcarbonilo, alquil(tiocarbonilo), alcoxi(tiocarbonilo), carbociclil(tiocarbonilo), carbociclilalquil(tiocarbonilo), heterociclil(tiocarbonilo), heterociclilalquil(tiocarbonilo), carbocicliloxi(tiocarbonilo), carbociclilalcoxi(tiocarbonilo), y aminoalquil(tiocarbonilo), donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido; y

A^2 y A^3, junto con el átomo de carbono al cual ambos están unidos, forman un heterociclilo optativamente sustituido que contiene entre 5 y 8 miembros en el anillo; y

E^1 se selecciona del grupo formado por -O-, $-S(O)_2-$, -S(O)-, $-N(R^1)-$, $-C(O)-N(R^1)-$, $-N(R^1)-C(O)-$, y $-C(R^1)(R^2)-$; y

E^2 se selecciona del grupo formado por alquilo, cicloalquilo, alquilcicloalquilo, cicloalquilalquilo, y alquilcicloalquilalquilo, donde cualquier miembro de dicho grupo es optativamente sustituido; y

E^2 comprende al menos dos átomos de carbono; y

E^5 es heterociclilo optativamente sustituido; y

1403

R^1 y R^2 se seleccionan independientemente del grupo formado por -H y alquilo, donde el alquilo es optativamente sustituido; y

ni R^1 ni R^2 forman una estructura de anillo con E^5.

373. Un compuesto o sal del mismo de acuerdo con la cláusula 372, en el cual

A^1 se selecciona del grupo formado por -H, C_1-C_8-alquilcarbonilo, C_1-C_8-alcoxicarbonilo, carbociclilcarbonilo, carbociclil-C_1-C_8-alquilcarbonilo, heterociclilcarbonilo, heterociclil-C_1-C_8-alquilcarbonilo, carbocicliloxicarbonilo, carbociclil-C_1-C_8-alcoxicarbonilo, $N(R^3)(R^4)$-C_1-C_8-alquilcarbonilo, C_1-C_8-alquil(tiocarbonilo), C_1-C_8-alcoxi(tiocarbonilo), carbociclil(tiocarbonilo), carbociclil-C_1-C_8-alquil(tiocarbonilo), heterociclil(tiocarbonilo), heterociclil-C_1-C_8-alquil(tiocarbonilo), carbocicliloxi(tiocarbonilo), carbociclil-C_1-C_8-alcoxi(tiocarbonilo), y $N(R^3)(R^4)$-C_1-C_8-alquil(tiocarbonilo); y

E^2 se selecciona del grupo formado por C_2-C_{20}-alquilo, cicloalquilo, C_1-C_{10}-alquil-cicloalquilo, cicloalquil-C_1-C_{10}-alquilo, y C_1-C_{10}-alquil-cicloalquil-C_1-C_{10}-alquilo, donde el cualquier miembro de dicho grupo es optativamente sustituido con uno o más halógenos; y

E^5 es heterociclilo que es:

optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, ceto, C_1-C_8-alquilo, halo-C_1-C_8-alquilo, C_1-C_8-alcoxi, halo-C_1-C_8-alcoxi, C_1-C_8-alcoxi-C_1-C_8-alquilo, C_1-C_8-alcoxi-C_1-C_8-alquilo sustituido con halógeno , $-N(R^5)(R^6)$, $-C(O)(R^7)$, $-S-R^5$, $-S(O)_2-R^5$, carbociclilo, halocarbociclilo, y carbociclil-C_1-C_8-alquilo, y/o

optativamente sustituido en el mismo átomo con dos sustituyentes seleccionados independientemente del grupo formado por alquilo y haloalquilo, donde los dos sustituyentes juntos forman C_5-C_8-cicloalquilo o halo-C_5-C_8-cicloalquilo; y

R^1 y R^2 se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, y halo-C_1-C_8-alquilo; y

R^3 y R^4 se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, C_1-C_8-alcoxicarbonilo, C_1-C_8-alquilcarbonilo, carbociclil-C_1-C_8-alquilo, y carbociclil-C_1-C_8-alcoxicarbonilo; y

R^5 y R^6 se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, carbociclilo, carbociclil-C_1-C_8-alquilo, heterociclilo, y heterociclil-C_1-C_8-alquilo, donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido con uno o más halógenos; y

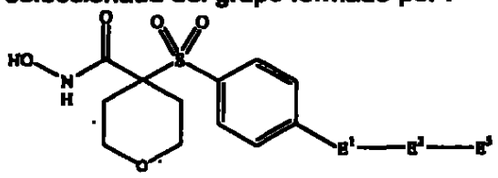
R^7 se selecciona del grupo formado por -H, C_1-C_8-alquilo, -O-R^8, -N(R^8)(R^9), carbociclil-C_1-C_8-alquilo, y heterociclil-C_1-C_8-alquilo, donde el C_1-C_8-alquilo, carbociclil-C_1-C_8-alquilo, o heterociclil-C_1-C_8-alquilo es optativamente sustituido con uno o más halógenos; y

R^8 y R^9 se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, carbociclilo, carbociclil-C_1-C_8-alquilo, heterociclilo, y heterociclil-C_1-C_8-alquilo, donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido con uno o más halógenos.

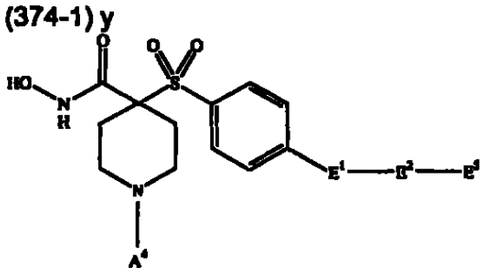
1405

374. Un compuesto o sal del mismo de acuerdo con la cláusula 373, en el cual

el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



(374-1) y



(374-2); y

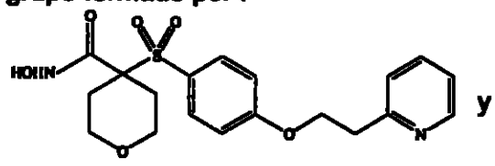
A^4 se selecciona del grupo formado por -H, alquilo, alquilcarbonilo, alquilcarbonilalquilo, alquilcarbonilalqulicarbonilo, alcoxicarbonilo, alcoxicarbonilalquilo, alcoxicarbonilalquilcarbonilo, alquilsulfonilo, alquiliminocarbonilo, alquenilo, alquinilo, alcoxialquilo, alquiltioalquilo, alquilsulfonilalquilo, alquilsufoxidoalquilo, alquiltioalquenilo, alquilsulfoxidoalquenilo, alquilsulfonilalquenilo, carbociclilo, carbociclilalquilo, carbociclilalcoxialquilo, carbociclilcarbonilo, carbociclilsulfonilo, carbociclliliminocarbonilo, carbocicliloxicarbonilo, carbocililtioalquilo, carbocililsulfoxidoalquilo, carbocililsulfonilalquilo, carbociclitioalquenilo, carbociclilsulfoxidoalquenilo, carbociclilsulfonilalquenilo, heterociclilo, heterociclilalquilo, heterociclilalcoxialquilo, heterociclilcarbonilo, heterociclitioalquilo, heterociclilsulfoxidoalquilo, heterociclilsulfonilalquilo,

1406

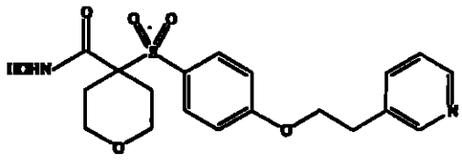
heterocicliltioalquenilo, heterociclilsulfoxidoalquenilo, heterociclilsulfonilalquenilo, heterociclilsulfonilo, heterocicliliminocarbonilo, heterociclilalquilcarbonilo, heterociclilcarbonilalquilcarbonilo, heterociclilsulfonilo, heterociclilcarbonilalquilo, aminoalquilcarbonilo, aminocarbonilo, aminocarbonilalquilcarbonilo, aminosulfonilo, aminosulfonilalquilo, aminoalquilo, aminocarbonilalquilo, y aminoalquilsulfonilo, donde

cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido.

375. Un compuesto o sal del mismo de acuerdo con la cláusula 374, en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por .



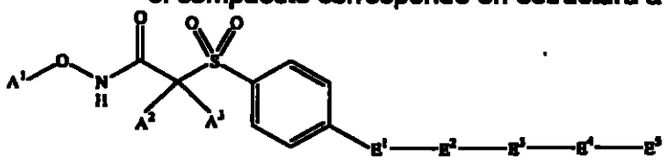
y



(375-1) (375-2).

376. Un compuesto o sal del mismo, en el cual

el compuesto corresponde en estructura a la Fórmula 376-1:



(376-1); y

A^1 se selecciona del grupo formado por -H, alquilcarbonilo, alcoxicarbonilo, carbociclilcarbonilo, carbociclilalquilcarbonilo, heterociclilcarbonilo, heterociclilalquilcarbonilo, carbociclioxicarbonilo,

1409

1277

carbociclilalcoxicarbonilo, aminoalquilcarbonilo, alquil(tiocarbonilo), alcoxi(tiocarbonilo), carbociclil(tiocarbonilo), carbociclilalquil(tiocarbonilo), heterociclil(tiocarbonilo), heterociclilalquil(tiocarbonilo), carbocicliloxi(tiocarbonilo), carbociclilalcoxi(tiocarbonilo), y aminoalquil(tiocarbonilo), donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido; y

A^2 y A^3, junto con el átomo de carbono al cual ambos están unidos, forman un heterociclilo optativamente sustituido que contiene entre 5 y 8 miembros en el anillo; y

E^1 se selecciona del grupo formado por -O-, $-S(O)_2-$, -S(O)-, -S-, $-N(R^1)-$, $-C(O)-N(R^1)-$, $-N(R^1)-C(O)-$, y $-C(R^1)(R^2)-$; y

E^2 se selecciona del grupo formado por alquilo, cicloalquilo, alquilcicloalquilo, cicloalquilalquilo, y alquilcicloalquilalquilo, donde cualquier miembro de dicho grupo es optativamente sustituido; y

E^3 se selecciona del grupo formado por -C(O)-, -O-(CO)-, -C(O)-O-, $-C(NR^3)-$, $-N(R^4)-$, $-N(R^4)-C(NR^3)-$, $-C(NR^3)-N(R^4)-$, $-C(O)-N(R^4)-$, $-N(R^4)-C(O)-$, $-N(R^4)-C(O)-N(R^5)-$, -S-, -S(O)-, $-N(R^4)-S(O)_2-$, $-S(O)_2-N(R^4)-$, $-C(O)-N(R^4)-N(R^5)-C(O)-$, $-C(R^4)(R^6)-C(O)-$, y $-C(R^7)(R^8)-$; y

E^4 se selecciona del grupo formado por un enlace, alquilo, y alquenilo, donde el alquilo o alquenilo es optativamente sustituido; y

E^5 se selecciona del grupo formado por carbociclilo y heterociclilo, donde el carbociclilo y heterociclilo son:

sustituido con un sustituyente seleccionado del grupo formado por carbociclilo optativamente sustituido, carbociclilalquilo optativamente sustituido,

heterociclilo optativamente sustituido, y heterociclilalquilo optativamente sustituido, y

optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, alquilo, alcoxi, alcoxialquilo, -$N(R^{11})(R^{12})$; -$C(O)(R^{13})$, -S-R^{11}, -$S(O)_2$-R^{11}, carbociclilo, carbociclilalquilo, haloalquilo, haloalcoxi, alcoxialquilo sustituido con halógeno, halocarbociclilo, carbociclilalquilo sustituido con halógeno, hidroxicarbociclilo, y heteroarilo; y

R^1 y R^2 se seleccionan independientemente del grupo formado por -H y alquilo, donde el alquilo es optativamente sustituido; y

R^3 se selecciona del grupo formado por -H y -OH; y

R^4 y R^5 se seleccionan independientemente del grupo formado por -H, alquilo, carbociclilo, carbociclilalquilo, heterociclilo, y heterociclilalquilo, donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido; y

R^6 se selecciona del grupo formado por -CN y -OH; y

R^7 se selecciona del grupo formado por -H, halógeno, -OH, alquilo, alcoxi, y alcoxialquilo, donde el alquilo , alcoxi, o alcoxialquilo es optativamente sustituido; y

R^8 se selecciona del grupo formado por -OH y alcoxi, en el cual el alcoxi es optativamente sustituido; y

R^{11} y R^{12} se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, carbociclilo, carbociclil-C_1-C_8-alquilo, heterociclilo, y heterociclil-C_1-C_8-alquilo, donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido con uno o más halógenos; y

1409

R^{13} se selecciona del grupo formado por -H, C_1-C_8-alquilo, -O-R^{14}, -N(R^{14})(R^{15}), carbociclil-C_1-C_8-alquilo, heterociclil-C_1-C_8-alquilo, halo-C_1-C_8-alquilo, carbociclil-C_1-C_8-alquilo sustituido con halógeno, y heterociclil-C_1-C_8-alquilo sustituido con halógeno; y

R^{14} y R^{15} se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, carbociclilo, carbociclil-C_1-C_8-alquilo, heterociclilo, y heterociclil-C_1-C_8-alquilo, donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido con uno o más halógenos; y

ni R^1 ni R^2 forman una estructura de anillo con E^2, E^3, E^4, o E^5; y

ni R^4 ni R^5 forman una estructura de anillo con E^2, E^4, o E^5.

377. Un compuesto o sal del mismo de acuerdo con la cláusula 376, en el cual

A^1 se selecciona del grupo formado por -H, C_1-C_8-alquilcarbonilo, C_1-C_8-alcoxicarbonilo, carbociclilcarbonilo, carbociclil-C_1-C_8-alquilcarbonilo, heterociclilcarbonilo, heterociclil-C_1-C_8-alquilcarbonilo, carbociclíloxicarbonilo, carbociclil-C_1-C_8-alcoxicarbonilo, N(R^9)(R^{10})-C_1-C_8-alquilcarbonilo, C_1-C_8-alquil(tiocarbonilo), C_1-C_8-alcoxi(tiocarbonilo), carbociclil(tiocarbonilo), carbociclil-C_1-C_8-alquil(tiocarbonilo), heterociclil(tiocarbonilo), heterociclil-C_1-C_8-alquil(tiocarbonilo), carbociclíloxi(tiocarbonilo), carbociclil-C_1-C_8-alcoxi(tiocarbonilo), y N(R^9)(R^{10})-C_1-C_8-alquil(tiocarbonilo); y

E^2 se selecciona del grupo formado por C_2-C_{20}-alquilo, cicloalquilo, C_1-C_{10}-alquilcicloalquilo, cicloalquil-C_1-C_{10}-alquilo, y C_1-C_{10}-alquilcicloalquil-C_1-C_{10}-alquilo, donde cualquier miembro de dicho grupo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, C_1-C_8-alquilo, y halo-C_1-C_8-alquilo; y

1410

E^4 se selecciona del grupo formado por un enlace, C_1-C_{20}-alquilo, y C_2-C_{20}-alquenilo, donde el C_1-C_{20}-alquilo o C_2-C_{20}-alquenilo es optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por:

halógeno, y

carbociclilo optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_8-alquilo, C_1-C_8-alcoxi, C_1-C_8-alcoxi-C_1-C_8-alquilo, carbociclilo, carbociclil-C_1-C_8-alquilo, halo-C_1-C_8-alquilo, halo-C_1-C_8-alcoxi, C_1-C_8-alcoxi-C_1-C_8-alquilo sustituido con halógeno , halocarbociclilo, y carbociclil-C_1-C_8-alquilo sustituido con halógeno; y

E^5 se selecciona del grupo formado por carbociclilo y heterociclilo, donde el carbociclilo y heterociclilo son:

sustituido con un sustituyente seleccionado del grupo formado por carbociclilo optativamente sustituido, optativamente-sustituido carbociclil-C_1-C_8-alquilo, heterociclilo optativamente sustituido, y heterociclilo optativamente sustituido-C_1-C_8-alquilo, y

optativamente sustituido con uno o más sustituyentes independientemente seleccionados del grupo formado por halógeno, -OH, -NO_2, -CN, C_1-C_8-alquilo, C_1-C_8-alcoxi, C_1-C_8-alcoxi-C_1-C_8-alquilo, -$N(R^{11})(R^{12})$, -$C(O)(R^{13})$, -S-R^{11}, -$S(O)_2$-R^{11}, carbociclilo, carbociclil-C_1-C_8-alquilo, halo-C_1-C_8-alquilo, halo-C_1-C_8-alcoxi, C_1-C_8-alcoxi-C_1-C_8-alquilo sustituido con halógeno , halocarbociclilo, carbociclil-C_1-C_8-alquilo sustituido con halógeno, hidroxicarbociclilo, y heteroarilo; y

1411

R^1 y R^2 se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, y halo-C_1-C_8-alquilo; y

R^4 y R^5 se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, carbociclilo, carbociclil-C_1-C_8-alquilo, heterociclilo, y heterociclil-C_1-C_8-alquilo, donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido con uno o más halógenos; y

R^7 se selecciona del grupo formado por -H, halógeno, -OH, C_1-C_8-alquilo, C_1-C_8-alcoxi, C_1-C_8-alcoxi-C_1-C_8-alquilo, halo-C_1-C_8-alquilo, halo-C_1-C_8-alcoxi, y C_1-C_8-alcoxi-C_1-C_8-alquilo sustituido con halógeno ; y

R^8 se selecciona del grupo formado por -OH, C_1-C_8-alcoxi, y halo-C_1-C_8-alcoxi; y

R^9 y R^{10} se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, C_1-C_8-alcoxicarbonilo, C_1-C_8-alquilcarbonilo, carbociclil-C_1-C_8-alquilo, y carbociclil-C_1-C_8-alcoxicarbonilo; y

R^{11} y R^{12} se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, carbociclilo, carbociclil-C_1-C_8-alquilo, heterociclilo, y heterociclil-C_1-C_8-alquilo, donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido con uno o más halógenos; y

R^{13} se selecciona del grupo formado por -H, C_1-C_8-alquilo, -O-R^{14}, -N(R^{14})(R^{15}), carbociclil-C_1-C_8-alquilo, heterociclil-C_1-C_8-alquilo, halo-C_1-C_8-alquilo, carbociclil-C_1-C_8-alquilo sustituido con halógeno, y heterociclil-C_1-C_8-alquilo sustituido con halógeno; y

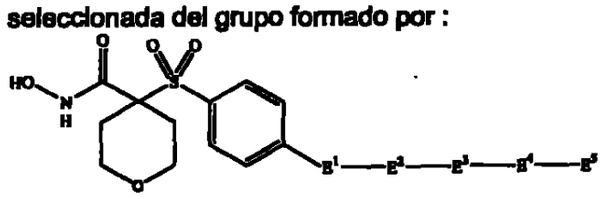
R^{14} y R^{15} se seleccionan independientemente del grupo formado por -H, C_1-C_8-alquilo, carbociclilo, carbociclil-C_1-C_8-alquilo, heterociclilo, y

1412

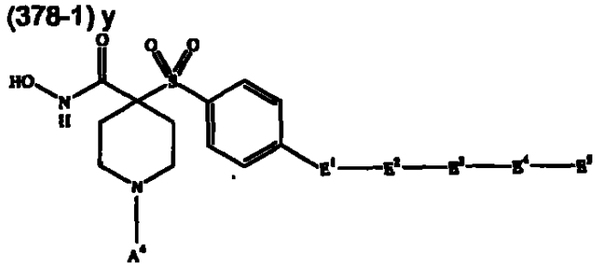
heterociclil-C_1-C_6-alquilo, donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido con uno o más halógenos.

378. Un compuesto o sal del mismo de acuerdo con la cláusula 377, en el cual

el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por :



(378-1) y



(378-2); y

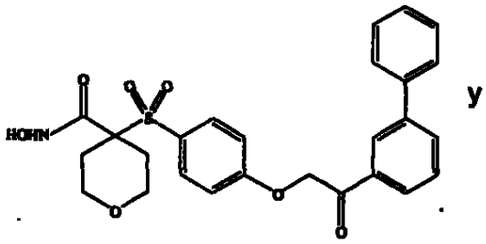
A^4 se selecciona del grupo formado por -H, alquilo, alquilcarbonilo, alquilcarbonilalquilo, alquilcarbonilalquilcarbonilo, alcoxicarbonilo, alcoxicarbonilalquilo, alcoxicarbonilalquilcarbonilo, alquilsulfonilo, alquiliminocarbonilo, alquenilo, alquinilo, alcoxialquilo, alquiltioalquilo, alquilsulfonilalquilo, alquilsufoxidoalquilo, alquiltioalquenilo, alquilsulfoxidoalquenilo, alquilsulfonilalquenilo, carbociclilo, carbociclilalquilo, carbociclilalcoxialquilo, carbociclilcarbonilo, carbociclilsulfonilo, carbociclliliminocarbonilo, carbociclioxicarbonilo, carbocililtioalquilo, carbociclilsulfoxidoalquilo, carbociclilsulfonilalquilo, carbociclitioalquenilo, carbociclilsulfoxidoalquenilo, carbociclilsulfonilalquenilo, heterociclilo,

1413

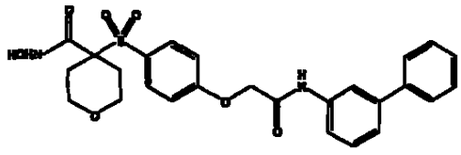
heterociclilalquilo, heterociclilalcoxialquilo, heterociclilcarbonilo, heterocicliltioalquilo, heterociclilsulfoxidoalquilo, heterociclilsulfonilalquilo, heterociclitioalquenilo, heterociclilsulfoxidoalquenilo, heterociclilsulfonilalquenilo, heterociclilsulfonilo, heterociclliminocarbonilo, heterociclilalquilcarbonilo, heterociclilcarbonilalquilcarbonilo, heterociclilsulfonilo, heterociclilcarbonilalquilo, aminoalquilcarbonilo, aminocarbonilo, aminocarbonilalquilcarbonilo, aminosulfonilo, aminosulfonilalquilo, aminoalquilo, aminocarbonilalquilo, y aminoalquilsulfonilo, donde

cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido.

379. Un compuesto o sal del mismo de acuerdo con la cláusula 378, en el cual el compuesto corresponde en estructura a una fórmula seleccionada del grupo formado por .



y



(379-2).

(379-1)

380. Un método para prevenir o tratar una condición vinculada con actividad patológica de la metaloproteasa de matriz en un mamífero afectado por dicha condición o predispuesto a adquirir dicha condición, en el cual

1414

el método comprende administrar un compuesto o una sal aceptable para uso farmacéutico del mismo en una cantidad eficaz en términos terapéuticos al mamífero; y

el compuesto se selecciona del grupo de compuestos enumerados en las cláusulas 1, 122, 225, 235, 250, 260, 267, 296, 303, 308, 322, 335, 337, 344, 354, 359, 361, 368,372, y 376.

381. Un método de acuerdo con la cláusula 380, en el cual el compuesto o sal inhibe la actividad de uno o más de MMP-2, MMP-9, y MMP-13, y al mismo tiempo exhibe substancialmente menos actividad inhibidora contra ambas MMP-1 y MMP-14.

382. Un método de acuerdo con la cláusula 381, en el cual el compuesto o sal inhibe la actividad de MMP-13, y al mismo tiempo exhibe substancialmente menos actividad inhibidora contra ambas MMP-1 y MMP-14.

383. Un método de acuerdo con la cláusula 382, en el cual la condición patológica comprende artritis o un trastorno cardiovascular.

384. Un método de acuerdo con la cláusula 381, en el cual el compuesto o sal inhibe la actividad de ambas MMP-2 y MMP-9, y al mismo tiempo exhibe substancialmente menos actividad inhibidora contra ambas MMP-1 y MMP-14.

385. Un método de acuerdo con la cláusula 384, en el cual la condición patológica comprende cáncer, una afección oftalmológica, o un trastorno cardiovascular.

386. Un método para prevenir o tratar una condición patológica en un mamífero que tiene la condición patológica o tiene predisposición a tener la condición patológica, en el cual

1415

el método comprende administrar un compuesto o una sal aceptable para uso farmacéutico del mismo en una cantidad eficaz en términos terapéuticos al mamífero; y

el compuesto se selecciona del grupo de compuestos enumerados en las cláusulas 1, 122, 225, 235, 250, 260, 267, 296, 303, 308, 322, 335, 337, 344, 354, 359, 361, 368,372, y 376; y

la condición patológica se selecciona del grupo formado por destrucción de tejidos, una enfermedad fibrótica, debilitamiento de la matriz, reparación deficiente de heridas, una enfermedad cardiovascular, una enfermedad pulmonar, una enfermedad renal, una enfermedad hepática, una enfermedad oftalmológica, y una enfermedad del sistema nervioso central.

387. Un método para prevenir o tratar una condición patológica en un mamífero que tiene la condición patológica o tiene predisposición a tener la condición patológica, en el cual

el método comprende administrar un compuesto o una sal aceptable para uso farmacéutico del mismo en una cantidad eficaz en términos terapéuticos al mamífero; y

el compuesto se selecciona del grupo de compuestos enumerados en las cláusulas 1, 122, 225, 235, 250, 260, 267, 296, 303, 308, 322, 335, 337, 344, 354, 359, 361, 368,372, y 376

la condición patológica se selecciona del grupo formado por osteoartritis, artritis reumatoide, artritis séptica, invasión tumoral, metástasis tumoral, angiogénesis tumoral, una úlcera de decubitus, una úlcera gástrica, una úlcera de córnea, enfermedad periodontal, cirrosis hepática, enfermedad

1416

fibrótica pulmonar, otoesclerosis, ateroesclerosis, esclerosis múltiple, cardiomiopatía dilatada, ulceración epidérmica, epidermólisis ampollar, aneurisma aórtico, reparación deficiente de heridas, una adherencia , escarificación, deficiencia cardíaca congestiva, infarto pos-miocardial, trombosis coronaria, enfisema, proteinuria, mal de Alzheimer, enfermedad ósea, y obstrucción pulmonar crónica.

388. Un método de acuerdo con la cláusula 387, en el cual la condición comprende artritis.

389. Un método de acuerdo con la cláusula 387, en el cual la condición comprende invasión tumoral, metástasis tumoral, o angiogénesis tumoral.

390. Un método de acuerdo con la cláusula 387, en el cual la condición comprende enfermedad periodontal.

391. Un método de acuerdo con la cláusula 387, en el cual la condición comprende ateroesclerosis.

392. Un método de acuerdo con la cláusula 387, en el cual la condición comprende esclerosis múltiple.

393. Un método de acuerdo con la cláusula 387, en el cual la condición comprende cardiomiopatía dilatada.

394. Un método de acuerdo con la cláusula 387, en el cual la condición comprende infarto pos-miocardial.

395. Un método de acuerdo con la cláusula 387, en el cual la condición comprende deficiencia cardíaca congestiva.

396. Un método de acuerdo con la cláusula 387, en el cual la condición comprende obstrucción pulmonar crónica.

397. Un método para prevenir o tratar una condición patológica asociada con la actividad patológica de TNF-α convertasa en un mamífero que tiene la condición patológica o tiene predisposición a adquirir dicha condición, en el cual

el método comprende administrar un compuesto o una sal aceptable para uso farmacéutico del mismo en una cantidad eficaz en términos terapéuticos al mamífero; y

el compuesto se selecciona del grupo de compuestos enumerados en las cláusulas 1, 122, 225, 235, 250, 260, 267, 296, 303, 308, 322, 335, 337, 344, 354, 359, 361, 368,372, y 376

398. Un método de acuerdo con la cláusula 397, en el cual la condición patológica se selecciona del grupo formado por inflamación, una enfermedad pulmonar, una enfermedad cardiovascular, una enfermedad autoinmune, rechazo a injertos, una enfermedad fibrótica, esclerosis múltiple, cáncer, una enfermedad infecciosa, fiebre, psoriasis, hemorragia, coagulación, daño por radiación, respuestas de fase aguda de shock y sepsis, anorexia, y caquexia.

399. Un método para prevenir o tratar una condición patológica asociada con actividad patológica de agrecanasa en un mamífero que tiene la condición patológica o tiene predisposición a tener la condición, en el cual

el método comprende administrar un compuesto o una sal aceptable para uso farmacéutico del mismo en una cantidad eficaz en términos terapéuticos al mamífero; y

el compuesto se selecciona del grupo de compuestos enumerados en las cláusulas 1, 122, 225, 235, 250, 260, 267, 296, 303, 308, 322, 335, 337, 344, 354, 359, 361, 368,372, y 376

1418

400. Un método de acuerdo con la cláusula 399, en el cual la condición comprende un trastorno inflamatorio o cáncer.

401. Un método de acuerdo con la cláusula 399, en el cual el método comprende además administrar el compuesto o sal del mismo para prevenir o tratar una condición vinculada con la actividad de metaloproteasas de matriz.

402. Una composición farmacéutica que comprende una cantidad eficaz en términos terapéuticos de un compuesto o una sal aceptable para uso farmacéutico del mismo , en el cual el compuesto se selecciona del grupo de compuestos enumerados en las cláusulas 1, 122, 225, 235, 250, 260, 267, 296, 303, 308, 322, 335, 337, 344, 354, 359, 361, 368,372, y 376.

403. Un uso de un compuesto o una sal aceptable para uso farmacéutico del mismo para preparar un medicamento para tratar una condición vinculada con actividad patológica de la metaloproteasa de matriz, en el cual el compuesto se selecciona del grupo de compuestos enumerados en las cláusulas 1, 122, 225, 235, 250, 260, 267, 296, 303, 308, 322, 335, 337, 344, 354, 359, 361, 368,372, y 376.

404. Un uso de un compuesto o una sal aceptable para uso farmacéutico del mismo para preparar un medicamento para tratar una condición vinculada con la actividad patológica TNF-α convertasa, en el cual el compuesto se selecciona del grupo de compuestos enumerados en las cláusulas 1, 122, 225, 235, 250, 260, 267, 296, 303, 308, 322, 335, 337, 344, 354, 359, 361, 368,372, y 376.

405. Un uso de un compuesto o una sal aceptable para uso farmacéutico del mismo para preparar un medicamento para tratar una condición vinculada con actividad patológica de agrecanasa, en el cual el compuesto se selecciona

1419

del grupo de compuestos enumerados en las cláusulas 1, 122, 225, 235, 250, 260, 267, 296, 303, 308, 322, 335, 337, 344, 354, 359, 361, 368,372, y 376.

1420

SULFONA-HIDROXAMATOS AROMÁTICOS Y SU USO COMO INHIBIDORES DE PROTEASAS

RESUMEN

Sulfona hidroxamatos aromáticos (también conocidos como "ácidos sulfona hidroxámicos aromáticos") y sales de los mismos que, entre otras propiedades, inhiben la actividad de metaloproteasas de matriz (también conocidas como "metaloproteasas de matriz" o "MMP") y/o la actividad de la agrecanasa. Esta invención también tiene como objeto un método de prevención o tratamiento que comprende administrar dicho compuesto o sal en una cantidad eficaz para inhibir las MMP y/o la agrecanasa en un animal, particularmente un animal afectado (o con predisposición a ser afectado) por una condición patológica asociada con la actividad de MMP y/o de agrecanasa.

1392

1380 p

1386.

1700 L.

1800 A.

1400 SD

142-30

1293

SUPERINTENDENCIA [illegible]
Radicacion : 03099304 00000000 Folios: 1.592
Fecha (MMDD): 2003-11-10 17:22:24
Tramite : 012 PCT-PATENT [illegible]
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

REQUISITOS NECESARIOS PARA PRESENTACION Y AGILIZACION DEL TRAMITE

	USUARIO	RADICADOR
PATENTE DE INVENCIÓN MODELO DE UTILIDAD	( )	(X)
- Indicación de que se solicita la concesión de una patente.	( )	(X)
- Datos de identificación del solicitante o de la persona que se presenta la solicitud.	( )	(X)
- Descripción de la invención.	( )	(X)
- Dibujos de ser estos pertinentes.	( )	(X)
- 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 y fotográfica del Diseño Industrial o muestra del Material que incorpora el diseño.	( )	( )
Comprobante de pago de las tasas establecidas	( )	( )
COMPLETA ( ) INCOMPLETA	( )	( )
ESQUEMA DE TRAZADO ( )		
- Indicación de que solicita el registro de un Esquema de trazado.	( )	( )
- Datos de identificación del solicitante o de la persona que presenta La solicitud.	( )	( )
Representación gráfica del esquema de trazado	( )	( )
Comprobante de pago de las tasas establecidas.	( )	( )
COMPLETA ( ) INCOMPLETA	( )	( )

Firma Responsable:

Eduar Navarro

Fecha: 10-11-2003

AS: 92.534

1412

Industria y Comer
SUPERINTENDENCI 03 099304 . 00

Radicacion : 0099304 00000000 Folios: 1392
Fecha (AMD): 2003-11-10 17:22:24
Tramite : 911 PCT-PATENT 1/9 FASE NACI 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

Rad 03-99304
10/11/2003
Fecha

FORMULARIO ÚNICO DE SOLICITUD DE PATENTE

PCT

ENTRADA EN FASE NACIONAL : 11/12/2003

1 SOLICITUD DE:

☒ Patente de Invención. ☐ Patente de Modelo de Utilidad.

☐ Capítulo I. ☒ Capítulo II.

2 SOLICITANTE (71)	Nombre: PHARMACIA CORPORATION Dirección: P.O. BOX 1027, Chesterfield, Missouri 63006, 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 y República China (Respectivamente)	

5 PCT (86)
Solicitud Internacional No. PCT/US02/15257 Fecha 10-05-2002
Publicación Internacional No. WO 02/092588 A3 Fecha 21-11-2002

6 Titulo (54): SULFONA-HIDROXAMATOS AROMÁTICOS Y SU USO COMO INHIBIDORES DE PROTEASAS

7 Clasificación Internacional (51) A61K31/357

8 Prioridad SI ☒ NO ☐	(33) País de Origen	(32) Fecha	(31) Número de Solicitud
	US	11-05-2001	60/290.375

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

Brigard & Castro
Abogados

1423

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: 92.534

LISTA DE INVENTORES

1. THOMAS E. BARTA
   1133 Maple Avenue, Apt.3-W
   Evanston, Illinois 60602
   Estados Unidos de América

2. DANIEL P. BECKER
   1800 Maplewood Lane
   Glenview, Illinois 60025
   Estados Unidos de América

3. LOUIS J. BEDELL
   208 E. Marion Avenue
   Mt. Prospect, Illinois 60070
   Estados Unidos de América

4. TERRI L. BOEHM
   928 Cleta Drive
   Ballwin, Missouri 63021
   Estados Unidos de América

5. JEFFERY N. CARROLL
   306 N. Rapp
   Columbia, Illinois 62236
   Estados Unidos de América

6. GARY A. DECRESCENZO
   7534 Spruce Hill Ct.
   St. Charles, Missouri 63304
   Estados Unidos de América

7. YVETTE M. FOBIAN
   580 Eagles Nest Ct.
   Wildwood, Missouri 63011
   Estados Unidos de América

8. JOHN N. FRESKOS
   7572 York
   Clayton, Missouri 63105
   Estados Unidos de América

9. SUSAN L. HOCKERMAN
   5319 W. Hutchingson
   Chicago, Illinois 60641
   Estados Unidos de América

10. DARREN J. KASSAB
    5 Park City Court
    O'Fallon, Missouri 63040
    Estados Unidos de América

11. STEVE A. KOLODZIEJ
    2448 Clarjon Road
    Ballwin, Missouri 63021
    Estados Unidos de América

12. JOSEPH J. MCDONALD
    1716 Timber Ridge Estate Dr.
    Wildwood, Missouri 63011
    Estados Unidos de América

13. DEBORAH A. MISCHKE
    25 White River Lane
    Defiance, Missouri 63341
    Estados Unidos de América

14. MONICA B. NORTON
    7777 Gissler Avenue
    St. Louis, Missouri 63117
    Estados Unidos de América

15. JOSEPH G. RICO
    524 Wetherby Terr. Dr.
    Ballwin, Missouri 63021
    Estados Unidos de América

16. JOHN J. TALLEY
    122 Hamilton St., Apt. 2
    Cambridge, Massachusetts
    02139, Estados Unidos

17. CLARA I. VILLAMIL
    813 Long Road
    Glenview, Illinois 60025
    Estados Unidos de América

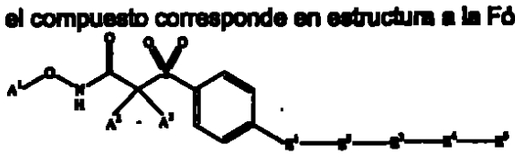
18. LIJUAN JANE WANG
    919 Crown Pointe Est. Dr
    Wildwood, Missouri 63021
    Estados Unidos de América

1424

REIVINDICACIONES

1. Un compuesto o sal del mismo en el cual:

el compuesto corresponde en estructura a la Fórmula 1-1:



(1-1); y

A^1 se selecciona del grupo formado por -H, alquilcarbonilo, alcoxicarbonilo, carbociclilcarbonilo, carbociclilalquilcarbonilo, heterociclilcarbonilo, heterociclilalquilcarbonilo, carbocicliloxicarbonilo, carbociclilalcoxicarbonilo, aminoalquilcarbonilo, alquil(tiocarbonilo), alcoxi(tiocarbonilo), carbociclil(tiocarbonilo), carbociclilalquil(tiocarbonilo), heterociclil(tiocarbonilo), heterociclilalquil(tiocarbonilo), carbociclioxi(tiocarbonilo), carbociclilalcoxi(tiocarbonilo), y aminoalquil(tiocarbonilo), donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido; y

A^2 y A^3, junto con el átomo de carbono al cual ambos están unidos, forman un heterociclilo optativamente sustituido que contiene entre 5 y 8 miembros en el anillo; y

E^1 se selecciona del grupo formado por -O-, $-S(O)_2-$, -S(O)-, -S-, $-N(R^1)-$, $-C(O)-N(R^1)-$, $-N(R^1)-C(O)-$, y $-C(R^1)(R^2)-$; y

E^2 se selecciona del grupo formado por alquilo, cicloalquilo, alquilcicloalquilo, cicloalquilalquilo, y alquilcicloalquilalquilo donde cualquier miembro de dicho grupo es optativamente sustituido; y

E^2 forma un enlace de al menos 2 átomos de carbono entre E^1 y E^2; y

E^3 se selecciona del grupo formado por -C(O)-, -O-(CO)-, -C(O)-O-, -C(NR^3)-, -N(R^4)-, -N(R^4)-C(NR^3)-, -C(NR^3)-N(R^4)-, -C(O)-N(R^4)-, -N(R^4)-C(O)-, -N(R^4)-C(O)-N(R^5)-, -S-, -S(O)-, -N(R^4)-S(O)$_2$-, -S(O)$_2$-N(R^4)-, -C(O)-N(R^4)-N(R^5)-C(O)-, -C(R^4)(R^6)-C(O)-, -C(R^7)(R^8)-; y

E^4 se selecciona del grupo formado por un enlace, alquilo, y alquenilo donde el alquilo o alquenilo es optativamente sustituido; y

E^5 se selecciona del grupo formado por -H, -OH, alquilo, alquenilo, alquinilo, alcoxi, alcoxialquilo, carbociclilo, y heterociclilo donde cualquier miembro (excepto -H o, -OH) de dicho grupo es optativamente sustituido; y

R^1 y R^2 se seleccionan independientemente del grupo formado por -H y alquilo donde el alquilo es optativamente sustituido; y

R^3 se selecciona del grupo formado por -H y -OH; y

R^4 y R^5 se seleccionan independientemente del grupo formado por -H, alquilo, carbociclilo, carbociclilalquilo, heterociclilo, y heterociclilalquilo donde cualquier miembro (excepto -H) de dicho grupo es optativamente sustituido; y

R^6 se selecciona del grupo formado por -CN y -OH; y

R^7 se selecciona del grupo formado por -H, halógeno, -OH, alquilo, alcoxi, y alcoxialquilo donde el alquilo , alcoxi, o alcoxialquilo es optativamente sustituido; y

R^8 se selecciona del grupo formado por -OH y alcoxi donde el alcoxi es optativamente sustituido; y

ni R^1 ni R^2 forman una estructura de anillo con E^2, E^3, E^4, o E^5; y

ni R^4 ni R^5 forman una estructura de anillo con E^2, E^4, o E^5; y

E^5 no es -H cuando E^3 es -C(R^7)(R^8)- y E^4 es un enlace.

Industria y Comercio
SUPERINTENDENCIA

1426 0970

2020
Bogotá, D.C.,

Doctor:
RAMIRO CASTRO DUQUE
Apoderado
PHARMACIA CORPORATION.

Oficio N°
01685

ASUNTO:	Radicación N°	03-99304
	Solicitud internacional	PCT/US2002/15257
	Fecha inicio fase nacional	11/12/2003
	Trámite	011
	Evento	379
	Actuación	430
	Folios	001

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

- La solicitud no contiene la copia del documento en que consta la cesión del derecho a la patente del inventor al solicitante o a su causante. (Art. 26-k) Decisión 486).
- La solicitud no contiene el poder debidamente otorgado, con el lleno de los requisitos exigidos por los artículos 63 y subsiguientes del Código de Procedimiento Civil. Adicionalmente, deberá presentar el documento que acredita la existencia y representación legal de la sociedad solicitante, cuando ésta fuere persona jurídica.

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

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

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

13 FEB. 200

El anterior requerimiento fue notificado por fijación en lista de fecha_____.

202057