

**FORMULARIO UNICO 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: AXYS
PHARMACEUTICALS, INC.
Dirección: 180-Kimball Way South
San Francisco, California 94080
Estados Unidos
Nacionalidad o domicilio: California,
Estados Unidos
Lugar de constitución: California,
Estados Unidos

IDENTIFICACIÓN

C.C. ☐ NIT: ☒

C.E. ☐ OTRO ☐

NÚMERO Cual

Teléfono: Fax:
E. Mail:

**3) REPRESENTANTE
O APODERADO**

Nombre: DILIA MARÍA RODRÍGUEZ
D'ALEMAN
Dirección: Carrera 11 N°. 93-43 Of.
404 Santafé de Bogotá D.C.

Teléfono: 6350835 Fax: 6350824
E. Mail:
clarkemodet@clarkemodet.com.co

IDENTIFICACIÓN

C.C. ☒ NIT: ☐

C.E. ☐ OTRO ☐

NÚMERO: 41.854.882
TP: 20824 CSJ

**4) INVENTOR (ES)
(72)**

Nombre: 1. PATTERSON, John, W. 2. ZIPFEL, Sheila
Dirección: 1. 1619 Montalto Drive, Mountain View, CA 94040
Estados Unidos. 2. 112 E. Middlefield Road, Unit B Mountain
View, CA 9403 Estados Unidos
Nacionalidad o Domicilio: California, Estados Unidos

5) PCT (86)

Solicitud Internacional No. PCT/US02/17922 Fecha: Junio 4, 2002

Publicación Internacional No. WO 02/098406 A 1 Fecha: Diciembre 12, 2002

**6) Título (54) COMPUESTOS Y COMPOSICIONES NOVEDOSAS COMO
INHIBIDORES DE CATEPSINA**

7) Clasificación Internacional: A61K 31/277, C07C 255/42

8) PRIORIDAD	33) País de Origen	(32) Fecha	(31) Número de Solicitud
	ESTADOS UNIDOS	JUNIO 4, 2001	60/295,744
SI ☒ NO ☐			

9) Comprobante de pago N°: 03-88.904 Fecha: DICIEMBRE 5, 2003

2

SUPERINDUSTRIA Y COMERCIO
Radicacion : 03113869 00000000 Folios: 201
Fecha (MM): 2003-12-08 15:42:42
Tramite : 011 PCI-PAIENT 379 FASE NUL3 411 PRESENTAC
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 03 - 88,904
FECHA : DICIEMBRE 5 DE 2003

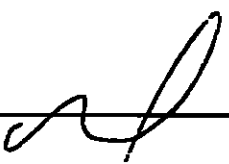
***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
CLARKE MODET Y CO. COLOMBIA	CONSIGNACION	BANCO POPULAR	050-00110-6	14329295	03/12/2003	9,754,000.00

***** CONCEPTO *****

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. _____

8504

10)

ANEXOS

- ☒ Comprobante de pago de la tasa de presentación de la solicitud
- ☐ Comprobante de pago por reivindicación de prioridad
- ☐ Documento que acredite la existencia y representación legal cuando el solicitante sea persona Jurídica
- ☐ Poderes, si fuera el caso
- ☐ Documento de cesión del inventor al solicitante o a su causante
- ☐ Declaraciones
- ☒ Copia de la solicitud Internacional. (Resumen, descripción, reivindicación, Dibujos).
- ☒ Traducción de la solicitud Internacional al castellano. (Resumen, descripción, reivindicación, Dibujos)
- ☐ Copia del examen preliminar efectuado por la IPEA
- ☐ De ser el caso, copia del contrato de acceso
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas
- ☐ De ser el caso, certificado de depósito del material biológico
- ☐ Arte final 12 x 12 y 6 x 6 cm
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionados parcial o totalmente con la invención de esta solicitud.
- ☐ Otros:
 1. Reporte de Búsqueda internacional
 2. opinión escrita
 3. Solicitud de modificación del solicitante
 4. Solicitud de modificación dirección de uno de los inventores

11) FIGURA CARACTERÍSTICA:

12) Solicitud concesión de la patente,

NOMBRE: DILIA RODRÍGUEZ D'ALEMAN

FIRMA:


C.C. 41.654.882 de Bogotá TP 20824 CSJ

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

NSC

PATENT COOPERATION TREATY

From the
INTERNATIONAL PRELIMINARY EXAMINING AUTHORITYTo:
NATHAN S. CASSELL
TOWNSEND AND TOWNSEND AND CREW LLP
TWO EMBARCADERO CENTER, 8TH FLOOR
SAN FRANCISCO, CALIFORNIA 94111-3834

PCT

WRITTEN OPINION

(PCT Rule 66)

Applicant's or agent's file reference 15058-34PC 015058-003400PC		Date of Mailing (day/month/year) 27 AUG 2003
International application No. PCT/US02/17922		REPLY DUE 9-27-03 within 1 month/days from the above date of mailing
International filing date (day/month/year) 04 June 2002 (04.06.2002)	Priority date (day/month/year) 04 June 2001 (04.06.2001)	
International Patent Classification (IPC) or both national classification and IPC IPC(7): A61K 31/277; C07C 253/42 and US Cl.: 514/621; 558/393		
Applicant CELERA		

1. This written opinion is the first (first, etc.) drawn by this International Preliminary Examining Authority.

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

- I ☒ Basis of the opinion
- 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 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 hereby 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 66.4 bis.
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: 04 October 2003 (04.10.2003)

Name and mailing address of the IPEA/US Commissioner of Patents and Trademarks Box PCT Washington, D.C. 20231 Facsimile No. (703)305-3230	Authorized officer <i>Rebecca L. Anderson</i> Telephone No. (703) 308-1235
---	--

Form PCT/IPEA/408 (cover sheet)(July 1998)

9-27-03
Response to Written opinion
DOCKETED BY AW

WRITTEN OPINION

International application No.

PCT/US02/17922

I. Basis of the opinion

1. With regard to the elements of the international application:*

- ☒ the international application as originally filed
- ☒ the description:
 pages 1-53, as originally filed
 pages NONE, filed with the demand
 pages NONE, filed with the letter of _____.
- ☒ the claims:
 pages 54-63, as originally filed
 pages NONE, as amended (together with any statement) under Article 19
 pages NONE, filed with the demand
 pages NONE, filed with the letter of _____.
- ☒ the drawings:
 pages NONE, as originally filed
 pages NONE, filed with the demand
 pages NONE, filed with the letter of _____.
- ☐ the sequence listing part of the description:
 pages NONE, as originally filed
 pages NONE, filed with the demand
 pages NONE, filed with the letter of _____.

2. With regard to the language, all the elements marked above were available or furnished to this Authority in the language in which the international application was filed, unless otherwise indicated under this item. These elements were available or furnished to this Authority in the following language _____ which is:

- ☐ the language of a translation furnished for the purposes of international search (under Rule 23.1(b)).
- ☐ the language of publication of the international application (under Rule 48.3(b)).
- ☐ the language of the translation furnished for the purposes of international preliminary examination (under Rules 55.2 and/or 55.3).

3. With regard to any nucleotide and/or amino acid sequence disclosed in the international application, the written opinion was drawn on the basis of the sequence listing:

- ☐ contained in the international application in printed form.
- ☐ filed together with the international application in computer readable form.
- ☐ furnished subsequently to this Authority in written form.
- ☐ furnished subsequently to this Authority in computer readable form.
- ☐ The statement that the subsequently furnished written sequence listing does not go beyond the disclosure in the international application as filed has been furnished.
- ☐ The statement that the information recorded in computer readable form is identical to the written sequence listing has been furnished.

4. ☐ The amendments have resulted in the cancellation of:

- ☐ the description, pages NONE
- ☐ the claims, Nos. NONE
- ☐ the drawings, sheets/fig NONE

5. ☐ This opinion has been drawn as if (some of) the amendments had not been made, since they have been considered to go beyond the disclosure as filed, as indicated in the Supplemental Box (Rule 70.2(c)).

* Replacement sheets which have been furnished to the receiving Office in response to an invitation under Article 14 are referred to in this opinion as "originally filed."

WRITTEN OPINION

International application No.

PCT/US02/17922

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

1. The question whether the claimed invention appears to be novel, to involve an inventive step (to be non-obvious), or to be industrially applicable have not been examined in respect of:

☐ the entire international application,

☒ claims Nos. 1-5 and 9

because:

☐ the said international application, or the said claim Nos. _____ relate to the following subject matter which does not require international preliminary examination (*specify*):

☐ the description, claims or drawings (*indicate particular elements below*) or said claims Nos. _____ are so unclear that no meaningful opinion could be formed (*specify*):

☐ the claims, or said claims Nos. _____ are so inadequately supported by the description that no meaningful opinion could be formed.

☒ no international search report has been established for said claims Nos. 1-5 and 9.

2. A written opinion cannot be drawn due to the failure of the nucleotide and/or amino acid sequence listing to comply with the standard provided for in Annex C of the Administrative Instructions:

☐ the written form has not been furnished or does not comply with the standard.

☐ the computer readable form has not been furnished or does not comply with the standard.

WRITTEN OPINION

International application No.
PCT/US02/17922

V. Reasoned statement under Rule 66.2(a)(ii) with regard to novelty, inventive step or industrial applicability; citations and explanations supporting such statement

1. STATEMENT

Novelty (N)	Claims <u>6-8 and 10</u>	YES
	Claims <u>NONE</u>	NO
Inventive Step (IS)	Claims <u>6-8 and 10</u>	YES
	Claims <u>NONE</u>	NO
Industrial Applicability (IA)	Claims <u>6-8 and 10</u>	YES
	Claims <u>NONE</u>	NO

2. CITATIONS AND EXPLANATIONS

Claims 6-8 and 10 meet the criteria set out in PCT Article 33(2)-(4), because the prior art does not teach or fairly suggest the compounds 2-butyl-N-cyanomethyl-N'-phenyl-malonamide, N-Cyanomethyl-2-cyclohexylmethyl-N'-phenyl-malonamide or N-Cyanomethyl-2-cyclohexylmethyl-N'-phenethyl-malonamide.

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WRITTEN OPINION

International application No.

PCT/US02/17922

VIII. Certain observations on the international application

The following observations on the clarity of the claims, description, and drawings or on the questions whether the claims are fully supported by the description, are made:

In these claims, the numerous variables (e.g. R1-R14, X1-X5, etc.) and their voluminous complex meanings and their seemingly endless permutations and combinations make it virtually impossible to determine the full scope and complete meaning of the claimed subject matter. As presented, the claimed subject matter cannot be regarded as being a clear and concise description for which protection is sought and as such the listed claims do not comply with the requirements of PCT article 6. Thus it is impossible to carry out a meaningful written opinion on same. The written opinion will be made on the first discernable invention of claims 6-8 and 10, which is the products, preparation and methods of use for the first 3 compounds of claim 6.

WRITTEN OPINION

International application No.
PCT/US02/17922

Supplemental Box
(To be used when the space in any of the preceding boxes is not sufficient)

TIME LIMIT:

The time limit set for response to a Written Opinion may not be extended. 37 CFR 1.484(d). Any response received after the expiration of the time limit set in the Written Opinion will not be considered in preparing the International Preliminary Examination Report.

**TOWNSEND
and
TOWNSEND
and
CREW**

LLP

Denver, Colorado
Tel 303 571-4000

Palo Alto, California
Tel 650 328-2400

Seattle, Washington
Tel 206 457-9600

San Francisco ^{12/10}

Two Embarcadero Cen
Eighth Floor
San Francisco
California 94111-3834
Tel 415 576-0200
Fax 415 576-0300

November 24, 2003

VIA EXPRESS MAIL

PCT International Application Processing Division
USPTO International Division
Commissioner for Patents
Mail Stop PCT
PO Box 1450
Alexandria, VA 22313-1450

**CHANGE OF REQUEST UNDER
92-bis**

RE: International Application No.: PCT/US02/17922
Title: NOVEL COMPOUNDS AND COMPOSITIONS AS CATHEPSIN INHIBITORS
Applicant: AXYS PHARMACEUTICALS, INC.
International Filing Date: 4 June 2002
Express Mail Label No.: EV 348 111 255 US
Date Mailing: November 24, 2003
Our File No.: 15058-34PC

Dear Sir or Madam:

Pursuant to Rule 92-bis, Applicants for the above-referenced application respectfully request to change Applicants' name of record to:

**AXYS PHARMACEUTICALS, INC.
180 Kimball Way
South San Francisco, California 94080
United States of America**

At this time, Applicants respectfully submits three (3) fully executed Powers of Attorney reflecting Applicants' change of name for the above-referenced application.

Applicants respectfully request a copy of Form PCT/IB/306 indicating the recordation of the above-referenced change.

Respectfully submitted,

Townsend and Townsend and Crew LLP


Nathan S. Cassell
Patent Agent Reg. No. 42,396

NSC/kec

Enclosures: Three (3) Powers of Attorney

cc: The International Bureau of WIPO via facsimile: 011-41-22-740-1435 (with enclosures).

60079012 v1

PCT

POWER OF ATTORNEY

(for an international application filed under the Patent Cooperation Treaty)

(PCT Rule 90.4)

The undersigned applicant(s) (names should be indicated as they appear in the request):

AXYS PHARMACEUTICALS, INC.
180 Kimball Way
South San Francisco, California 94080
United States of America

hereby appoints (appoint) the following person 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.)

Nathan S. Cassell Reg. No. 42,396, William B. Kezer, Reg. No. 37,369, Joel Ackerman Reg. No. 24,307, Scott L. Ausenhus Reg. No. 42,271, Kevin Bastain Reg. No. 34,774, Rosemarie L. Celli Reg. No. 42,397, Harrison Dillon Reg. No. 46,661, Todd Esker Reg. No. 46,690, Carol Fang Reg. No. 48,631, Chuan Gao Reg. No. 54,111, Eugenia Garrett-Wackowski Reg. No. 37,330, Brigitte Hajos Reg. No. 50,971, Matthew Hinsch Reg. No. 47,651, Laurence Hyman Reg. No. 35,551, Kenneth Jenkins Reg. No. 51,846, Beth L. Kelly Reg. No. 51,868, Jean Lockyer Reg. No. 44,879, Jeffry Mann Reg. No. 42,837, Frank Mycroft Reg. No. 46,946, Annette Parent Reg. No. 42,058, Donald Schelling Reg. No. 53,558, Joseph Synder Reg. No. 39,381, Kenneth Weber Reg. No. 31,677

TOWNSEND AND TOWNSEND AND CREW LLP
Two Embarcadero Center, 8th Floor
San Francisco, California 94111-3834
United States of America

to represent the undersigned before

☒ all the competent International Authorities

☐ the International Searching Authority only

☐ the International Preliminary Examining Authority only

in connection with the international application identified below:

Title of the invention: NOVEL COMPOUNDS AND COMPOSITIONS AS CATHEPSIN INHIBITORS

Applicant's or agent's file reference: 15058-34PC

International application number (if already available): PCT/US02/17922

filed with the following Office US as receiving Office and to make or receive payments on behalf of the undersigned.

Signature of the applicant(s) (where there are several applicants, each of them must sign; 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 or this power):

By



Name: Wayne Montgomery

Title: Vice President, Intellectual Property

Date:



12

PCT

POWER OF ATTORNEY

(for an international application filed under the Patent Cooperation Treaty)

(PCT Rule 90.4)

The undersigned applicant(s) (names should be indicated as they appear in the request):

John W. Patterson
1619 Montalto Drive
Mountain View, California 94040
United States of America

hereby appoints (appoint) the following person 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.)

Nathan S. Cassell Reg. No. 42,396, William B. Kezer, Reg. No. 37,369, Joel Ackerman Reg. No. 24,307, Scott L. Auschus Reg. No. 42,271, Kevin Bastain Reg. No. 34,774, Rosemarie L. Celli Reg. No. 42,397, Harrison Dillon Reg. No. 46,661, Todd Eaker Reg. No. 46,690, Carol Pang Reg. No. 48,631, Chuan Gao Reg. No. 54,111, Eugenia Garrett-Wackowski Reg. No. 37,330, Brigitte Hajos Reg. No. 50,971, Matthew Hinsch Reg. No. 47,651, Laurence Hyman Reg. No. 35,551, Kenneth Jenkins Reg. No. 51,846, Beth L. Kelly Reg. No. 51,868, Jean Lockyer Reg. No. 44,879, Jeffry Mann Reg. No. 42,837, Frank Mycroft Reg. No. 46,946, Annette Parent Reg. No. 42,058, Donald Schelling Reg. No. 53,558, Joseph Synder Reg. No. 39,381, Kenneth Weber Reg. No. 31,677

TOWNSEND AND TOWNSEND AND CREW LLP

Two Embarcadero Center, 8th Floor
San Francisco, California 94111-3834
United States of America

to represent the undersigned before:

☒ all the competent International Authorities

☐ the International Searching Authority only

☐ the International Preliminary Examining Authority only

in connection with the international application identified below:

Title of the invention: NOVEL COMPOUNDS AND COMPOSITIONS AS CATHEPSIN INHIBITORS

Applicant's or agent's file reference: 15058-34PC

International application number (if already available): PCT/US02/17922

filed with the following Office US as receiving Office and to make or receive payments on behalf of the undersigned.

Signature of the applicant(s) (where there are several applicants, each of them must sign; 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 or this power):

By John W. Patterson

Name: John W. Patterson

Title: Inventor/Applicant (for U.S. only)

Date: Nov 20, 2003

13

PCT

POWER OF ATTORNEY

(for an international application filed under the Patent Cooperation Treaty)

(PCT Rule 90.4)

The undersigned applicant(s) (names should be indicated as they appear in the request):

Sheila Zipfel
112 E Middlefield Rd., Unit B
Mountain View, CA 94043
United States of America

hereby appoints (appoint) the following person 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.)

Nathan S. Cassell Reg. No. 42,396, William B. Kezer, Reg. No. 37,369, Joel Ackerman Reg. No. 24,307, Scott L. Ausenhus Reg. No. 42,271, Kevin Bastain Reg. No. 34,774, Rosemarie L. Celli Reg. No. 42,397, Harrison Dillon Reg. No. 46,661, Todd Esker Reg. No. 46,690, Carol Fang Reg. No. 48,631, Chuan Gao Reg. No. 54,111, Eugenia Garrett-Wackowski Reg. No. 37,330, Brigitte Hajos Reg. No. 50,971, Matthew Hinsch Reg. No. 47,651, Laurence Hyman Reg. No. 35,551, Kenneth Jenkins Reg. No. 51,846, Beth L. Kelly Reg. No. 51,868, Jean Lockyer Reg. No. 44,879, Jeffry Mann Reg. No. 42,837, Frank Mycroft Reg. No. 46,946, Annette Parent Reg. No. 42,058, Donald Schelling Reg. No. 53,558, Joseph Synder Reg. No. 39,381, Kenneth Weber Reg. No. 31,677

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Two Embarcadero Center, 8th Floor
San Francisco, California 94111-3834
United States of America

to represent the undersigned before

☒ all the competent International Authorities

☐ the International Searching Authority only

☐ the International Preliminary Examining Authority only

in connection with the international application identified below:

Title of the invention: NOVEL COMPOUNDS AND COMPOSITIONS AS CATHEPSIN INHIBITORS

Applicant's or agent's file reference: 15058-34PC

International application number (if already available): PCT/US02/17922

filed with the following Office US as receiving Office and to make or receive payments on behalf of the undersigned.

Signature of the applicant(s) (where there are several applicants, each of them must sign; 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 or this power):

By

Name: Sheila Zipfel

Title: Inventor/Applicant (for U.S. only)

Date:

4/20/03

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/17922

A. CLASSIFICATION OF SUBJECT MATTER

IPC(7) : A61K 31/277; C07C 255/42
US CL : 514/621; 558/393

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

B. FIELDS SEARCHED

Minimum documentation searched (classification system followed by classification symbols)
U.S. : 514/621; 558/393

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

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
Please See Continuation Sheet

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category *	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	WO 01/019796 A1 (AXYS PHARMACEUTICALS, INC.) 22 March 2001 pages 1-3; claims 1, 11, 12 and 14.	6-8, 10



Further documents are listed in the continuation of Box C.



See patent family annex.

Special categories of cited documents:	
"A" document defining the general state of the art which is not considered to be of particular relevance	"T" later document published after the international filing date or priority date and not in conflict with the application but cited to underscore the principle or theory underlying the invention
"B" earlier application or patent published on or after the international filing date	"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
"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)	"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
"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	"E" document member of the same patent family

Date of the actual completion of the international search

05 September 2002 (05.09.2002)

Date of mailing of the international search report

18 OCT 2002

Name and mailing address of the ISA/US

Consultation of Patents and Trademarks
Box PCT
Washington, D.C. 20531

Facsimile No. (703)305-3230

Authorized officer

Rebecca L. Anderson

Telephone No. (703) 605-1157

INTERNATIONAL SEARCH REPORT

International application No.

PCT/US02/17922

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

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

1. ☒ Claim Nos.: 9
because they relate to subject matter not required to be searched by this Authority, namely:
because it is a use claim which is an improper definition of a process claim
2. ☒ Claim Nos.: 1-5
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:
Please See Continuation Sheet
3. ☐ Claim 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

PCT/US02/17922

Continuation of Box I Reason 2:

In these claims, the numerous variables (e.g. R1-R14, X1-X5, etc.) and their voluminous complex meanings and their seemingly endless permutations and combinations make it virtually impossible to determine the full scope and complete meaning of the claimed subject matter. As presented, the claimed subject matter cannot be regarded as being a clear and concise description for which protection is sought and as such the listed claims do not comply with the requirements of PCT article 6. Thus it is impossible to carry out a meaningful search on same. A search will be made on the first discernable invention of claims 6-8 and 10, which is the products, preparation, and methods of use for the first 3 compounds of claim 6.

Continuation of B. FIELDS SEARCHED Item 3:

CAS ONLINE

STN structure search

**TOWNSEND
and
TOWNSEND
and
CREW**

LLP

San Francisco, California
Tel 415 576-0200

San Diego, California
Tel 858 350-6100

Walnut Creek, California
Tel 925 472-5000

Denver, Colorado
Tel 303 571-4000

Seattle, Washington
Tel 206 467-9800

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**CHANGE OF REQUEST UNDER
92-bis**

Re: International Application No.: PCT/US02/17922
Title: NOVEL COMPOUNDS AND COMPOSITIONS AS CATHEPSIN INHIBITORS
Applicant: AXYS PHARMACEUTICALS, INC.
International Filing Date: 04 June 2002
Express Mail Label: EV 348 112 945 US
Date Mailing: 24 November 2003
Our File No.: 15058-34PC

Dear Sir or Madam:

Pursuant to Rule 92-bis, Inventor/Applicant (for U.S. only) for the above-referenced application respectfully request that a change in mailing address be recorded for inventor/applicant Sheila Zipfel from

Sheila Zipfel
380 Edlee Avenue
Palo Alto, CA 94306

to

Sheila Zipfel
112 E. Middlefield Road, Unit B
Mountain View, CA 9403

At this time, Inventor/Applicant (for U.S. only) respectfully submits the fully executed Power of Attorney reflecting Inventor/Applicant (for U.S. only) address change for the above-referenced application.

Applicant respectfully request a copy of Form PCT/IB/306 indicating the recordation of the above-referenced changes.

Very truly yours,



Nathan S. Cassell
Patent Agent Reg. No. 42, 396

Enclosure: One (1) Power of Attorney
NSC/kcc

cc: The International Bureau of WIPO via facsimile: 011-41-22-740-1435 (with enclosure).
6008842 v1

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POWER OF ATTORNEY

(for an international application filed under the Patent Cooperation Treaty)

(PCT Rule 90.4)

The undersigned applicant(s) (names should be indicated as they appear in the request):

Sheila Zipfel
112 E Middlefield Rd., Unit B
Mountain View, CA 94043
United States of America

hereby appoints (appoint) the following person 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.)

Nathan S. Cassell Reg. No. 42,396, William B. Kezer, Reg. No. 37,369, Joel Ackerman Reg. No. 24,307, Scott L. Ausenhus Reg. No. 42,271, Kevin Bastain Reg. No. 34,774, Rosemarie L. Celli Reg. No. 42,397, Harrison Dillon Reg. No. 46,661, Todd Esker Reg. No. 46,690, Carol Fang Reg. No. 48,631, Chuan Gao Reg. No. 54,111, Eugenia Garrett-Wackowski Reg. No. 37,330, Brigitte Hajos Reg. No. 50,971, Matthew Hinsch Reg. No. 47,651, Laurence Hyman Reg. No. 35,551, Kenneth Jenkins Reg. No. 51,846, Beth L. Kelly Reg. No. 51,868, Jean Lockyer Reg. No. 44,879, Jeffry Mann Reg. No. 42,837, Frank Mycroft Reg. No. 46,946, Annette Parent Reg. No. 42,058, Donald Schelling Reg. No. 53,558, Joseph Synder Reg. No. 39,381, Kenneth Weber Reg. No. 31,677

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United States of America

to represent the undersigned before

☒ all the competent International Authorities

☐ the International Searching Authority only

☐ the International Preliminary Examining Authority only

in connection with the international application identified below:

Title of the invention: NOVEL COMPOUNDS AND COMPOSITIONS AS CATHEPSIN INHIBITORS

Applicant's or agent's file reference: 15058-34PC

International application number (if already available): PCT/US02/17922

filed with the following Office US as receiving Office and to make or receive payments on behalf of the undersigned.

Signature of the applicant(s) (where there are several applicants, each of them must sign; 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 or this power):

By Sheila Zipfel

Name: Sheila Zipfel

Title: Inventor/Applicant (for U.S. only)

Date: 4/20/03

COMPUESTOS Y COMPOSICIONES NOVEDOSAS COMO INHIBIDORES DE CATEPSINA

LA INVENCION

Esta solicitud se relaciona con compuestos y composiciones para tratar enfermedades asociadas con actividad de cisteína proteasa, particularmente enfermedades asociadas con enfermedad de catepsina S.

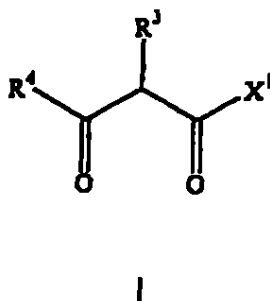
DESCRIPCION DEL CAMPO

Las proteasas de cisteína representan una clase de peptidasa caracterizada por la presencia de un residuo de cisteína en el sitio catalítico de la enzima. Las proteasas de cisteína están asociadas con la elaboración normal y el procesamiento de proteína. La actividad aberrante de las proteasas de cisteína, por ejemplo, como resultado de la expresión de incremento o activación mejorada, sin embargo, puede tener consecuencias patológicas. A este respecto, ciertas cisteínas proteasas están asociadas con un número de estados de enfermedad, incluyendo artritis, distrofia

muscular, inflamación, invasión tumoral, glomerulonefritis, mamaria, enfermedad periodontal, leucodistrofia metacromática y otros. Un incremento en la actividad de catepsina S contribuye a la patología y/o sintomatología de numerosas enfermedades. De acuerdo con esto, las moléculas que exhiben la actividad de la proteasa catepsina S son útiles como agentes terapéuticos en el tratamiento de tales enfermedades.

RESUMEN DE LA INVENCION

Esta solicitud se relaciona con compuestos de Fórmula I:



En el cual:

X^1 es $-NHC(R^1)(R^2)X^2$ o $-NHX^3$;

X^2 es clano, $-C(R^7)(R^8)X^3$, $-C(R^7)(R^8)CF_3$, $-C(R^7)(R^8)CF_2CF_2R^9$, $-CH=CHS(O)_2R^5$, $-C(O)CF_2C(O)NR^5R^5$, $-C(O)C(O)NR^5R^6$, $-C(O)C(O)OR^5$, $-C(O)CH_2OR^5$, $-C(O)CH_2N(R^9)SO_2R^5$ o $-C(O)C(O)R^5$; en donde R^5 es alquilo (C_{1-4}), arilo (C_{5-10}) alquilo (C_{0-8}) o heteroarilo (C_{5-10}) alquilo (C_{0-8}); R^6 es hidrógeno o alquilo (C_{1-8}); R^7 es hidrógeno o alquilo (C_{1-4}) y R^8 es hidroxil o R^7 y R^8 juntos forman oxo; R^9 es hidrógeno, halo, alquilo (C_{1-4}), arilo (C_{5-10}) alquil (C_{0-8}) o heteroarilo (C_{5-10}) alquilo (C_{0-8});

X^3 comprende un anillo heteromonocíclico que contiene 4 a 6 miembros del anillo o un sistema de anillo heterobicíclico fusionado que contiene 8 a 14 átomos miembros del anillo y cualquier cetona carbocíclica, Iminocetona o tiocetona derivado de esta;

En donde dentro de R^5 , X^2 o X^3 cualquier sistema de anillo alicíclico o aromático puede ser sustituida adicionalmente por 1 a 5 radicales independientemente seleccionados de alquilo (C_{1-8}),

alquilideno (C_{1-6}), ciano, halo, alquilo (C_{1-6}) halo-sustituído, nitró, $-X^4NR^{12}R^{12}$, $-X^4NR^{12}C(O)R^{12}$, $-X^4NR^{12}C(O)OR^{12}$, $-X^4NR^{12}C(O)NR^{12}R^{12}$, $-X^4NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^4OR^{12}$, $-X^4SR^{12}$, $-X^4C(O)OR^{12}$, $-X^4C(O)R^{12}$, $-X^4OC(O)R^{12}$, $-X^4C(O)NR^{12}R^{12}$, $-X^4S(O)_2NR^{12}R^{12}$, $-X^4NR^{12}S(O)_2R^{12}$, $-X^4P(O)(OR^{12})OR^{12}$, $O-X^4OP(O)(OR^{12})OR^{12}$, $-X^4NR^{12}C(O)R^{13}$, $-X^4S(O)R^{13}$ y $-X^4S(O)_2R^{13}$ y/o 1 radical seleccionado de $-R^{14}$, $-X^4OR^{14}$, $-X^4SR^{14}$, $-X^4S(O)R^{14}$, $-X^4S(O)_2R^{14}$, $-X^4C(O)R^{14}$, $-X^4C(O)OR^{14}$, $-X^4OC(O)R^{14}$, $-X^4NR^{14}R^{12}$, $-X^4NR^{12}C(O)R^{14}$, $-X^4NR^{12}C(O)OR^{14}$, $-X^4C(O)NR^{12}R^{12}$, $-X^4S(O)_2NR^{14}R^{12}$, $-X^4NR^{12}S(O)_2R^{14}$, $-X^4NR^{12}C(O)NR^{14}R^{12}$ y $-X^4NR^{12}C(NR^{12})NR^{14}R^{12}$, en donde X^4 es un enlace o alquilo (C_{1-6}); R^{12} en cada ocurrencia Independientemente es hidrógeno, alquilo (C_{1-6}), o alquilo (C_{1-6}) halo-sustituído; R^{13} es alquilo (C_{1-6}) o alquilo (C_{1-6}) halo-sustituído; y R^{14} es cicloalquilo (C_{3-10}) alquilo (C_{6-8}), hetero (C_{3-10}) cicloalquilo (C_{6-8}) alquilo, arilo (C_{6-10}) alquilo (C_{6-8}), hetero arilo (C_{5-10}) alquilo (C_{6-8}), bicicloarilo (C_{8-10}) alquilo (C_{6-8}) o hetero (C_{8-10}) bicicloarilo (C_{6-8}) alquilo;

R^1 es hidrógeno, halo o (C_{1-6}) alquilo y R^2 se selecciona del grupo que consiste de hidrógeno, ciano halo, $-X^4NR^{12}R^{12}$, $-X^4NR^{12}C(O)R^{12}$, $-X^4NR^{12}C(O)OR^{12}$, $-4X^4NR^{12}C(O)NR^{12}R^{12}$, $-X^4NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^4OR^{12}$, $-X^4SR^{12}$, $-X^4C(O)OR^{12}$, $-X^4C(O)R^{12}$, $-X^4OC(O)R^{12}$, $-X^4C(O)NR^{12}R^{12}$, $-X^4S(O)_2NR^{12}R^{12}$, $-X^4NR^{12}S(O)_2R^{12}$, $-X^4P(O)(OR^{12})OR^{12}$, $-X^4OP(O)(OR^{12})OR^{12}$, $-X^4NR^{12}C(O)R^{12}$, $-X^4S(O)R^{13}$, $-X^4S(O)_2R^{13}$, $-R^{14}$, $-X^4OR^{14}$, $-X^4SR^{14}$, $-X^4S(O)R^{14}$, $-X^4S(O)_2R^{14}$, $-$

$X^4C(O)OR^4$, $-X^4C(O)OR^{14}$, $-X^4OC(O)R^{14}$, $-X^4NR^{14}R^{12}$, $X^4NR^{12}C(O)R^{14}$, $-X^4NR^{12}C(O)OR^{14}$, $-X^4C(O)NR^{12}R^{12}$, $-X^4S(O)_2NR^{14}R^{12}$, $-X^4NR^{12}S(O)_2R^{14}$, $-XNR^{12}C(O)NR^{14}R^{12}$ y $-X^4NR^{12}C(NR^{12})NR^{14}R^{12}$, en donde X^4 , R^2 , R^{13} y R^{14} son como se definió anteriormente; o R^1 y R^2 tomados juntos con el átomo de carbono al cual tanto R^1 y R^2 están unidos forman cicloalquilleno (C_{3-8}) o heterocicloalquilleno (C_{3-8}); en donde dentro de dicho R^2 cualquier heteroarilo, arilo, cicloalquilo, heterocicloalquilo, cicloalquilleno o heterocicloalquilleno es opcionalmente sustituido con 1 a 3 radicales independientemente seleccionados de alquilo (C_{1-6}), alquildieno (C_{1-6}), clano, halo alquilo (C_{1-6}) halo-sustituido, nitro, $-X^4NR^{12}R^{12}$, $-X^4NR^{12}C(O)R^{12}$, $-X^4NR^{12}C(O)OR^{12}$, $-X^4NR^{12}C(O)NR^{12}R^{12}$, $-X^4NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^4OR^{12}$, $-X^4SR^{12}$, $-X^4C(O)OR^{12}$, $-X^4C(O)R^{12}$, $-X^4OC(O)R^{12}$, $-X^4C(O)NR^{12}R^{12}$, $-X^4S(O)_2NR^{12}R^{12}$, $-X^4NR^{12}S(O)_2R^{12}$, $-X^4P(O)(OR^{12})OR^{12}$, $-X^4OP(O)(OR^{12})OR^{12}$, $-X^4NR^{12}C(O)R^{13}$, $-X^4S(O)R^{13}$, $-X^4S(O)_2R^{13}$ y $-X^4C(O)R^{13}$, en donde X^4 , R^{12} y R^{13} son como se definió anteriormente;

R^3 es $-C(R^6)(R^6)X^5$, en donde R^6 es como se definió anteriormente y X^5 se selecciona de $-X^4NR^{12}R^{12}$, $-X^4NR^{12}C(O)R^{12}$, $-X^4NR^{12}C(O)OR^{12}$, $-X^4NR^{12}C(O)NR^{12}R^{12}$, $-X^4NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^4OR^{12}$, $-X^4SR^{12}$, $-X^4C(O)OR^{12}$, $-X^4C(O)R^{12}$, $-X^4OC(O)R^{12}$, $-X^4C(O)NR^{12}R^{12}$, $-X^4S(O)_2NR^{12}R^{12}$, $-X^4NR^{12}S(O)_2R^{12}$, $-X^4P(O)(OR^{12})OR^{12}$, $-X^4R^{12}$, $-X^4OP(O)(OR^{12})OR^{12}$, $-X^4C(O)R^{13}$, $-X^4NR^{12}C(O)R^{13}$,

$X^4S(O)R^{13}$ y $-X^4S(O)_2R^{13}$, $-R^{14}$, $-X^4OR^{14}$, $-X^4SR^{14}$, $-X^4S(O)R^{14}$, $-X^4S(O)_2R^{14}$, $-X^4C(O)R^{14}$, $-X^4C(O)OR^{14}$, $-X^4OC(O)R^{14}$, $-X^4NR^{14}R^{12}$, $-X^4NR^{12}C(O)R^{14}$, $-X^4NR^{12}C(O)OR^{14}$, $-XC(O)NR^{14}R^{12}$, $-X^4S(O)_2NR^{14}R^{12}$, $-X^4NR^{12}S(O)_2R^{14}$, $-X^4NR^{12}C(O)NR^{14}R^{12}$ y $-X^4NR^{12}C(NR^{12})NR^{14}R^{12}$ en donde X^4 , R^{12} , R^{13} y R^{14} son como se definió anteriormente;

R^4 es $-NR^8R$, $-NR^8R^{14}$, $-NR^8R^{15}$ o $-NR^8X^5C(O)R^{14}$ en donde R^8 , X^5 y R^{14} son como se definió anteriormente y R^{15} es hidrógeno, alquilo (C_{1-6}) o $-X^5OR^8$ en donde X^5 es como se describió anteriormente; o R^8 y R^{15} junto con el átomo de nitrógeno al cual R^8 y R^{15} están unidos de hetero cicloalquilo (C_{3-6}), heteroarilo (C_{5-6}) o hetero bicicloarilo (C_{8-10});

Dentro de R^3 y R^4 cualquier sistema de anillos aromáticos pueden ser sustituidos adicionalmente por 1-5 radicales Independientemente seleccionados de alquilo (C_{1-6}), alquillideno (C_{1-6}), ciano, halo, alquilo (C_{1-6}) halo-sustituido, nitro, $-X^4NR^{12}R^{12}$, $-X^4NR^{12}C(O)R^{12}$, $-X^4NR^{12}C(O)OR^{12}$, $-X^4NR^{12}C(O)NR^{12}R^{12}$, $-X^4NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^4OR^2$, $-X^4SR^{12}$, $-X^4C(O)OR^{12}$, $-X^4C(O)R^{12}$, $-X^4OC(O)R^{12}$, $-X^4C(O)NR^{12}R^{12}$, $-X^4S(O)_2NR^{12}R^{12}$, $-X^4NR^{12}SO_2R^{12}$, $-X^4P(O)(OR^{12})OR^{12}$, $-X^4OP(O)(OR^{12})OR^{12}$, $-NX^4NR^{12}C(O)R^{13}$, $-X^4S(O)R^{13}$, $-X^4C(O)R^{13}$ y $-X^4S(O)_2R^{13}$ y/o 1 radical seleccionado de $-R^{14}$, $-X^4OR^{14}$, $-X^4SR^{14}$, $-X^4S(O)R^{14}$, $-X^4S(O)_2R^{14}$, $-XC(O)R^{14}$, $-$

$X^4C(O)OR^{14}$, $-X^4OC(O)R^{14}$, $-X^4NR^{14}R^{12}$, $-X^4NR^{12}C(O)R^{14}$, $-X^4NR^{12}C(O)OR^{14}$ -
 $X^4C(O)NR^{14}R^{12}$, $-X^4S(O)_2NR^{14}R^{12}$, $-X^4NR^{12}S(O)_2R^{14}$, $-X^4NR^{12}C(O)NR^{14}R^{12}$ y -
 $X^4NR^{12}C(NR^{12})NR^{14}R^{12}$; y dentro de R^3 y R^4 cualquier porción alifática
 puede ser sustituida adicionalmente por 1-5 radicales
 Independientemente seleccionados de clano, halo, nitro, $-NR^{12}R^{12}$, -
 $NR^{12}C(O)R^{12}$, $-NR^{12}C(O)OR^{12}$, $-NR^{12}C(O)NR^{12}R^{12}$, $-NR^{12}C(NR^{12})NR^{12}R^{12}$, $-OR^{12}$, -
 SR^{12} , $-C(O)O^{12}$, $-C(O)R^{12}$, $-OC(O)R^{12}$, $-C(O)NR^{12}R^{12}$, $-S(O)_2NR^{12}R^{12}$, $-NR^{12}S(O)_2R^{12}$,
 $-P(O)(OR^{12})OR^{12}$, $-OP(O)(OR^{12})OR^{12}$, $-NR^{12}C(O)R^{13}$, $-S(O)R^{13}$ y $-S(O)_2R^{13}$; en
 donde X^4 , R^{12} , R^{13} y R^{14} son como se describió anteriormente;

Con la condición de solamente una estructura de anillo bicíclica
 está presente dentro de R^3 y R^4 ; y los derivados de N-óxido,
 derivados de prodroga, derivados protegidos, isómeros
 Inhibidores y mezclas de isómeros de estos; y las sales
 farmacéuticamente aceptables y solvatos (por ejemplo hidratos)
 de tales compuestos y los derivados de N-óxido, derivados de
 prodroga, derivados protegidos, isómeros individuales y mezclas
 de isómeros de estos.

Un segundo aspecto de la Invención es una composición
 farmacéutica que contiene un compuesto de Fórmula I o un
 derivado de N-óxido, isómero individual o mezcla de isómero de

esto, una sal farmacéuticamente aceptable de estos, en mezcla con uno o más excipientes adecuados.

Un tercer aspecto de la invención es un método para tratar una enfermedad en un animal en el cual la inhibición de catepsina S puede prevenir, inhibir o mejorar la patología y/o la sintomatología de la enfermedad, cuyo método comprende administrar al animal una cantidad terapéuticamente efectiva del compuesto de Fórmula I o un derivado de N-óxido, isómeros individual o mezcla de isómero de estos; o una sal farmacéuticamente aceptable de esta.

Un cuarto aspecto de la invención es el proceso para preparar compuestos de Fórmula I y los derivados de N-óxido, derivados de prodroga, derivados protegidos, isómeros individuales y mezclas de isómeros de estos; y sales farmacéuticamente aceptables de estos.

DESCRIPCIÓN DETALLADA DE LA INVENCION

Definiciones:

A menos que se establezca otra cosa, los siguientes términos utilizados en la especificación y reivindicaciones son definidos para los propósitos de esta solicitud y tienen los siguientes significados.

"Alcíclico" significa una porción caracterizada por la disposición de los átomos de carbono en las estructuras de anillo no aromático cerrado que tiene propiedades que semejan aquellos de los alifáticos y pueden ser saturados o parcialmente saturados con dos o más dobles o triples enlaces.

"Alifático" significa una porción caracterizada por una disposición de cadena recta o ramificada de los átomos de carbono constituyentes y pueden ser saturados o parcialmente insaturados con dos o más dobles o triples enlaces.

"Alquilo" representado por sí mismo significa un radical alifático recto o ramificado saturado o insaturado, que tiene el número de átomos de carbono indicado (por ejemplo, alquilo (C1-6) incluye metilo, etilo, propilo, isopropilo, butilo, sec-butilo, isobutilo, terc-butilo, vinilo, alilo, 1-propenilo, isopropenilo, 1-butenilo, 2-butenilo, 3-butenilo, 2-metilalilo, etinilo, 1-propinilo, 2-propinilo, y

similares). El Alquillo representado junto con otro radical (por ejemplo, como un arilalquillo) significa un radical divalente alifático recto o ramificado, saturado o insaturado que tiene el número de átomos indicado o cuando no se indican átomos significa un enlace (por ejemplo, arillo (C_{6-10}) alquillo (C_{2-3}) Incluye fenilo, benzilo, fenetilo, 1-fenetil 3-fenilpropilo y similares).

"Alquilleno", a menos que se indique otra cosa significa un radical divalente recto o ramificado, saturado o insaturado, alifático que tiene el número de átomos de carbono indicado (por ejemplo alquilleno (C1-6) Incluye metileno ($-CH_2-$), etileno ($-CH_2CH_2-$), trimetileno ($-CH_2CH_2CH_2-$), tetrametileno ($-CH_2CH_2CH_2CH_2-$) 2-butenileno ($-CH_2CH=CHCH_2-$), 2-metiltetrametileno ($-CH_2CH(CH_3)CH_2CH_2-$), pentametileno ($-CH_2CH_2CH_2CH_2CH_2-$) y similares).

"Alquillideno" significa un radical divalente recto o ramificado saturado o insaturado, alifático, que tiene el número de átomos de carbono indicado (por ejemplo, alquillideno (C_{1-8}) incluye metilideno ($=CH_2$), etilideno ($=CHCH_3$), isopropilideno ($=C(CH_3)_2$), propilideno ($=CHCH_2CH_3$), alilideno ($=CHCH=CH_2$), y similares).

"Amino" significa el radical $-NH_2$, a menos que se indique otra cosa, los compuestos de la invención que contienen porciones amino incluyen derivados protegidos de este. Los grupos protectores adecuados para porciones aminas incluyen acetilo, terc-butoxicarbonilo, benziloxycarbonilo, y similares.

"Animal" incluye humanos, mamíferos no humanos (por ejemplo perros, gatos, conejos, ganado, caballos, ovejas, cabras, cerdos, venados y similares) y no mamíferos (por ejemplo pájaros y similares).

"Aromáticos" significa una porción en donde los átomos constituyentes caracterizan un sistema de anillo insaturado, todos los átomos en el sistema de anillo son sp^2 hibridizados y el número total de electrones π es igual a $4n + 2$.

"Arillo" significa una agrupación de anillo monocíclico o bicíclico fusionado que contiene el número total de átomos de carbono de anillo indicado, en donde cada anillo está comprendido de 6 átomos de carbono de anillo y es aromático o cuando se fusiona con un segundo anillo forma una agrupación de anillo aromático. Por ejemplo, arillo (C_{8-10}) opcionalmente sustituido como se utilizó

en esta solicitud incluye, pero no está limitado a, bifenil-2-ilo, 2-bromofenilo, 2-bromocarbonilfenilo, 2-bromo-5-fluorofenilo, 4-terc-butilfenilo, 4-carbamoilfenilo, 4-carboxi-2-nitrofenilo, 2-clorofenilo, 4-clorofenilo, 3-clorocarbonilfenilo, 4-clorocarbonilfenilo, 2-cloro-4-fluorofenilo, 2-cloro-6-fluorofenilo, 4-cloro-2-nitrofenilo, 6-cloro-2-nitrofenilo, 2,6-dibromofenilo, 2,3-diclorofenilo, 2,5-diclorofenilo, 3,4-diclorofenilo, 2-difluorometoxifenilo, 3,5-dimetilfenilo, 2-etoxycarbonilfenilo, 2-fluorofenilo, 2-yodofenilo, 4-isopropilfenilo, 2-metoxifenilo, 4-metoxifenilo, 2-metilfenilo, 3-metilfenilo, 4-metilfenilo, 5-metil-2-nitrofenilo, 4-metilsulfonilfenilo, naft-2-ilo, 2-nitrofenilo, 3-nitrofenilo, 4-nitrofenilo, 2,3,4,5,6-pentafluorofenilo, fenilo, 2-trifluorometoxifenilo, 3-trifluorometoxifenilo, 4-trifluorometoxifenilo, 2-trifluorometilfenilo, 3-trifluorometilfenilo, 4-trifluorometilfenilo, 2-trifluorometilsulfanilfenilo, 4-trifluorometilsulfanilfenilo, y similares. Arilo (C_{6-10}) opcionalmente sustituido como se utiliza en esta solicitud incluye 3-acetilfenilo, 3-terc-butoxycarbonilaminometilfenilo, bifenil-4-ilo, 3-hidroxifenilo, 4-hidroxifenilo, 3-metoxifenilo, naft-2-ilo, 3-fenoxifenilo, fenilo, y similares.

"Bicicloarilo" significa una agrupación de anillos bicíclico que contiene el número de átomos de carbono de anillo indicado, en donde los anillos están ligados por un enlace simple o fusionado y al menos uno de los anillos que comprende la agrupación es aromático y cualquier derivado de cetona carboxídica, tiocetona o imidocetona de este (por ejemplo bicicloarilo (C₈₋₁₀) incluye ciclohexilfenilo, 1,2-dihidronaftilo, 2,4-dioxo-1,2,3,4-tetrahidronaftilo, indanilo, indenilo, 1,2,3,4-tetrahidronaftilo, y similares.

"Carbamilo" significa el radical $-C(O)NH_2$. A menos que se indique otra cosa, los compuestos que contienen porciones carbamilo contienen derivados protegidos de este. Los grupos protectores adecuados para porciones carbamilo incluyen acetilo, terc-butoxicarbonilo, benziloxicarbonilo, y similares y ambos los derivados protegidos y no protegidos caben dentro del alcance de la invención.

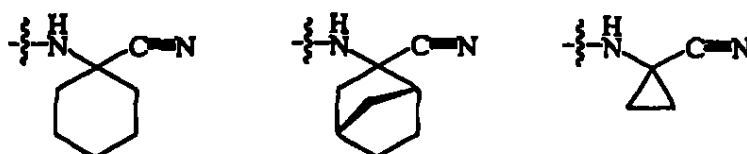
"Derivados de Cetona Carboxídicos" significa un derivado que contienen la porción $-C(O)-$.

"Carboxi" significa el radical $-C(O)OH$. A menos que se indique otra cosa, los compuestos de la invención que contiene porciones carboxi incluyen derivados protegidos de este. Los grupos protectores adecuados para las porciones carboxi incluyen benzilo, terc-butilo, y similares.

"Cicloalquilo" significa una agrupación de anillo saturado o parcialmente insaturado, monocíclico, bicíclico fusionado o policíclico puenteado que contiene el número de átomos de carbono del anillo indicado, y cualquier cetona carboxídica, tiocetona o derivados de iminocetona de este (por ejemplo, cicloalquilo (C3-10) incluye ciclopropilo, ciclobutilo, ciclopentilo, ciclohexilo, ciclohexenilo, 2,5-ciclohexadienilo, biciclo[2.2.2]octilo, adamantan-1-ilo, decahidronaftilo, oxociclohexilo, dioxociclohexilo, tiociclohexilo, 2-oxobiciclo[2.2.1]hept-1-ilo y similares).

"Cicloalquilleno" significa un anillo divalente saturado o parcialmente insaturado, monocíclico o una agrupación de anillo policíclico puenteado que contiene el número de átomos de carbono del anillo indicado, y cualquier cetonacarboxídica, tiocetona o iminocetona derivada de este. Por ejemplo, el caso en

donde "R¹ y R² juntos con el átomo de carbono al cual ambos R¹ y R² están unidos forman cicloalquileo (C₃₋₈)" Incluyen, pero no están limitados a, lo siguiente:



"Enfermedad" específicamente incluye cualquier condición no saludable de un animal o parte de este e incluye una condición no saludable y puede ser originada por, o ser incidente de, terapia médica o veterinaria aplicada a ese animal, es decir, los "Efectos colaterales" de tal terapia.

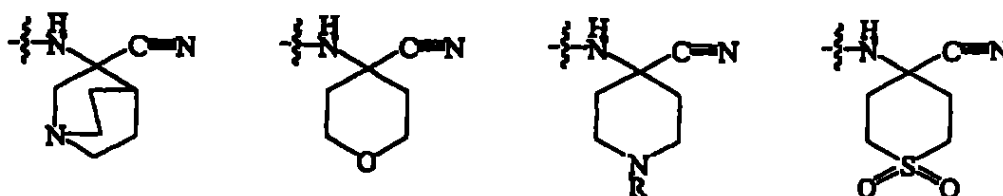
"Halo" significa fluoro, cloro, bromo, o yodo.

"Alquilo sustituido por Halo" es un grupo alilado o parte de un grupo mayor, significa "alquilo" sustituido por uno o más átomos "halo", tal como los términos se definen en esta solicitud. Alquilo halo-sustituido incluye haloalquilo, dihaloalquilo, trihaloalquilo, perhaloalquilo y similar (por ejemplo alquilo (C₁₋₃) halosustituido incluye clorometilo, diclorometilo, difluorometilo, trifluorometilo,

2,2,2-trifluoroetilo, percloroetilo, 2,2-trifluoro-1,1-dicloroetilo, y similares).

"Porciones de Heteroátomo" Incluye $-N=$, $-NR-$, $-O-$, $-S-$ o $-S(O)_2-$, en donde R es hidrógeno alquilo (C_{1-8}) o un grupo protector.

"Heterocicloalquilenos" significa cicloalquilenos, como se definió en esta solicitud, siempre y cuando uno o más de los átomos de carbono miembros del anillo indicado, se reemplace por una porción de heteroátomos seleccionado de $-N=$, $-NR-$, $-O-$, $-S-$ o $-S(O)_2-$, en donde R es hidrógeno o alquilo (C_{1-8}). Por ejemplo, el caso en donde R^1 y R^2 junto con el átomo de carbono al cual ambos R^1 y R^2 están unidos forman hetero (C_{3-8})cicloalquilo" incluyen pero no están limitados a, lo siguiente:



en el cual R es hidrógeno, alquilo (C_{1-8}) o un grupo protector.

"Heteroarilo" significa arilo, como se definió en esta solicitud, siempre y cuando uno o más de los átomos de carbono en el anillo indicado serán reemplazados por una función de heteroátomo seleccionada de -N=, -NR-, -O- o -S-, en donde R es hidrógeno, alquilo (C_{1-6}), un grupo protector o represente la valencia de que sirve como el punto de unión a un nitrógeno del anillo, y cada anillo que esté comprendido de 5 o 6 átomos de anillo. Por ejemplo, el hetero arilo (C_{5-10}) opcionalmente sustituido como se utilizó en esta solicitud incluye, pero no está limitado a, 4-amino-2-hidroxi pirimidin-5-ilo, benzotiazol-2-ilo, 1H-benzimidazol-2-ilo, 2-bromopirid-5-ilo, 5-bromopirid-2-ilo, 4-carbamotiazol-2-ilo, 3-carboxipirid-4-ilo, 5-carboxi-2,6-dimetilpirid-3-ilo, 3,5-dimetilisoxazol-4-ilo, 5-etoxi-2, 6-dimetilpirid-3-ilo, 5-fluoro- 6-hidroxi pirimidin-4-ilo, fur-2-ilo, fur-3-ilo, 5-hidroxi-4,6-dimetilpirid-3-ilo, 8-hidroxi-5,7-dimetilquinolin-2-ilo, 5-hidroxi metilisoxazol-3-ilo, 3-hidroxi-6-metilpirid-2-ilo, 3-hidroxi pirid-2-ilo, 1H-imidazol-2-ilo, 1H-imidazol-4-ilo, 1H-indol-3-ilo, isotiazol-4-ilo, isoxazol-4-ilo, 2-metilfur-3-ilo, 5-metilfur-2-ilo, 1-metil-1H-imidazol-2-ilo, 5-metil-3H-imidazol-4-ilo, 5-metilisoxazol-3-ilo, 5-metil-2h-pirazol-3-ilo, 3-metilpirid-2-ilo, 4-metilpirid-2-ilo, 5-metilpirid-2-ilo, 6-metilpirid-2-ilo, 2-metilpirid-3-ilo, 2-metiltiazol-4-ilo, 5-nitropirid-2-ilo, 2H-pirazol-3-ilo, 3H-pirazol-4-ilo, piridazin-3-ilo,

pirid-2-ilo, pirid-3-ilo, pirid-4-ilo, 5-pirid-3-il-2H-[1,2,4]triazol-3-ilo, pirimidin-4-ilo, pirimidin-5-ilo, 1H-pirrol-3-ilo, quinolin-2-ilo, 1H-tetrazol-5-ilo, tiazol-2-ilo, tiazol-5-ilo, tien-2-ilo, tien-3-ilo, 2H-[1,2,4]triazol-3-ilo, 3H-[1,2,3]triazol-4-ilo, 5-trifluorometilpirid-2-ilo, y similares. Los grupos protectores adecuados incluyen terc-butoxicarbonilo, benziloxicarbonilo, benzilo, 4-metoxibenzilo, 2-nitrobenzilo, y similares. Hetero arilo (C_{5-10}) como se utiliza en esta solicitud para definir R^4 incluye benzofur-2-ilo, fur-2-ilo, fur-3-ilo, pirid-3-ilo, pirid-4-ilo, quinol-2-ilo, quinol-3-ilo, tien-2-ilo, tien-3-ilo, y similares.

"Heterobicicloarilo" significa bicicloarilo, como se definió en esta solicitud, siempre y cuando uno o más de los átomos de carbono del anillo indicado sean reemplazados por la función de heteroátomo seleccionado de $-N=$, $-NR-$, $-O-$ o $-S-$, en donde R es hidrógeno, alquilo (C_{1-4}), un grupo protector o representa una valencia libre que representa un punto de unión a un nitrógeno del anillo, y cualquier cetona carboxídica, tiocetona o Iminocetona derivada de este. Por ejemplo, el hetero bicicloarilo (C_{8-10}) opcionalmente sustituido como se utiliza en esta solicitud incluye, pero no está limitado a 2-amino-4-oxo-3,4-dihidropteridín-6-ilo, y similares. En general, el término heterobicicloarilo como se

utiliza en esta solicitud incluye, por ejemplo, benzo [1,3]dioxol-5-ilo, 3,4-dihidro-2H-[1,8]naftiridinilo, 3,4-dihidro-2H-quinolinilo, 2,4-dioxo-3,4-dihidro-2H-quinazolinilo, 1,2,3,4,5,6-hexahidro[2,2']bipiridinililo, 3-oxo-2,3-dihidrobencol[1,4]oxazinilo, 5,6,7,8-tetrahidroquinolinilo, y similares.

"Heterocicloalquilo" significa cicloalquilo, como se definió en esta solicitud, siempre y cuando uno o más de los átomos de carbono del anillo de indicado son reemplazados por una porción heteroátomo seleccionada de -N=, -NR-, -O- o -S-, en donde R es hidrógeno, alquilo (C₁₋₆), un grupo protector o representa una valencia libre que representa un punto de unión a un nitrógeno del anillo, y cualquier cetona carboxílica, tiocetona o iminocetona derivada de este. Por ejemplo, "el hetero cicloalquilo (C₃₋₁₀) incluye imidazolinilo, morfolinilo, piperazinilo, piperidilo, pirrolidinilo, pirrolinilo, quinuclidinilo, y similares). Los grupos protectores adecuados incluyen terc-butoxicarbonilo, benziloxicarbonilo, benzilo, 4-metoxibenzilo, 2-nitrobenzilo, y similares. Tanto los derivados no protegidos, como protegidos caen dentro del alcance de la invención.

"Hidroxi" significa el radical $-OH$. A menos que se indique otra cosa, los compuestos de la invención que contienen radicales hidroxilo incluyen derivados protegidos de este. Los grupos protectores adecuados, para las funciones hidroxilo incluyen benzilo y similares.

"Derivados de iminocetona" significa un derivado que contiene la función $-C(NR)-$, en donde R es hidrógeno o alquilo (C_{1-4}).

"Isómero" significa compuestos de Fórmula I que tienen fórmulas moleculares idénticas pero difieren en la naturaleza de secuencia de unión de sus átomos o en la disposición de sus átomos en el espacio. Los isómeros que difieren en la disposición de sus átomos en el espacio son denominados "estereoisómeros". Los estereoisómeros que no son imágenes especulares uno del otro son denominados "diastereoisómeros" y los estereoisómeros que no son imágenes especulares no superimpuestas no denominados "enantiómeros" o algunas veces "isómeros ópticos". Un átomo de carbono unido a 4 sustituyentes no idénticos se denomina un "centro quiral". Un compuesto por un centro quiral tiene dos formas enantioméricas de quiralidad opuesta se denomina una "mezcla racémica". Un compuesto que tiene más de un centro quiral tiene 2^R pares enantioméricos, en donde R es el número de

centros quirales. Los compuestos con más de un centro quiral pueden existir bien sea como diastereómeros individuales o como una mezcla de diastereómeros, denominada una "mezcla diastereomérica". Cuando está presente un centro quiral un estereoisómero se puede caracterizar por la configuración absoluta de ese centro quiral. La configuración absoluta se refiere a una disposición en el espacio de los sustituyentes unidos al centro quiral. Los enantiómeros se caracterizan por la configuración absoluta de sus centros quirales y se describen por las reglas de Cahn, Ingold y Prelog secuenciales R- y S-. Las convenciones para nomenclatura estereoquímica, los métodos para la determinación de la estereoquímica y la separación de los estereoisómeros son bien conocidos en la técnica (por ejemplo, ver "Advanced Organic Chemistry", 4^{ta} edición, Marzo, Jerry, John Wiley & Sons, New York, 1992). Se entiende que los nombres e ilustración utilizados en esta solicitud para describir los compuestos de Fórmula I pretenden comprender todos los posibles estereoisómeros. Así, por ejemplo, el nombre N-[1-(1-benzilcarbamoil-metanollo)-propil-4-morfolin-4-il-4-oxo-2-fenilmetanosulfonilmetil-butiramida] pretende incluir N-[1-(1-benzilcarbamoil-metanollo)-propil-4-morfolin-4-il-4-oxo-2-fenilmetanosulfonilmetil-butiramida] y N-[1-(1-benzilcarbamoil-

metanol)-propil-4-morfolin-4-il-4-oxo-2-fenilmetanosulfonilmetil-butiramida y una mezcla, racémica u otras, de estos.

"Derivado de Cetona" significa un derivado que contiene una porción $-C(O)-$. Por ejemplo, en esta solicitud X^3 puede ser 2-acetoxi-acetidin-3-il. El "derivado de cetona carboxílico" de este ejemplo de X^3 sería 2-acetoxi-4-oxo-acetidin-3-il (ver tabla 3, C3).

"Nitro" significa el radical $-NO_2$.

"Opcional" o "opcionalmente" significa que el evento subsecuentemente descrito o circunstancia puede o no ocurrir, y que la descripción incluye ejemplos donde el evento o circunstancia ocurre y casos en el cual este no ocurre. Por ejemplo, la frase "en donde dentro de R^3 y R^4 cualquier sistema de anillo abicíclico o aromático puede ser sustituido adicionalmente por 1-5 radicales..." significa que R^3 y R^4 pueden ser o no sustituidos con el fin de caer dentro del alcance de la invención.

"Oxoalquilo" significa alquilo, como se definió anteriormente, mientras uno del número de átomos de carbono ubicado se

reemplaza por un grupo oxígeno (-O-), por ejemplo, oxo (C_{2-8}) Incluye metoximetilo, etc.

"Derivados de N-óxido" significa derivados de compuestos de Fórmula I en el cual los nitrógenos están en un estado oxidado (es decir, O-N) y que poseen la actividad Farmacológica deseada.

"Patología" de la enfermedad significa la naturaleza esencial, causas y desarrollo de la enfermedad así como también cambios estructurales y funcionales que dan como resultado de los procesos de la enfermedad.

"farmacéuticamente aceptable" significa que lo que es útil en la preparación de una composición farmacéutica que es generalmente seguro, ni biológicamente tóxico ni indeseable de cualquier otra forma e incluye aquello que es aceptable para uso veterinario así como también uso farmacéutico en humanos.

"Sales farmacéuticamente aceptables" significan sales de compuestos de Fórmula I que son farmacéuticamente aceptables, como se definió anteriormente, y que posee la actividad farmacológica deseada. Tales sales incluyen sales de adición ácida

formada con ácidos inorgánicos tales como ácido clorhídrico, ácido bromhídrico, ácido sulfúrico, ácido nítrico, ácido fosfórico, y similares; o con ácidos orgánicos tales como ácido acético, ácido fosfórico, ácido hexanoico, ácido heptanoico, ácido ciclopentanopropiónico, ácido glicólico, ácido pirúvico, ácido láctico, ácido malónico, ácido succínico, ácido málico, ácido maléico, ácido fumárico, ácido tartárico, ácido cítrico, ácido benzoico, ácido O-(4-hidroxibenzol)benzoico, ácido cinnámico, ácido maléico, ácido metanosulfónico, ácido etanosulfónico, ácido 1,2-etanodisulfónico, ácido 2-hidroxietanosulfónico, ácido bencenosulfónico, ácido p-clorobencenosulfónico, ácido 2-naftalenosulfónico, ácido p-toluenosulfónico, ácido camforsulfónico, ácido 4-metilbicyclo[2.2.2]oct-2-eno-1-carboxílico, ácido glucoheptónico, ácido 4,4'-metileno bis (3-hidroxi-2-eno-1-carboxílico), ácido 3-fenilpropiónico, ácido trimetilacético, ácido butilacético terciario, ácido laurilsulfúrico, ácido glucónico, ácido glutámico, ácido hidroxilactónico, ácido salicílico, ácido esteárico, ácido mucónico y similares.

Las sales farmacéuticamente aceptables también incluyen sales de adición de base que se pueden formar cuando los protones ácidos presentes son capaces de reaccionar con bases inorgánicas u

orgánicas. Las bases inorgánicas aceptables incluyen hidróxido de sodio, carbonato de sodio, hidróxido de potasio, hidróxido de aluminio e hidróxido de calcio. Las bases orgánicas aceptables incluyen etanolamina, dietanolamina, trietanolamina, trometamina, N-metilglucamina y similares.

"Prodroga" significa un compuesto que es convertible in vivo por medios metabólicos (por ejemplo por hidrólisis a un compuesto de Fórmula I. Por ejemplo un éster de un compuesto de Fórmula I que contiene un grupo hidroxilo puede ser convertible mediante hidrólisis in vivo a la molécula padre. Alternativamente un éster de un compuesto de Fórmula I que contiene un grupo carboxilo puede ser convertible mediante hidrólisis in vivo a la molécula padre. Los ésteres adecuados de los compuestos de Fórmula I que contienen un grupo hidroxilo, son por ejemplo acetatos, citratos, lactatos, tartratos, malonatos, oxalatos, salicilatos, propionatos, succinatos, fumaratos, maleatos, metileno-bis-b-hidroxi-naftoatos, gentisatos, isetionatos, di-p-toluoiltartratos, metanosulfonatos, etanosulfonatos, benzenosulfonatos, p-toluenosulfonatos, ciclohexilsulfamatos y quinatos. Los ésteres adecuados de compuestos de Fórmula I que contienen un grupo carboxilo, son por ejemplo aquellos descritos por F.J. Leinweber, Drug Metab.

Reset., 1987, 18, página 379. Una clase especialmente útil de ésteres de compuestos de Fórmula I que contienen grupo hidroxil, se pueden formar de porciones ácidas seleccionadas de aquellas descritas por Bundgaard et al., J. Med. Chem., 1989, 32, página 2503-2507, e incluye (aminometil)-benzoatos sustituidos, por ejemplo, dialquilamino-metilbenzoatos en los cuales los dos grupos alquilo se pueden unir juntos y/o interrumpidos por un átomo de oxígeno o por un átomo de nitrógeno opcionalmente sustituido, por ejemplo un átomo de nitrógeno alquilado, más especialmente (morfolino-metil)benzoatos, por ejemplo 3- o 4-(morfolinometil)-benzoatos, y (4- alquilpiperazin-11)-benzoatos, por ejemplo 3- o 4-(4-alkilpiperazin-1-11)-benzoatos.

"Derivados Protegidos" significa derivados de compuestos de Fórmula I en el cual un sitio o sitios de activos son bloqueados por grupos protectores. Los derivados protegidos de los compuestos de Fórmula I son útiles en la preparación de compuestos de Fórmula I en ellos mismos pueden estar los inhibidores de catepsina S activos. Una lista comprehensiva de grupos protectores adecuados se pueden encontrar en T.W. Greene, Protecting Groups in Organic Synthesis, 3ra edición, John Wiley & Sons, Inc. 1999.

"Cantidad terapéuticamente efectiva" significa aquella cantidad que, cuando se administra a un animal para tratar una enfermedad, es suficiente para efectuar tal tratamiento para la enfermedad.

"Derivado de Tlocetona" significa un derivado que contiene la porción -C(S)-.

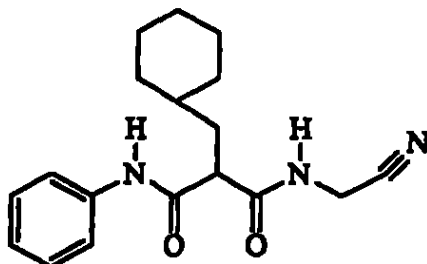
"Tratamiento" o **"tratar"** significa cualquier administración de un compuesto de la presente Invención e Incluye:

- (1) evitar que la enfermedad ocurra en un animal que puede estar predispuesto a la enfermedad pero que no la ha experimentado aún o muestra la patología o sintomatología de la enfermedad,
- (2) Inhibir la enfermedad en un animal que está experimentando o mostrando la patología o sintomatología de la enfermedad (es decir impidiendo el desarrollo adicional de la patología y/o sintomatología), o

(3) mejorando la enfermedad en un animal que está experimentando o mostrando la patología o sintomatología de la enfermedad (es decir reversando la patología y/o sintomatología).

Nomenclatura:

Los compuestos de Fórmula I y los intermedios y materiales de partida utilizados en su preparación son denominados de acuerdo con las reglas IUPAC de nomenclatura en las cuales los grupos característicos tienen prioridad decreciente para cita como el grupo de principio como sigue: ácido, ésteres, amidas, etc. alternativamente, los compuestos son denominados mediante AutoNom 4.0 (Bellstein Information Systems, Inc.). Por ejemplo, un compuesto de Fórmula I en el cual X^1 es $-NHC(R^1)(R^2)X^2$ (R^1 y R^2 son cada uno hidrógeno), X^2 es clano, R^3 es ciclohexilmetilo, y R^4 es fenilamino; que es, un compuesto que tiene la siguiente estructura:



se denomina N-cianometil-2-ciclohexilmetil-N'-fenil-malonamida.

Modalidades Actualmente Preferidas:

Aunque la definición más amplia de la Invención se establece en el resumen de la Invención, ciertos aspectos de la invención son preferidos. Por ejemplo, X^1 es $-NHC(R^1)(R^2)X^2$ o $-NHX^3$; X^2 es ciano, $-C(O)X^3$, $-C(O)CF_3$, $-C(O)CF_2CF_2R^5$, $-CH=CHS(O)_2R^5$, $-C(O)CF_2C(O)NR_5R$, $-C(O)C(O)NR^5R^6$, $-C(O)C(O)OR^5$, $-C(O)CH_2OR^5$, $-C(O)CH_2N(R^6)SO_2R^5$ o $-C(O)C(O)R^5$; en donde R^5 y R^6 son como se describió anteriormente; X^3 comprende un anillo heteromonocíclico que contiene 4 a 6 átomos y miembros del anillo o un sistema de anillo heterobifcíclico fusionado que contiene 8 a 14 átomos miembros del anillo y cualquier cetona carboxílica, iminocetona o tioacetona derivada de este; en donde dentro de R^5 , X^2 o X^3 cualquier sistema de anillo alifcíclico o aromático puede ser sustituido

adicionalmente por 1 a 5 radicales independientemente seleccionados de alquilo (C_{1-6}) o $-X^4OC(O)R^2$ y/o 1 radical seleccionado de $-R^{14}$, $-X^4C(O)R^{14}$ o $-X^4OC(O)R^{14}$; en donde X^4 , R^{12} y R^{14} son como se describió anteriormente; R^1 es hidrógeno o alquilo (C_{1-6}) y R^2 es hidrógeno, $-X^4OR^{12}$, (C_{5-10}) heteroaril (C_{6-9}) alquilo, (C_{5-10}) aril (C_{6-9}) alquilo, (C_{5-10}) cicloalquil (C_{6-9}) alquilo, (C_{5-10}) heterocicloalquil (C_{6-9}) alquilo o alquilo (C_{1-6}); o R^1 y R^2 tomados juntos con el átomo de carbono al cual ambos R^1 y R^2 están unidos forman el cicloalquilleno (C_{3-8}) o heterocicloalquilleno (C_{3-8}); en donde dentro de dicho R^2 cualquier heteroarilo, arilo, cicloalquilo, heterocicloalquilo, cicloalquilleno o heterocicloalquilleno está opcionalmente sustituido con uno o más radicales independientemente seleccionados de alquilo (C_{1-6}) e hidroxil; R^3 es $-CH_2X^5$, en donde X^5 en cada ocurrencia independientemente se selecciona de $-X^4SR^{12}$, $-X^4C(O)NR^{12}R^{12}$, $-X^4S(O)_2R^{13}$, $-X^4C(O)R^{13}$, $-X^4SR^{14}$, $-X^4R^{12}$, $-R^{12}$, $-X^4S(O)_2R^{14}$, $-X^4C(O)R^{14}$, $-X^4C(O)NR^{14}R^{12}$, en donde X^4 , R^{12} , R^{13} y R^{14} son como se definió anteriormente; R^4 es $-NR^6R^6$, $-NR^6R^{14}$, $-NR^6R^{15}$ o $-NR^6X^5C(O)R^{14}$ en donde R^6 , X^5 y R^{14} son como se definió anteriormente y R^{15} es hidrógeno, alquilo (C_{1-6}) o $-X^6OR^6$ en donde X^5 es como se describió anteriormente; o R^6 y R^{15} juntos con el átomo de nitrógeno al cual R^6 y R^{15} están unidos forman hetero (C_{3-10}) cicloalquilo, hetero (C_{5-10}) arilo o hetero (C_{6-10}) bicicloarilo; en

donde dentro de R^3 y R^4 cualquier sistema de anillo alifático o aromático puede ser sustituido adicionalmente por 1 - 5 radicales independientemente seleccionados de alquilo (C_{1-4}), ciano, halo, nitro, alquilo (C_{1-4}) halo-sustituido, $-X^4OR^{12}$, $-X^4C(O)OR^{12}$, $-X^4C(O)R^{13}$, $-X^4C(O)NR^{12}R^{12}$, $-X^4NR^{12}S(O)_2R^{12}$ y/o 1 radical seleccionado de $-R^{14}$, $-X^4OR^{14}$ y $-X^4C(O)NR^{14}R^{12}$; dentro de R y R^4 cualquier porción alifática puede ser sustituida adicionalmente por 1 - 5 radicales independientemente seleccionados de ciano; en donde X^4 , OR^{12} , R^{13} y R^{14} son como se describió anteriormente; con la condición de que solo una estructura de anillos bicíclica está presente dentro de R^3 o R^4 .

En particular, X^1 es $-NHC(R^1)(R^2)X^2$ o NHX^2 ; X^2 es clano, $-C(O)X^3$, $-CF_3$, $-CF_2CF_3$, (E)-2-benzenesulfonil-vinilo, 2-dimetilcarbamoyl-2,2-difluoro-acetilo, 1-benzilcarbamoyl-metanoilo, 1-benziloxi (oxali), 2-benziloxi-acetilo, 2-benzenesulfonilamino-etanoyl o 2-oxo-2-fenil-etanoyl; X^3 es 1H-benzimidazol-2-ilo, pirimidin-2-ilo, benzooxazol-2-ilo, benzotiazol-2-ilo, piridazin-3-ilo, 3-fenil-1,2,4-ioxadiazol-5-ilo, 3-etil-1,2,4-ioxadiazol-5-ilo, 2-metil-4-oxo-tetrahidro-furan-3-ilo, 2-etil-4-oxo-tetrahidro-furan-3-ilo, 4-oxo-1-(1-fenil-metanoil)-pirrolidin-3-il o (S)-2-acetoxi-4-oxo-azetidin-3-il; R^1 es hidrógeno o metilo y R^2 es hidrógeno, metoximetilo, alquilo (C_{1-4}), fenetilo,

tiofen-2-il o 5-metil-furan-2-ilo, o (ii) R^1 y R^2 tomados juntos con el átomo de carbono al cual ambos R^1 y R^2 están unidos del ciclopropileno, tetrahidro-pirán-4-ileno o metil-piperidín-4-ileno.

R^3 es más preferiblemente tiofene-2-sulfonilmetilo, 3-cloro-2-fluoro-fenilmetanosulfonilmetilo, benzenesulfonilmetilo, fenilmetanosulfonilmetilo, 2-(1,1-difluoro-metoxi)-fenilmetanosulfonilmetilo, 2-benzenesulfonil-etilo, 2-(piridino-2-sulfonil)-etilo, 2-(piridino-4-sulfonil)-etilo, 2-fenilmetanosulfonil-etilo, oxi-piridin-2-ilmetanosulfonilmetilo, prop-2-ene-1-sulfonilmetilo, 4-metoxi-fenilmetanosulfonilmetilo, p-tolilmetilesulfonilmetilo, 4-cloro-fenilmetanosulfonilmetilo, o-tolilmetanosulfonilmetilo, 3,5-dimetil-fenilmetanosulfonilmetilo, 4-trifluorometil-fenilmetanosulfonilmetilo, 4-trifluorometoxi-fenilmetanosulfonilmetilo, 2-bromo-fenilmetanosulfonilmetilo, piridin-2-ilmetanosulfonilmetilo, piridin-3-ilmetanosulfonilmetilo, piridin-4-ilmetanosulfonilmetilo, naftalen-2-ilmetanosulfonilmetilo, 3-metil-fenilmetanosulfonilmetilo, 3-trifluorometil-fenilmetanosulfonilmetilo, 3-trifluorometoxi-fenilmetanosulfonilmetilo, 4-fluoro-2-trifluorometoxi-fenilmetanosulfonilmetilo, 2-fluoro-6-trifluorometil-fenilmetanosulfonilmetilo, 3-cloro-fenilmetanosulfonilmetilo, 2-

fluoro-fenilmetanosulfonilmetilo, 2-trifluoro-
fenilmetanosulfonilmetilo, 2-ciano-fenilmetanosulfonilmetilo, 4-
terc-butil-fenilmetanosulfonilmetilo, 2-fluoro-3-metil-
fenilmetanosulfonilmetilo, 3-fluoro-fenilmetanosulfonilmetilo, 4-
fluoro-fenilmetanosulfonilmetilo, 2-cloro-
fenilmetanosulfonilmetilo, 2,5-difluoro-fenilmetanosulfonilmetilo,
2,6-difluoro-fenilmetanosulfonilmetilo, 2, 5-dicloro-
fenilmetanosulfonilmetilo, 3, 4-dicloro-fenilmetanosulfonilmetilo,
2-(1,1-difluoro-metoxi)-fenilmetanosulfonilmetilo, 2-ciano-
fenilmetanosulfonilmetilo, 3-ciano-fenilmetanosulfonilmetilo, 2-
trifluorometoxi-fenilmetanosulfonilmetilo, 2,3-difluoro-
fenilmetanosulfonilmetilo, 2,5-difluoro-fenilmetanosulfonilmetilo,
bifenil-2-ilmetanosulfonilmetilo, ciclohexilmetilo, 3-fluoro-
fenilmetanosulfonilmetilo, 3,4-difluoro-fenilmetanosulfonilmetilo,
2,4-difluoro-fenilmetanosulfonilmetilo, 2,4,6-trifluoro-
fenilmetanosulfonilmetilo, 2,4,5-trifluoro-
fenilmetanosulfonilmetilo, 2,3,4-trifluoro-
fenilmetanosulfonilmetilo, 2,3,5-trifluoro-
fenilmetanosulfonilmetilo, 2,5,6-trifluoro-
fenilmetanosulfonilmetilo, 2-cloro-5-
trifluorometilfenilmetanosulfonilmetilo, 2-metil-propano-1-
sulfonilo, 2-fluoro-3-trifluorometilfenilmetanosulfonilmetilo, 2-

fluoro-4-trifluorometilfenilmetanosulfonilmetilo, 2-fluoro-5-
 trifluorometilfenilmetanosulfonilmetilo, 4-fluoro-3-
 trifluorometilfenilmetanosulfonilmetilo, 2-metoxi-
 fenilmetanosulfonilmetilo, 3,5 bis-trifluorometil-
 fenilmetanosulfonilmetilo, 4-difluorometoxi-
 fenilmetanosulfonilmetilo, 2-difluorometoxi-
 fenilmetanosulfonilmetilo, 3-difluorometoxi-
 fenilmetanosulfonilmetilo, 2,6-dicloro-fenilmetanosulfonilmetilo,
 bifenil-4-ilmetanosulfonilmetilo, 3,5-dimetil-isoxazol-4-
 ilmetanosulfonilmetilo, 5-cloro-tiofen-2-ilmetanosulfonilmetilo, 2-
 [4-(1,1-difluoro-metoxi)-benzenesulfonil]-etil, 2-[2-(1,1-difluoro-
 metoxi)-benzenesulfonil]-etil, 2-[3-(1,1-difluoro-metoxi)-
 benzenesulfonil]-etil, 2-(4-trifluorometoxi-benzenesulfonil)-etil,
 2-(3-trifluorometoxi-benzenesulfonil)-etil, 2-(2-trifluorometoxi-
 benzenesulfonil)-etil, (cianometil-metil-carbamol)-metilo, butilo,
 bifenil-3-ilmetilo, 2-oxo-2-pirrolidin-1-il-etilo, 2-benzenesulfonil-
 etilo, isobutilsulfanilmetilo, 2-fenilsulfanil-etilo,
 ciclohexilmetanosulfonilmetilo, 2-ciclohexil-etanesulfonilo,
 benzilo, naftalen-2-ilo, benzilsulfanilmetilo, 2-trifluorometil-
 benzilsulfanilmetilo, 5-bromo-tiofen-2-ilmetilo, fenilsulfanil-etil y
 ciclopropilmetanosulfonilmetil.

R⁴ más preferiblemente es fenilamino, benzilamino, 4-fenoxi-fenilamino, fenetilamino, 3-fenil-propilamino, morfolln-4-ilo, ciclohexilamino, naftalen-1-ilmetil-amino, piridin-3-ilamino, 6-metoxi-piridin-3-ilamino, diisobutilamino, 4-nitro-benzilamino, 2-tiofen-2-il-etilamino, 3-fenoxi-fenilamino, clonometil-amino, (piridin-3-ilmetil)-amino, 5,6,7,8-tetrahidro-naftalen-1-ilamino, 2-piridin-2-il-etilamino, 2,3-dihidro-indol-1-ilo, 3,4-dihidro-1H-Isoquinolln-2-ilo, ciclohexilmetil-amino, 2-metoxi-benzilamino, 1-fenil-etilamino, (piridin-4-ilmetil)-amino, benzil-metil-amino, 3-nitro-benzilamino, 4-metoxi-fenilamino, 3-carbamoll-fenilamino, 4-carbamoll-fenilamino, (tetrahidro-furan-2-ilmetil)-amino, 3,4-dihidro-2H-quinolln-1-ilo, dimetilamino, butilmetilamino, diisopropilamino, propilmetilamino, 1-(benzooxazol-2-carbonil)-propilamino e isobutilmetilamino.

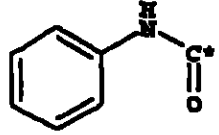
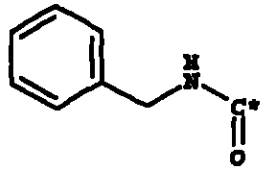
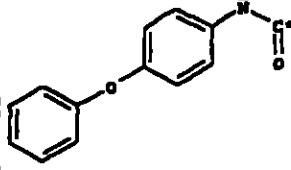
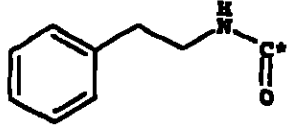
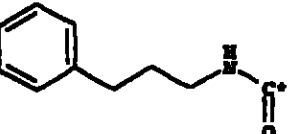
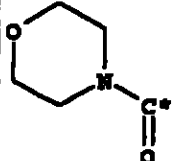
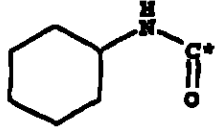
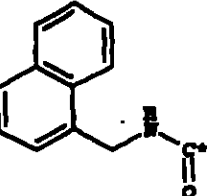
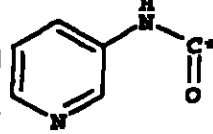
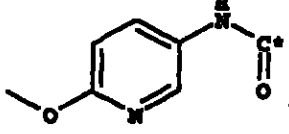
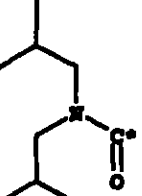
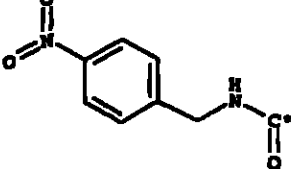
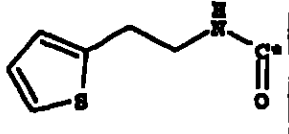
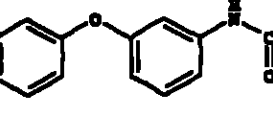
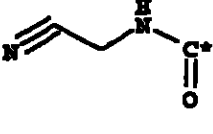
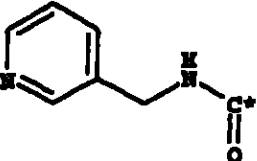
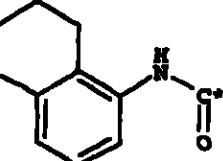
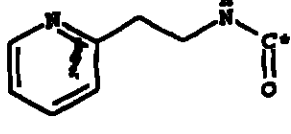
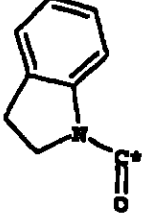
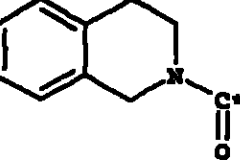
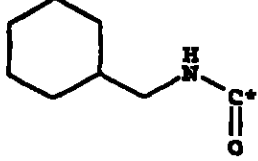
Referencia a las modalidades establecidas anteriormente significa que incluyen todas las combinaciones de los grupos particulares preferidos.

Los compuestos particulares de la invención son seleccionados de los compuestos formados por la unión del átomo carbono del

acilo (C*) de uno de los fragmentos (A1 a A37) mostrados en la Tabla 1 al átomo de carbono metino (*CH*) de uno de los fragmentos (B1 a B88) mostrados en la tabla 2, y uniendo el átomo de carbono metino (*HC*) de uno de los fragmentos (B1 a B88) mostrados en la tabla en la tabla 2 al átomo de carbono acilo (*C) de uno de los fragmentos (C1 a C36) descrito en la tabla 3.

Las siguientes tablas pretenden suministrar guía para llevar a cabo la presente invención. Sin embargo, ellas no limitan el alcance de la invención. Los expertos pueden selectivamente hacer compuestos particulares al unir uno de los fragmentos mostrados en la tabla 1 a uno cualquiera de los fragmentos mostrados en la tabla 2 y luego unir los fragmentos mostrados en la tabla 2 a cualquiera uno de los fragmentos de la tabla 3.

TABLE 1

A1		A2		A3	
A4		A5		A6	
A7		A8		A9	
A10		A11		A12	
A13		A14		A15	
A16		A17		A18	
A19		A20		A21	

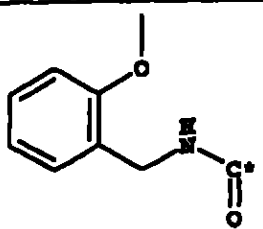
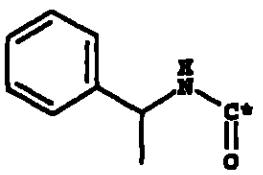
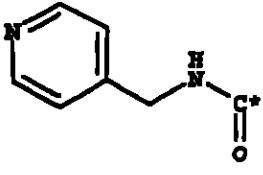
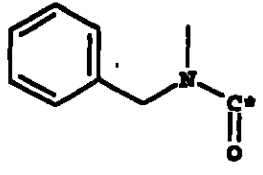
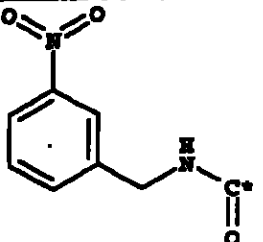
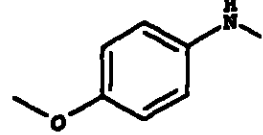
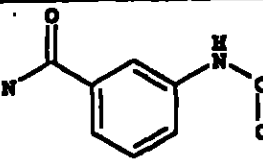
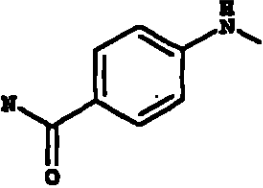
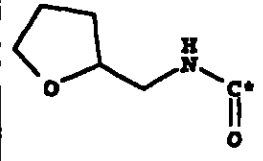
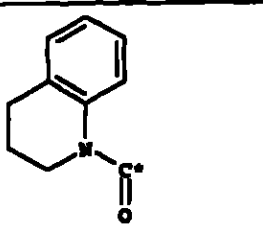
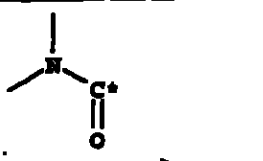
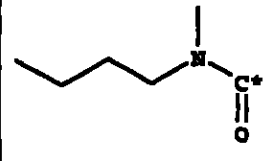
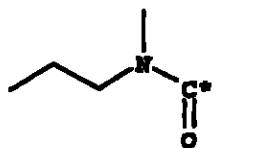
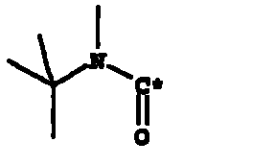
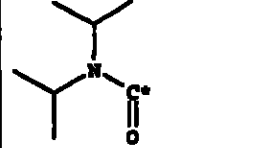
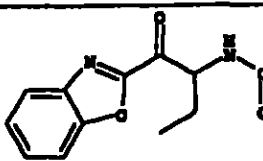
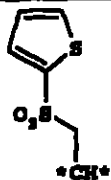
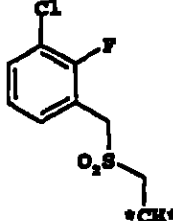
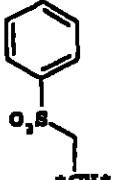
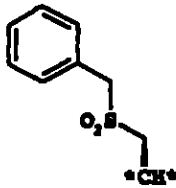
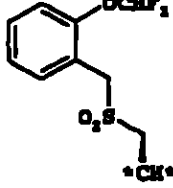
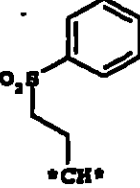
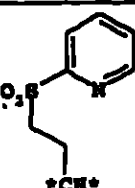
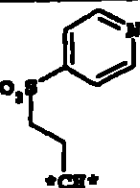
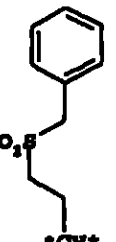
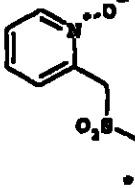
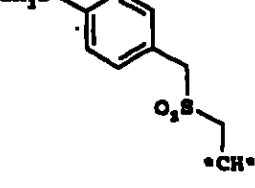
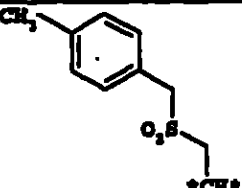
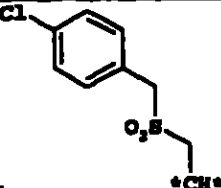
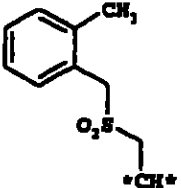
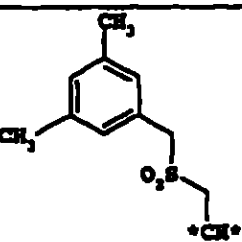
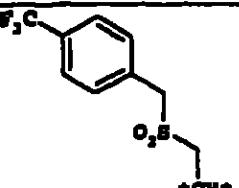
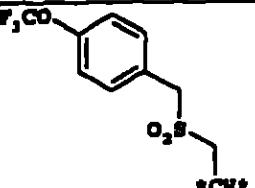
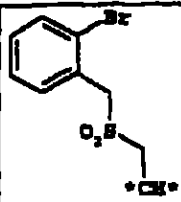
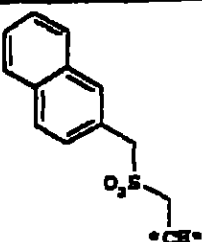
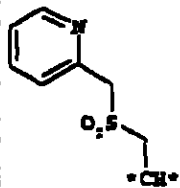
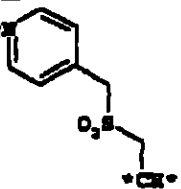
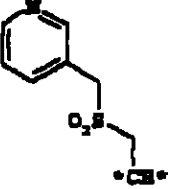
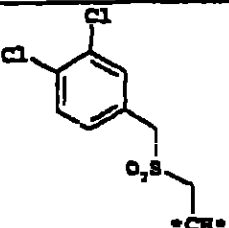
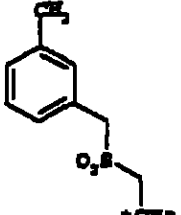
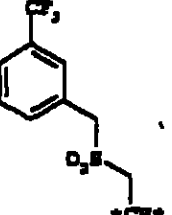
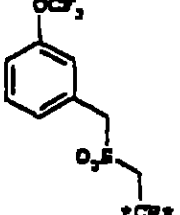
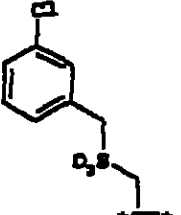
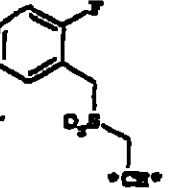
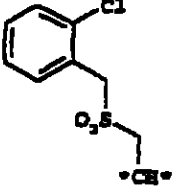
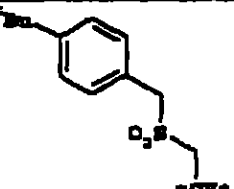
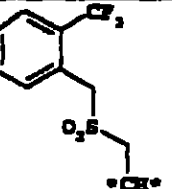
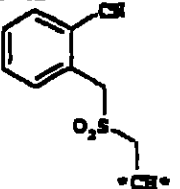
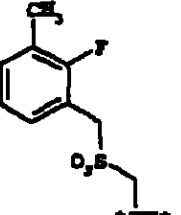
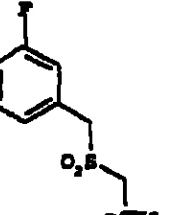
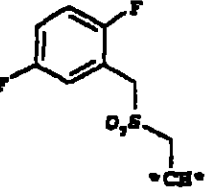
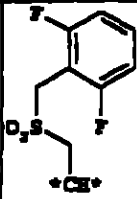
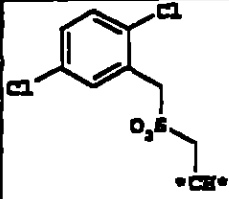
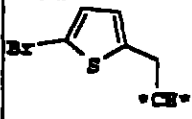
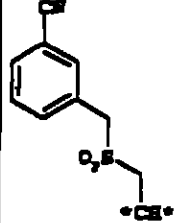
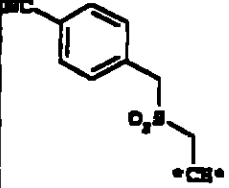
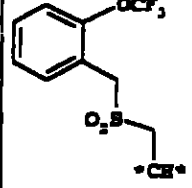
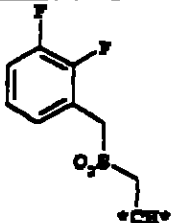
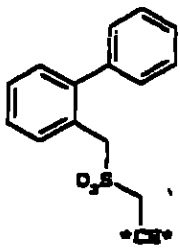
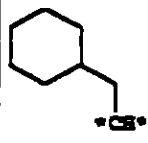
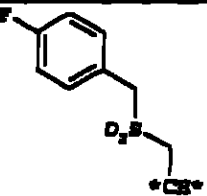
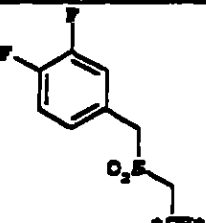
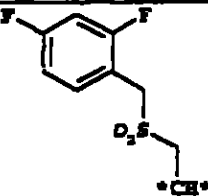
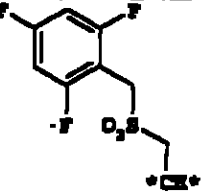
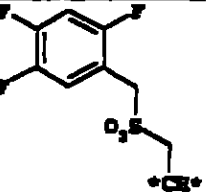
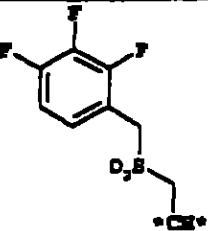
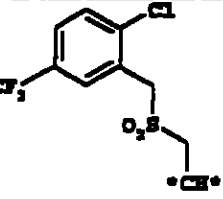
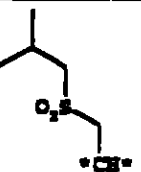
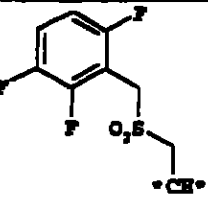
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A25		A26		A27	
A28		A29		A30	
A31		A32		A33	
A34		A35		A36	
A37					

TABLE 2

B1		B2		B3	
B4		B5		B6	
B7		B8		B9	
B10		B11		B12	
B13		B14		B15	
B16		B17		B18	

B19		B20		B21	
B22		B23		B24	
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B28		B29		B30	
B31		B32		B33	
B34		B35		B36	

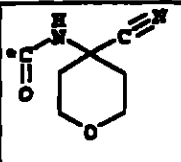
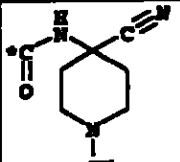
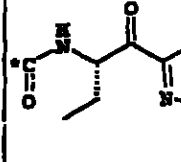
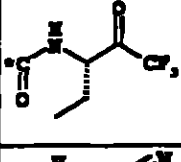
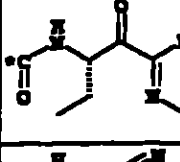
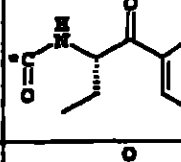
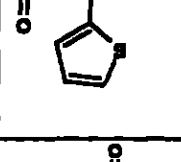
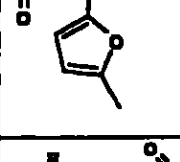
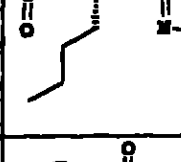
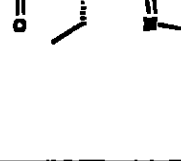
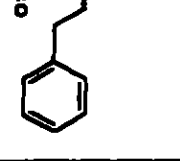
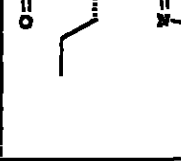
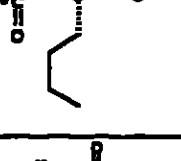
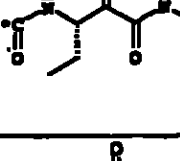
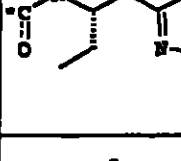
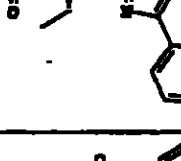
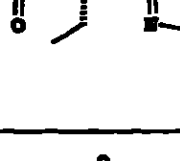
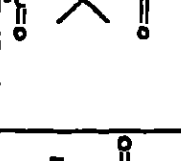
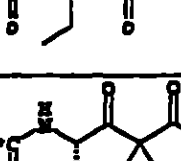
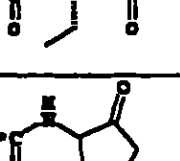
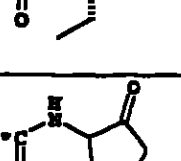
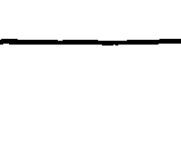
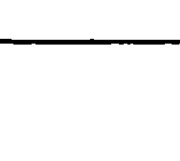
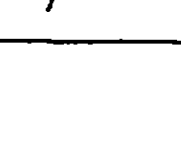
B37		B38		B39	
B40		B41		B42	
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B46		B47		B48	
B49		B50		B51	
B52		B53		B54	

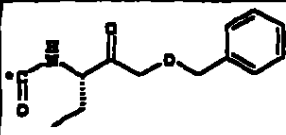
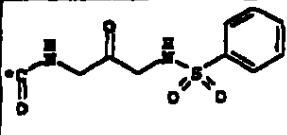
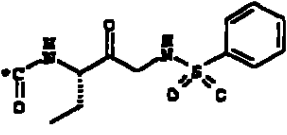
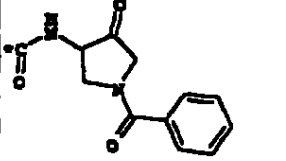
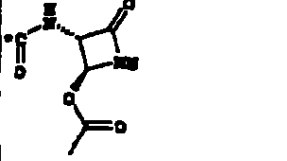
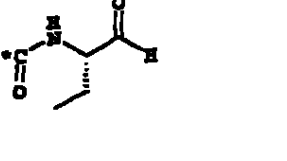
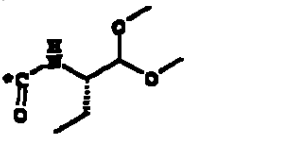
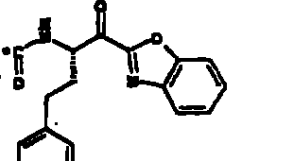
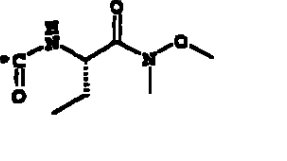
B55		B56		B57	
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B61		B62		B63	
B64		B65		B66	
B67		B68		B69	
B70		B71		B72	

B73		B74		B75	
B76		B77		B78	
B79		B80		B81	
B82		B83		B84	
B85		B86		B87	
B88					

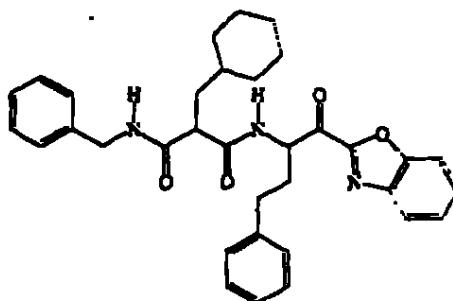
TABLA 3

C1		C2		C3	
----	--	----	--	----	--

C4		C5		C6	
C7		C8		C9	
C10		C11		C12	
C13		C14		C15	
C16		C17		C18	
C19		C20		C21	
C22		C23		C24	
C25		C26		C27	

C28		C29		C30	
C31		C32		C33	
C34		C35		C36	

Así, por ejemplo, en la tabla 4 el compuesto denotado como A2-B45-C35 e el producto de la combinación del grupo A2 de la tabla 1 y B45 en la tabla 2 y C35 en la tabla 3, a saber N-[1-(1-benzoxazol-2-il-metanol)-3-fenil-propil]-N'-benzil-2-ciclohexilmetil-malonamida:



Preferidos adicionalmente son los compuestos de Fórmula I seleccionados del grupo que consiste de:

2-butil-N-clanometil-N'-fenil-malonamida (compuesto 1; denotado como A1-B88-C1);

N-clanometil-2-ciclohexilmetil-N'-fenil-malonamida (compuesto 2; denotado como A1-B45-C1);

N-clanometil-2-ciclohexilmetil-N'-fenetil-malonamida (compuesto 3; denotado como A4-B45-C1);

N-clanometil-2-ciclohexilmetil-N'-piridina-4-ilmetil-malonamida (compuesto 4; denotado como A24-B45-C1);

N-(1-(benzoxazole-2-carbonil)-3-fenilpropil)-N'-benzil-2-ciclohexilmetil-malonamida (compuesto 5; denotado como A2-B45-C35);

N-clanometil-N'-ciclohexil-2-ciclohexilmetil-malonamida (compuesto 6; denotado como A7-B45-C1);

N-benzil-N'-cianometil-2-ciclohexilmetil-malonamida (compuesto 7;
denotado como A2-B45-C1);

N-cianometil-2-ciclohexilmetil-N'-(4-fenoxi-fenil)-malonamida
(compuesto 8; denotado como A3-B45-C1);

N-cianometil-2-ciclohexilmetil-N'-(3-fenil-propil)-malonamida
(compuesto 9; denotado como A5-B45-C1);

N-cianometil-2-ciclohexilmetil-3-morfolin-4-il-3-oxo-propionamida
(compuesto 10; denotado como A6-B45-C1);

N-cianometil-2-ciclohexilmetil-N'-Nafthalen-1-ilmetil-malonamida
(compuesto 11; denotado como A8-B45-C1);

N-cianometil-2-ciclohexilmetil-N'-piridin-3-il-malonamida
(compuesto 12; denotado como A9-B45-C1);

N-cianometil-2-ciclohexilmetil-N',N'-diisobutil-malonamida
(compuesto 13; denotado como A11-B45-C1);

N-clanometil-2-ciclohexilmetil-N',N'-diisopropil-malonamida

(compuesto 14; denotado como A36-B45-C1);

N-clanometil-2-ciclohexilmetil-N'-(6-methoxi-piridin-3-il)-

malonamida (compuesto 15; denotado como A10-B45-C1);

N-clanometil-2-ciclohexilmetil-N'-(2-tiofen-2-il-etil)-malonamida

(compuesto 16; denotado como A13-B45-C1);

N-clanometil-2-ciclohexilmetil-N'-(3-fenoxi-fenil)-malonamida

(compuesto 17; denotado como A14-B45-C1);

N-clanometil-2-ciclohexilmetil-N'-(4-Nitro-benzil)-malonamida

(compuesto 18; denotado como A12-B45-C1);

N,N-bis-clanometil-2-ciclohexilmetil-malonamida (compuesto 19;

denotado como A15-B45-C1);

N-clanometil-2-ciclohexilmetil-N'-(5,6,7,8-tetrahidro-naftalen-1-il)-

malonamida (compuesto 20; denotado como A17-B45-C1);

N-cianometil-2-ciclohexilmetil-N'-(2-piridin-2-il-etil)-malonamida
(compuesto 21; denotado como A18-B45-C1);

N-cianometil-2-ciclohexilmetil-3-(2,3-dihidro-indol-1-il)-3-oxo-propionamida (compuesto 22; denotado como A19-B45-C1);

N-cianometil-2-ciclohexilmetil-3-(3,4-dihidro-1h-isoguinoiln-2-il)-3-oxo-propionamida (compuesto 23; denotado como A20-B45-C1);

N-cianometil-2,N'-bis-ciclohexilmetil-malonamida (compuesto 24; denotado como A21-B45-C1);

N-cianometil-2-ciclohexilmetil-N'-(2-methoxi-benzil)-malonamida
(compuesto 25; denotado como A22-B45-C1);

N-cianometil-2-ciclohexilmetil-N'-(1-fenil-etil)-malonamida
(compuesto 26; denotado como A23-B45-C1);

N-benzil-N'-cianometil-2-ciclohexilmetil-N-metil-malonamida
(compuesto 27; denotado como A25-B45-C1);

N-cianometil-2-ciclohexilmetil-N'-(3-Nitro-benzil)-malonamida

(compuesto 28; denotado como A26-B45-C1);

N-cianometil-2-ciclohexilmetil-N'-(4-methoxi-benzil)-malonamida

(compuesto 29; denotado como A27-B45-C1);

N-(3-carbamoil-fenil)-N'-cianometil-2-ciclohexilmetil-malonamida

(compuesto 30; denotado como A28-B45-C1);

N-cianometil-2-ciclohexilmetil-N'-piridin-3-ilmetil-malonamida

(compuesto 31; denotado como A16-B45-C1);

N-(4-carbamoilfenil)-N'-cianometil-2-ciclohexilmetilmalonamida

(compuesto 32; denotado como A29-B45-C1);

N-cianometil-2-ciclohexilmetil-N'-tetrahidrofur-2-

ilmetilmalonamida (compuesto 33; denotado como A30-B45-C1);

N-cianometil-2-ciclohexilmetil-3-(3,4-dihidro-2h-quinolín-1-il)-3-

oxopropionamida (compuesto 34; denotado como A31-B45-C1);

N-tert-butil-N'-cianometil-2-ciclohexilmetil-N-metilmalonamida

(compuesto 35; denotado como A35-B45-C1);

N-cianometil-2-ciclohexilmetil-N'-metil-N'-propilmalonamida

(compuesto 36; denotado como A34-B45-C1);

N-butil-N'-cianometil-2-ciclohexilmetil-N-metilmalonamida

(compuesto 37; denotado como A33-B45-C1);

N-cianometil-2-ciclohexmetil-N',N'-dimetilmalonamida (compuesto

38; denotado como A32-B45-C1);

N-benzil-N'-cianometil-2-(2-fenilsulfaniletil)malonamida (compuesto

39 ; denotado como A2-B80-C1);

2-(2-fenilsulfoniletil)-N-benzil-N'-cianometilmalonamida (compuesto

40; denotado como A2-B6-C1);

2-(2-benzenesulfonil-etil)-N-[(s)-1-(1-benzoxazol-2-il-metanoil)-pentil]-

N'-benzil-malonamida (compuesto 41; denotado como A2-B6-C12);

N,N'-bis-[(S)-1-(1-benzoxazol-2-yl-metanoil)-propyl]-2-ciclohexilmetil-malonamida (compuesto 42; denotado como A37-B45-C13);

Y los derivados de N-óxido, los derivados de prodrogas, los derivados protegidos, los estereoisómeros individuales y las mezclas de isómeros de estos; y las sales farmacéuticamente aceptables y solvatos (por ejemplo hidratos) de tales compuestos y los derivados N-óxido, los derivados prodroga, los derivados protegidos, los isómeros individuales y las mezclas de isómeros de estos.

Farmacología y Utilidad:

Los compuestos de la invención son Inhibidores selectivos de catepsina S y, como tales, son útiles para tratar enfermedades en las cuales la actividad de la catepsina a veces contribuye a la patología y/o sintomatología de la enfermedad. Por ejemplo, los compuestos de la invención son útiles para tratar desórdenes autoinmunes, incluyendo, pero no limitados a, ataques de diabetes juvenil, esclerosis múltiple, fenfigus vulgaris, enfermedad de Graves, miastenia gravis, lupus eritematosos

sistémico, artritis reumatoide y tiroiditis de Hashimoto, desórdenes alérgicos, incluyendo, pero no limitados, a asma, y respuestas inmunes halogénicas, incluyendo, pero no limitadas a, transplantes de órganos o injertos de tejidos.

La catepsina S también está implicada en desordenes que involucran el astollis excesiva, tal como enfermedad pulmonar obstructiva crónica (por ejemplo, enfisema), bronquiolitis, elastolisis aérea excesiva en asma y bronquitis, neumonitis y enfermedad cardiovascular tal como ruptura de placa y ateroma. La catepsina S está implicada en formación de fibrilo y, por lo tanto, los inhibidores de la catepsina S son de uso en tratamiento de amiloidosis sistémica.

Las actividades inhibitorias de la cisteína proteasa de los compuestos de la invención se pueden determinar mediante métodos conocidos por aquellos expertos en la técnica. Los ensayos in vitro adecuados para la medición de actividades de proteasa y la inhibición de esta mediante compuestos de ensayos son conocidos. Típicamente, las mediciones de ensayo de proteasa inducida por hidrólisis de un péptido basado en sustrato.

Los detalles de los ensayos para medición de actividad inhibitoria de proteasa se establecen en los ejemplos 6-9, *Infra*.

Administración y Composiciones Farmacéuticas:

En general, los compuestos de Fórmula I serán administrados en cantidades terapéuticamente efectivas por vía de cualquiera de los modos usuales y aceptables conocidos en la técnica, o simplemente en combinación con uno o más agentes terapéuticos. Una cantidad terapéuticamente efectiva puede variar ampliamente dependiendo de la severidad de la enfermedad, la edad, y la salud de relativa del sujeto, la potencia del compuesto utilizado y otros factores. Por ejemplo, las cantidades terapéuticamente efectivas de un compuesto de la fórmula 1 pueden variar desde aproximadamente un microgramo por kilogramo de peso de cuerpo ($\mu\text{g/kg}$) por día a aproximadamente 1 miligramo de peso de cuerpo (mg/kg) por día, típicamente desde aproximadamente 10 $\mu\text{g/kg/día}$ a aproximadamente 0,1 mg/kg/día . Por lo tanto, una cantidad terapéuticamente efectiva para un paciente humano de 80 kg puede variar desde aproximadamente 100 $\mu\text{g/día}$ a

aproximadamente 100 mg/día típicamente desde aproximadamente 1 μ g/día a aproximadamente 10 μ g/día. En general un experto en la técnica, que actúa con fiabilidad de su conocimiento personal y la descripción de esta solicitud, será capaz de determinar una cantidad terapéuticamente efectiva de un compuesto de Fórmula I para tratar una enfermedad dada.

Los compuestos de la Fórmula I se pueden administrar como composiciones farmacéuticas por una de las siguientes rutas: oral, sistémica (por ejemplo, transdérmica, intranasal o mediante supositorio) o parenteral (por ejemplo, intramuscular, intravenosa o subcutánea). Las composiciones pueden tomar la forma de tabletas, píldoras, cápsulas, semisólidos, polvos, formulaciones de liberación sostenida, soluciones, suspensiones, elixires, aerosoles, o cualquier otra composición apropiada y están comprendidas de, en general, un compuesto de Fórmula I en combinación con al menos un excipiente farmacéuticamente aceptable. Los excipientes aceptables son no tóxicos, administrados de ayuda, y no afectan adversamente el beneficio terapéutico del ingrediente activo. Tal excipiente puede ser cualquier sólido, líquido, semisólido o, en el caso de una composición de aerosol,

excipiente gaseoso que está generalmente disponible a un experto en la técnica.

Los excipientes farmacéuticos sólidos incluyen almidón, celulosa, talco, glucosa, lactosa, sucrosa, gelatina, malta, arroz, harina, yeso, sílica gel, estearato de magnesio, estearato de sodio, monoestearato de glicerol, cloruro de sodio, leche de nata seca y similares. Excipientes líquidos y semisólidos se pueden seleccionar de agua, etanol, glicerol, propilenglicol y aceites varios, incluyendo aquellos de petróleo, origen vegetal o sintético (por ejemplo, aceite de maní, aceite de soja, aceite mineral, aceite de sésamo y similares). Los portadores líquidos preferidos, particularmente para soluciones inyectables, incluyen agua, solución salina, dextrosa acuosa y glicoles.

La cantidad de un compuesto de fórmula 1 en la composición puede variar ampliamente dependiendo del tipo de formulación, tamaño y dosis unitaria, clase de excipientes y otros factores conocidos por aquellos expertos en la técnica de ciencias farmacéuticas. En general, la composición de un compuesto de fórmula 1 para tratar una enfermedad dada comprenderá de 0,01% en peso a 10% en peso, preferiblemente 0,3% en peso a 1%

en peso, de Ingrediente activo siendo el resto el excipiente o excipientes. Preferiblemente la composición farmacéutica se administra en una forma de dosis unitaria simple para tratamiento continuo o en una forma de dosis unitaria ad limitum cuando se requiere específicamente el alivio de los síntomas. Las formulaciones representativas farmacéuticas que contienen un compuesto de Fórmula I se describen en el ejemplo 10.

Química:

Los procesos de la elaboración de los compuestos de Fórmula I:

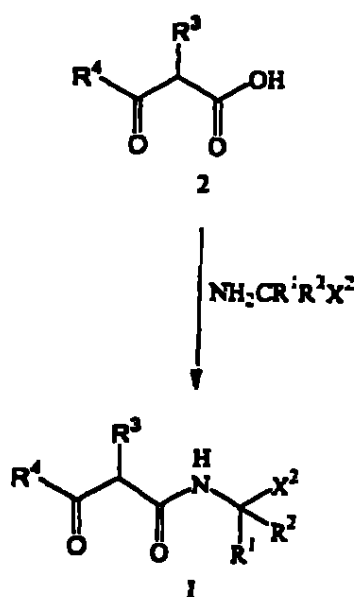
Los compuestos de la invención se pueden preparar mediante la aplicación o adaptación de métodos conocidos, mediante lo cual significan métodos utilizados en lo sucesivo o descritos en la literatura, por ejemplo aquellos descritos por R.C. Larock en Comprehensive Organic Transformations, VCH publishers, 1989.

En las reacciones descritas en lo sucesivo puede ser necesario proteger los grupos funcionales reactivos, por ejemplo hidroxil, amino, imino, tio o grupos carboxil, donde estos son deseados en

el producto final, para evitar su participación no requerida en las reacciones. Los grupos protectores convencionales se pueden utilizar de acuerdo con la práctica estándar, por ejemplo ver T.W. Greene y P.G.M. Wuts en "Protective Groups In Organic Chemistry" John Wiley and Sons, 1991.

Los compuestos de Fórmula I, donde X¹ es -NHC(R¹)(R²)X², se pueden preparar mediante los procedimientos como en el siguiente esquema de reacción 1:

Esquema de Reacción 1

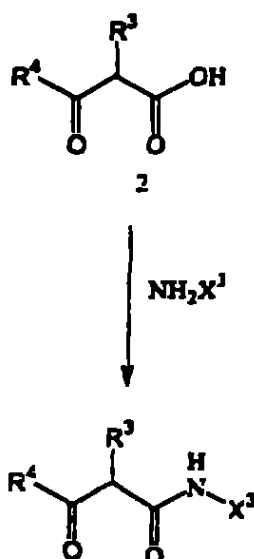


En la cual X², R¹, R², R³ y R⁴ son como se definió en el resumen de la invención.

Los compuestos de Fórmula I se pueden preparar al condensar un ácido de fórmula 2 con un compuesto de fórmula $\text{NH}_2\text{CR}^1\text{R}^2\text{X}^3$. la reacción de condensación se puede efectuar con agente de acoplamiento apropiado (por ejemplo hexafluorofosfato de benzotriazol-1-iloxitrispirrolidino-fosfonio (PyBOP®), clorhidrato de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (EDCI), hexafluorofosfato de O-benzotriazol-1-il-N,N,N',N'-tetrametiluronio (HBTU), 1,3-diciclohexil-carbodiimida (DCC), o similares) y opcionalmente un catalizador apropiado (por ejemplo, 1-hydroxibenzotriazol (HOBt), 1-hidroxi-7-azabenzotriazol (HOAt), y similares) y base no nucleofílica (por ejemplo, N-metilmorfolino, trietilamina, o similares, o cualquier combinación adecuada de estos) en un solvente adecuado (N-metilpirrolidinona, o similares) a temperatura ambiente y requiere 3 a 10 horas para completar la reacción. Una descripción detallada para la síntesis de un compuesto de Fórmula I por los procesos en el Esquema de Reacción 1 se establece en el Ejemplo, *infra*.

Los compuestos de Fórmula I, en donde X^3 es $-\text{NHX}^3$, puede ser preparado procediendo como en el siguiente Esquema de Reacción 2:

Esquema de Reacción 2



Los compuestos de Fórmula I, en donde X^1 es $-\text{NHX}^3$. La reacción de condensación puede ser efectuada con un agente de acoplamiento apropiado (por ejemplo, hexafluorofosfato de benzotriazol-1-iloxitrispiroldino-fosfonilo (PyBOP[®]), hidrocloruro de 1-(3-dimetilaminopropil)-3-etilcarbodiimida (EDCI), hexafluorofosfato de O-benzotriazol-1-il-N,N,N',N'-tetrametiluronio (HBTU), 1,3-diciclohexil-carbodiimida (DCC), o similares) y opcionalmente un catalizador apropiado (por ejemplo, 1-hidroxibenzotriazol (HOBt), 1-hidroxil-7-azabenzotriazol (HOAt), o similares) y una base no nucleofílica (por ejemplo N-

metilmorfonina, trietilamina, o similar, o cualquier combinación adecuada de ellas) en un disolvente adecuado (N-metilpirrolidona, o similares) a temperatura ambiente y requiere 3 a 10 horas para completar la reacción. Una descripción detallada para la síntesis del compuesto de Fórmula I por los procesos en el Esquema de Reacción 1 se establece en los ejemplos, *infra*.

Procesos Adicionales para Preparar Compuestos de Fórmula I:

Un compuesto de Fórmula I puede ser preparado como una sal de adición de ácido farmacéuticamente aceptable al hacer reaccionar la forma de base libre del compuesto con un ácido orgánico o inorgánico farmacéuticamente aceptable. Alternativamente, una sal de adición de base farmacéuticamente aceptable de un compuesto de fórmula puede se preparado por hacer reaccionar la forma de ácido libre del compuesto con una base orgánica o inorgánica farmacéuticamente aceptable. Los ácidos orgánicos e inorgánicos y las bases orgánicas e inorgánicas adecuadas por la preparación de las sales farmacéuticamente aceptables de los compuestos de Fórmula I se establecen en la sección de definiciones de esta solicitud. Alternativamente, las

formas de sal de los compuestos de Fórmula I pueden ser preparadas usando sales de materiales de partida o Intermedios.

Las formas de ácidos libres o bases libres de los compuestos de Fórmula I pueden ser preparadas a partir de la fórmula de sal de adición de ácido o sal de adición de base correspondiente. Por ejemplo, un compuesto de Fórmula I en una forma de sal de adición de ácido puede ser convertida a la base libre correspondiente tratándolo con una base adecuada (por ejemplo, una solución de hidróxido de amonio, hidróxido de sodio, o similares). Un compuesto de Fórmula I en una forma de sal de adición de base puede ser convertida al ácido libre correspondiente tratándolo con un ácido adecuado (por ejemplo, ácido clorhídrico, etc.).

Los N-óxidos de los compuestos de Fórmula I pueden ser preparados por métodos conocidos por aquellos versados en la técnica. Por ejemplo, los N-óxidos pueden ser preparados tratando una forma no oxidada del compuesto de Fórmula I con un agente oxidante (por ejemplo ácido trifluoroperacético, ácido permaleico, ácido perbenzoico, ácido peracético, ácido meta-

cloroperoxibenzoico, o similares) en un disolvente orgánico Inerte (por ejemplo, un hidrocarburo halogenado tal como diclorometano) a aproximadamente 0° C. Alternativamente, los N-óxidos de los compuestos de Fórmula I pueden ser preparados a partir de N-óxido de un material de partida apropiado.

Los compuestos de Fórmula I en la forma no oxidada pueden ser preparados a partir de N-óxidos de compuestos de Fórmula I por medio de tratarlos con un agente reductor (por ejemplo azufre, dióxido de azufre, trifenilfosfina, borohidruro de litio, borohidruro de sodio, tricloruro de fosforoso, tribromuro o similares) en un disolvente orgánico inerte adecuado, (por ejemplo, acetonitrilo, etanol, dioxano acuoso, o similares) entre 0 a 80° C.

Los derivados de prodrogas de los compuestos de Fórmula I pueden se preparados por métodos conocidos por aquellos versados en la técnica (por ejemplo, para mayores detalles ver Saulnier et al. (1994), Bioorganic and Medicinal Chemistry Letters, Vol. 4, p. 1985). Por ejemplo, las prodrogas apropiadas pueden ser preparadas por medio de hacer reaccionar un compuesto no

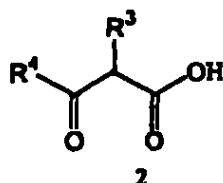
derivado de Fórmula I con un agente carbamillante adecuado (por ejemplo, 1,1-aclloxialquillcarbonoclorhidrato, carbonato de para-nitrofenilo, o similares).

Los derivados protegidos de los compuestos de Fórmula I pueden ser hechos por medios conocidos por aquellos versados en la técnica. Una descripción detallada de las técnicas aplicables para la creación de grupos protectores y su remoción pueden encontrarse en T.W. Greene, *Protecting Group In Organic Synthesis*, 3ra edición, John Wiley & Sons, Inc. 1999. Los compuestos de la presente Invención pueden ser preparados convenientemente, o formados durante el proceso de la Invención, como solvatos (por ejemplo hidratos). Los hidratos de compuestos de la presente Invención pueden ser preparados convenientemente por medio de recristalización a partir de una mezcla de solvente acuosa/orgánica usando disolventes orgánicos tales como dioxina, tetrahidrofurano o metanol. Los compuestos de Fórmula I pueden ser preparados como sus estereoisómeros individuales por medio de hacer reaccionar una mezcla racémica de compuestos con un agente de resolución activa ópticamente para formar un par de compuestos diastereoisoméricos, separando los diastereómeros y recuperando el enantiómero ópticamente puro. Aunque la

resolución de enantiómeros puede ser llevada a cabo usando derivados de diastereoméricos covalentes de los compuestos de Fórmula I, complejos disociables son preferidos (por ejemplo sales diastereoisoméricas cristalinas). Los diastereómeros tienen propiedades físicas distintas (por ejemplo, puntos de fusión, puntos de ebullición, solubilidad, reactividad, etc.) y pueden ser separados fácilmente teniendo en cuenta las ventajas de estas disimilitudes. Los diastereómeros pueden ser separados por cromatografía, o, preferiblemente por técnicas de separación/resolución con base en las diferencias de solubilidades. El enantiómero ópticamente puro es entonces recuperado junto con el agente de resolución, por cualquier medio práctico que no resulte en racemización. Una descripción más detallada de las técnicas aplicables a la resolución del estereoisómero de los compuestos a partir de sus mezclas racémicas puede encontrarse en Jean Jacques Andre Collet, Samuel H. Wilen, *Enantiomers, Racemates and Resolutions*, John Wiley & Sons, Inc. (1981).

En resumen, los compuestos de Fórmula I están hechos por un proceso que comprende:

(A) hacer reaccionar un compuesto de Fórmula 2:



con un compuesto de fórmula $\text{NH}_2\text{CR}^1\text{R}^2\text{X}^2$, en los cuales R^1 , R^2 , R^3 , R^4 y X^2 son según se definió en el resumen de la invención para la Fórmula I; o

(B) hacer reaccionar un compuesto de Fórmula 2 con un compuesto de Fórmula NH_2X^3 , en el cual R^3 , R^4 y X^3 son según se describió en el resumen de la invención para la Fórmula I; y

(C) convertir opcionalmente un compuesto de Fórmula I en una sal farmacéuticamente aceptable;

(D) convertir opcionalmente una forma de sal de un compuesto de Fórmula I a una forma no salina;

(E) convertir opcionalmente una forma no oxidada de un compuesto de Fórmula I en un N-óxido farmacéuticamente aceptable;

- (F) convertir opcionalmente una forma N-óxido de un compuesto de Fórmula I en su forma no oxidada;
- (G) resolver opcionalmente un isómero individual de un compuesto de Fórmula I a partir de mezcla de isómeros;
- (H) convertir opcionalmente un compuesto no derivado de Fórmula I en un derivado farmacéuticamente de prodroga; y
- (I) convertir opcionalmente un derivado de prodroga de un compuesto de Fórmula I en su forma no derivada.

EJEMPLOS:

La presente invención se ejemplifica adicionalmente, pero no se limita por, los siguientes ejemplos que ilustran la preparación de compuestos de Fórmula I (Ejemplos) e intermedios (Referencias) de acuerdo con la invención.

REFERENCIA 1

Ácido 2-Fenilcarbamoil-hexanoico

Una solución de anilina (5,47 ml, 60 mmoles) y trietilamina (8,36 ml, 60 mmoles) en cloruro de metileno (150 ml) fue enfriado -20 °C y tratado con metilmalonilcloruro (8,36 ml, 60 mmoles) en cloruro de metileno (20 ml). La mezcla de reacción se le permitió calentarse a temperatura ambiente durante 3 horas y luego fue vertida en 1N HCL frío. La capa orgánica fue separada y lavada con bicarbonato de sodio acuoso y luego salmuera y secada sobre sulfato de magnesio y evaporada para dar 2-fenilcarbamoilacetato de metilo.

Una mezcla de 2-fenilcarbamoilacetato de metilo (1,159g, 6 mmoles) hidróxido de litio (0,43g, 18 mmoles) y 1-yodobutano (0,91 ml, 8 mmoles) en N-metilpirrolidinona (10 ml) fue agitada a temperatura ambiente durante 1,5 horas. La mezcla de reacción fue vertida en agua con hielo, extraída con etilacetato (2 veces, 50 ml cada una). Los extractos combinados fueron lavados con salmuera, secados sobre sulfato de magnesio y evaporados. El residuo fue purificado por cromatografía flash sobre gel de sílice eluyendo con 20% de etilacetato/hexano para dar 2-fenilcarbamoilhexanoato de metilo (0,715g, 48% de producción).

Una solución de 2-fenilcarbamoilhexanoato de metilo (0,98g, 3,9 mmoles) en metanol (10 ml) fue tratada con hidróxido de sodio (4 ml, 4 mmoles) a temperatura ambiente durante 17 horas. El metanol fue removido bajo presión reducida y el residuo fue tratado con 1N HCl y extraído con etilacetato (2 veces, 50 ml cada uno). Las capas orgánicas fueron lavadas con salmuera, secadas sobre sulfato de magnesio y evaporadas para dar ácido 2-fenilcarbamoilhexanoico (0,68g, 2,9 mmoles, 74% de producto).

REFERENCIA 2

Ácido 2-Ciclohexilmetil-N-fenil-manolámico

Una mezcla de 2-fenilcarbamoilacetato de metilo (preparada como en la referencia Ejemplo 1) (4,39g, 22,7 mmoles), hidróxido de litio (1,08g, 45 mmoles) y bromometilciclohexano (3,76 ml, 27 mmoles), en N-metilpirrolidinona (25 ml) fue agitado a temperatura ambiente durante 17 horas. La mezcla de reacción fue vertida en agua con hielo y extraída con éter (3 veces, 100 ml cada una). Los extractos fueron lavados con agua y luego

salmuera, secados sobre sulfato de magnesio y evaporados. El residuo fue purificado por cromatografía flash sobre gel de sílice eludiendo con 10% de etilacetato (hexano) para dar malonamato de 2-ciclohexilmetil-N-fenilo (1,89g, 6,5 mmoles, 29% de producto). La capa acuosa anterior fue enfriada sobre hielo y acidificada a un pH2 con 1N HCL. La capa acuosa fue extraída con éter (3 veces, 100 ml cada uno) y los extractos fueron lavados con agua, luego salmuera, secados sobre sulfato de magnesio y evaporados para dar ácido 2-ciclohexilmetil-N-fenilmalonámico (1,12g, 18% de producto).

REFERENCIA 3

Ácido 2-Ciclohexilmetil-N-fenetil-manolámico

Sodio (6,9g, 0,3 moles), disuelto en etanol (300 ml) y luego dietilmalonato (50,3 ml, 0,3 moles) se agregó. Bromometilciclohexano (46 ml, 0,33 moles) fue agregado y la mezcla de reacción fue calentada a 70° C durante 14 horas. La mezcla de reacción fue enfriada y el etanol removido por evaporación. La masa resultante fue disuelta en agua con hielo y

luego extraída con etilacetato. Las capas orgánicas fueron lavadas con agua, luego salmuera y secadas sobre sulfato de magnesio. Los disolventes fueron removidos bajo presión reducida para dar malonato de dietilciclohexilo.

Una solución de malonato de dietilciclohexilo (12,8g, 0,05 moles) en etanol (100 ml) fue tratada con una solución de hidróxido de litio (1,2g, 0,05 moles) en agua (50 ml) y luego agitada a temperatura ambiente durante 15 horas. El etanol fue removido a presión reducida y agua (50 ml) se agregó al residuo. La mezcla de reacción fue extraída con éter, enfriada sobre hielo y acidificada a un pH 1,5 con HCL. La fase acuosa fue saturada con NaCl y extraída con acetato de etilo (2 veces, 150 ml cada uno). Secando sobre sulfato de magnesio y evaporando el disolvente dio 2-ciclohexilmalonato de etilo (8,52g, 37 mmoles, 74% de producto).

El 2-ciclohexilmalonato de etilo (8,52g, 37 mmoles) en etilacetato (80 ml) fue enfriado a 0° C y tratado con dimetilformado (50 μ L) y luego oxalilcloruro (3,93 ml, 45 mmoles). La temperatura de reacción fue elevada a temperatura ambiente y después de 2

horas los disolventes fueron removidos bajo presión reducida para dar 2-ciclohexilmalonil cloruro de etilo.

El malonilcloruro anterior fue diluido en un volumen de 28 ml con etilacetato y 2 ml de esa solución se agregó a una solución de fenetilamina (0,376 ml, 3 mmoles) y N-metilmorfolina (0,40g, 4 mmoles) en acetato de etilo (4 ml) a -20° C. después de 15 minutos la mezcla de reacción se le permitió calentarse a temperatura ambiente durante la noche. La mezcla de reacción fue diluida con acetato de etilo (5 ml) y agua con hielo (5 ml). La capa orgánica fue separada y lavada con HCl al 0,05 N frío, luego NaHCO₃ acuoso, luego salmuera, secado sobre sulfato de magnesio y evaporado bajo presión reducida. El residuo fue purificado por cromatografía radial para dar 2-ciclohexilmetil-N-fenetil malanmato de etilo (0,366g, 1,10 mmoles, 42% de producto).

El éster anterior (0,366g, 1,10 mmoles) en etanol (10 ml) fue tratado a temperatura ambiente con hidróxido de sodio acuoso (1,3 ml de 1N) durante 2,5 horas. La mezcla de reacción fue diluida con agua (30 ml) y lavada con éter (3 veces, 30 ml cada uno). La capa acuosa fue enfriada, acidificada con HCl al 1N (2 ml) y extraída

con acetato de etilo (3 veces, 30 ml cada uno). Los extractos de acetato de etilo fueron lavados con salmuera, secados sobre sulfato de magnesio y evaporados para dar ácido 2-ciclohexilmetil-N-femetil malonámico (0,138g, 0,46 mmoles, 42% de producto).

REFERENCIA 4

Ácido 2-Ciclohexilmetil-N-piridin-4-ilmetil-malonámico

2-ciclohexilmetilmalonil cloruro de etilo, preparado como en la Referencia 3 (0,307g, 1,25 mmoles), fue condensado con 4-aminometil piridina usando el método de la Referencia 3 para dar 2-ciclohexilmetil-4-piridin-4-ilmetil malonamato de etilo (0,237g, 0,74 mmoles, 58% de producto).

Este ester fue hidrolizado con hidróxido de sodio usando el método de la Referencia 3 para dar ácido de 2-ciclohexilmetil-N-piridin-4-ilmetilmalanámico (0,048g, 0,14 mmoles, 19% de producto).

Procediendo como en los ejemplos de referencia anterior se suministran los siguientes compuestos:

Ácido N-benzil-2-ciclohexilmetil-malonámico ;

Ácido 2-ciclohexilmetil-N-(4-fenoxi-fenil)-malonámico;

Ácido 2-ciclohexilmetil-N-(3-fenil-propil)-malonámico;

Ácido 2-ciclohexilmetil-3-morfolin-4-il-3-oxo-propionico;

Ácido N-ciclohexil-2-ciclohexilmetil-malonámico;

Ácido 2-ciclohexilmetil-N-naftalen-1-ilmetil-malonámico;

Ácido 2-ciclohexilmetil-N-piridin-3-il-malonámico;

Ácido 2-ciclohexilmetil-N,N-diisobutil-malonámico;

Ácido 2-ciclohexilmetil-N-(6-metoxi-piridin-3-il)-malonámico;

Ácido 2-ciclohexilmetil-N-(2-tiofen-2-il-etil)-malonámico;

Ácido 2-ciclohexilmetil-N-(3-fenoxi-fenil)-malonámico;

Ácido 2-ciclohexilmetil-N-(4-nitro-benzil)-malonámico;

Ácido N-clanometil-2-ciclohexilmetil-malonámico;

Ácido 2-ciclohexilmetil-N-(5,6,7,8-tetrahidro-naftalen-1-il)-malonámico;

Ácido 2-ciclohexilmetil-N-(2-piridin-2-il-etil)-malonámico;

Ácido 2-ciclohexilmetil-3-(2,3-dihidro-indol-1-il)-3-oxo-propionico;

Ácido 2-ciclohexilmetil-3-(3,4-dihidro-1h-isoquinolin-2-il)-3-oxo-propionico;

2,N-bis-ciclohexilmetil-3-oxo-butiramida;

2-ciclohexilmetil-N-(2-metoxi-benzil)-3-oxo-butiramida;

Ácido 2-ciclohexilmetil-N-(1-fenil-etil)-malonámico;

Ácido N-benzil-2-ciclohexilmetil-N-metil-malonámico;

2-ciclohexilmetil-N-(3-nitro-benzil)-3-oxo-butiramida;

Ácido 2-ciclohexilmetil-N-(4-metoxi-benzil)-malonámico;

Ácido N-(3-carbamoyl-fenil)-2-ciclohexilmetil-malonámico;

Ácido 2-ciclohexilmetil-N-piridin-3-ilmetil-malonámico;

Ácido N-(4-carbamoyl-fenil)-2-ciclohexilmetil-malonámico;

Ácido 2-ciclohexilmetil-N-(tetrahidro-furan-2-ilmetil)-malonámico;

Ácido 2-ciclohexilmetil-3-(3,4-dihidro-2H-quinolin-1-il)-3-oxo-propiónico;

Ácido N-terc-butil-2-ciclohexilmetil-N-metil-malonámico;

Ácido 2-ciclohexilmetil-N-metil-N-propil-malonámico;

Ácido N-butil-2-ciclohexilmetil-N-metil-malonámico;

Ácido 2-ciclohexilmetil-N,N-dimetil-malonámico;

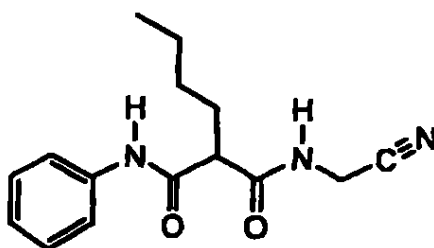
Ácido (R)-2-benzilcarbamoil-4-fenilsulfanil-butírico; y

Ácido 4-benzenesulfonil-2-benzilcarbamoil-butírico;

EJEMPLO 1

2-Butil-N-clanometil-N'-fenilmalonamida

(Compuesto 1)

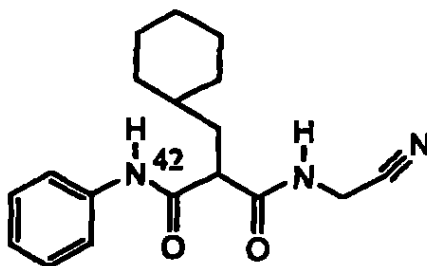


Una solución comprendida de ácido 2-fenilcarbamoil-hexanoico (188g, 0,8 mmoles), preparada como en la Referencia 1, en DMF (5. ml) fue tratada con PyBOP® (425g, 0,8 mmoles), bisulfato de aminoacetonitrilo (140 mg, 0,9 mmoles) y trietilamina (600 μ L, 4,3 mmoles). La mezcla fue agitada durante 3 horas y luego particionada entre agua (20 ml) y acetato de etilo (50 ml). La capa orgánica fue separada y lavada con una solución de bicarbonato de sodio saturado al 1 M, una solución de ácido clorhídrico al 1 M y agua, secado (MgSO₄) y concentrado. El producto fue purificado a partir del residuo por una columna flash sobre gel de sílice (60°A) con 50% de acetato de etilo en hexano para suministrar 2-butil-N-clanometil-N'-fenilmalonamida (125 mg, 57% de producto). ¹H RMN: (DMSO) 10,01 (s, 1H), 7,59 (d, J=8Hz, 2H), 7,31 (t, J=7Hz, 2H), 7,06 (t, J=7Hz, 1H), 4,13 (d, J=6Hz, 2H), 3,32 (t, J=8Hz, 1H), 1,80 (m, 2H), 1,25 (m, 4H), 0,86 (t, J=7Hz, 3H). MS: m/e 273,9.

EJEMPLO 2

N-clanometil-2-clclohexilmetil-N'-fenil-malonamida

(Compuesto 2);

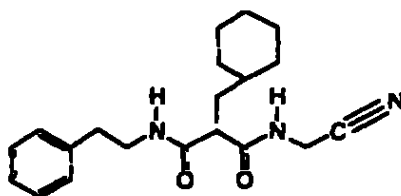


Una solución comprendida de ácido 2-ciclohexilmetil-N-fenil-malonámico (350 mg, 1,2 mmoles), preparado como en la Referencia 2, DESI (250 mg, 1,3 mmoles), hidrato HOBt (199 mg, 1,3 mmoles), bisulfato de aminoacetoniitrilo (200 mg, 1,3 mmoles) y N-metilmorfolina (0,30 ml, 2,7 mmoles) en N,N-dimetilpirrolidinona (5 ml) fue agitada a temperatura ambiente durante 15 horas. La mezcla de reacción fue vertida en IN HCl frío y extraída con acetato de etilo. La fase orgánica fue lavada con bicarbonato de sodio saturado acuoso y luego salmuera (50 ml cada uno) secado sobre sulfato de magnesio y evaporado. El residuo fue purificado por cromatografía radial usando 50% de acetato de etilo/hexano como eluyente para suministrar N-cianometil-2-ciclohexil-metil-N'-fenil-malonamida (179 mg, 48% de producto). ^1H RMN: (DMSO) 10,01 (s, 1H), 8,47 (t, $J=5\text{Hz}$, 1H), 7,59 (d, $J=7\text{Hz}$, 2H), 7,31 (t, $J=8\text{Hz}$, 2H), 7,07 (t, $J=7\text{Hz}$, 1H), 4,13 (d, $J=5\text{Hz}$, 2H), 3,47 (t, $J=7\text{Hz}$, 1H), 1,6 (m, 7H), 1,1 (m, 4H), 0,9 (m, 2H). MS: m/e 313,2.

EJEMPLO 3

N-cianometil-2-ciclohexilmetil-N'-fenetilmalonamida

(Compuesto 3)

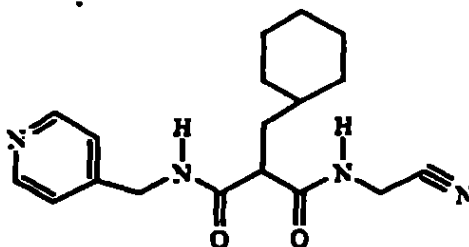


Una solución comprendida de ácido 2-ciclohexilmetil-N-fenetilmalónico (138 mg, 0,46 mmoles), preparado como en la Referencia 3, DESI (115 mg, 0,60 mmoles), hidrato de HOBt (92 mg, 0,60 mmoles), N-metilmorfolina (0,115 ml, 1,38 mmoles) en N,N-dimetilpirrolidina (4 ml) fue agitado a temperatura ambiente durante 10 minutos. Se agregó bisulfato de aminoacetoniitrilo (106 mg, 0,69 mmoles). La mezcla de reacción fue agitada a temperatura ambiente durante 2 horas, luego se vertió en 1N HCl frío y se extrajo 2 veces con acetato de etilo (50 ml cada uno). La fase orgánica fue lavada con bicarbonato de sodio acuoso y luego salmuera (50 ml cada uno) secado sobre sulfato de magnesio y evaporado. El residuo fue purificado por cromatografía radial usando 50% de acetato de etilo/hexano como eluyente para

suministrar N-cianometil-2-ciclohexilometil-N'-fenetilmalonamida (56 mg, 36% de producto). ^1H RMN: (DMSO) 8,38 (t, $J=5\text{Hz}$, 1H), 7,98 (t, $J=6\text{Hz}$, 1H), 7,25 (m, 5H), 4,10 (d, $J=6\text{Hz}$, 2H), 3,2 (m, 3H), 2,71 (t, $J=7\text{Hz}$, 2H), 1,6 (m, 7H), 1,1 (m, 4H), 0,85 (m, 2H). MS: m/e 342,10.

EJEMPLO 4

N-cianometil-2-ciclohexilmetil-N'-pirid-4-ilmetilmalonamida
(Compuesto 4)

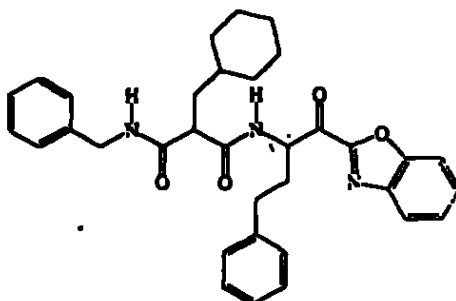


Una solución comprendida de ácido 2-ciclohexilmetil-N-piridin-4-ilmetil-malónico (41 mg, 0,14 mmoles), preparado como en la Referencia 4, fue acoplado a aminoacetoniitrilo como se describió en el Ejemplo 3 para suministrar N-cianometil-2-ciclohexilmetil-N'-pirid-4-ilmetilmalonamida (13 mg, 28% de producto). ^1H RMN: (DMSO) 8,5 (m, 4H), 7,20 (d, $J=6\text{Hz}$, 2H), 4,3 (m, 2H), 4,13 (d, $J=5\text{Hz}$, 2H), 3,3 (m, 1H), 1,6 (m, 7H), 1,1 (m, 4H), 0,83 (m, 2H). MS: m/e 329,08.

EJEMPLO 5

N-[1-(1-benzooxazol-2-il-metanoil)-3-fenil-propil]-N'-benzil-2-
ciclohexilmetil-malonamida

(Compuesto 5)



Una mezcla de ácido N-benzil-2-ciclohexilmetil-malonámico (200mg, 0,69 mmoles), HOBt (159mg, 1,04 mmoles), EDC (146mg, 0,76 mmoles), 2-amino-1-benzoxazol-2-il-4-fenil-butan-1-ona (195 mg, 0,69 mmoles), diclorometano (3 ml) y trietilamina (106 μ L, 0,76 mmoles) se le permitió agitarse durante 2 horas. El producto fue extraído con acetato de etilo (60 ml) y lavado con dos porciones de 15 ml de HCl al 1N, y dos porciones de 15 ml de NaHSO₃ saturado, secado sobre MgSO₄ y concentrada. El acetato de etilo (5 ml) fue agregado y un precipitado blanco se formó y fue

recolectado para dar N-[1-(1-benzoxazol-2-il-1-hidroxi-metil)-3-fenil-propil]-N'-benzil-2-ciclohexilmetil-malonamida (81 mg, 0,12 mmoles, 21% de producto).

N-[1-(1-benzoxazol-2-il-1-hidroxi-metil)-3-fenil-propil]-N'-benzil-2-ciclohexilmetil-malonamida (70 mg, 0,126 mmoles) fue disuelto en 0,6 ml diclorometano y tratado con periodinano Dess Martin (107 mg, 0,253 mmoles). La mezcla fue agitada durante 2 horas y luego se agregó 8 ml $\text{Na}_2\text{S}_2\text{O}_3$ al 0,26M en NaHSO_3 saturado y la mezcla fue extraída con dos porciones de 15 ml de acetato de etilo y lavada con dos porciones de 4 ml de NaHSO_3 saturado. La capa orgánica fue secada sobre MgSO_4 y concentrada. El producto fue recristalizado a partir de acetato de etilo y hexano para dar N-[1-(1-benzoxazol-2-il-metanol)-3-fenil-propil]-N'-benzil-2-ciclohexilmetil-malonamida (40 mg, 0,072 mmoles, 57% de producto); ^1H RMN: (DMSO) 7,88 (m, 1H), 7,68-7,40 (m, 3H), 7,35-7,10 (m, 10H), 6,90 (m, 1H), 5,65 (m, 1H), 4,43 (d, $J=5,7\text{Hz}$, 2H), 3,25 (m, 1H), 2,74 (t, $J=8,0\text{Hz}$, 1H), 2,46 (m, 1H), 2,17 (m, 1H), 1,77 (t, $J=7,4\text{Hz}$, 1H), 1,64 (m, 7H), 1,22 (m, 4H), 0,87 (m, 2H); MS: ($\text{M}^+ + 1$) 552,8; 551,68.

Los siguientes compuestos de Fórmula I fueron suministrados por medio de proceder tal como en los ejemplos anteriores:

N-cianometil-N'-ciclohexil-2-ciclohexilmetilmalonamida (Compuesto 6); ^1H RMN (DMSO): 8,31 (t, J = 6Hz, 1H), 7,82 (d, J = 8Hz, 1H), 4,10 (d, J = 8Hz, 2H), 3,52 (m, 1H), 3,20 (t, J = 7Hz, 1H), 1,6 (m, 12H), 1,1 (m, 9H), 0,83 (m, 2H); MS (m/e) = 320,11;

N-benzil-N'-cianometil-2-ciclohexilmetilmalonamida (Compuesto 7); ^1H RMN (DMSO): 8,45 (m, 2H), 7,3 (m, 5H), 4,33 (dd, J = 6,15Hz, 1H), 4,23 (dd, J = 6,15Hz, 1H), 4,12 (d, 2H), 3,3 (m, 1H), 1,6 (m, 7H), 1,1 (m, 4H), 0,85 (m, 2H); MS (m/e) = 328,15, P. M. = 327,43;

N-cianometil-2-ciclohexilmetil-N'-(4-fenoxifenil)malonamida (Compuesto 8); ^1H RMN (DMSO): 10,1 (s, 1H), 8,50 (t, J = 5Hz, 1H), 7,61 (d, J = 7Hz, 2H), 7,37 (t, J = 7Hz, 2H), 7,11 (t, J = 7Hz, 1H), 7,0 (m, 4H), 4,14 (d, J = 5Hz, 2H), 3,47 (t, J = 7Hz, 1H), 1,7 (m, 7H), 1,1 (m, 4H), 0,92 (m, 2H); MS (m/e) = 406,10, P. M. = 405,49;

N-cianometil-2-ciclohexilmetil-N'-(3-fenilpropil)malonamida

(Compuesto 9); ^1H RMN (DMSO): 8,38 (t, $J = 6\text{Hz}$, 1H), 8,00 (t, $J = 6\text{Hz}$, 1H), 7,2 (m, 5H), 4,10 (d, $J = 5\text{Hz}$, 2H), 3,23 (t, $J = 7\text{Hz}$, 1H), 3,1 (m, 2H), 2,5 (m, 2H), 1,6 (m, 9H), 1, 1 (m, 4H), 0,85 (m, 2H); MS (m/e) = 356,02;

N-cianometil-2-ciclohexilmetil-3-morfolin-4-il-3-oxopropionamida

(Compuesto 10); ^1H RMN (DMSO): 8,54 (t, $J = 4\text{Hz}$, 1H), 4,12 (d, $J = 5\text{Hz}$, 2H), 3,5 (m, 8H), 1,65 (m, 8H), 1,15 (m, 4H), 0,85 (m, 2H); MS (m/e) = 308,05;

N-cianometil-2-ciclohexilmetil-N'-naft-1-ilmetilmalonamida

(Compuesto 11); ^1H RMN (DMSO): 8,53 (t, $J = 5\text{Hz}$, 1H), 8,43 (t, $J = 6\text{Hz}$, 1H), 8, 04 (m, 1H), 7,94 (m, 1H), 7,86 (d, $J = 8\text{Hz}$, 1H), 7,5 (m, 4H), 4,85 (dd, $J = 6,15\text{Hz}$, 1H), 4,65 (dd, $J = 5, 15\text{Hz}$, 1H), 4,12 (d, $J = 3\text{Hz}$, 2H), 3,3 (M, 1H), 1,6 (m, 8H), 1,0 (m, 5H); MS (m/e) = 378,18, P. M. 377,18;

N-cianometil-2-ciclohexilmetil-N'-pirid-3-ilmalonamida (Compuesto

12); ^1H RMN (DMSO): 10,24 (s, 1H), 8, 75 (s, 1H), 8, 54 (t, $J = 5\text{Hz}$, 1H),

8,29 (d, $J = 5\text{Hz}$, 1H), 8,04 (d, $J = 7\text{Hz}$, 1H), 7,36 (m, 1H), 4,13 (d, $J = 5\text{Hz}$, 2H), 3,49 (t, $J = 7\text{Hz}$, 1H), 1,7 (m, 7H), 1,1 (m, 4H), 0,9 (m, 2H); MS (m/e) = 314,91;

N-cianometil-2-ciclohexilmetil-N',N'-diisobutilmalonamida

(Compuesto 13); ^1H RMN (DMSO): 8,50 (t, $J = 4\text{Hz}$, 1H), 4,09 (m, 2H), 3,63 (t, $J = 7\text{Hz}$, 1H), 3,2 (m, 2H), 3,05 (m, 2H), 1,9 (m, 2H), 1,6 (m, 7H), 1,1 (m, 4H), 0,8 (m, 14H); MS (m/e) = 350,08, P. M. 349,51;

N-cianometil-2-ciclohexilmetil-N',N'-diisopropilmalonamida

(Compuesto 14); ^1H RMN (DMSO): 8,45 (t, $J = 5\text{Hz}$, 1H), 4,1 (m, 3H), 3,55 (t, $J = 7\text{Hz}$, 1H), 3,46 (m, 1H), 1,6 (m, 7H), 1,27 (d, $J = 7\text{Hz}$, 6H), 1,11 (m, 10H), 0,85 (m, 2H); MS (m/e) = 321,99, P. M. 321,24;

N-cianometil-2-ciclohexilmetil-N'-(6-metoxipirid-3-il)malonamida

(Compuesto 15); ^1H RMN (DMSO): 10,04 (s, 1H), 8,50 (t, $J = 5\text{Hz}$, 1H), 8,35 (s, 1H), 7,88 (d, $J = 9\text{Hz}$, 1H), 6,80 (d, $J = 9\text{Hz}$, 1H), 4,13 (m, 2H), 3,81 (s, 3H), 3,44 (t, $J = 8\text{Hz}$, 1H), 1,7 (m, 7H), 1,1 (m, 4H), 0,91 (m, 2H); MS (m/e) = 345,01, P. M. 344,18;

N-cianometil-2-ciclohexilmetil-N'-(2-tien-2-iletil)malonamida

(Compuesto 16); ^1H RMN (DMSO): 8,40 (t, $J = 5\text{Hz}$, 1H), 8,07 (t, $J = 5\text{Hz}$, 1H), 7,33 (d, $J = 5\text{Hz}$, 1H), 6,95 (m, 1H), 6,87 (m, 1H), 4,10 (d, $J = 5\text{Hz}$, 2H), 3,3 (m, 3H), 3,21 (t, $J = 7\text{Hz}$, 2H), 1,6 (m, 7H), 1,1 (m, 4H), 0,85 (m, 2H); MS (m/e) = 348,09, P. M. 347,48;

N-cianometil-2-ciclohexilmetil-N'-(3-fenoxifenil)malonamida

(Compuesto 17); ^1H RMN (DMSO): 10,1 (s, 1H), 8,45 (t, $J = 5\text{Hz}$, 1H), 7,41 (t, $J = 8\text{Hz}$, 2H), 7,33 (m, 3H), 7,16 (t, $J = 7\text{Hz}$, 1H), 7,03 (d, $J = 8\text{Hz}$, 2H), 6,73 (m, 1H), 4,1 (m, 2H), 3,42 (t, $J = 7\text{Hz}$, 1H), 1,6 (m, 7H), 1,1 (m, 4H), 0,85 (m, 2H); MS (M/E) = 406,04, P. M. 405,49;

N-cianometil-2-ciclohexilmetil-N'-(4-nitrobenzil)malonamida

(Compuesto 18); ^1H RMN (DMSO): 8,61 (t, $J = 6\text{Hz}$, 1H), 8,53 (t, $J = 6\text{Hz}$, 1H), 8,17 (d, $J = 9\text{Hz}$, 2H), 7,47 (d, $J = 9\text{Hz}$, 2H), 4,41 (d, $J = 6\text{Hz}$, 2H), 4,14 (d, $J = 6\text{Hz}$, 2H), 3,3 (m, 1H), 1,6 (m, 7H), 1,1 (m, 4H), 0,87 (m, 2H); MS (M/E) = 373,02, P. M. 372,42;

N,N'-biscianometil-2-ciclohexilmetilmalonamida (Compuesto 19); ^1H

RMN (DMSO): 8,59 (t, $J = 5\text{Hz}$, 2H), 4,14 (d, $J = 6\text{Hz}$, 4H), 3,28 (t, $J =$

8Hz, 1H), 1,6 (m, 7H), 1,1 (m, 4H), 0,86 (m, 2H); MS (m/e) = 276,99, P. M. 276,34;

N-cianometil-2-ciclohexilmetil-N'-(5,6,7,8-tetrahidronaft-1-

il)malonamida (Compuesto 20); ^1H RMN (DMSO): 9,28 (s, 1H), 8,57 (t, J = 6Hz, 1H), 7,21 (d, J = 8Hz, 1H), 7,05 (t, J = 8Hz, 1H), 6,90 (d, J = 7Hz, 1H), 4,16 (d, J = 6Hz, 2H), 3,49 (t, J = 7Hz, 1H), 2,7 (m, 2H), 2,5 (m, 2H), 1,7 (m, 11H), 1,1 (m, 4H), 0,91 (m, 2H); MS (m/e) = 368, 04, P. M. 367,48;

N-cianometil-2-ciclohexilmetil-N'-(2-pirid-2-iletil)malonamida

(Compuesto 21); ^1H RMN (DMSO): 8,49 (m, 1H), 8,40 (t, J = 6Hz, 1H), 8,00 (t, J = 5Hz, 1H), 7,68 (dt, J = 2,8Hz, 1H), 7,2 (m, 2H), 4,09 (d, J = 6Hz, 2H), 3,42 (m, 2H), 3,17 (t, J = 8Hz, 1H), 2,85 (t, J = 7Hz, 2H), 1,6 (m, 7H), 1,07 (m, 4H), 0,83 (m, 2H); MS (m/e) = 343,04, P. M. 342,44;

N-cianometil-2-ciclohexilmetil-3-(2,3-dihidroindol-1-il)-3-

oxopropionamida (Compuesto 22); ^1H RMN (DMSO): 8,73 (t, J = 5Hz, 1H), 8,06 (d, J = 8Hz, 1H), 7,24 (d, J = 7Hz, 1H), 7,15 (t, J = 7Hz, 1H), 7,00 (t, J = 7Hz, 1H), 4,15 (d, J = 5Hz, 2H), 4,1 (m, 2H), 3,66 (t, J =

7Hz, 1H), 3,14 (m, 2H), 1,6 (m, 7H), 1,1 (m, 4H), 0,91 (m, 2H); MS (M/E) = 340,07, P. M. 339,19;

N-cianometil-2-ciclohexilmetil-3,4-dihidro-1H-isoquinolin-2-il)-3-oxopropionamida (Compuesto 23); ^1H RMN (DMSO): 8,64 (t, $J = 5\text{Hz}$, 1H), 7,15 (s, 4H), 4,65 (m, 2H), 4,11 (t, $J = 6\text{Hz}$, 2H), 3,77 (m, 2H), 2,8 (m, 2H), 1,7 (m, 7H), 1,1 (m, 4H), 0,89 (m, 2H), 3,54 (m, 1H); MS (M/E) = 354,05, P. M. 353,46;

N-cianometil-2,N'-bisciclohexilmetilmalonamida (Compuesto 24); ^1H RMN (DMSO): 8,34 (t, $J = 5\text{Hz}$, 1H), 7,93 (t, $J = 5\text{Hz}$, 1H), 4,09 (d, $J = 6\text{Hz}$, 2H), 3,23 (dd, $J = 7,9\text{Hz}$, 1H), 3,0 (m, 1H), 2,8 (m, 1H), 1,6 (m, 12H), 1,4 (m, 1H), 1,1 (m, 7H), 0,86 (m, 4H); MS (m/e) = 334,00, P. M. 333,47;

N-cianometil-2-ciclohexilmetil-N'-92-metoxibenzil)malonamida (Compuesto 25); ^1H RMN (DMSO): 8,44 (t, $J = 5\text{Hz}$, 1H), 8,27 (t, $J = 6\text{Hz}$, 1H), 7,24 (dt, $J = 2,7\text{Hz}$, 1H), 7,10 (dd, $J = 2,7\text{Hz}$, 1H), 6,96 (d, $J = 7\text{Hz}$, 1H), 6,88 (dt, $J = 7,1\text{Hz}$, 1H), 4,30 (dd, $J = 6,16\text{Hz}$, 1H), 4,20

(dd, $J = 5,16\text{Hz}$, 1H), 4,12 (d, $J = 6\text{Hz}$, 2H), 3,79 (s, 3H), 3,3 (m, 1H), 1,6 (m, 7H), 1, 1 (m, 4H), 0,85 (m, 2H); MS (m/e) = 358,03, P. M. 357,45;

N-clanometil-2-ciclohexilmetil-N'-(1-feniletil)malonamida

(Compuesto 26); ^1H RMN (DMSO): 8,25 (m, 1H), 7,4 (m, 5H), 4,02 (m, 2H), 3,18 (s, 3H), 3,25 (m, 1H), 1,6 (m, 7H), 1,1 (m, 4H), 0,7 (m, 2H); MS (m/e) = 328,08, P. M. 327,42;

N-benzil-N'-clanometil-2-ciclohexilmetil-N-metilmalonamida

(Compuesto 27); ^1H RMN (DMSO): 8,62 (m, 1H), 7,3 (m, 5H), 4,5 (m, 2H), 4,13 (d, $J = 6\text{Hz}$, 2H), 3,7 (m, 1H), 2,93 (s, 3H), 1,6 (m, 7H), 1,1 (m, 4H), 0,88 (m, 2H); MS (m/e) = 342,09, P. M. 341,45;

N-clanometil-2-ciclohexilmetil-N'-(3-nitrobenzil)malonamida

(Compuesto 28); ^1H RMN (DMSO): 8,6 (t, 1H), 8,5 (t, 1H), 8,1 (m, 2H), 7,6 (m, 2H), 4,1 (m, 2H), 1,6 (m, 7H), 1,1 (m, 4H), 0,8 (m, 2H); MS (m/e) = 373,07, P. M. 372,42;

N-cianometil-2-ciclohexilmetil-N'-(4-metoxibenzil)malonamida

(Compuesto 29); ^1H RMN (DMSO): 8,42 (t, $J = 5\text{Hz}$, 1H), 8,38 (t, $J = 6\text{Hz}$, 1H), 7,14 (d, $J = 9\text{Hz}$, 2H), 6,86 (d, $J = 9\text{Hz}$, 2H), 4,25 (dd, $J = 6, 15\text{Hz}$, 1H), 4,15 (dd, $J = 7, 16\text{Hz}$, 1H), 3,71 (s, 3H), 3,27 (t, $J = 8\text{Hz}$, 1H), 1,6 (m, 7H), 1,1 (m, 4H), 0,84 (m, 2H), 4,11 (d, $J = 6\text{Hz}$, 2H); MS (M/E) = 356,97, P. M. 357,45;

N-(3-carbamolifenil)-N'-cianometil-2-ciclohexilmetilmalonamida

(Compuesto 30); ^1H RMN (DMSO): 10,14 (s, 1H), 8,48 (t, 1H), 8,03 (s, 1H), 7,75 (d, 1H), 7,54 (d, 1H), 7,35 (m, 2H), 4,12 (d, 2H), 3,4 (t, 1H), 1,6 (m, 7H), 1,1 (m, 4H), 0,9 (m, 2H), 3,29 (s, 3H); MS (m/e) = 357,11, P. M. 356,42;

N-cianometil-2-ciclohexilmetil-N'-pirid-3-ilmetilmalonamida

(Compuesto 31); ^1H RMN (DMSO): 8,4 (m, 4H), 7,55 (d, 1H), 7,25 (dd, 1H), 4,28 (dd, 1H), 4,18 (dd, 1H), 4,05 (d, 2H), 3,2 (m, 1H), 1,6 (m, 7H), 1,01 (m, 4H), 0,78 (m, 2H); MS (M/E) = 329,03, P. M. 328,41;

N-(4-carbamolifenil)-N'-cianometil-2-ciclohexilmetilmalonamida

(Compuesto 32); ^1H RMN (DMSO): 10,22 (s, 2H), 8,50 (t, $J = 6\text{Hz}$, 1H),

7,83 (d, J = 9Hz 2H), 7,64 (d, J = 9Hz, 2H), 7,52 (s, 1H), 4,13 (d, J = 6Hz, 2H), 3,48 (t, J = 7Hz, 1H), 1,7 (m, 7H), 1,1 (M, 4H), 0,9 (m, 2H); MS (m/e) = 357,04, P. M. 356,42;

N-clanometil-2-ciclohexilmetil-N'-tetrahidrofur-2-

ilmetilmalonamida (Compuesto 33); ^1H RMN (DMSO): 8,38 (t, J = 5Hz, 1H), 7,98 (t, J = 4Hz, 1H), 4,10 (d, J = 6Hz 2H), 3,8 (m, 2H), 3,6 (m, 1H), 3,2 (m, 4H), 1,8 (m, 3H), 1,6 (m, 7H), 1,1 (m, 4H), 0,85 (m, 2H); MS (m/e) = 322,02, P. M. 321,41;

N-clanometil-2-ciclohexilmetil-3-(3,4-dihidro-2H-quinolin-1-il)-3-

oxopropionamida (Compuesto 34); ^1H RMN (DMSO): 8,5 (m, 1H), 7,35 (m, 1H), 7,2 (M,,4H), 4,1 (m, 2H), 3,82 (dd, 1H), 2,78 (t, 1H), 2,72 (t, 1H), 2,59 (m, 1H), 1,8 (m, 2H), 1,5 (m, 7H), 1,0 (m, 4H), 0,7 (m, 2H); MS (m/e) = 354,02, P. M. 353,46;

N-terc-butil-N'-clanometil-2-ciclohexilmetil-N-metilmalonamida

(Compuesto 35); ^1H RMN (DMSO): 8,41 (t, J = 5Hz, 1H), 4,09 (d, J = 5Hz, 1H), 3,56 (t, J = 7Hz, 1H), 2,86 (s, 3H), 1,6 (m, 7H), 1,31 (s, 9H), 1,1 (m, 4H), 0,8 (m, 2H); MS (M/E) = 308,04, P. M. 307,43;

N-clanometil-2-ciclohexilmetil-N'-metil-N'-propilmalonamida

(Compuesto 36); ^1H RMN (DMSO): 8,5 (m, 1H), 4,10 (m, 2H), 3,60 (t, $J = 7\text{Hz}$, 1H), 3,2 (m, 2H), 2,96 (s, 3H), 1,65 (m, 7H), 1,45 (m, 2H), 1,1 (m, 4H), 0,8 (m, 5H); MS (m/e) = 294,02, P. M. 293,40;

N-butil-N'-clanometil-2-ciclohexilmetil-N-metilmalonamida

(Compuesto 37); ^1H RMN (DMSO): 8,5 (m, 1H), 4,10 (d, $J = 5\text{Hz}$, 2H), 3,60 (t, 1H), 3,3 (m, 2H), 2,95 (s, 3H), 1,6 (m, 7H), 1,4 (m, 2H), 1,1 (m, 6H), 0,8 (m, 5H); MS (m/e) = 308,01, P. M. 307,43;

N-clanometil-2-ciclohexilmetil-N',N'-dimetilmalonamida

(Compuesto 38); ^1H RMN (DMSO): 8,55 (t, $J = 5\text{Hz}$, 1H), 4,11 (d, $J = 7\text{Hz}$, 2H), 3,62 (t, $J = 8\text{Hz}$, 1H), 2,99 (s, 3H), 2,81 (s, 3H), 1,6 (m, 7H), 1,1 (m, 4H), 0,85 (m, 2H); MS (m/e) = 266,01, P. M. 265,18;

N-benzil-N'-clanometil-2-(2-fenilsulfaniletil)malonamida (Compuesto

39); ^1H RMN (DMSO): 8,56 (t, $J = 6\text{Hz}$, 1H), 8,49 (t, $J = 6\text{Hz}$, 1H), 7,3 (m, 10H), 4,29 (d, $J = 6\text{Hz}$, 2H), 4,14 (d, $J = 6\text{Hz}$, 2H), 3,40 (t, $J = 7\text{Hz}$, 1H), 2,86 (t, $J = 8\text{Hz}$, 2H), 2,05 (m, 2H); MS (M/E) = 368,02, P. M. 367,14; γ

2-(2-fenilsulfoniletil)-N-benzil-N'-cianometilmalonamida

(Compuesto 40); ^1H RMN (DMSO): 8,56 (t, $J = 6\text{Hz}$, 1H), 8,43 (t, $J = 6\text{Hz}$, 1H), 7,86 (d, $J = 7\text{Hz}$, 2H), 7,79 (t, $J = 5\text{Hz}$, 1H), 7,68 (t, $J = 8\text{Hz}$, 2H), 7,25 (m, 5H), 4,26 (d, $J = 6\text{Hz}$, 2H), 4,13 (d, $J = 6\text{Hz}$, 2H), 3,36 (m, 1H), 3,19 (m, 2H), 2,00 (m, 2H); MS (m/e) = 400,04, P. M. 399,47;

2-(2-Benzenesulfoniletil)-N-((S)-1-(1-benzooxazol-2-il-metanil)-pentil)-

N'-benzil-malonamida (Compuesto 41) ^1H RMN (DMSO): 8,56 (d, $J = 6\text{Hz}$, 1H), 8,2 (m, 1H), 8,0-7,5 (m, 9H), 7,3-7,1 (m, 5H), 5,3 (m, 1H), 4,24 (t, $J = 6\text{Hz}$, 2H), 3,41 (t, $J = 7\text{Hz}$, 1H), 3,18 (m, 2H), 1,96 (m, 3H), 1,67 (m, 1H), 1,30 (m, 4H), 0,82 (m, 3H); MS (m/e) = 576,27, P. M. 575,21; γ

N,N-bis-((S)-1-(1-benzooxazol-2-il-metanil)-propil)-2-ciclohexilmetil-
malonamida (Compuesto 42) ^1H RMN (DMSO): 8,41 (d, $J = 6\text{Hz}$, 2H), 8,00 (d, $J = 8\text{Hz}$, 2H), 7,89 (d, $J = 8\text{Hz}$, 2H), 7,65 (t, $J = 7\text{Hz}$, 2H), 7,53 (t, $J = 8\text{Hz}$, 2H), 5,19 (m, 2H), 3,42 (t, $J = 8\text{Hz}$, 1H), 1,98 (m, 2H), 1,74 (m, 2H), 1,52 (m, 7H), 0,94 (m, 10H), 0,77 (m, 2H); MS (m/e) = 572,26, P. M. 573,4.

EJEMPLO 6

Ensayo de Catepsina S

Soluciones de los compuestos de ensayo en concentraciones diversas fueron preparados en 10 μ l de dimetilsulfóxido (DMSO) y luego diluidos en un amortiguador de ensayo (40 μ l, que comprende: MES, 50 mM (pH 6,5); EDTA, 2,5 mM; y NaCl, 100 mM). La catepsina S humana (0,158 pmoles en 25 μ l de amortiguador de ensayo fue agregada a las diluciones. Las soluciones de ensayo fueron mezcladas durante 5 a 10 segundos sobre una placa agitadora cubierta e incubada durante 30 minutos a temperatura ambiente. Se agregó Z-Val-Val-Arg-AMC (9 nMoles en 256 μ l de amortiguador de ensayo) a las soluciones de ensayo y la hidrólisis fue seguida espectrofotométricamente en (λ 460 nm) durante 5 minutos. Las constantes de Inhibición aparentes (K_i) fueron calculadas para las curvas de progreso de enzima usando modelos matemáticos estándar.

EJEMPLO 7

Ensayo de Catepsina B

Las soluciones de los compuestos de ensayo en concentraciones variadas fueron preparadas en 10 μ l de dimetilsulfóxido (DMSO) y luego diluidas en un amortiguador de ensayo (40 μ l, que comprende; ácido N,N-bis(2-hidroxietil)-2-aminoetanosulfónico (BES), 50 mM (pH 6); monolaurato de polioxietilenesorbitan, 0,05%; y ditiotretiol (DTT), 2,5 mM). La catepsina B humana (0,025 pmoles en 25 μ l de amortiguador de ensayo) se agregó a las diluciones. Las soluciones de ensayo fueron mezcladas durante 5 y 10 segundos sobre una placa agitadora, cubierta e incubada durante 30 minutos a temperatura ambiente. Se agregó Z-FR-AMC (20 mmoles en 25 μ l en amortiguador de ensayo) a las soluciones de ensayo y la hidrólisis fue seguida espectrofotométricamente en (λ 460 nm) durante 5 minutos. Las constantes de inhibición aparentes (K_i) fueron calculadas a partir de las curvas de progreso de la enzima usando modelos matemáticos estándar.

EJEMPLO 8

Ensayo de Catepsina K

Las soluciones de los compuestos de ensayo en concentraciones variadas fueron preparadas en 10 μ l de dimetilsulfóxido (DMSO) y luego diluidas en el amortiguador de ensayo (40 μ l, que comprende: MES, 50 mM (pH 5,5); EDTA, 2,5 mM; y DTT, 2,5 mM). Se agregó la catepsina K humana (0,0906 pmoles en 25 μ l de amortiguador de ensayo) a las diluciones. Las soluciones de ensayo fueron mezcladas durante 5 a 10 segundos en una placa agitadora, cubiertas e incubadas durante 30 minutos a temperatura ambiente. Se agregó Z-Phe-Arg-AMC (4 nMoles en 25 μ l de amortiguador de ensayo) a las soluciones de ensayo y la hidrólisis fue seguida espectrofotométricamente en (λ 460 nm) durante 5 minutos. Las constantes de inhibición aparentes (K_i) fueron calculadas a partir de las curvas de progreso de enzima usando modelos matemáticos estándar.

EJEMPLO 9

Ensayo de Catepsina L

Las soluciones de los compuestos de ensayo en concentraciones variadas fueron preparadas en 10 μ l de dimetilsulfóxido (DMSO) y luego diluidas en el amortiguador de ensayo (40 μ l, que

comprende: MES, 50 mM (pH 5,5); EDTA, 2,5 mM; y DTT, 2,5 mM). Se agregó la catepsina L humana (0,05 pmoles en 25 μ l de amortiguador de ensayo) a las diluciones. Las soluciones de ensayo fueron mezcladas durante 5 a 10 segundos en una placa agitadora, cubiertas e incubadas durante 30 minutos a temperatura ambiente. Se agregó Z-Phe-Arg-AMC (1 nMoles en 25 μ l de amortiguador de ensayo) a las soluciones de ensayo y la hidrólisis fue seguida espectrofotométricamente en (λ 460 nm) durante 5 minutos. Las constantes de Inhibición aparentes (K_i) fueron calculadas a partir de las curvas de progreso de enzima usando modelos matemáticos estándar.

Los compuestos de la Invención fueron ensayados de acuerdo con los ensayos anteriormente descritos para la Inhibición de proteasa y fueron observados en que exhibían una actividad Inhibitoria selectiva de catepsina S. por ejemplo, los compuestos de la Invención se encontraron que Inhibían la actividad de la proteasa de catepsina S en concentraciones de por lo menos 50 veces menos que aquellas concentraciones requeridas para producir una Inhibición equiactiva de la actividad de la proteasa de catepsina K. Las constantes de Inhibición aparente (K_i) para los

compuestos de la Invención, contra la catepsina S estuvieron en rango entre cerca de 10^{-10} M a cerca de 10^{-7} M.

EJEMPLO 10

Formulaciones farmacéuticas representativas que contienen un compuesto de Fórmula I.

FORMULACIÓN ORAL

Compuesto de Fórmula I	10 – 100 mg
Monohidrato de Ácido Cítrico	105 mg
Hidróxido de Sodio	18 mg
Saborizante	
Agua	q.s. a 100 ml

FORMULACIÓN INTRAVENOSA

Compuesto de Fórmula I	0,1 – 10 mg
Monohidrato de dextrosa	q.s. para hacerla Isotónica
Monohidrato de ácido Cítrico	1,05 mg

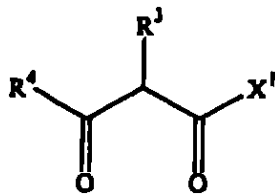
Hidróxido de sodio	0,18 mg
Agua para Inyección	q.s. a 1,0 ml

FORMULACIÓN DE TABLETA

Compuesto de Fórmula I	1%
Celulosa Microsistalina	73%
Ácido esteárico	25%
Sílice coloidal	1%

REIVINDICACIONES

1. Un compuesto de Fórmula I:



I

En la cual

X^1 es $-NHC(R^1)(R^2)X^2$ o $-NHX^2$;

X^2 es clano, $-C(R^7)(R^8)X^3$, $-C(R^7)(R^8)CF_3$, $-C(R^7)(R^8)CF_2CF_2R^9$, $-CH=CHS(O)_2R^5$, $-C(O)CF_2C(O)NR^5R^5$, $-C(O)C(O)NR^5R^6$, $-C(O)C(O)OR^5$, $-C(O)CH_2OR^5$, $-C(O)CH_2N(R^6)SO_2R^5$ o $-C(O)C(O)R^5$; en donde R^5 es alquilo (C_{1-4}), arilo (C_{5-10}) alquilo (C_{6-9}) o heteroarilo (C_{5-10}) alquilo (C_{6-9}); R^6 es hidrógeno o alquilo (C_{1-4}); R^7 es hidrógeno o alquilo (C_{1-4}) y R^8 es hidroxil o R^7 y R^8 juntos forman oxo; R^9 es

hidrógeno, halo, alquilo (C_{1-4}), arilo (C_{5-10}) alquil (C_{0-8}) o heteroarilo (C_{5-10}) alquilo (C_{0-8});

X^3 comprende un anillo heteromonocíclico que contiene 4 a 6 miembros del anillo o un sistema de anillo heterobifclico fusionado que contiene 8 a 14 átomos miembros del anillo y cualquier cetona carbocíclica, iminocetona o tiocetona derivado de esta;

En donde dentro de R^5 , X^2 o X^3 cualquier sistema de anillo alifclico o aromático puede ser sustituida adicionalmente por 1 a 5 radicales Independientemente seleccionados de alquilo (C_{1-8}), alquillideno (C_{1-8}), clano, halo, alquilo (C_{1-4}) halo-sustituído, nitro, $-X^4NR^{12}R^{12}$, $-X^4NR^{12}C(O)R^{12}$, $-X^4NR^{12}C(O)OR^{12}$, $-X^4NR^{12}C(O)NR^{12}R^{12}$, $-X^4NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^4OR^{12}$, $-X^4SR^{12}$, $-X^4C(O)OR^{12}$, $-X^4C(O)R^{12}$, $-X^4OC(O)R^{12}$, $-X^4C(O)NR^{12}R^{12}$, $-X^4S(O)_2NR^{12}R^{12}$, $-X^4NR^{12}S(O)_2R^{12}$, $-X^4P(O)(OR^{12})OR^{12}$, $O-X^4OP(O)(OR^{12})OR^{12}$, $-X^4NR^{12}C(O)R^{13}$, $-X^4S(O)R^{13}$ y $-X^4S(O)_2R^{13}$ y/o 1 radical seleccionado de $-R^{14}$, $-X^4OR^{14}$, $-X^4SR^{14}$, $-X^4S(O)R^{14}$, $-X^4S(O)_2R^{12}$, $-X^4C(O)R^{14}$, $-X^4C(O)OR^{14}$, $-X^4OC(O)R^{14}$, $-X^4NR^{14}R^{12}$, $-X^4NR^{12}C(O)R^{14}$, $-X^4NR^{12}C(O)OR^{14}$, $-X^4C(O)NR^{12}R^{12}$, $-X^4S(O)_2NR^{14}R^{12}$, $-X^4NR^{12}S(O)_2R^{14}$, $-X^4NR^{12}C(O)NR^{14}R^{12}$ y

$-X^4NR^{12}C(NR^{12})NR^{14}R^{12}$, en donde X^4 es un enlace o alquilo (C_{1-8}); R^{12} en cada ocurrencia independientemente es hidrógeno, alquilo (C_{1-8}), o alquilo (C_{1-8}) halo-sustituido; R^{13} es alquilo (C_{1-8}) o alquilo (C_{1-8}) halo-sustituido; y R^{14} es cicloalquilo (C_{3-10}) alquilo (C_{0-8}), hetero (C_{3-10}) cicloalquilo (C_{0-3}) alquilo, arilo (C_{6-10}) alquilo (C_{0-8}), hetero arilo (C_{3-10}) alquilo (C_{0-8}), bicicloarilo (C_{8-10}) alquilo (C_{0-8}) o hetero (C_{8-10}) bicicloarilo (C_{0-8}) alquilo;

R^1 es hidrógeno, halo o (C_{1-8}) alquilo y R^2 se selecciona del grupo que consiste de hidrógeno, clano halo, $-X^4NR^{12}R^{12}$, $-X^4NR^{12}C(O)R^{12}$, $-X^4NR^{12}C(O)OR^{12}$, $-4X^4NR^{12}C(O)NR^{12}R^{12}$, $-X^4NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^4OR^{12}$, $-X^4SR^{12}$, $-X^4C(O)OR^{12}$, $-X^4C(O)R^{12}$, $-X^4OC(O)R^{12}$, $-X^4C(O)NR^{12}R^{12}$, $-X^4S(O)_2NR^{12}R^{12}$, $-X^4NR^{12}S(O)_2R^{12}$, $-X^4P(O)(OR^{12})OR^{12}$, $-X^4OP(O)(OR^{12})OR^{12}$, $-X^4NR^{12}C(O)R^{12}$, $-X^4S(O)R^{13}$, $-X^4S(O)_2R^{13}$, $-R^{14}$, $-X^4OR^{14}$, $-X^4SR^{14}$, $-X^4S(O)R^{14}$, $-X^4S(O)_2R^{14}$, $-X^4C(O)OR^{14}$, $-X^4C(O)R^{14}$, $-X^4OC(O)R^{14}$, $-X^4NR^{14}R^{12}$, $X^4NR^{12}C(O)R^{14}$, $-X^4NR^{12}C(O)OR^{14}$, $-X^4C(O)NR^{12}R^{12}$, $-X^4S(O)_2NR^{14}R^{12}$, $-X^4NR^{12}S(O)_2R^{14}$, $-XNR^{12}C(O)NR^{14}R^{12}$ y $-X^4NR^{12}C(NR^{12})NR^{14}R^{12}$, en donde X^4 , R^2 , R^{13} y R^{14} son como se definió anteriormente; o R^1 y R^2 tomados juntos con el átomo de carbono al cual tanto R^1 y R^2 están unidos forman cicloalquilleno (C_{3-8}) o heterocicloalquilleno(C_{3-8}); en donde dentro de dicho R^2 cualquier heteroarilo, arilo, cicloalquilo,

heterocicloalquillo, cicloalquileno o heterocicloalquilleno es opcionalmente sustituido con 1 a 3 radicales Independientemente seleccionados de alquilo (C_{1-6}), alquildieno (C_{1-6}), clano, halo alquilo (C_{1-6}) halo-sustituido, nítro, $-X^4NR^{12}R^{12}$, $-X^4NR^{12}C(O)R^{12}$, $-X^4NR^{12}C(O)OR^{12}$, $-X^4NR^{12}C(O)NR^{12}R^{12}$, $-X^4NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^4OR^{12}$, $-X^4SR^{12}$, $-X^4C(O)OR^{12}$, $-X^4C(O)R^{12}$, $-X^4OC(O)R^{12}$, $-X^4C(O)NR^{12}R^{12}$, $-X^4S(O)_2NR^{12}R^{12}$, $-X^4NR^{12}S(O)_2R^{12}$, $-X^4P(O)(OR^{12})OR^{12}$, $-X^4OP(O)(OR^{12})OR^{12}$, $-X^4NR^{12}C(O)R^{13}$, $-X^4S(O)R^{13}$, $-X^4S(O)_2R^{13}$ y $-X^4C(O)R^{13}$, en donde X^4 , R^{12} y R^{13} son como se definió anteriormente;

R^3 es $-C(R^6)(R^6)X^5$, en donde R^6 es como se definió anteriormente y X^5 se selecciona de $-X^4NR^{12}R^{12}$, $-X^4NR^{12}C(O)R^{12}$, $-X^4NR^{12}C(O)OR^{12}$, $-X^4NR^{12}C(O)NR^{12}R^{12}$, $-X^4NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^4OR^{12}$, $-X^4SR^{12}$, $-X^4C(O)OR^{12}$, $-X^4C(O)R^{12}$, $-X^4OC(O)R^{12}$, $-X^4C(O)NR^{12}R^{12}$, $-X^4S(O)_2NR^{12}R^{12}$, $-X^4NR^{12}S(O)_2R^{12}$, $-X^4P(O)(OR^{12})OR^{12}$, $-X^4R^{12}$, $-X^4OP(O)(OR^{12})OR^{12}$, $-X^4C(O)R^{13}$, $-X^4NR^{12}C(O)R^{13}$, $-X^4S(O)R^{13}$ y $-X^4S(O)_2R^{13}$, $-R^{14}$, $-X^4OR^{14}$, $-X^4SR^{14}$, $-X^4S(O)R^{14}$, $-X^4S(O)_2R^{14}$, $-X^4C(O)R^{14}$, $-X^4C(O)OR^{14}$, $-X^4OC(O)R^{14}$, $-X^4NR^{14}R^{12}$, $-X^4NR^{12}C(O)R^{14}$, $-X^4NR^{12}C(O)OR^{14}$, $-XC(O)NR^{14}R^{12}$, $-X^4S(O)_2NR^{14}R^{12}$, $-X^4NR^{12}S(O)_2R^{14}$, $-X^4NR^{12}C(O)NR^{14}R^{12}$ y $-X^4NR^{12}C(NR^{12})NR^{14}R^{12}$ en donde X^4 , R^{12} , R^{13} y R^{14} son como se definió anteriormente;

R^4 es $-NR^6R$, $-NR^6R^{14}$, $-NR^6R^{15}$ o $-NR^6X^5C(O)R^{14}$ en donde R^6 , X^5 y R^{14} son como se definió anteriormente y R^{15} es hidrógeno, alquilo (C_{1-8}) o $-X^5OR^6$ en donde X^5 es como se describió anteriormente; o R^6 y R^{15} junto con el átomo de nitrógeno al cual R^6 y R^{15} están unidos de hetero cicloalquilo (C_{3-6}), hetero arilo (C_{5-6}) o hetero bicicloarilo (C_{8-10});

Dentro de R^3 y R^4 cualquier sistema de anillos aromáticos pueden ser sustituidos adicionalmente por 1-5 radicales Independientemente seleccionados de alquilo (C_{1-8}), alquillideno (C_{1-8}), clano, halo, alquilo (C_{1-4}) halo-sustituido, nitro, $-X^4NR^{12}R^{12}$, $-X^4NR^{12}C(O)R^{12}$, $-X^4NR^{12}C(O)OR^{12}$, $-X^4NR^{12}C(O)NR^{12}R^{12}$, $-X^4NR^{12}C(NR^{12})NR^{12}R^{12}$, $-X^4OR^2$, $-X^4SR^{12}$, $-X^4C(O)OR^{12}$, $-X^4C(O)R^{12}$, $-X^4OC(O)R^{12}$, $-X^4C(O)NR^{12}R^{12}$, $-X^4S(O)_2NR^{12}R^{12}$, $-X^4NR^{12}SO_2R^{12}$, $-X^4P(O)(OR^{12})OR^{12}$, $-X^4OP(O)(OR^{12})OR^{12}$, $-NX^4NR^{12}C(O)R^{13}$, $-X^4S(O)R^{13}$, $-X^4C(O)R^{13}$ y $-X^4S(O)_2R^{13}$ y/o 1 radical seleccionado de $-R^{14}$, $-X^4OR^{14}$, $-X^4SR^{14}$, $-X^4S(O)R^{14}$, $-X^4S(O)R^{14}$, $-XC(O)R^{14}$, $-X^4C(O)OR^{14}$, $-X^4OC(O)R^{14}$, $-X^4NR^{14}R^{12}$, $-X^4NR^{12}C(O)R^{14}$, $-X^4NR^{12}C(O)OR^{14}$, $-X^4C(O)NR^{14}R^{12}$, $-X^4S(O)_2NR^{14}R^{12}$, $-X^4NR^{12}S(O)_2R^{14}$, $-X^4NR^{12}C(O)NR^{14}R^{12}$ y $-X^4NR^{12}C(NR^{12})NR^{14}R^{12}$; y dentro de R^3 y R^4 cualquier porción alifática puede ser sustituida

adicionalmente por 1-5 radicales independientemente seleccionados de ciano, halo, nitro, $-\text{NR}^{12}\text{R}^{12}$, $-\text{NR}^{12}\text{C}(\text{O})\text{R}^{12}$, $-\text{NR}^{12}\text{C}(\text{O})\text{OR}^{12}$, $-\text{NR}^{12}\text{C}(\text{O})\text{NR}^{12}\text{R}^{12}$, $-\text{NR}^{12}\text{C}(\text{NR}^{13})\text{NR}^{12}\text{R}^{12}$, $-\text{OR}^{12}$, $-\text{SR}^{12}$, $-\text{C}(\text{O})\text{O}^{12}$, $-\text{C}(\text{O})\text{R}^{12}$, $-\text{OC}(\text{O})\text{R}^{12}$, $-\text{C}(\text{O})\text{NR}^{12}\text{R}^{12}$, $-\text{S}(\text{O})_2\text{NR}^{12}\text{R}^{12}$, $-\text{NR}^{12}\text{S}(\text{O})_2\text{R}^{12}$, $-\text{P}(\text{O})(\text{OR}^{12})\text{OR}^{12}$, $-\text{OP}(\text{O})(\text{OR}^{12})\text{OR}^{12}$, $-\text{NR}^{12}\text{C}(\text{O})\text{R}^{13}$, $-\text{S}(\text{O})\text{R}^{13}$ y $-\text{S}(\text{O})_2\text{R}^{13}$; en donde X^4 , R^{12} , R^{13} y R^{14} son como se describió anteriormente;

Con la condición de solamente una estructura de anillo bicíclica está presente dentro de R^3 y R^4 ; y los derivados de N-óxido, derivados de prodroga, derivados protegidos, Isómeros Inhibidores y mezclas de Isómeros de estos; y las sales farmacéuticamente aceptables y solvatos de tales compuestos y los derivados de N-óxido, derivados de prodroga, derivados protegidos, isómeros Individuales y mezclas de isómeros de estos.

2. El compuesto de la Reivindicación 1 en la cual:

X^1 es $-\text{NHC}(\text{R}^1)(\text{R}^2)\text{X}^2$ o $-\text{NHX}^3$;

X^2 es clano, $-C(O)X^3$, $-C(O)CF_3$, $-C(O)CF_2CF_2R^9$, $-CH=CHSi(O)_2R^5$, $-C(O)CF_2C(O)NR^5R$, $-C(O)C(O)NR^5R^6$; $-C(O)C(O)OR^5$, $-C(O)CH^2OR^5$, $-C(O)CH_2N(R^9)SO_2R^5$ o $-C(O)C(O)R^5$; en donde R^5 y R^6 son como se describió anteriormente;

X^3 comprende un anillo heteromonocíclico que contiene 4 a 6 átomos y miembros del anillo o un sistema de anillo heterobícíclico fusionado que contiene 8 a 14 átomos miembros del anillo y cualquier cetona carboxídica, iminocetona o tioacetona derivada de este;

En donde dentro de R^5 , X^2 o X^3 cualquier sistema de anillo alicíclico o aromático puede ser sustituido adicionalmente por 1 a 5 radicales independientemente seleccionados de alquilo (C_{1-6}) o $-X^4OC(O)R^{12}$ y/o 1 radical seleccionado de $-R^{14}$, $-X^4C(O)R^{14}$ o $-X^4OC(O)R^{14}$;

En donde X^4 , R^{12} y R^{14} son como se describió anteriormente;

R^1 es hidrógeno o alquilo (C_{1-6}) y R^2 es hidrógeno, $-X^4OR^{12}$, (C_{5-10}) heteroaril (C_{6-9}) alquilo, (C_{5-10}) aril (C_{6-9}) alquilo, (C_{5-10}) cicloalquil (C_{6-9}) alquilo, (C_{5-10}) heterocicloalquil (C_{6-9}) alquilo o alquilo (C_{1-6});

o R^1 y R^2 tomados juntos con el átomo de carbono al cual ambos R^1 y R^2 están unidos forman el cicloalquilleno (C_{3-8}) o heterocicloalquilleno (C_{3-8}); en donde dentro de dicho R^2 cualquier heteroarilo, arilo, cicloalquilo, heterocicloalquilo, cicloalquilleno o heterocicloalquilleno está opcionalmente sustituido con uno o más radicales independientemente seleccionados de alquilo (C_{1-4}) e hidroxil;

R^3 es $-CH_2X^5$, en donde X^5 en cada ocurrencia independientemente se selecciona de $-X^4SR^{12}$, $-X^4C(O)NR^{12}R^{12}$, $-X^4S(O)_2R^{13}$, $-X^4C(O)R^{13}$, $-X^4SR^{14}$, $-R^{14}$, $-X^4S(O)_2R^{14}$, X^4R^{12} , $-X^4C(O)R^{14}$, $-X^4C(O)NR^{14}R^{12}$, en donde X^4 , R^{12} , R^{13} y R^{14} son como se definió anteriormente;

R^4 es $-NR^6R^6$, $-NR^6R^{14}$, $-NR^6R^{15}$ o $-NR^6X^5C(O)R^{14}$ en donde R^6 , X^5 y R^{14} son como se definió anteriormente y R^{15} es hidrógeno, alquilo (C_{1-4}) o $-X^5OR^6$ en donde X^5 es como se describió anteriormente; o R^6 y R^{15} juntos con el átomo de nitrógeno al cual R^6 y R^{15} están unidos forman hetero (C_{3-10})cicloalquilo, hetero (C_{5-10}) arilo o hetero (C_{8-10}) bicicloarilo;

En donde dentro de R^3 y R^4 cualquier sistema de anillo alicíclico o aromático puede ser sustituido adicionalmente por 1 - 5 radicales independientemente seleccionados de alquilo (C_{1-6}), ciano, halo, nitro, alquilo (C_{1-6}) halo-sustituido, $-X^4OR^{12}$, $-X^4C(O)OR^{12}$, $-X^4C(O)R^{13}$, $-X^4C(O)NR^{12}R^{12}$, $-X^4NR^{12}S(O)_2R^{12}$ y/o 1 radical seleccionado de $-R^{14}$, $-X^4OR^{14}$ y $-X^4C(O)NR^{14}R^{12}$; dentro de R^3 y R^4 cualquier porción alifática puede ser sustituida adicionalmente por 1 - 5 radicales independientemente seleccionados de ciano; en donde X^4 , R^{12} , R^{13} y R^{14} son como se describió anteriormente; con la condición de que solo una estructura de anillos bicíclica está presente dentro de R^3 o R^4 ; y los derivados N-óxido, derivados de prodrogas, derivados de prodrogas, isómeros individuales y mezclas de isómeros de estos; y las sales farmacéuticamente aceptables y solvatos de tales compuestos y los derivados de N-óxido, derivados de prodrogas, derivados protegidos, isómeros individuales y mezclas de estos isómeros.

3. El compuesto de la reivindicación 2 en el cual:

X^1 es $-NHC(R^1)(R^2)X^2$ o NHX^3 ;

X^2 es ciano, $-C(O)X^3$, $-CF_3$, $-CF_2CF_3$, (E)-2-benzenesulfonil-vinilo, 2-dimetilcarbamoil-2,2-difluoro-acetilo, 1-benzilcarbamoil-metanolo, 1-benziloxi (oxalil), 2-benziloxi-acetilo, 2-benzenesulfonilamino-etanol o 2-oxo-2-fenil-etanol;

X^3 es 1H-benzimidazol-2-ilo, pirimidin-2-ilo, benzooxazol-2-ilo, benzotiazol-2-ilo, piridazin-3-ilo, 3-fenil-[1,2,4]oxadiazol-5-ilo, 3-etil-[1,2,4]oxadiazol-5-ilo, 2-metil-4-oxo-tetrahidro-furan-3-ilo, 2-etil-4-oxo-tetrahidro-furan-3-ilo, 4-oxo-1-(1-fenil-metanol)-pirrolidin-3-il o (S)-2-acetoxi-4-oxo-azetidín-3-il;

R^1 es hidrógeno o metilo y R^2 es hidrógeno, metoximetilo, alquilo (C_{1-6}), fenetilo, tiofen-2-il o 5-metil-furan-2-ilo, o (ii) R^1 y R^2 tomados juntos con el átomo de carbono al cual ambos R^1 y R^2 están unidos del ciclopropano, tetrahidro-piran-4-ileno o metil-piperidín-4-ileno.

4. El compuesto de la reivindicación 3 en el cual R^3 se selecciona de tiofene-2-sulfonilmetilo, 3-cloro-2-fluoro-

fenilmetanosulfonilmetilo,	benzenesulfonilmetilo,
fenilmetanosulfonilmetilo,	2-(1,1-difluoro-metoxi)-
fenilmetanosulfonilmetilo,	2-benzenesulfonil-etilo, 2-
(piridino-2-sulfonil)-etilo,	2-(piridino-4-sulfonil)-etilo, 2-
fenilmetanosulfonil-etilo,	oxi-piridin-2-
ilmetanosulfonilmetilo,	prop-2-ene-1-sulfonilmetilo, 4-
metoxi-fenilmetanosulfonilmetilo,	p-
tolilmetilesulfonilmetilo,	4-cloro-
fenilmetanosulfonilmetilo,	o-tolilmetanosulfonilmetilo,
3,5-dimetil-fenilmetanosulfonilmetilo,	4-trifluorometil-
fenilmetanosulfonilmetilo,	4-trifluorometoxi-
fenilmetanosulfonilmetilo,	2-bromo-
fenilmetanosulfonilmetilo,	piridin-2-
ilnotanosulfonilmetilo,	piridin-3-ilmetanosulfonilmetilo,
piridin-4-ilmetanosulfonilmetilo,	naftalen-2-
ilmetanosulfonilmetilo,	3-metil-
fenilmetanosulfonilmetilo,	3-trifluorometil-
fenilmetanosulfonilmetilo,	3-trifluorometoxi-
fenilmetanosulfonilmetilo,	4-fluoro-2-trifluorometoxi-
fenilmetanosulfonilmetilo,	2-fluoro-6-trifluorometil-
fenilmetanosulfonilmetilo,	3-cloro-
fenilmetanosulfonilmetilo,	2-fluoro-

fenilmetanosulfonilmetilo,		2-trifluoro-
fenilmetanosulfonilmetilo,		2-ciano-
fenilmetanosulfonilmetilo,		4-terc-butil-
fenilmetanosulfonilmetilo,		2-fluoro-3-metil-
fenilmetanosulfonilmetilo,		3-fluoro-
fenilmetanosulfonilmetilo,		4-fluoro-
fenilmetanosulfonilmetilo,		2-cloro-
fenilmetanosulfonilmetilo,		2,5-difluoro-
fenilmetanosulfonilmetilo,		2,6-difluoro-
fenilmetanosulfonilmetilo,	2,	5-dicloro-
fenilmetanosulfonilmetilo,	3,	4-dicloro-
fenilmetanosulfonilmetilo,	2-(1,1-difluoro-metoxi)-	
fenilmetanosulfonilmetilo,		2-ciano-
fenilmetanosulfonilmetilo,		3-ciano-
fenilmetanosulfonilmetilo,		2-trifluorometoxi-
fenilmetanosulfonilmetilo,		2,3-difluoro-
fenilmetanosulfonilmetilo,		2,5-difluoro-
fenilmetanosulfonilmetilo,		bifenil-2-
ilmetanosulfonilmetilo,	ciclohexilmetilo,	3-fluoro-
fenilmetanosulfonilmetilo,		3,4-difluoro-
fenilmetanosulfonilmetilo,		2,4-difluoro-
fenilmetanosulfonilmetilo,		2,4,6-trifluoro-

fenilmetanosulfonilmetilo,	2,4,5-trifluoro-
fenilmetanosulfonilmetilo,	2,3,4-trifluoro-
fenilmetanosulfonilmetilo,	2,3,5-trifluoro-
fenilmetanosulfonilmetilo,	2,5,6-trifluoro-
fenilmetanosulfonilmetilo,	2-cloro-5-
trifluorometilfenilmetanosulfonilmetilo, 2-metil-propano-	
1-sulfonilo,	2-fluoro-3-
trifluorometilfenilmetanosulfonilmetilo,	2-fluoro-4-
trifluorometilfenilmetanosulfonilmetilo,	2-fluoro-5-
trifluorometilfenilmetanosulfonilmetilo,	4-fluoro-3-
trifluorometilfenilmetanosulfonilmetilo,	2-metoxi-
fenilmetanosulfonilmetilo,	3,5 bis-trifluorometil-
fenilmetanosulfonilmetilo,	4-difluorometoxi-
fenilmetanosulfonilmetilo,	2-difluorometoxi-
fenilmetanosulfonilmetilo,	3-difluorometoxi-
fenilmetanosulfonilmetilo,	2,6-dicloro-
fenilmetanosulfonilmetilo,	bifenil-4-
ilmetanosulfonilmetilo,	3,5-dimetil-isoxazol-4-
ilmetanosulfonilmetilo,	5-cloro-tiofen-2-
ilmetanosulfonilmetilo,	2-[4-(1,1-difluoro-metoxi)-
benzenesulfonil]-etilo,	2-[2-(1,1-difluoro-metoxi)-
benzenesulfonil]-etilo,	2-[3-(1,1-difluoro-metoxi)-

benzenesulfonil)-etilo, 2-(4-trifluorometoxi-
benzenesulfonil)-etilo, 2-(3-trifluorometoxi-
benzenesulfonil)-etilo, 2-(2-trifluorometoxi-
benzenesulfonil)-etilo, (cianometil-metil-carbamol)-
metilo, butilo, bifenil-3-ilmetilo, 2-oxo-2-pirrolidin-1-il-
etilo, 2-benzenesulfonil-etilo, isobutilsulfanilmetilo, 2-
fenilsulfanil-etilo, ciclohexilmetanosulfonilmetilo, 2-
ciclohexil-étanesulfonilo, benzilo, naftalen-2-ilo,
benzilsulfanilmetilo, 2-trifluorometil-benzilsulfanilmetilo,
5-bromo-tiofen-2-ilmetilo, fenilsulfanil-etil y
ciclopropilmetanosulfonilmetil.

5. El compuesto de la reivindicación 4 en que R⁴ se
selecciona de fenilamino, benzilamino, 4-fenoxi-
fenilamino, fenetilamino, 3-fenil-propilamino, morfolin-4-
ilo, ciclohexilamino, naftalen-1-ilmetil-amino, piridin-3-
ilamino, 6-metoxi-piridin-3-ilamino, diisobutilamino, 4-
nitro-benzilamino, 2-tiofen-2-il-etilamino, 3-fenoxi-
fenilamino, cianometil-amino, (piridin-3-ilmetil)-amino,
5,6,7,8-tetrahidro-naftalen-1-ilamino, 2-piridin-2-il-
etilamino, 2,3-dihidro-Indol-1-ilo, 3,4-dihidro-1H-
Isoquinolin-2-ilo, ciclohexilmetil-amino, 2-metoxi-

benzilamino, 1-fenil-etilamino, (piridin-4-ilmetil)-amino, benzil-metil-amino, 3-nitro-benzilamino, 4-metoxi-fenilamino, 3-carbamoil-fenilamino, 4-carbamoil-fenilamino, (tetrahidro-furan-2-ilmetil)-amino, 3,4-dihidro-2H-quinolin-1-ilo, dimetilamino, butilmetilamino, diisopropilamino, propilmetilamino, 1-(benzooxazol-2-carbonil)-propilamino e isobutilmetilamino.

6. El compuesto de la reivindicación 5 seleccionado del grupo que consiste de: 6. 2-butil-N-cianometil-N'-fenil-malonamida; N-cianometil-2-ciclohexilmetil-N-fenil-malonamida; N-cianometil-2-ciclohexilmetil-N-fenetil-malonamida; N-cianometil-2-ciclohexilmetil-N'-piridin-4-ilmetil-malonamida; N-1-(benzooxazol-2-carbonil)-3-fenil-propil-N'-benzil-2-ciclohexilmetil-malonamida; N-cianometil-N-ciclohexil-2-ciclohexilmetil-malonamida; N-benzil-N-cianometil-2-ciclohexilmetil-malonamida; N-cianometil-2-ciclohexilmetil-N-(4-fenoxi-fenil)-malonamida; N-cianometil-2-ciclohexilmetil-N-(3-fenil-propil)-malonamida; N-cianometil-2-ciclohexilmetil-3-morfolin-4-il-3-oxo-propionamida; N-cianometil-2-ciclohexilmetil-N-naftalen-1-ilmetil-malonamida; N-cianometil-2-

ciclohexilmetil-N-piridin-3-il-malonamida; N-cianometil-2-
 ciclohexilmetil-N',N'-diisobutil-malonamida; N-cianometil-
 2-ciclohexilmetil-N',N'-diisopropil-malonamida; N-
 cianometil-2-ciclohexilmetil-N'-(6-metoxi-piridin-3-il)-
 malonamida; N-cianometil-2-ciclohexilmetil-N'-(2-tiofen-2-
 il-etil)-malonamida; N-cianometil-2-ciclohexilmetil-N'-(3-
 fenoxi-fenil)-malonamida; N-cianometil-2- ciclohexilmetil-
 N'-(4-nitro-benzil)-malonamida; N,N'-bis-cianometil-2-
 ciclohexilmetil-malonamida; N-cianometil-2-
 ciclohexilmetil-N'-(5,6,7,8-tetrahidro-naftalen-1-il)-
 malonamida; N-cianometil-2-ciclohexilmetil-N-(2-piridin-2-
 il-etil)-malonamida; N-cianometil-2-ciclohexilmetil-3-(2,3-
 dihidro-indol-1-il)-3-oxo-propionamida; N-cianometil-2-
 ciclohexilmetil-3-(3,4-dihidro-1H-Isoquinolin-2-il)-3-oxo-
 propionamida; N-cianometil-2,N'-bis-ciclohexilmetil-
 malonamida; N-cianometil-2-ciclohexilmetil-N-(2-metoxi-
 benzil)-malonamida; N-cianometil-2-ciclohexilmetil-N-(1-
 fenil-etil)-malonamida; N-benzil-N-cianometil-2-
 ciclohexilmetil-N-metil-malonamida; N-cianometil-2-
 ciclohexilmetil-N'-(3-nitro-benzil)-malonamida; N-
 cianometil-2-ciclohexilmetil-N'-(4-metoxi-benzil)-
 malonamida; N-(3-carbamoil-fenil)-N-cianometil-2-

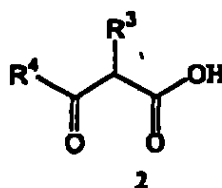
ciclohexylmetil-malonamida; N-cianometil-2-
 ciclohexilmetil-N'-piridin-3-ilmetil-malonamida; N-(4-
 carbamoylfenil)-N-cianometil-2-ciclohexilmetilmalonamida;
 N-cianometil-2-ciclohexilmetil-N-tetrahidrofur-2-
 ilmetilmalonamida; N-cianometil-2-ciclohexilmetil-3-(3,4-
 dihidro-2H-quinolin-1-il)-3-oxopropionamida; N-terc-butil-
 N'-cianometil-2-ciclohexilmetil-N-metilmalonamida; N-
 cianometil-2-ciclohexilmetil-N'-metil-N'-propilmalonamida;
 N-butil-N'-cianometil-2-ciclohexilmetil-N-metilmalonamida;
 N-cianometil-2-ciclohexylmetil-N',N'- dimetilmalonamida;
 N-benzil-N-cianometil-2-(2-fenilsulfaniletil)malonamida; 2-
 (2-fenilsulfoniletil)-N-benzil-N'-cianometilmalonamida; 2-(2-
 benzenesulfonil-etil)-N-[(S)-1-(1-benzooxazol-2-il-metanoil)-
 pentil]-N-benzil-malonamida; N,N'-bis-[(S)-1-(1-benzooxazol-
 2-il-metanoil)-propil]-2-ciclohexilmetil-malonamida; y los
 derivados N-óxido, derivados de prodroga, derivados
 protegidos, isómeros individuales y mezclas de isómeros
 de estos; y sales farmacéuticamente aceptables y solvatos
 de tales compuestos y los derivados N-óxido, derivados
 de prodrogas, derivados protegidos, isómeros
 individuales y mezclas de isómeros de estos.

7. Una composición farmacéutica comprende una cantidad terapéuticamente efectiva de un compuesto de la reivindicación 1 en combinación con un excipiente farmacéuticamente aceptable.
8. Un método para tratar una enfermedad en un animal en el que la inhibición de la Catepsina S puede prevenir, inhibir o aminorar la patología y/o sintomatología de la enfermedad, que el método comprende administrar al animal una cantidad terapéuticamente efectiva del compuesto de la reivindicación 1 o un derivado de N-óxido o isómero individual o mezcla de isómeros de estos; o sales farmacéuticamente aceptables y solvatos de tales compuestos y los derivados N-óxido, derivados de prodrogas, derivados protegidos, isómeros individuales y mezclas de isómeros de estos.
9. El uso de un Compuesto de la Reivindicación 1 en la fabricación de un medicamento para tratar una enfermedad en un animal en el que la actividad de la

Catepsina S contribuye a la patología y/o sintomatología de la enfermedad.

10. Un proceso para preparar un compuesto de Fórmula I:

(A) hacer reaccionar un compuesto de Fórmula 2:



con un compuesto de fórmula $\text{NH}_2\text{CR}^1\text{R}^2\text{X}^2$, en los cuales R^1 , R^2 , R^3 , R^4 y X^2 son según se definió en el resumen de la Invención para la Fórmula I; o

(B) hacer reaccionar un compuesto de Fórmula 2 con un compuesto de Fórmula NH_2X^3 , en el cual R^3 , R^4 y X^3 son según se describió en el resumen de la Invención para la Fórmula I;

y

- (C) convertir opcionalmente un compuesto de Fórmula I en una sal farmacéuticamente aceptable;
- (D) convertir opcionalmente una forma de sal de un compuesto de Fórmula I a una forma no salina;
- (E) convertir opcionalmente una forma no oxidada de un compuesto de Fórmula I en un N-óxido farmacéuticamente aceptable;
- (F) convertir opcionalmente una forma N-óxido de un compuesto de Fórmula I en su forma no oxidada;
- (G) resolver opcionalmente un isómero individual de un compuesto de Fórmula I a partir de mezcla de isómeros;
- (H) convertir opcionalmente un compuesto no derivado de Fórmula I en un derivado farmacéuticamente de prodroga;
- y
- (I) convertir opcionalmente un derivado de prodroga de un compuesto de Fórmula I en su forma no derivada.

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(54) Title: NOVEL COMPOUNDS AND COMPOSITIONS AS CATHEPSIN INHIBITORS

(57) Abstract: The present invention relates to novel selective cathepsin S inhibitors, the pharmaceutically acceptable salts and N-oxides thereof, their uses as therapeutic agents and the methods of their making.

NOVEL COMPOUNDS AND COMPOSITIONS AS CATHEPSIN INHIBITORS

THE INVENTION

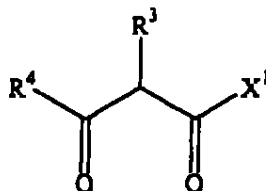
5 This Application relates to compounds and compositions for treating diseases associated with cysteine protease activity, particularly diseases associated with activity of cathepsin S.

DESCRIPTION OF THE FIELD

10 Cysteine proteases represent a class of peptidases characterized by the presence of a cysteine residue in the catalytic site of the enzyme. Cysteine proteases are associated with the normal degradation and processing of proteins. The aberrant activity of cysteine proteases, e.g., as a result of increase expression or enhanced activation, however, may
15 have pathological consequences. In this regard, certain cysteine proteases are associated with a number of disease states, including arthritis, muscular dystrophy, inflammation, tumor invasion, glomerulonephritis, malaria, periodontal disease, metachromatic leukodystrophy and others. An increase in cathepsin S activity contributes to the pathology and/or symptomatology of a number of diseases. Accordingly, molecules that
20 inhibit the activity of cathepsin S protease are useful as therapeutic agents in the treatment of such diseases.

SUMMARY OF THE INVENTION

This Application relates to compounds of Formula I:



I

5 in which:

X^1 is $-NHC(R^1)(R^2)X^2$ or $-NHX^2$;

X^2 is cyano, $-C(R^7)(R^8)X^3$, $-C(R^7)(R^8)CF_3$, $-C(R^7)(R^8)CF_2CF_2R^9$, $-CH=CHS(O)_2R^5$,
 $-C(O)CF_2C(O)NR^4R^5$, $-C(O)C(O)NR^4R^6$, $-C(O)C(O)OR^5$, $-C(O)CH_2OR^5$,
 $-C(O)CH_2N(R^6)SO_2R^5$ or $-C(O)C(O)R^5$; wherein R^4 is (C_{1-4}) alkyl, (C_{3-10}) aryl (C_{0-6}) alkyl or
 10 (C_{3-10}) heteroaryl (C_{0-6}) alkyl; R^6 is hydrogen or (C_{1-4}) alkyl; R^7 is hydrogen or (C_{1-4}) alkyl and
 R^8 is hydroxy or R^7 and R^8 together form oxo; R^9 is hydrogen, halo, (C_{1-4}) alkyl,
 (C_{3-10}) aryl (C_{0-6}) alkyl or (C_{3-10}) heteroaryl (C_{0-6}) alkyl;

X^3 comprises a heteromonocyclic ring containing 4 to 6 ring member atoms or a
 fused heterobicyclic ring system containing 8 to 14 ring member atoms and any
 15 carbocyclic ketone, iminoketone or thioketone derivative thereof;

wherein within R^4 , X^2 or X^3 any alicyclic or aromatic ring system may be
 substituted further by 1 to 5 radicals independently selected from (C_{1-4}) alkyl,
 (C_{1-4}) alkylidene, cyano, halo, halo-substituted (C_{1-4}) alkyl, nitro, $-X^4NR^{12}R^{13}$,
 $-X^4NR^{12}C(O)R^{12}$, $-X^4NR^{12}C(O)OR^{12}$, $-X^4NR^{12}C(O)NR^{12}R^{12}$, $-X^4NR^{12}C(NR^{12})NR^{12}R^{12}$,
 20 $-X^4OR^{12}$, $-X^4SR^{12}$, $-X^4C(O)OR^{12}$, $-X^4C(O)R^{12}$, $-X^4OC(O)R^{12}$, $-X^4C(O)NR^{12}R^{12}$,
 $-X^4S(O)_2NR^{12}R^{12}$, $-X^4NR^{12}S(O)_2R^{12}$, $-X^4P(O)(OR^{12})OR^{12}$, $-X^4OP(O)(OR^{12})OR^{12}$,
 $-X^4NR^{12}C(O)R^{12}$, $-X^4S(O)R^{12}$ and $-X^4S(O)_2R^{12}$ and/or 1 radical selected from $-R^{14}$, $-X^4OR^{14}$,
 $-X^4SR^{14}$, $-X^4S(O)R^{14}$, $-X^4S(O)_2R^{14}$, $-X^4C(O)R^{14}$, $-X^4C(O)OR^{14}$, $-X^4OC(O)R^{14}$, $-X^4NR^{14}R^{12}$,
 $-X^4NR^{12}C(O)R^{14}$, $-X^4NR^{12}C(O)OR^{14}$, $-X^4C(O)NR^{12}R^{12}$, $-X^4S(O)_2NR^{14}R^{12}$, $-X^4NR^{12}S(O)_2R^{14}$,
 25 $-X^4NR^{12}C(O)NR^{14}R^{12}$ and $-X^4NR^{12}C(NR^{12})NR^{14}R^{12}$, wherein X^4 is a bond or (C_{1-4}) alkyl; R^{12}
 at each occurrence independently is hydrogen, (C_{1-4}) alkyl or halo-substituted (C_{1-4}) alkyl; R^{13}
 is (C_{1-4}) alkyl or halo-substituted (C_{1-4}) alkyl; and R^{14} is (C_{3-10}) cycloalkyl (C_{0-6}) alkyl,

hetero(C₃₋₁₀)cycloalkyl(C₆₋₈)alkyl, (C₆₋₁₀)aryl(C₆₋₈)alkyl, hetero(C₃₋₁₀)aryl(C₆₋₈)alkyl, (C₃₋₁₀)bicycloaryl(C₆₋₈)alkyl or hetero(C₃₋₁₀)bicycloaryl(C₆₋₈)alkyl;

R¹ is hydrogen, halo or (C₁₋₆)alkyl and R² is selected from a group consisting of hydrogen, cyano, halo, -X⁴NR¹²R¹², -X⁴NR¹²C(O)R¹³, -X⁴NR¹²C(O)OR¹³,
 5 -X⁴NR¹²C(O)NR¹²R¹², -X⁴NR¹²C(NR¹²)NR¹²R¹², -X⁴OR¹², -X⁴SR¹², -X⁴C(O)OR¹²,
 -X⁴C(O)R¹², -X⁴OC(O)R¹², -X⁴C(O)NR¹²R¹², -X⁴S(O)₂NR¹²R¹², -X⁴NR¹²S(O)₂R¹²,
 -X⁴P(O)(OR¹³)OR¹², -X⁴OP(O)(OR¹³)OR¹², -X⁴NR¹²C(O)R¹³, -X⁴S(O)R¹³, -X⁴S(O)₂R¹³,
 -R¹⁴, -X⁴OR¹⁴, -X⁴SR¹⁴, -X⁴S(O)R¹⁴, -X⁴S(O)₂R¹⁴, -X⁴C(O)R¹⁴, -X⁴C(O)OR¹⁴, -X⁴OC(O)R¹⁴,
 -X⁴NR¹⁴R¹², -X⁴NR¹²C(O)R¹⁴, -X⁴NR¹²C(O)OR¹⁴, -X⁴C(O)NR¹²R¹², -X⁴S(O)₂NR¹⁴R¹²,
 10 -X⁴NR¹²S(O)₂R¹⁴, -X⁴NR¹²C(O)NR¹⁴R¹² and -X⁴NR¹²C(NR¹²)NR¹⁴R¹², wherein X⁴, R¹², R¹³
 and R¹⁴ are as defined above; or R¹ and R² taken together with the carbon atom to which
 both R¹ and R² are attached form (C₃₋₆)cycloalkylene or (C₃₋₆)heterocycloalkylene; wherein
 within said R² any heteroaryl, aryl, cycloalkyl, heterocycloalkyl, cycloalkylene or
 heterocycloalkylene is optionally substituted with 1 to 3 radicals independently selected
 15 from (C₁₋₆)alkyl, (C₁₋₆)alkylidene, cyano, halo, halo-substituted(C₁₋₆)alkyl, nitro,
 -X⁴NR¹²R¹², -X⁴NR¹²C(O)R¹², -X⁴NR¹²C(O)OR¹², -X⁴NR¹²C(O)NR¹²R¹²,
 -X⁴NR¹²C(NR¹²)NR¹²R¹², -X⁴OR¹², -X⁴SR¹², -X⁴C(O)OR¹², -X⁴C(O)R¹², -X⁴OC(O)R¹²,
 -X⁴C(O)NR¹²R¹², -X⁴S(O)₂NR¹²R¹², -X⁴NR¹²S(O)₂R¹², -X⁴P(O)(OR¹³)OR¹²,
 -X⁴OP(O)(OR¹³)OR¹², -X⁴NR¹²C(O)R¹³, -X⁴S(O)R¹³, -X⁴S(O)₂R¹³ and -X⁴C(O)R¹³, wherein
 20 X⁴, R¹² and R¹³ are as defined above;

R³ is -C(R⁶)(R⁶)X⁵, wherein R⁶ is as defined above and X⁵ is selected from
 -X⁴NR¹²R¹², -X⁴NR¹²C(O)R¹², -X⁴NR¹²C(O)OR¹², -X⁴NR¹²C(O)NR¹²R¹²,
 -X⁴NR¹²C(NR¹²)NR¹²R¹², -X⁴OR¹², -X⁴SR¹², -X⁴C(O)OR¹², -X⁴C(O)R¹², -X⁴OC(O)R¹²,
 -X⁴C(O)NR¹²R¹², -X⁴S(O)₂NR¹²R¹², -X⁴NR¹²S(O)₂R¹², -X⁴P(O)(OR¹³)OR¹², -X⁴R¹²,
 25 -X⁴OP(O)(OR¹³)OR¹², -X⁴C(O)R¹³, -X⁴NR¹²C(O)R¹³, -X⁴S(O)R¹³ and -X⁴S(O)₂R¹³, -R¹⁴,
 -X⁴OR¹⁴, -X⁴SR¹⁴, -X⁴S(O)R¹⁴, -X⁴S(O)₂R¹⁴, -X⁴C(O)R¹⁴, -X⁴C(O)OR¹⁴, -X⁴OC(O)R¹⁴,
 -X⁴NR¹⁴R¹², -X⁴NR¹²C(O)R¹⁴, -X⁴NR¹²C(O)OR¹⁴, -X⁴C(O)NR¹⁴R¹², -X⁴S(O)₂NR¹⁴R¹²,
 -X⁴NR¹²S(O)₂R¹⁴, -X⁴NR¹²C(O)NR¹⁴R¹² and -X⁴NR¹²C(NR¹²)NR¹⁴R¹² wherein X⁴, R¹², R¹³
 and R¹⁴ are as defined above;

30 R⁴ is -NR⁶R⁶, -NR⁶R¹⁴, -NR⁶R¹⁵ or -NR⁶X⁵C(O)R¹⁴ wherein R⁶, X⁵ and R¹⁴ are
 as described above and R¹⁵ is hydrogen, -(C₁₋₆)alkyl or -X⁵OR⁶ wherein X⁵ is as described

above; or R^6 and R^{15} together with the nitrogen atom to which R^6 and R^{15} are attached form hetero(C_{3-10})cycloalkyl, hetero(C_{3-10})aryl or hetero(C_{3-10})bicycloaryl;

wherein within R^3 and R^4 any alicyclic or aromatic ring system may be substituted further by 1-5 radicals independently selected from (C_{1-6})alkyl, (C_{1-6})alkylidene, cyano, halo, halo-substituted(C_{1-6})alkyl, nitro, $-X^4NR^{12}R^{13}$, $-X^4NR^{12}C(O)R^{13}$, $-X^4NR^{12}C(O)OR^{13}$, $-X^4NR^{12}C(O)NR^{13}R^{14}$, $-X^4NR^{12}C(NR^{13})NR^{13}R^{14}$, $-X^4OR^{13}$, $-X^4SR^{13}$, $-X^4C(O)OR^{13}$, $-X^4C(O)R^{13}$, $-X^4OC(O)R^{13}$, $-X^4C(O)NR^{13}R^{14}$, $-X^4S(O)_2NR^{13}R^{14}$, $-X^4NR^{12}S(O)_2R^{13}$, $-X^4P(O)(OR^{13})OR^{13}$, $-X^4OP(O)(OR^{13})OR^{13}$, $-X^4NR^{12}C(O)R^{13}$, $-X^4S(O)R^{13}$, $-X^4C(O)R^{13}$ and $-X^4S(O)_2R^{13}$ and/or 1 radical selected from $-R^{14}$, $-X^4OR^{14}$, $-X^4SR^{14}$, $-X^4S(O)R^{14}$, $-X^4S(O)_2R^{14}$, $-X^4C(O)R^{14}$, $-X^4C(O)OR^{14}$, $-X^4OC(O)R^{14}$, $-X^4NR^{14}R^{12}$, $-X^4NR^{12}C(O)R^{14}$, $-X^4NR^{12}C(O)OR^{14}$, $-X^4C(O)NR^{14}R^{12}$, $-X^4S(O)_2NR^{14}R^{12}$, $-X^4NR^{12}S(O)_2R^{14}$, $-X^4NR^{12}C(O)NR^{14}R^{12}$ and $-X^4NR^{12}C(NR^{13})NR^{14}R^{12}$; and within R^3 and R^4 any aliphatic moiety may be substituted further by 1-5 radicals independently selected from cyano, halo, nitro, $-NR^{12}R^{13}$, $-NR^{12}C(O)R^{13}$, $-NR^{12}C(O)OR^{13}$, $-NR^{12}C(O)NR^{13}R^{14}$, $-NR^{12}C(NR^{13})NR^{13}R^{14}$, $-OR^{13}$, $-SR^{13}$, $-C(O)OR^{13}$, $-C(O)R^{13}$, $-OC(O)R^{13}$, $-C(O)NR^{13}R^{14}$, $-S(O)_2NR^{13}R^{14}$, $-NR^{12}S(O)_2R^{13}$, $-P(O)(OR^{13})OR^{13}$, $-OP(O)(OR^{13})OR^{13}$, $-NR^{12}C(O)R^{13}$, $-S(O)R^{13}$ and $-S(O)_2R^{13}$; wherein X^4 , R^{12} , R^{13} and R^{14} are as described above;

with the proviso that only one bicyclic ring structure is present within R^3 or R^4 ; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates (e.g. hydrates) of such compounds and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

A second aspect of the invention is a pharmaceutical composition which contains a compound of Formula I or a *N*-oxide derivative, individual isomer or mixture of isomers thereof, or a pharmaceutically acceptable salt thereof, in admixture with one or more suitable excipients.

A third aspect of the invention is a method for treating a disease in an animal in which inhibition of cathepsin S can prevent, inhibit or ameliorate the pathology and/or symptomatology of the disease, which method comprises administering to the animal a therapeutically effective amount of compound of Formula I or a *N*-oxide derivative, individual isomer or mixture of isomers thereof; or a pharmaceutically acceptable salt

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thereof.

A fourth aspect of the invention is the processes for preparing compounds of Formula I and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts thereof.

DETAILED DESCRIPTION OF THE INVENTION

Definitions:

Unless otherwise stated, the following terms used in the specification and claims are defined for the purposes of this Application and have the following meanings.

"Alicyclic" means a moiety characterized by arrangement of the carbon atoms in closed non-aromatic ring structures having properties resembling those of aliphatics and may be saturated or partially unsaturated with two or more double or triple bonds.

"Aliphatic" means a moiety characterized by a straight or branched chain arrangement of the constituent carbon atoms and may be saturated or partially unsaturated with two or more double or triple bonds.

"Alkyl" represented by itself means a straight or branched, saturated or unsaturated, aliphatic radical having the number of carbon atoms indicated (e.g., (C₁₋₆)alkyl includes methyl, ethyl, propyl, isopropyl, butyl, *sec*-butyl, isobutyl, *tert*-butyl, vinyl, allyl, 1-propenyl, isopropenyl, 1-butenyl, 2-butenyl, 3-butenyl, 2-methylallyl, ethynyl, 1-propynyl, 2-propynyl, and the like). Alkyl represented along with another radical (e.g., as in arylalkyl) means a straight or branched, saturated or unsaturated aliphatic divalent radical having the number of atoms indicated or when no atoms are indicated means a bond (e.g., (C₆₋₁₀)aryl(C₁₋₃)alkyl includes phenyl, benzyl, phenethyl, 1-phenylethyl, 3-phenylpropyl, and the like).

"Alkylene", unless indicated otherwise, means a straight or branched, saturated or unsaturated, aliphatic, divalent radical having the number of carbon atoms indicated (e.g., (C₁₋₆)alkylene includes methylene (-CH₂-), ethylene (-CH₂CH₂-), trimethylene (-CH₂CH₂CH₂-), tetramethylene (-CH₂CH₂CH₂CH₂-) 2-butenylene (-CH₂CH=CHCH₂-),

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2-methyltetramethylene $(-\text{CH}_2\text{CH}(\text{CH}_3)\text{CH}_2\text{CH}_2-)$, pentamethylene
 $(-\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2\text{CH}_2-)$ and the like).

"Alkylidene" means a straight or branched saturated or unsaturated, aliphatic, divalent radical having the number of carbon atoms indicated (e.g. (C_{1-6}) alkylidene
 5 includes methyldiene $(=\text{CH}_2)$, ethylidene $(=\text{CHCH}_3)$, isopropylidene $(=\text{C}(\text{CH}_3)_2)$, propylidene $(=\text{CHCH}_2\text{CH}_3)$, allylidene $(=\text{CHCH}=\text{CH}_2)$, and the like).

"Amino" means the radical $-\text{NH}_2$. Unless indicated otherwise, the compounds of the invention containing amino moieties include protected derivatives thereof. Suitable protecting groups for amino moieties include acetyl, *tert*-butoxycarbonyl,
 10 benzyloxycarbonyl, and the like.

"Animal" includes humans, non-human mammals (e.g., dogs, cats, rabbits, cattle, horses, sheep, goats, swine, deer, and the like) and non-mammals (e.g., birds, and the like).

"Aromatic" means a moiety wherein the constituent atoms make up an unsaturated ring system, all atoms in the ring system are sp^2 hybridized and the total number of pi
 15 electrons is equal to $4n+2$.

"Aryl" means a monocyclic or fused bicyclic ring assembly containing the total number of ring carbon atoms indicated, wherein each ring is comprised of 6 ring carbon atoms and is aromatic or when fused with a second ring forms an aromatic ring assembly.

For example, optionally substituted (C_{6-10}) aryl as used in this Application includes, but is
 20 not limited to, biphenyl-2-yl, 2-bromophenyl, 2-bromocarbonylphenyl, 2-bromo-5-fluorophenyl, 4-*tert*-butylphenyl, 4-carbamoylphenyl, 4-carboxy-2-nitrophenyl, 2-chlorophenyl, 4-chlorophenyl, 3-chlorocarbonylphenyl, 4-chlorocarbonylphenyl, 2-chloro-4-fluorophenyl, 2-chloro-6-fluorophenyl, 4-chloro-2-nitrophenyl, 6-chloro-2-nitrophenyl, 2,6-dibromophenyl, 2,3-dichlorophenyl, 2,5-dichlorophenyl,
 25 3,4-dichlorophenyl, 2-difluoromethoxyphenyl, 3,5-dimethylphenyl, 2-ethoxycarbonylphenyl, 2-fluorophenyl, 2-iodophenyl, 4-isopropylphenyl, 2-methoxyphenyl, 4-methoxyphenyl, 2-methylphenyl, 3-methylphenyl, 4-methylphenyl, 5-methyl-2-nitrophenyl, 4-methylsulfonylphenyl, naphth-2-yl, 2-nitrophenyl, 3-nitrophenyl, 4-nitrophenyl, 2,3,4,5,6-pentafluorophenyl, phenyl,
 30 2-trifluoromethoxyphenyl, 3-trifluoromethoxyphenyl, 4-trifluoromethoxyphenyl, 2-trifluoromethylphenyl, 3-trifluoromethylphenyl, 4-trifluoromethylphenyl,

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2-trifluoromethylsulfanylphenyl, 4-trifluoromethylsulfanylphenyl, and the like. Optionally substituted (C_{6-10})aryl as used in this Application includes 3-acetylphenyl, 3-*tert*-butoxycarbonylaminoethylphenyl, biphenyl-4-yl, 3-hydroxyphenyl, 4-hydroxyphenyl, 3-methoxyphenyl, naphth-2-yl, 3-phenoxyphenyl, phenyl, and the like.

5 "Bicycloaryl" means a bicyclic ring assembly containing the number of ring carbon atoms indicated, wherein the rings are linked by a single bond or fused and at least one of the rings comprising the assembly is aromatic, and any carbocyclic ketone, thioketone or iminoketone derivative thereof (e.g., (C_{7-10})bicycloaryl includes cyclohexylphenyl, 1,2-dihydronaphthyl, 2,4-dioxo-1,2,3,4-tetrahydronaphthyl, indanyl, indenyl,
10 1,2,3,4-tetrahydronaphthyl, and the like).

"Carbamoyl" means the radical $-C(O)NH_2$. Unless indicated otherwise, the compounds of the invention containing carbamoyl moieties include protected derivatives thereof. Suitable protecting groups for carbamoyl moieties include acetyl, *tert*-butoxycarbonyl, benzyloxycarbonyl, and the like and both the unprotected and
15 protected derivatives fall within the scope of the invention.

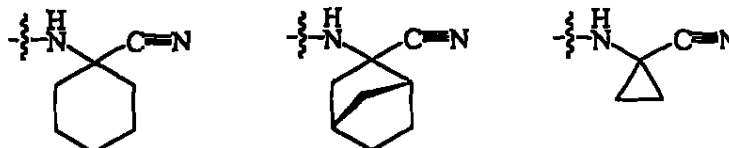
"Carbocyclic ketone derivative" means a derivative containing the moiety $-C(O)-$.

"Carboxy" means the radical $-C(O)OH$. Unless indicated otherwise, the compounds of the invention containing carboxy moieties include protected derivatives thereof. Suitable protecting groups for carboxy moieties include benzyl, *tert*-butyl, and the
20 like.

"Cycloalkyl" means a saturated or partially unsaturated, monocyclic, fused bicyclic or bridged polycyclic ring assembly containing the number of ring carbon atoms indicated, and any carbocyclic ketone, thioketone or iminoketone derivative thereof (e.g.,
25 (C_{3-10})cycloalkyl includes cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, cyclohexenyl, 2,5-cyclohexadienyl, bicyclo[2.2.2]octyl, adamantan-1-yl, decahydronaphthyl, oxocyclohexyl, dioxocyclohexyl, thiocyclohexyl, 2-oxobicyclo[2.2.1]hept-1-yl, and the like).

"Cycloalkylene" means a divalent saturated or partially unsaturated, monocyclic
30 ring or bridged polycyclic ring assembly containing the number of ring carbon atoms indicated, and any carbocyclic ketone, thioketone or iminoketone derivative thereof. For

example, the instance wherein "R¹ and R² together with the carbon atom to which both R¹ and R² are attached form (C₃₋₆)cycloalkylene" includes, but is not limited to, the following:



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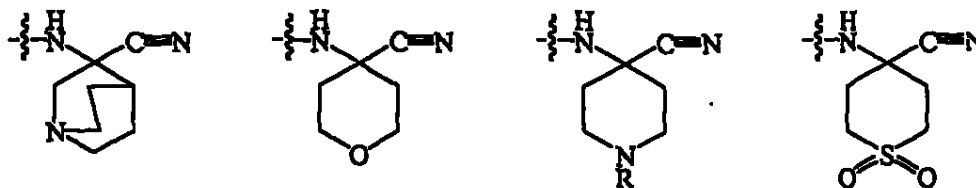
"Disease" specifically includes any unhealthy condition of an animal or part thereof and includes an unhealthy condition that may be caused by, or incident to, medical or veterinary therapy applied to that animal, i.e., the "side effects" of such therapy.

"Halo" means fluoro, chloro, bromo or iodo.

- 10 "Halo-substituted alkyl", as an isolated group or part of a larger group, means "alkyl" substituted by one or more "halo" atoms, as such terms are defined in this Application. Halo-substituted alkyl includes haloalkyl, dihaloalkyl, trihaloalkyl, perhaloalkyl and the like (e.g. halo-substituted (C₁₋₃)alkyl includes chloromethyl, dichloromethyl, difluoromethyl, trifluoromethyl, 2,2,2-trifluoroethyl, perfluoroethyl,
- 15 2,2,2-trifluoro-1,1-dichloroethyl, and the like).

"Heteroatom moiety" includes -N=, -NR-, -O-, -S- or -S(O)₂-, wherein R is hydrogen, (C₁₋₆)alkyl or a protecting group.

- "Heterocycloalkylene" means cycloalkylene, as defined in this Application, provided that one or more of the ring member carbon atoms indicated, is replaced by
- 20 heteroatom moiety selected from -N=, -NR-, -O-, -S- or -S(O)₂-, wherein R is hydrogen or (C₁₋₆)alkyl. For example, the instance wherein R¹ and R² together with the carbon atom to which both R¹ and R² are attached form hetero(C₃₋₆)cycloalkyl" includes, but is not limited to, the following:



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in which R is hydrogen, (C₁₋₆)alkyl, or a protecting group.

"Heteroaryl" means aryl, as defined in this Application, provided that one or more of the ring carbon atoms indicated are replaced by a heteroatom moiety selected from -N=, -NR-, -O- or -S-, wherein R is hydrogen, (C₁₋₆)alkyl, a protecting group or represents the free valence which serves as the point of attachment to a ring nitrogen, and each ring is comprised of 5 or 6 ring atoms. For example, optionally substituted hetero(C₅₋₁₀)aryl as used in this Application includes, but is not limited to, 4-amino-2-hydroxypyrimidin-5-yl, benzothiazol-2-yl, 1*H*-benzimidazol-2-yl, 2-bromopyrid-5-yl, 5-bromopyrid-2-yl, 4-carbamoylthiazol-2-yl, 3-carboxypyrid-4-yl, 5-carboxy-2,6-dimethylpyrid-3-yl, 3,5-dimethylisoxazol-4-yl, 5-ethoxy-2,6-dimethylpyrid-3-yl, 5-fluoro-6-hydroxypyrimidin-4-yl, fur-2-yl, fur-3-yl, 5-hydroxy-4,6-dimethylpyrid-3-yl, 8-hydroxy-5,7-dimethylquinolin-2-yl, 5-hydroxymethylisoxazol-3-yl, 3-hydroxy-6-methylpyrid-2-yl, 3-hydroxypyrid-2-yl, 1*H*-imidazol-2-yl, 1*H*-imidazol-4-yl, 1*H*-indol-3-yl, isothiazol-4-yl, isoxazol-4-yl, 2-methylfur-3-yl, 5-methylfur-2-yl, 1-methyl-1*H*-imidazol-2-yl, 5-methyl-3*H*-imidazol-4-yl, 5-methylisoxazol-3-yl, 5-methyl-2*H*-pyrazol-3-yl, 3-methylpyrid-2-yl, 4-methylpyrid-2-yl, 5-methylpyrid-2-yl, 6-methylpyrid-2-yl, 2-methylpyrid-3-yl, 2-methylthiazol-4-yl, 5-nitropyrid-2-yl, 2*H*-pyrazol-3-yl, 3*H*-pyrazol-4-yl, pyridazin-3-yl, pyrid-2-yl, pyrid-3-yl, pyrid-4-yl, 5-pyrid-3-yl-2*H*-[1,2,4]triazol-3-yl, pyrimidin-4-yl, pyrimidin-5-yl, 1*H*-pyrrol-3-yl, quinolin-2-yl, 1*H*-tetrazol-5-yl, thiazol-2-yl, thiazol-5-yl, thien-2-yl, thien-3-yl, 2*H*-[1,2,4]triazol-3-yl, 3*H*-[1,2,3]triazol-4-yl, 5-trifluoromethylpyrid-2-yl, and the like. Suitable protecting groups include *tert*-butoxycarbonyl, benzyloxycarbonyl, benzyl, 4-methoxybenzyl, 2-nitrobenzyl, and the like. Optionally substituted hetero(C₅₋₁₀)aryl as used in this Application to define R⁴ includes benzofur-2-yl, fur-2-yl, fur-3-yl, pyrid-3-yl, pyrid-4-yl, quinol-2-yl, quinol-3-yl, thien-2-yl, thien-3-yl, and the like.

"Heterobicycloaryl" means bicycloaryl, as defined in this Application, provided that one or more of the ring carbon atoms indicated are replaced by a heteroatom moiety selected from -N=, -NR-, -O- or -S-, wherein R is hydrogen, (C₁₋₆)alkyl, a protecting group or represents the free valence which serves as the point of attachment to a ring nitrogen, and any carbocyclic ketone, thioketone or iminoketone derivative thereof. For example, optionally substituted hetero(C₈₋₁₀)bicycloaryl as used in this Application includes, but is

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not limited to, 2-amino-4-oxo-3,4-dihydropteridin-6-yl, and the like. In general, the term heterobicycloaryl as used in this Application includes, for example, benzo[1,3]dioxol-5-yl, 3,4-dihydro-2H-[1,8]naphthyridinyl, 3,4-dihydro-2H-quinolinyl, 2,4-dioxo-3,4-dihydro-2H-quinazolinyl, 1,2,3,4,5,6-hexahydro[2,2']bipyridinyl, 3-oxo-2,3-dihydrobenzo[1,4]oxazinyl, 5,6,7,8-tetrahydroquinolinyl, and the like.

"Heterocycloalkyl" means cycloalkyl, as defined in this Application, provided that one or more of the ring carbon atoms indicated are replaced by a heteroatom moiety selected from -N=, -NR-, -O- or -S-, wherein R is hydrogen, (C₁₋₄)alkyl, a protecting group or represents the free valence which serves as the point of attachment to a ring nitrogen, and any carbocyclic ketone, thioketone or iminoketone derivative thereof (e.g., the term hetero(C₃₋₁₀)cycloalkyl includes imidazolidinyl, morpholinyl, piperazinyl, piperidyl, pyrrolidinyl, pyrrolinyl, quinuclidinyl, and the like). Suitable protecting groups include *tert*-butoxycarbonyl, benzyloxycarbonyl, benzyl, 4-methoxybenzyl, 2-nitrobenzyl, and the like. Both the unprotected and protected derivatives fall within the scope of the invention.

"Hydroxy" means the radical -OH. Unless indicated otherwise, the compounds of the invention containing hydroxy radicals include protected derivatives thereof. Suitable protecting groups for hydroxy moieties include benzyl and the like.

"Iminoketone derivative" means a derivative containing the moiety -C(NR)-, wherein R is hydrogen or (C₁₋₄)alkyl.

"Isomers" mean compounds of Formula I having identical molecular formulae but differ in the nature or sequence of bonding of their atoms or in the arrangement of their atoms in space. Isomers that differ in the arrangement of their atoms in space are termed "stereoisomers". Stereoisomers that are not mirror images of one another are termed "diastereomers" and stereoisomers that are nonsuperimposable mirror images are termed "enantiomers" or sometimes "optical isomers". A carbon atom bonded to four nonidentical substituents is termed a "chiral center". A compound with one chiral center has two enantiomeric forms of opposite chirality is termed a "racemic mixture". A compound that has more than one chiral center has 2ⁿ enantiomeric pairs, where *n* is the number of chiral centers. Compounds with more than one chiral center may exist as either an individual diastereomers or as a mixture of diastereomers, termed a "diastereomeric mixture". When one chiral center is present a stereoisomer may be characterized by the absolute

configuration of that chiral center. Absolute configuration refers to the arrangement in space of the substituents attached to the chiral center. Enantiomers are characterized by the absolute configuration of their chiral centers and described by the *R*- and *S*-sequencing rules of Cahn, Ingold and Prelog. Conventions for stereochemical nomenclature, methods
5 for the determination of stereochemistry and the separation of stereoisomers are well known in the art (e.g., see "Advanced Organic Chemistry", 4th edition, March, Jerry, John Wiley & Sons, New York, 1992). It is understood that the names and illustration used in this Application to describe compounds of Formula I are meant to be encompassed all possible stereoisomers. Thus, for example, the name *N*-[1-(1-Benzylcarbamoyl-
10 methanoyl)-propyl]-4-morpholin-4-yl-4-oxo-2-phenylmethanesulfonylmethyl-butylamide is meant to include *N*-[(*S*)-1-(1-Benzylcarbamoyl-methanoyl)-propyl]-4-morpholin-4-yl-4-oxo-2-phenylmethanesulfonylmethyl-butylamide and *N*-[(*R*)-1-(1-Benzylcarbamoyl-methanoyl)-propyl]-4-morpholin-4-yl-4-oxo-2-phenylmethanesulfonylmethyl-butylamide and any mixture, racemic or otherwise, thereof.

15 "Ketone derivative" means a derivative containing the moiety -C(O)-. For example, in this Application X^3 can be 2-acetoxy-azetidin-3-yl. The "carbocyclic ketone derivative" of this example of X^3 would be 2-acetoxy-4-oxo-azetidin-3-yl (see Table 3, C32).

"Nitro" means the radical -NO₂.

20 "Optional" or "optionally" means that the subsequently described event or circumstance may or may not occur, and that the description includes instances where the event or circumstance occurs and instances in which it does not. For example, the phrase "wherein within R³ and R⁴ any alicyclic or aromatic ring system may be substituted further by 1-5 radicals..." means that R³ and R⁴ may or may not be substituted in order to fall
25 within the scope of the invention.

"Oxoalkyl" means alkyl, as defined above, wherein one of the number of carbon atoms indicated is replaced by an oxygen group (-O-), e.g., oxo(C₂₋₆)alkyl includes methoxymethyl, etc.

"*N*-oxide derivatives" means derivatives of compounds of Formula I in which
30 nitrogens are in an oxidized state (i.e., O-N) and which possess the desired pharmacological activity.

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"Pathology" of a disease means the essential nature, causes and development of the disease as well as the structural and functional changes that result from the disease processes.

5 "Pharmaceutically acceptable" means that which is useful in preparing a pharmaceutical composition that is generally safe, non-toxic and neither biologically nor otherwise undesirable and includes that which is acceptable for veterinary use as well as human pharmaceutical use.

"Pharmaceutically acceptable salts" means salts of compounds of Formula I which are pharmaceutically acceptable, as defined above, and which possess the desired
10 pharmacological activity. Such salts include acid addition salts formed with inorganic acids such as hydrochloric acid, hydrobromic acid, sulfuric acid, nitric acid, phosphoric acid, and the like; or with organic acids such as acetic acid, propionic acid, hexanoic acid, heptanoic acid, cyclopentanepropionic acid, glycolic acid, pyruvic acid, lactic acid, malonic acid, succinic acid, malic acid, maleic acid, fumaric acid, tartatic acid, citric acid,
15 benzoic acid, *o*-(4-hydroxybenzoyl)benzoic acid, cinnamic acid, maleic acid, methanesulfonic acid, ethanesulfonic acid, 1,2-ethanedisulfonic acid, 2-hydroxyethanesulfonic acid, benzenesulfonic acid, *p*-chlorobenzenesulfonic acid, 2-naphthalenesulfonic acid, *p*-toluenesulfonic acid, camphorsulfonic acid, 4-methylbicyclo[2.2.2]oct-2-ene-1-carboxylic acid, glucoheptonic acid,
20 4,4'-methylenebis(3-hydroxy-2-ene-1-carboxylic acid), 3-phenylpropionic acid, trimethylacetic acid, tertiary butylacetic acid, lauryl sulfuric acid, gluconic acid, glutamic acid, hydroxynaphthoic acid, salicylic acid, stearic acid, muconic acid and the like.

Pharmaceutically acceptable salts also include base addition salts which may be formed when acidic protons present are capable of reacting with inorganic or organic
25 bases. Acceptable inorganic bases include sodium hydroxide, sodium carbonate, potassium hydroxide, aluminum hydroxide and calcium hydroxide. Acceptable organic bases include ethanolamine, diethanolamine, triethanolamine, tromethamine, *N*-methylglucamine and the like.

"Prodrug" means a compound which is convertible in vivo by metabolic means
30 (e.g. by hydrolysis) to a compound of Formula I. For example an ester of a compound of Formula I containing a hydroxy group may be convertible by hydrolysis in vivo to the

parent molecule. Alternatively an ester of a compound of Formula I containing a carboxy group may be convertible by hydrolysis in vivo to the parent molecule. Suitable esters of compounds of Formula I containing a hydroxy group, are for example acetates, citrates, lactates, tartrates, malonates, oxalates, salicylates, propionates, succinates, fumarates, maleates, methylene-bis-b-hydroxynaphthoates, gentisates, isethionates, di-*p*-toluoyltartrates, methanesulphonates, ethanesulphonates, benzenesulphonates, *p*-toluenesulphonates, cyclohexylsulphamates and quinate. Suitable esters of compounds of Formula I containing a carboxy group, are for example those described by F.J. Leinweber, *Drug Metab. Res.*, 1987, 18, page 379. An especially useful class of esters of compounds of Formula I containing a hydroxy group, may be formed from acid moieties selected from those described by Bundgaard et al., *J. Med. Chem.*, 1989, 32, page 2503-2507, and include substituted (aminomethyl)-benzoates, for example, dialkylaminomethylbenzoates in which the two alkyl groups may be joined together and/or interrupted by an oxygen atom or by an optionally substituted nitrogen atom, e.g. an alkylated nitrogen atom, more especially (morpholino-methyl)benzoates, e.g. 3- or 4-(morpholinomethyl)-benzoates, and (4-alkylpiperazin-1-yl)benzoates, e.g. 3- or 4-(4-alkylpiperazin-1-yl)-benzoates.

"Protected derivatives" means derivatives of compounds of Formula I in which a reactive site or sites are blocked with protecting groups. Protected derivatives of compounds of Formula I are useful in the preparation of compounds of Formula I or in themselves may be active cathepsin S inhibitors. A comprehensive list of suitable protecting groups can be found in T.W. Greene, *Protecting Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons, Inc. 1999.

"Therapeutically effective amount" means that amount which, when administered to an animal for treating a disease, is sufficient to effect such treatment for the disease.

"Thioketone derivative" means a derivative containing the moiety -C(S)-.

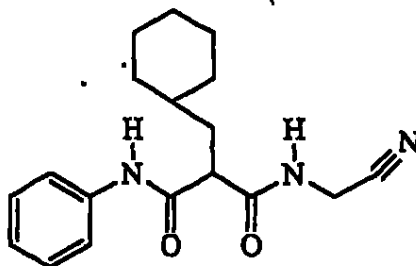
"Treatment" or "treating" means any administration of a compound of the present invention and includes:

- (1) preventing the disease from occurring in an animal which may be predisposed to the disease but does not yet experience or display the pathology or symptomatology of the disease,

- (2) inhibiting the disease in an animal that is experiencing or displaying the pathology or symptomatology of the diseased (i.e., arresting further development of the pathology and/or symptomatology), or
- (3) ameliorating the disease in an animal that is experiencing or displaying the pathology or symptomatology of the diseased (i.e., reversing the pathology and/or symptomatology).

Nomenclature:

The compounds of Formula I and the intermediates and starting materials used in their preparation are named in accordance with IUPAC rules of nomenclature in which the characteristic groups have decreasing priority for citation as the principle group as follows: acids, esters, amides, etc. Alternatively, the compounds are named by AutoNqm 4.0 (Beilstein Information Systems, Inc.). For example, a compound of Formula I in which X^1 is $-NHC(R^1)(R^2)X^2$ (R^1 and R^2 are each hydrogen), X^2 is cyano, R^3 is cyclohexylmethyl, and R^4 is phenylamino; that is, a compound having the following structure:



is named N-cyanomethyl-2-cyclohexylmethyl-N'-phenyl-malonamide.

Presently Preferred Embodiments:

While the broadest definition of the invention is set forth in the Summary of the Invention, certain aspects of the invention are preferred. For example, X^1 is $-NHC(R^1)(R^2)X^2$ or $-NHX^3$; X^2 is cyano, $-C(O)X^3$, $-C(O)CF_3$, $-C(O)CF_2CF_2R^9$, $-CH=CHS(O)_2R^5$, $-C(O)CF_2C(O)NR^5R^6$, $-C(O)C(O)NR^5R^6$, $-C(O)C(O)OR^5$, $-C(O)CH_2OR^5$, $-C(O)CH_2N(R^6)SO_2R^5$ or $-C(O)C(O)R^5$; wherein R^5 and R^6 are as described

above; X^3 comprises a heteromonocyclic ring containing 4 to 6 ring member atoms or a fused heterobicyclic ring system containing 8 to 14 ring member atoms and any carbocyclic ketone, iminoketone or thioketone derivative thereof; wherein within R^5 , X^2 or X^3 any alicyclic or aromatic ring system may be substituted further by 1 to 5 radicals independently selected from (C_{1-6}) alkyl or $-X^4OC(O)R^{12}$ and/or 1 radical selected from $-R^{14}$, $-X^4C(O)R^{14}$ or $-X^4OC(O)R^{14}$; wherein X^4 , R^{12} and R^{14} are as described above; R^1 is hydrogen or (C_{1-6}) alkyl and R^2 is hydrogen, $-X^4OR^{12}$, (C_{5-10}) heteroaryl (C_{6-6}) alkyl, (C_{5-10}) aryl (C_{6-6}) alkyl, (C_{5-10}) cycloalkyl (C_{6-6}) alkyl, (C_{5-10}) heterocycloalkyl (C_{6-6}) alkyl or (C_{1-6}) alkyl; or R^1 and R^2 taken together with the carbon atom to which both R^1 and R^2 are attached form (C_{3-6}) cycloalkylene or (C_{3-6}) heterocycloalkylene; wherein within said R^2 any heteroaryl, aryl, cycloalkyl, heterocycloalkyl, cycloalkylene or heterocycloalkylene is optionally substituted with 1 to 3 radicals independently selected from (C_{1-6}) alkyl and hydroxy; R^3 is $-CH_2X^5$, wherein X^5 at each occurrence independently is selected from $-X^4SR^{12}$, $-X^4C(O)NR^{12}R^{12}$, $-X^4S(O)_2R^{12}$, $-X^4C(O)R^{12}$, $-X^4SR^{14}$, $-X^4R^{12}$, $-R^{14}$, $-X^4S(O)_2R^{14}$, $-X^4C(O)R^{14}$, $-X^4C(O)NR^{14}R^{12}$, wherein X^4 , R^{12} , R^{13} and R^{14} are as defined above; R^4 is $-NR^6R^6$, $-NR^6R^{14}$, $-NR^6R^{15}$ or $-NR^6X^4C(O)R^{14}$ wherein R^6 , X^5 and R^{14} are as described above and R^{15} is hydrogen, (C_{1-6}) alkyl or $-X^5OR^6$ wherein X^5 is as described above; or R^6 and R^{15} together with the nitrogen atom to which R^6 and R^{15} are attached form hetero (C_{5-10}) cycloalkyl, hetero (C_{5-10}) aryl or hetero (C_{5-10}) bicycloaryl; wherein within R^1 and R^4 any alicyclic or aromatic ring system may be substituted further by 1-5 radicals independently selected from (C_{1-6}) alkyl, cyano, halo, nitro, halo-substituted (C_{1-6}) alkyl, $-X^4OR^{12}$, $-X^4C(O)OR^{12}$, $-X^4C(O)R^{12}$, $-X^4C(O)NR^{12}R^{12}$, $-X^4NR^{12}S(O)_2R^{12}$ and/or 1 radical selected from $-R^{14}$, $-X^4OR^{14}$ and $-X^4C(O)NR^{14}R^{12}$; within R^3 and R^4 any aliphatic moiety may be substituted further by 1-5 radicals independently selected from cyano; wherein X^4 , R^{12} , R^{13} and R^{14} are as described above; with the proviso that only one bicyclic ring structure is present within R^3 or R^4 .

In particular, X^1 is $-NHC(R^1)(R^2)X^2$ or $-NHX^3$; X^2 is cyano, $-C(O)X^1$, $-CF_3$, $-CF_2CF_3$, (E)-2-benzenesulfonyl-vinyl, 2-dimethylcarbamoyl-2,2-difluoro-acetyl, 1-benzylcarbamoyl-methanoyl, 1-benzyloxy(oxalyl), 2-benzyloxy-acetyl, 2-benzenesulfonylamino-ethanoyl or 2-oxo-2-phenyl-ethanoyl; X^3 is 1H-benzoimidazol-2-yl, pyrimidin-2-yl, benzooxazol-2-yl, benzothiazol-2-yl,

- pyridazin-3-yl, 3-phenyl-[1,2,4]oxadiazol-5-yl, 3-ethyl-[1,2,4]oxadiazol-5-yl, 2-methyl-4-oxo-tetrahydro-furan-3-yl, 2-ethyl-4-oxo-tetrahydro-furan-3-yl, 4-oxo-1-(1-phenyl-methanoyl)-pyrrolidin-3-yl or (S)-2-Acetoxy-4-oxo-azetidin-3-yl; R¹ is hydrogen or methyl and R² is hydrogen, methoxymethyl, (C₁₋₆)alkyl, phenethyl, thiophen-2-yl or 5-methyl-furan-2-yl, or (ii) R¹ and R² taken together with the carbon atom to which both R¹ and R² are attached form cyclopropylene, tetrahydro-pyran-4-ylene or methyl-piperidin-4-ylene.
- R³ more preferably is thiophene-2-sulfonylmethyl, 3-chloro-2-fluoro-phenylmethanesulfonylmethyl, benzenesulfonylmethyl, phenylmethanesulfonylmethyl, 2-(1,1-difluoro-methoxy)-phenylmethanesulfonylmethyl, 2-benzenesulfonyl-ethyl, 2-(pyridine-2-sulfonyl)-ethyl, 2-(pyridine-4-sulfonyl)-ethyl, 2-phenylmethanesulfonyl-ethyl, oxy-pyridin-2-ylmethanesulfonylmethyl, prop-2-ene-1-sulfonylmethyl, 4-methoxy-phenylmethanesulfonylmethyl, *p*-tolylmethanesulfonylmethyl, 4-chloro-phenylmethanesulfonylmethyl, *o*-tolylmethanesulfonylmethyl, 3,5-dimethyl-phenylmethanesulfonylmethyl, 4-trifluoromethyl-phenylmethanesulfonylmethyl, 4-trifluoromethoxy-phenylmethanesulfonylmethyl, 2-bromo-phenylmethanesulfonylmethyl, pyridin-2-ylmethanesulfonylmethyl, pyridin-3-ylmethanesulfonylmethyl, pyridin-4-ylmethanesulfonylmethyl, naphthalen-2-ylmethanesulfonylmethyl, 3-methyl-phenylmethanesulfonylmethyl, 3-trifluoromethyl-phenylmethanesulfonylmethyl, 3-trifluoromethoxy-phenylmethanesulfonylmethyl, 4-fluoro-2-trifluoromethoxy-phenylmethanesulfonylmethyl, 2-fluoro-6-trifluoromethyl-phenylmethanesulfonylmethyl, 3-chloro-phenylmethanesulfonylmethyl, 2-fluoro-phenylmethanesulfonylmethyl, 2-trifluoro-phenylmethanesulfonylmethyl, 2-cyano-phenylmethanesulfonylmethyl, 4-*tert*-butyl-phenylmethanesulfonylmethyl, 2-fluoro-3-methyl-phenylmethanesulfonylmethyl, 3-fluoro-phenylmethanesulfonylmethyl, 4-fluoro-phenylmethanesulfonylmethyl, 2-chloro-phenylmethanesulfonylmethyl, 2,5-difluoro-phenylmethanesulfonylmethyl, 2,6-difluoro-phenylmethanesulfonylmethyl, 2,5-dichloro-phenylmethanesulfonylmethyl, 3,4-dichloro-phenylmethanesulfonylmethyl,

- 2-(1,1-difluoro-methoxy)-phenylmethanesulfonylmethyl,
2-cyano-phenylmethanesulfonylmethyl, 3-cyano-phenylmethanesulfonylmethyl,
2-trifluoromethoxy-phenylmethanesulfonylmethyl,
2,3-difluoro-phenylmethanesulfonylmethyl, 2,5-difluoro-phenylmethanesulfonylmethyl,
5 biphenyl-2-ylmethanesulfonylmethyl, cyclohexylmethyl,
3-fluoro-phenylmethanesulfonylmethyl, 3,4-difluoro-phenylmethanesulfonylmethyl,
2,4-difluoro-phenylmethanesulfonylmethyl, 2,4,6-trifluoro-phenylmethanesulfonylmethyl,
2,4,5-trifluoro-phenylmethanesulfonylmethyl,
2,3,4-trifluoro-phenylmethanesulfonylmethyl,
10 2,3,5-trifluoro-phenylmethanesulfonylmethyl,
2,5,6-trifluoro-phenylmethanesulfonylmethyl,
2-chloro-5-trifluoromethylphenylmethanesulfonylmethyl, 2-methyl-propane-1-sulfonyl,
2-fluoro-3-trifluoromethylphenylmethanesulfonylmethyl,
2-fluoro-4-trifluoromethylphenylmethanesulfonylmethyl,
15 2-fluoro-5-trifluoromethylphenylmethanesulfonylmethyl,
4-fluoro-3-trifluoromethylphenylmethanesulfonylmethyl,
2-methoxy-phenylmethanesulfonylmethyl, 3,5
bis-trifluoromethyl-phenylmethanesulfonylmethyl,
4-difluoromethoxy-phenylmethanesulfonylmethyl,
20 2-difluoromethoxy-phenylmethanesulfonylmethyl,
3-difluoromethoxy-phenylmethanesulfonylmethyl,
2,6-dichloro-phenylmethanesulfonylmethyl, biphenyl-4-ylmethanesulfonylmethyl,
3,5-dimethyl-isoxazol-4-ylmethanesulfonylmethyl,
5-chloro-thiophen-2-ylmethanesulfonylmethyl,
25 2-[4-(1,1-Difluoro-methoxy)-benzenesulfonyl]-ethyl,
2-[2-(1,1-Difluoro-methoxy)-benzenesulfonyl]-ethyl,
2-[3-(1,1-Difluoro-methoxy)-benzenesulfonyl]-ethyl,
2-(4-trifluoromethoxy-benzenesulfonyl)-ethyl,
2-(3-trifluoromethoxy-benzenesulfonyl)-ethyl,
30 2-(2-trifluoromethoxy-benzenesulfonyl)-ethyl, (cyanomethyl-methyl-carbamoyl)-methyl,
butyl, biphenyl-3-ylmethyl, 2-oxo-2-pyrrolidin-1-yl-ethyl, 2-benzenesulfonyl-ethyl,

isobutylsulfanylmethyl, 2-phenylsulfanyl-ethyl, cyclohexylmethanesulfonylmethyl, 2-cyclohexyl-ethanesulfonyl, benzyl, naphthalen-2-yl, benzylsulfanylmethyl, 2-trifluoromethyl-benzylsulfanylmethyl, 5-bromo-thiophen-2-ylmethyl, phenylsulfanyl-ethyl and cyclopropylmethanesulfonylmethyl.

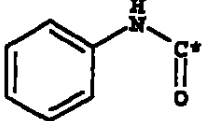
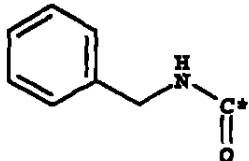
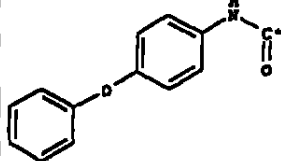
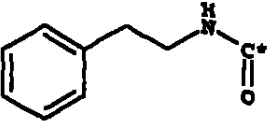
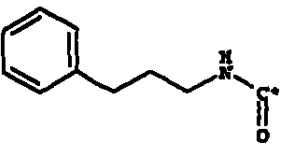
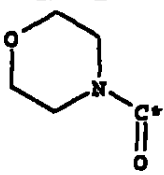
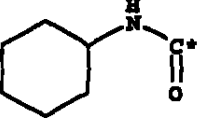
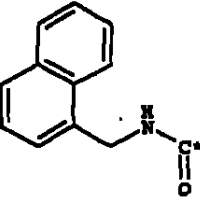
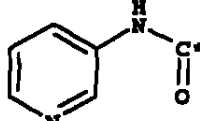
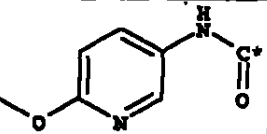
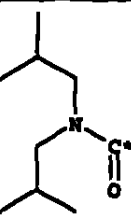
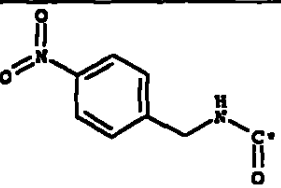
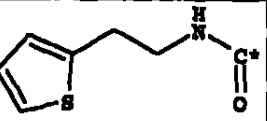
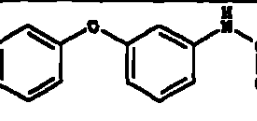
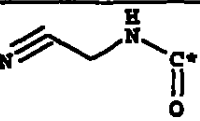
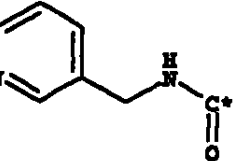
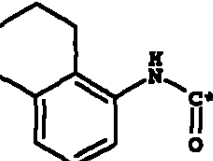
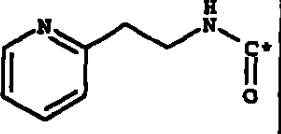
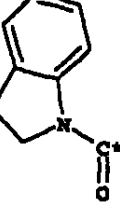
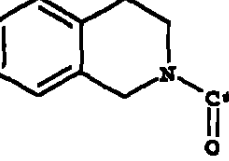
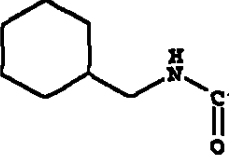
5 R⁴ more preferably is phenylamino, benzylamino, 4-phenoxy-phenylamino, phenethylamino, 3-phenyl-propylamino, morpholin-4-yl, cyclohexylamino, naphthalen-1-ylmethyl-amino, pyridin-3-ylamino, 6-methoxy-pyridin-3-ylamino, diisobutylamino, 4-nitro-benzylamino, 2-thiophen-2-yl-ethylamino, 3-phenoxy-phenylamino, cyanomethyl-amino, (pyridin-3-ylmethyl)-amino, 5,6,7,8-tetrahydro-naphthalen-1-ylamino, 2-pyridin-2-yl-ethylamino, 2,3-dihydro-indol-1-yl, 3,4-dihydro-1H-isoquinolin-2-yl, 10 cyclohexylmethyl-amino, 2-methoxy-benzylamino, 1-phenyl-ethylamino, (pyridin-4-ylmethyl)-amino, benzyl-methyl-amino, 3-nitro-benzylamino, 4-methoxy-phenylamino, 3-carbamoyl-phenylamino, 4-carbamoyl-phenylamino, (tetrahydro-furan-2-ylmethyl)-amino, 3,4-dihydro-2H-quinolin-1-yl, dimethylamino, butylmethylamino, 15 diisopropylamino, propylmethylamino, 1-(benzooxazole-2-carbonyl)-propylamino and isobutylmethylamino.

Reference to the preferred embodiments set forth above is meant to include all combinations of particular and preferred groups.

20 Particular compounds of the invention are selected from the compounds formed by joining the acyl carbon atom (C*) of one of the fragments (A1 to A37) shown in Table 1 to the methine carbon atom (*CH*) of one of the fragments (B1 to B88) shown in Table 2, and joining the methine carbon atom (*CH*) of one of the fragments (B1 to B88) shown in Table 2 to the acyl carbon atom (C*) of one of the fragments (C1 to C36) depicted in Table 3.

25 The following tables are intended to provide guidance to better carry out the present invention. However, they do not limit the scope of the invention. People of ordinary skill may selectively make particular compounds by joining of one of the fragments shown in Table 1 to any one of the fragments shown in Table 2, and then joining the fragments shown in Table 2 to the any of one of the fragments Table 3.

TABLE I

A1		A2		A3	
A4		A5		A6	
A7		A8		A9	
A10		A11		A12	
A13		A14		A15	
A16		A17		A18	
A19		A20		A21	

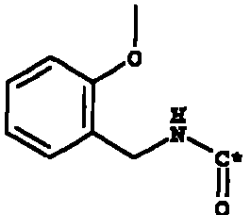
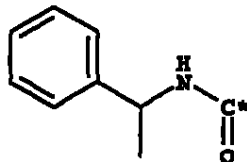
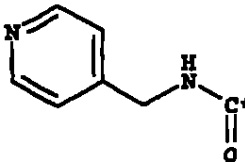
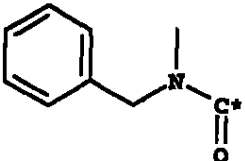
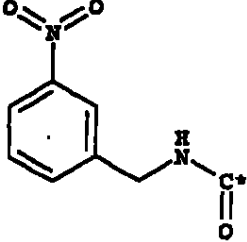
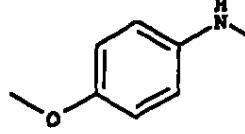
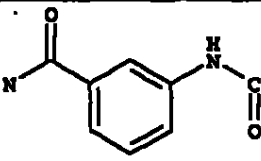
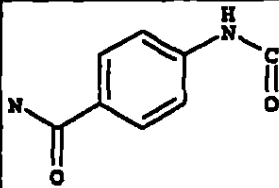
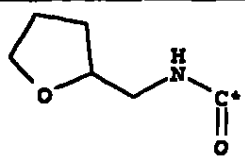
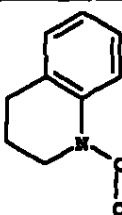
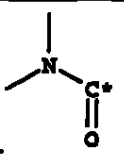
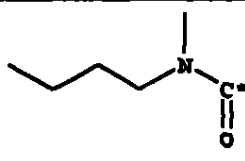
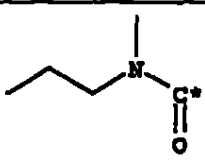
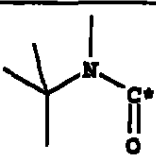
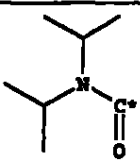
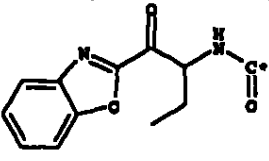
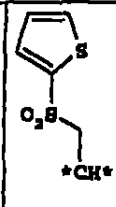
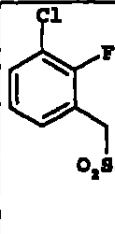
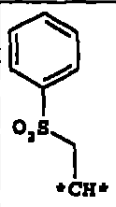
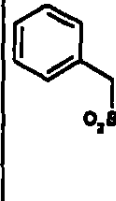
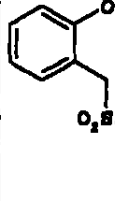
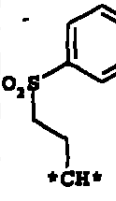
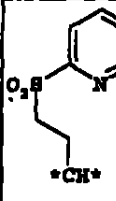
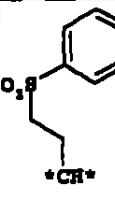
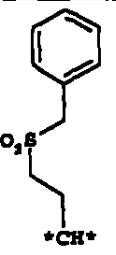
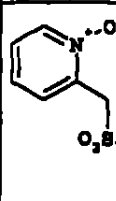
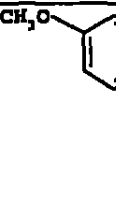
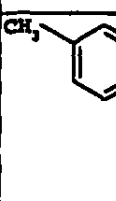
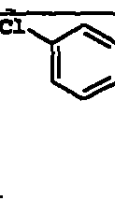
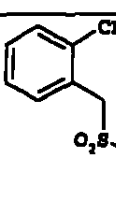
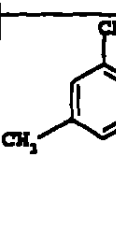
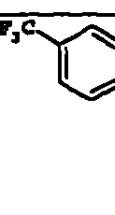
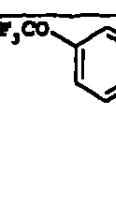
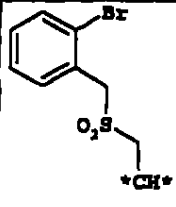
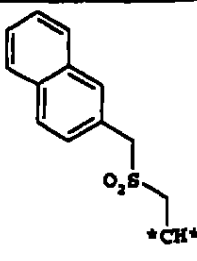
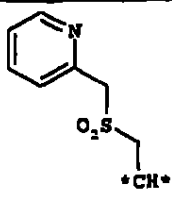
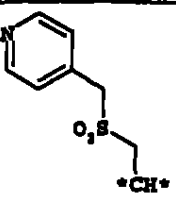
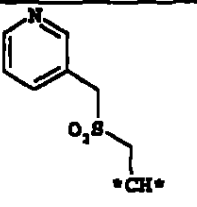
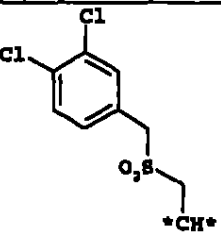
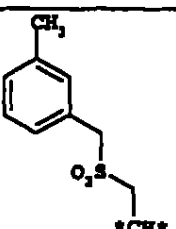
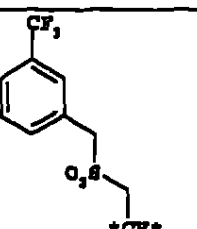
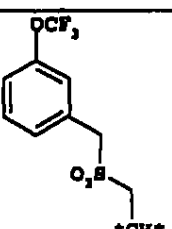
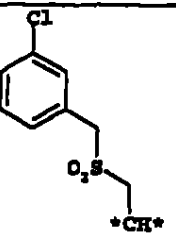
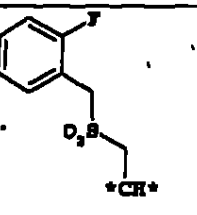
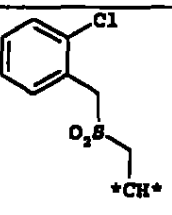
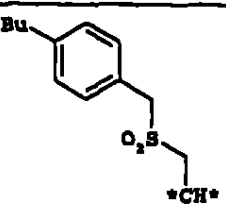
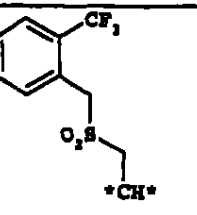
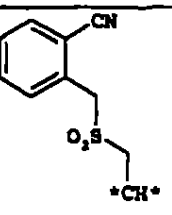
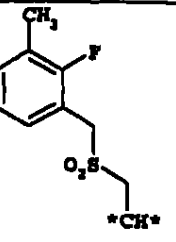
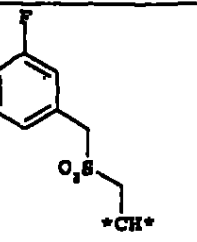
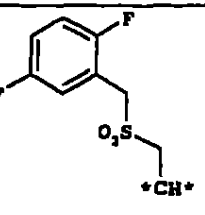
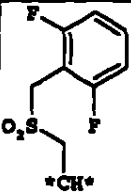
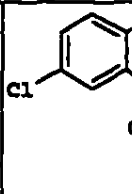
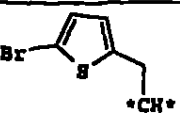
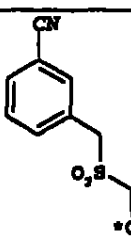
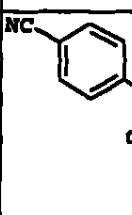
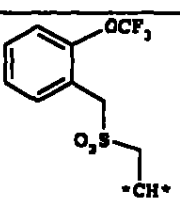
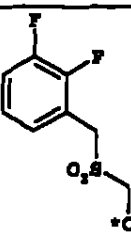
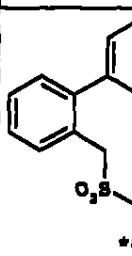
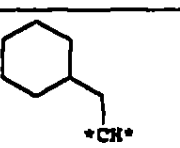
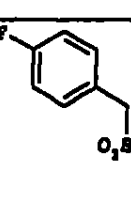
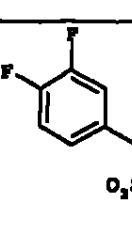
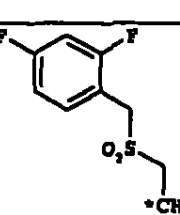
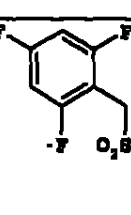
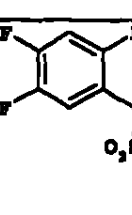
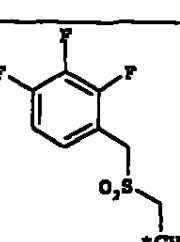
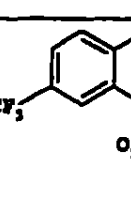
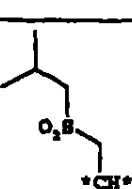
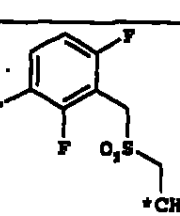
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A28		A29		A30	
A31		A32		A33	
A34		A35		A36	
A37					

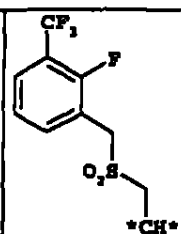
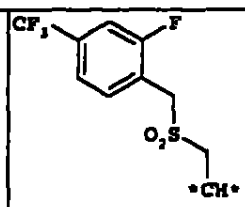
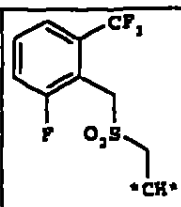
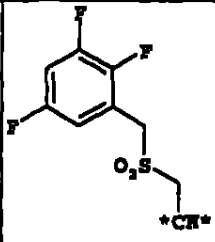
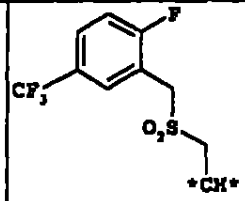
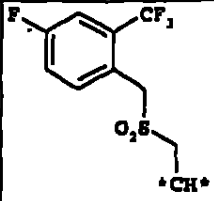
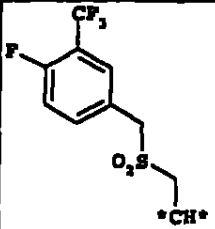
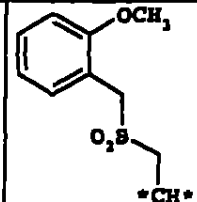
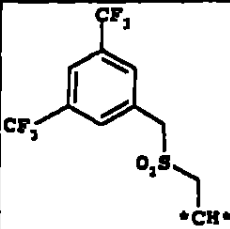
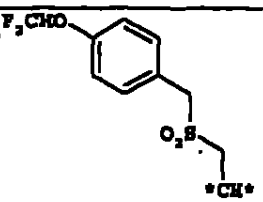
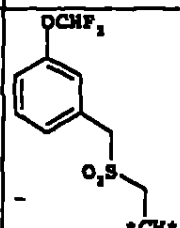
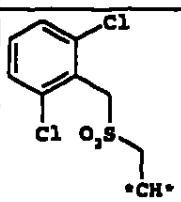
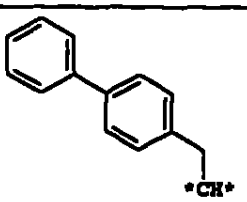
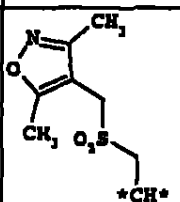
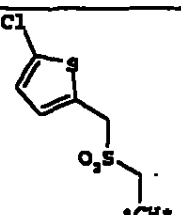
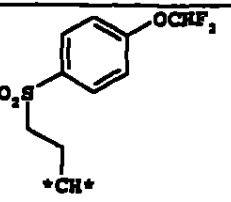
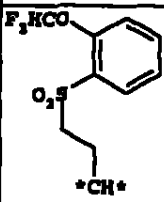
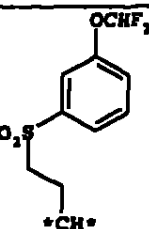
TABLE 2

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159

B1		B2		B3	
B4		B5		B6	
B7		B8		B9	
B10		B11		B12	
B13		B14		B15	
B16		B17		B18	

B19		B20		B21	
B22		B23		B24	
B25		B26		B27	
B28		B29		B30	
B31		B32		B33	
B34		B35		B36	

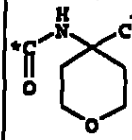
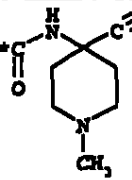
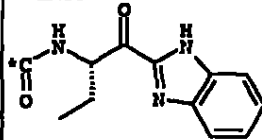
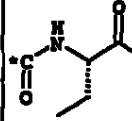
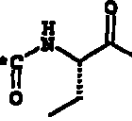
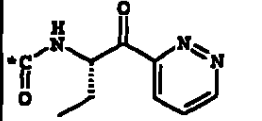
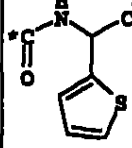
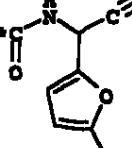
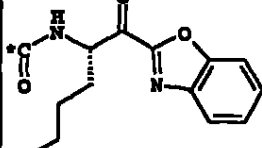
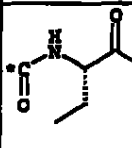
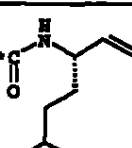
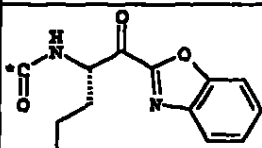
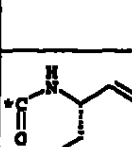
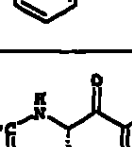
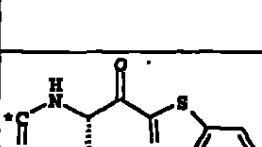
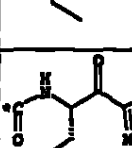
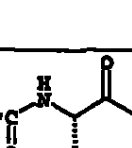
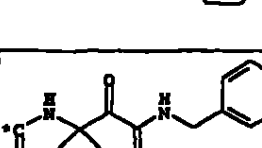
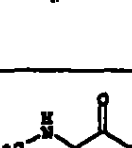
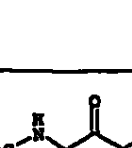
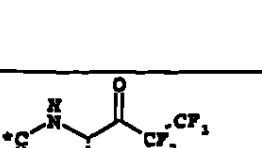
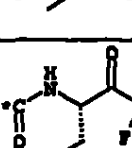
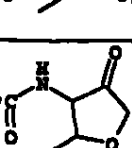
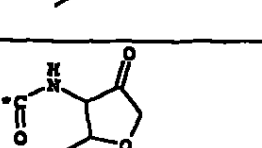
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B40		B41		B42	
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B46		B47		B48	
B49		B50		B51	
B52		B53		B54	

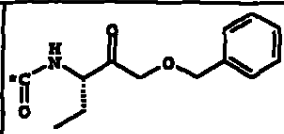
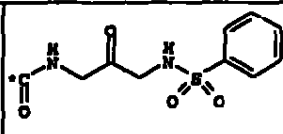
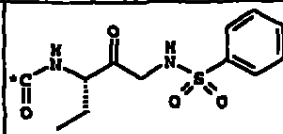
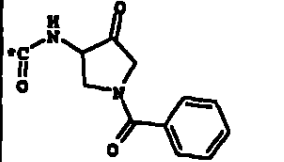
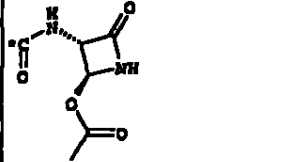
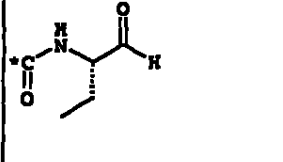
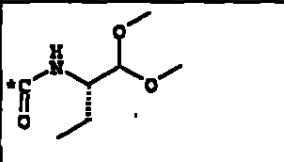
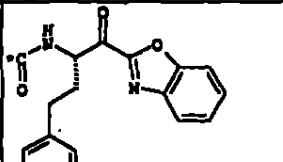
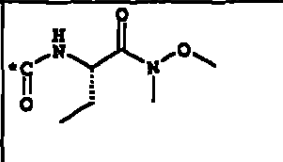
B55		B56		B57	
B58		B59		B60	
B61		B62		B63	
B64		B65		B66	
B67		B68		B69	
B70		B71		B72	

B73		B74		B75	
B76		B77		B78	
B79		B80		B81	
B82		B83		B84	
B85		B86		B87	
B88					

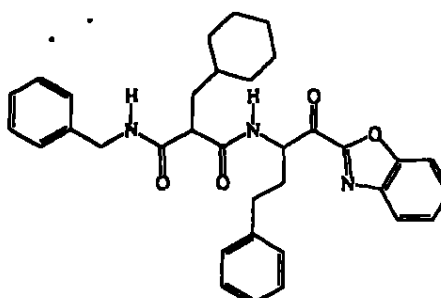
TABLE 3

C1		C2		C3	
----	--	----	--	----	--

C4		C5		C6	
C7		C8		C9	
C10		C11		C12	
C13		C14		C15	
C16		C17		C18	
C19		C20		C21	
C22		C23		C24	
C25		C26		C27	

C28		C29		C30	
C31		C32		C33	
C34		C35		C36	

Thus, for example, in table 4 the compound denoted as A2-B45-C35 is the product of the combination of group A2 in Table 1 and B45 in Table 2 and C35 in Table 3, namely N-[1-(1-benzooxazol-2-yl)-methanoyl]-3-phenyl-propyl]-N'-benzyl-2-cyclohexylmethyl-malonamide:



Further preferred are compounds of Formula I selected from a group consisting of:

2-butyl-N-cyanomethyl-N'-phenyl-malonamide (Compound 1; denoted as A1-B88-C1);

N-Cyanomethyl-2-cyclohexylmethyl-N'-phenyl-malonamide (Compound 2; denoted as A1-B45-C1);

N-Cyanomethyl-2-cyclohexylmethyl-N'-phenethyl-malonamide (Compound 3; denoted as A4-B45-C1);

- N-Cyanomethyl-2-cyclohexylmethyl-N'-pyridin-4-ylmethyl-malonamide
(Compound 4; denoted as A24-B45-C1);
- N-[1-(Benzooxazole-2-carbonyl)-3-phenyl-propyl]-N'-benzyl-2-cyclohexylmethyl-malonamide (Compound 5; denoted as A2-B45-C35);
- 5 N-Cyanomethyl-N'-cyclohexyl-2-cyclohexylmethyl-malonamide (Compound 6; denoted as A7-B45-C1);
- N-Benzyl-N'-cyanomethyl-2-cyclohexylmethyl-malonamide (Compound 7; denotes as A2-B45-C1);
- N-Cyanomethyl-2-cyclohexylmethyl-N'-(4-phenoxy-phenyl)-malonamide
10 (Compound 8; denoted as A3-B45-C1);
- N-Cyanomethyl-2-cyclohexylmethyl-N'-(3-phenyl-propyl)-malonamide
(Compound 9; denoted as A5-B45-C1);
- N-Cyanomethyl-2-cyclohexylmethyl-3-morpholin-4-yl-3-oxo-propionamide
(Compound 10; denoted as A6-B45-C1);
- 15 N-Cyanomethyl-2-cyclohexylmethyl-N'-naphthalen-1-ylmethyl-malonamide
(Compound 11; denoted as A8-B45-C1);
- N-Cyanomethyl-2-cyclohexylmethyl-N'-pyridin-3-yl-malonamide (Compound 12; denoted as A9-B45-C1);
- N-Cyanomethyl-2-cyclohexylmethyl-N',N'-diisobutyl-malonamide (Compound
20 13; denoted as A11-B45-C1);
- N-Cyanomethyl-2-cyclohexylmethyl-N',N'-diisopropyl-malonamide (Compound 14; denoted as A36-B45-C1);
- N-Cyanomethyl-2-cyclohexylmethyl-N'-(6-methoxy-pyridin-3-yl)-malonamide
(Compound 15; denoted as A10-B45-C1);
- 25 N-Cyanomethyl-2-cyclohexylmethyl-N'-(2-thiophen-2-yl-ethyl)-malonamide
(Compound 16; denoted as A13-B45-C1);
- N-Cyanomethyl-2-cyclohexylmethyl-N'-(3-phenoxy-phenyl)-malonamide
(Compound 17; denoted as A14-B45-C1);
- N-Cyanomethyl-2-cyclohexylmethyl-N'-(4-nitro-benzyl)-malonamide
30 (Compound 18; denoted as A12-B45-C1);
- N,N'-Bis-cyanomethyl-2-cyclohexylmethyl-malonamide (Compound 19;

denoted as A15-B45-C1);

N-Cyanomethyl-2-cyclohexylmethyl-N'-(5,6,7,8-tetrahydro-naphthalen-1-yl)-malonamide (Compound 20; denoted as A17-B45-C1);

N-Cyanomethyl-2-cyclohexylmethyl-N'-(2-pyridin-2-yl-ethyl)-malonamide
5 (Compound 21; denoted as A18-B45-C1);

N-Cyanomethyl-2-cyclohexylmethyl-3-(2,3-dihydro-indol-1-yl)-3-oxo-propionamide (Compound 22; denoted as A19-B45-C1);

N-Cyanomethyl-2-cyclohexylmethyl-3-(3,4-dihydro-1H-isquinolin-2-yl)-3-oxo-propionamide (Compound 23; denoted as A20-B45-C1);

10 N-Cyanomethyl-2,N'-bis-cyclohexylmethyl-malonamide (Compound 24; denoted as A21-B45-C1);

N-Cyanomethyl-2-cyclohexylmethyl-N'-(2-methoxy-benzyl)-malonamide
(Compound 25; denoted as A22-B45-C1);

N-Cyanomethyl-2-cyclohexylmethyl-N'-(1-phenyl-ethyl)-malonamide
15 (Compound 26; denoted as A23-B45-C1);

N-Benzyl-N'-cyanomethyl-2-cyclohexylmethyl-N-methyl-malonamide
(Compound 27; denoted as A25-B45-C1);

N-Cyanomethyl-2-cyclohexylmethyl-N'-(3-nitro-benzyl)-malonamide
(Compound 28; denoted as A26-B45-C1);

20 N-Cyanomethyl-2-cyclohexylmethyl-N'-(4-methoxy-benzyl)-malonamide
(Compound 29; denoted as A27-B45-C1);

N-(3-Carbamoyl-phenyl)-N'-cyanomethyl-2-cyclohexylmethyl-malonamide
(Compound 30; denoted as A28-B45-C1);

N-Cyanomethyl-2-cyclohexylmethyl-N'-pyridin-3-ylmethyl-malonamide
25 (Compound 31; denoted as A16-B45-C1);

N-(4-carbamoylphenyl)-N'-cyanomethyl-2-cyclohexylmethylmalonamide
(Compound 32; denoted as A29-B45-C1);

N-cyanomethyl-2-cyclohexylmethyl-N'-tetrahydrofur-2-ylmethylmalonamide
(Compound 33; denoted as A30-B45-C1);

30 N-cyanomethyl-2-cyclohexylmethyl-3-(3,4-dihydro-2H-quinolin-1-yl)-3-oxopropionamide (Compound 34; denoted as A31-B45-C1);

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N-tert-butyl-N'-cyanomethyl-2-cyclohexylmethyl-N-methylmalonamide

(Compound 35; denoted as A35-B45-C1);

N-cyanomethyl-2-cyclohexylmethyl-N'-methyl-N'-propylmalonamide

(Compound 36; denoted as A34-B45-C1);

5 *N-butyl-N'-cyanomethyl-2-cyclohexylmethyl-N-methylmalonamide*

(Compound 37; denoted as A33-B45-C1);

N-cyanomethyl-2-cyclohexylmethyl-N,N'-dimethylmalonamide (Compound 38;
denoted as A32-B45-C1);

10 *N-benzyl-N'-cyanomethyl-2-(2-phenylsulfonylethyl)malonamide* (Compound
39; denoted as A2-B80-C1);

2-(2-phenylsulfonylethyl)-N-benzyl-N'-cyanomethylmalonamide (Compound
40; denoted as A2-B6-C1);

*2-(2-Benzenesulfonyl-ethyl)-N-[(S)-1-(1-benzooxazol-2-yl-methanoyl)-pentyl]-
N'-benzyl-malonamide* (Compound 41; denoted as A2-B6-C12);

15 *N,N'-Bis-[(S)-1-(1-benzooxazol-2-yl-methanoyl)-propyl]-2-cyclohexylmethyl-
malonamide* (Compound 42; denoted as A37-B45-C13);

and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual
stereoisomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts
and solvates (e.g. hydrates) of such compounds and the N-oxide derivatives, prodrug
20 derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

Pharmacology and Utility:

The compounds of the invention are selective inhibitors of cathepsin S and, as
25 such, are useful for treating diseases in which cathepsin S activity contributes to the
pathology and/or symptomatology of the disease. For example, the compounds of the
invention are useful in treating autoimmune disorders, including, but not limited to,
juvenile onset diabetes, multiple sclerosis, pemphigus vulgaris, Graves' disease,
myasthenia gravis, systemic lupus erythematosus, rheumatoid arthritis and Hashimoto's
30 thyroiditis, allergic disorders, including, but not limited to, asthma, and allogeneic immune
responses, including, but not limited to, organ transplants or tissue grafts.

Cathepsin S also is implicated in disorders involving excessive elastolysis, such as

chronic obstructive pulmonary disease (e.g., emphysema), bronchiolitis, excessive airway elastolysis in asthma and bronchitis, pneumonitis and cardiovascular disease such as plaque rupture and atheroma. Cathepsin S is implicated in fibril formation and, therefore, inhibitors of cathepsins S are of use in treatment of systemic amyloidosis.

5 The cysteine protease inhibitory activities of the compounds of the invention can be determined by methods known to those of ordinary skill in the art. Suitable *in vitro* assays for measuring protease activity and the inhibition thereof by test compounds are known. Typically, the assay measures protease induced hydrolysis of a peptide based substrate. Details of assays for measuring protease inhibitory activity are set forth in
10 Examples 6-9, *infra*.

Administration and Pharmaceutical Compositions:

In general, compounds of Formula I will be administered in therapeutically effective amounts via any of the usual and acceptable modes known in the art, either singly
15 or in combination with one or more therapeutic agents. A therapeutically effective amount may vary widely depending on the severity of the disease, the age and relative health of the subject, the potency of the compound used and other factors. For example, therapeutically effective amounts of a compound of Formula I may range from about 1 micrograms per kilogram body weight ($\mu\text{g/kg}$) per day to about 1 milligram per kilogram
20 body weight (mg/kg) per day, typically from about 10 $\mu\text{g/kg/day}$ to about 0.1 mg/kg/day . Therefore, a therapeutically effective amount for a 80 kg human patient may range from about 100 $\mu\text{g/day}$ to about 100 mg/day , typically from about 1 $\mu\text{g/day}$ to about 10 mg/day . In general, one of ordinary skill in the art, acting in reliance upon personal knowledge and the disclosure of this Application, will be able to ascertain a therapeutically effective
25 amount of a compound of Formula I for treating a given disease.

The compounds of Formula I can be administered as pharmaceutical compositions by one of the following routes: oral, systemic (e.g., transdermal, intranasal or by suppository) or parenteral (e.g., intramuscular, intravenous or subcutaneous). Compositions can take the form of tablets, pills, capsules, semisolids, powders, sustained
30 release formulations, solutions, suspensions, elixirs, aerosols, or any other appropriate composition and are comprised of, in general, a compound of Formula I in combination

with at least one pharmaceutically acceptable excipient. Acceptable excipients are non-toxic, aid administration, and do not adversely affect the therapeutic benefit of the active ingredient. Such excipient may be any solid, liquid, semisolid or, in the case of an aerosol composition, gaseous excipient that is generally available to one of skill in the art.

5 Solid pharmaceutical excipients include starch, cellulose, talc, glucose, lactose, sucrose, gelatin, malt, rice, flour, chalk, silica gel, magnesium stearate, sodium stearate, glycerol monostearate, sodium chloride, dried skim milk, and the like. Liquid and semisolid excipients may be selected from water, ethanol, glycerol, propylene glycol and various oils, including those of petroleum, animal, vegetable or synthetic origin (e.g.,
10 peanut oil, soybean oil, mineral oil, sesame oil, and the like). Preferred liquid carriers, particularly for injectable solutions, include water, saline, aqueous dextrose and glycols.

The amount of a compound of Formula I in the composition may vary widely depending upon the type of formulation, size of a unit dosage, kind of excipients and other factors known to those of skill in the art of pharmaceutical sciences. In general, a
15 composition of a compound of Formula I for treating a given disease will comprise from 0.01%w to 10%w, preferably 0.3%w to 1%w, of active ingredient with the remainder being the excipient or excipients. Preferably the pharmaceutical composition is administered in a single unit dosage form for continuous treatment or in a single unit dosage form ad libitum when relief of symptoms is specifically required. Representative
20 pharmaceutical formulations containing a compound of Formula I are described in Example 10.

Chemistry:

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Processes for Making Compounds of Formula I:

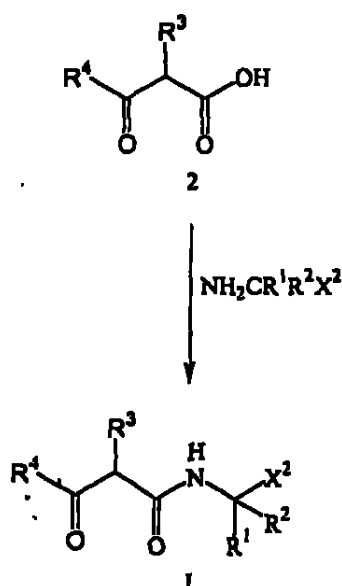
Compounds of the invention may be prepared by the application or adaptation of known methods, by which is meant methods used heretofore or described in the literature, for example those described by R.C. Larock in Comprehensive Organic Transformations,
30 VCH publishers, 1989.

In the reactions described hereinafter it may be necessary to protect reactive functional groups, for example hydroxy, amino, imino, thio or carboxy groups, where these

are desired in the final product, to avoid their unwanted participation in the reactions. Conventional protecting groups may be used in accordance with standard practice, for examples see T.W. Greene and P. G. M. Wuts in "Protective Groups in Organic Chemistry" John Wiley and Sons, 1991.

- 5 Compounds of Formula I, where X^1 is $-NHC(R^1)(R^2)X^2$, can be prepared by proceeding as in the following Reaction Scheme 1:

Reaction Scheme 1



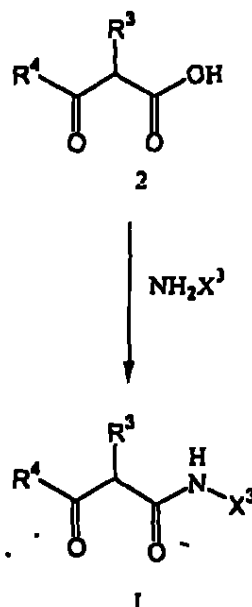
in which X^1 , R^1 , R^2 , R^3 and R^4 are as defined in the Summary of the Invention.

- 10 Compounds of Formula I can be prepared by condensing an acid of Formula 2 with a compound of formula NH₂CR¹R²X². The condensation reaction can be effected with an appropriate coupling agent (e.g., benzotriazol-1-yloxytrispyrrolidino-phosphonium hexafluorophosphate (PyBOP®), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI), *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium
- 15 hexafluorophosphate (HBTU), 1,3-dicyclohexyl-carbodiimide (DCC), or the like) and optionally an appropriate catalyst (e.g., 1-hydroxybenzotriazole (HOBt), 1-hydroxy-7-azabenzotriazole (HOAt), or the like) and non-nucleophilic base (e.g., *N*-methylmorpholine, triethylamine, or the like, or any suitable combination thereof) in a suitable solvent (*N*-methylpyrrolidinone, or the like) at ambient temperature and requires

3 to 10 hours to complete the reaction. A detailed description for the synthesis of a compound of Formula I by the processes in Reaction Scheme 1 is set forth in the Examples, *infra*.

Compounds of Formula I, where X^1 is $-NHX^3$, can be prepared by proceeding
5 as in the following Reaction Scheme 2:

Reaction Scheme 2



in which X^3 , R^3 and R^4 are as defined in the Summary of the Invention.

10 Compounds of Formula I can be prepared by condensing an acid of Formula 2 with a compound of formula NH_2X^3 . The condensation reaction can be effected with an appropriate coupling agent (e.g., benzotriazol-1-yloxytrispyrrolidino-phosphonium hexafluorophosphate (PyBOP®), 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide hydrochloride (EDCI), *O*-benzotriazol-1-yl-*N,N,N',N'*-tetramethyluronium
15 hexafluorophosphate (HBTU), 1,3-dicyclohexyl-carbodiimide (DCC), or the like) and optionally an appropriate catalyst (e.g., 1-hydroxybenzotriazole (HOBt), 1-hydroxy-7-azabenzotriazole (HOAt), or the like) and non-nucleophilic base (e.g., *N*-methylmorpholine, triethylamine, or the like, or any suitable combination thereof) in a suitable solvent (*N*-methylpyrrolidinone, or the like) at ambient temperature and requires

3 to 10 hours to complete the reaction. A detailed description for the synthesis of a compound of Formula I by the processes in Reaction Scheme 1 is set forth in the Examples, *infra*.

5 Additional Processes for Preparing Compounds of Formula I:

A compound of Formula I can be prepared as a pharmaceutically acceptable acid addition salt by reacting the free base form of the compound with a pharmaceutically acceptable inorganic or organic acid. Alternatively, a pharmaceutically acceptable base addition salt of a compound of Formula I can be prepared by reacting the free acid form
10 of the compound with a pharmaceutically acceptable inorganic or organic base. Inorganic and organic acids and bases suitable for the preparation of the pharmaceutically acceptable salts of compounds of Formula I are set forth in the definitions section of this Application. Alternatively, the salt forms of the compounds of Formula I can be prepared using salts of the starting materials or intermediates.

15 The free acid or free base forms of the compounds of Formula I can be prepared from the corresponding base addition salt or acid addition salt form. For example, a compound of Formula I in an acid addition salt form can be converted to the corresponding free base by treating with a suitable base (e.g., ammonium hydroxide solution, sodium hydroxide, and the like). A compound of Formula I in a base addition salt form can be
20 converted to the corresponding free acid by treating with a suitable acid (e.g., hydrochloric acid, etc).

The *N*-oxides of compounds of Formula I can be prepared by methods known to those of ordinary skill in the art. For example, *N*-oxides can be prepared by treating an unoxidized form of the compound of Formula I with an oxidizing agent (e.g.,
25 trifluoroperacetic acid, permaleic acid, perbenzoic acid, peracetic acid, *meta*-chloroperoxybenzoic acid, or the like) in a suitable inert organic solvent (e.g., a halogenated hydrocarbon such as dichloromethane) at approximately 0°C. Alternatively, the *N*-oxides of the compounds of Formula I can be prepared from the *N*-oxide of an appropriate starting material.

30 Compounds of Formula I in unoxidized form can be prepared from *N*-oxides of compounds of Formula I by treating with a reducing agent (e.g., sulfur, sulfur dioxide,

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triphenyl phosphine, lithium borohydride, sodium borohydride, phosphorus trichloride, tribromide, or the like) in an suitable inert organic solvent (e.g., acetonitrile, ethanol, aqueous dioxane, or the like) at 0 to 80°C.

5 Prodrug derivatives of the compounds of Formula I can be prepared by methods known to those of ordinary skill in the art (e.g., for further details see Saulnier *et al.* (1994), *Bioorganic and Medicinal Chemistry Letters*, Vol. 4, p. 1985). For example, appropriate prodrugs can be prepared by reacting a non-derivatized compound of Formula I with a suitable carbamylating agent (e.g., 1,1-acyloxyalkylcarbonochloridate, *para*-nitrophenyl carbonate, or the like).

10 Protected derivatives of the compounds of Formula I can be made by means known to those of ordinary skill in the art. A detailed description of the techniques applicable to the creation of protecting groups and their removal can be found in T.W. Greene, *Protecting Groups in Organic Synthesis*, 3rd edition, John Wiley & Sons, Inc. 1999.

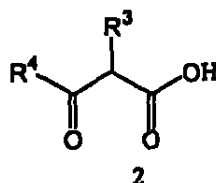
15 Compounds of the present invention may be conveniently prepared, or formed during the process of the invention, as solvates (e.g. hydrates). Hydrates of compounds of the present invention may be conveniently prepared by recrystallisation from an aqueous/organic solvent mixture, using organic solvents such as dioxin, tetrahydrofuran or methanol.

Compounds of Formula I can be prepared as their individual stereoisomers by reacting a racemic mixture of the compound with an optically active resolving agent to form a pair
20 of diastereoisomeric compounds, separating the diastereomers and recovering the optically pure enantiomer. While resolution of enantiomers can be carried out using covalent diastereomeric derivatives of compounds of Formula I, dissociable complexes are preferred (e.g., crystalline diastereoisomeric salts). Diastereomers have distinct physical properties (e.g., melting points, boiling points, solubilities, reactivity, etc.) and can be readily
25 separated by taking advantage of these dissimilarities. The diastereomers can be separated by chromatography or, preferably, by separation/resolution techniques based upon differences in solubility. The optically pure enantiomer is then recovered, along with the resolving agent, by any practical means that would not result in racemization. A more detailed description of the techniques applicable to the resolution of stereoisomers of
30 compounds from their racemic mixture can be found in Jean Jacques Andre Collet, Samuel H. Wilen, *Enantiomers, Racemates and Resolutions*, John Wiley & Sons, Inc. (1981).

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In summary, the compounds of Formula I are made by a process which comprises:

- (A) reacting a compound of Formula 2:



- 5 with a compound of formula $\text{NH}_2\text{CR}^1\text{R}^2\text{X}^2$, in which R^1 , R^2 , R^3 , R^4 and X^2 are as defined in the Summary of the Invention for Formula I; or
- (B) reacting a compound of Formula 2 with a compound of Formula NH_2X^3 , in which R^1 , R^4 and X^3 are as described in the Summary of the Invention for Formula I; and
- 10 (C) optionally converting a compound of Formula I into a pharmaceutically acceptable salt;
- (D) optionally converting a salt form of a compound of Formula I to non-salt form;
- (E) optionally converting an unoxidized form of a compound of Formula I into a pharmaceutically acceptable *N*-oxide;
- 15 (F) optionally converting an *N*-oxide form of a compound of Formula I its unoxidized form;
- (G) optionally resolving an individual isomer of a compound of Formula I from a mixture of isomers;
- (H) optionally converting a non-derivatized compound of Formula I into a
- 20 pharmaceutically prodrug derivative; and
- (I) optionally converting a prodrug derivative of a compound of Formula I to its non-derivatized form.

Examples:

- 25 The present invention is further exemplified, but not limited by, the following examples that illustrate the preparation of compounds of Formula I (Examples) and intermediates (References) according to the invention.

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REFERENCE 1

2-Phenylcarbamoyl-hexanoic acid

A solution of aniline (5.47 ml, 60 mmol) and triethylamine (8.36 ml, 60 mmol) in methylene chloride (150 ml) was cooled to -20°C and treated with methylmalonylchloride (8.36 ml, 60mmol) in methylene chloride (20 ml). The reaction mixture was allowed to warm to ambient temperature for 3 hours and then poured into cold 1N HCl. The organic layer was separated and washed with aqueous sodium bicarbonate then brine and dried over magnesium sulfate and evaporated to give methyl 2-phenylcarbamoylacetate.

A mixture of methyl 2-phenylcarbamoylacetate (1.159g, 6 mmol) lithium hydroxide (0.43g, 18 mmol) and 1-iodobutane (0.91 ml, 8 mmol) in *N*-methylpyrrolidinone (10 ml) was stirred at ambient temperature for 1.5 hours. The reaction mixture was poured into ice water, extracted with ethylacetate (twice, 50 ml each). The combined extracts were washed with brine, dried over magnesium sulfate and evaporated. The residue was purified by flash chromatography on silica gel eluting with 20% ethylacetate/hexane to give methyl 2-phenylcarbamoylhexanoate (0.715g, 48% yield).

A solution of methyl 2-phenylcarbamoylhexanoate (0.98g 3.9 mmol) in methanol (10 ml) was treated with sodium hydroxide (4 ml, 4 mmol) at ambient temperature for 17 hours. The methanol was removed under reduced pressure and the residue was treated with 1N HCl and extracted with ethylacetate (twice, 50 ml each). The organic layers were washed with brine, dried over magnesium sulfate and evaporated to give 2-phenylcarbamoylhexanoic acid (0.68 g, 2.9 mmol, 74% yield):

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REFERENCE 2

2-Cyclohexylmethyl-N-phenyl-malonamic acid

A mixture of methyl 2-phenylcarbamoylacetate (prepared as in reference Example 1) (4.39 g, 22.7 mmol), lithium hydroxide (1.08 g, 45 mmol) and bromomethylcyclohexane (3.76 ml, 27 mmol), in *N*-methylpyrrolidinone (25 ml) was stirred at ambient temperature

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for 17 hours. The reaction mixture was poured into ice water and extracted with ether (three times, 100 ml each). The extracts were washed with water then brine, dried over magnesium sulfate and evaporated. The residue was purified by flash chromatography on silica gel eluting with 10% ethylacetate (hexane) to give methyl 2-cyclohexylmethyl-*N*-phenyl malonamate (1.89 g, 6.5 mmol, 29% yield). The aqueous layer above was cooled on ice and acidified to pH 2 with 1N HCl. The aqueous layer was extracted with ether (3 times, 100 ml each) and the extracts were washed with water, then brine, dried over magnesium sulfate and evaporated to give 2-cyclohexylmethyl-*N*-phenyl malonamic acid (1.12 g, 18% yield).

10

REFERENCE 3

2-Cyclohexylmethyl-*N*-phenethyl-malonamic acid

Sodium (6.9 g, 0.3 mol), dissolved in ethanol (300 ml), and then diethylmalonate (50.3 ml, 0.3 mol) was added. Bromomethylcyclohexane (46 ml, 0.33 mol) was added and the reaction mixture was heated at 70°C for 14 hours. The reaction mixture was cooled and the ethanol removed by evaporation. The resulting mass was dissolved in ice water and then extracted with ethylacetate. The organic layers were washed with water, then brine and dried over magnesium sulfate. The solvents were removed under reduced pressure to give diethylcyclohexyl malonate.

A solution of diethylcyclohexylmalonate (12.8 g, 0.05 mol) in ethanol (100 ml) was treated with a solution of lithium hydroxide (1.2 g, 0.05 moles) in water (50 ml) and then stirred at ambient temperature for 15 hours. The ethanol was removed at reduced pressure and water (50 ml) was added to the residue. The reaction mixture was extracted with ether, cooled on ice and acidified to pH 1.5 with HCl. The aqueous phase was saturated with NaCl and extracted with ethylacetate (twice, 150 ml each). Drying over magnesium sulfate and evaporating the solvent gave ethyl 2-cyclohexylmalonate (8.52 g, 37 mmol, 74% yield).

The ethyl 2-cyclohexylmalonate (8.52 g, 37 mmol) in ethylacetate (80 ml) was cooled to 0° C and treated with dimethylformamide (50 µL) and then oxalylchloride (3.93 ml, 45 mmol). The reaction temperature was raised to room temperature and after 2 hours the

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solvents were removed under reduced pressure to give ethyl 2-cyclohexylmalonyl chloride.

The malonylchloride above was diluted to 28 ml volume with ethylacetate and 2 ml of that solution was added to a solution of phenethylamine (0.376 ml, 3 mmol) and *N*-methylmorpholine (0.40 g, 4 mmol) in ethylacetate (4 ml) at -20°C. After 15 minutes the reaction mixture was allowed to warm to ambient temperature overnight. The reaction mixture was diluted with ethylacetate (5 ml) and ice water (5 ml). The organic layer was separated and washed with cold 0.05 N HCl, then aqueous NaHCO₃, then brine, dried over magnesium sulfate and evaporated under reduced pressure. The residue was purified by radial chromatography to give ethyl 2-cyclohexylmethyl-*N*-phenethyl malonamate (0.366 g, 1.10 mmol, 42% yield).

The ester above (0.366 g, 1.10 mmol) in ethanol (10 ml) was treated at ambient temperature with aqueous sodium hydroxide (1.3 ml of 1N) for 2.5 hours. The reaction mixture was diluted with water (30 ml) and washed with ether (3 times, 30 ml each). The aqueous layer was cooled, acidified with 1N HCl (2 ml) and extracted with ethylacetate (3 times, 30 ml each). The ethylacetate extracts were washed with brine, dried over magnesium sulfate and evaporated to give 2-cyclohexylmethyl-*N*-phenethyl malonamic acid (0.138 g, 0.46 mmol, 42% yield).

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REFERENCE 4

2-Cyclohexylmethyl-*N*-pyridin-4-ylmethyl-malonamic acid

Ethyl 2-cyclohexylmethylmalonyl chloride, prepared as in Reference 3 (0.307 g, 1.25 mmol), was condensed with 4-aminomethyl pyridine using the method of Reference 3 to give ethyl 2-cyclohexylmethyl-4-pyridin-4-ylmethylmalonamate (0.237 g, 0.74 mmol, 58% yield).

This ester was hydrolyzed with sodium hydroxide using the method of Reference 3 to give 2-cyclohexylmethyl-*N*-pyridin-4-ylmethylmalonamic acid (0.041 g, 0.14 mmol, 19% yield).

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Proceeding as in the above referenced examples provided the following compounds:

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- N*-Benzyl-2-cyclohexylmethyl-malonamic acid;
2-Cyclohexylmethyl-*N*-(4-phenoxy-phenyl)-malonamic acid;
2-Cyclohexylmethyl-*N*-(3-phenyl-propyl)-malonamic acid;
2-Cyclohexylmethyl-3-morpholin-4-yl-3-oxo-propionic acid;
5 *N*-Cyclohexyl-2-cyclohexylmethyl-malonamic acid;
2-Cyclohexylmethyl-*N*-naphthalen-1-ylmethyl-malonamic acid;
2-Cyclohexylmethyl-*N*-pyridin-3-yl-malonamic acid;
2-Cyclohexylmethyl-*N,N*-diisobutyl-malonamic acid;
2-Cyclohexylmethyl-*N*-(6-methoxy-pyridin-3-yl)-malonamic acid;
10 2-Cyclohexylmethyl-*N*-(2-thiophen-2-yl-ethyl)-malonamic acid;
2-Cyclohexylmethyl-*N*-(3-phenoxy-phenyl)-malonamic acid;
2-Cyclohexylmethyl-*N*-(4-nitro-benzyl)-malonamic acid;
N-Cyanomethyl-2-cyclohexylmethyl-malonamic acid;
2-Cyclohexylmethyl-*N*-(5,6,7,8-tetrahydro-naphthalen-1-yl)-malonamic acid;
15 2-Cyclohexylmethyl-*N*-(2-pyridin-2-yl-ethyl)-malonamic acid;
2-Cyclohexylmethyl-3-(2,3-dihydro-indol-1-yl)-3-oxo-propionic acid;
2-Cyclohexylmethyl-3-(3,4-dihydro-1*H*-isoquinolin-2-yl)-3-oxo-propionic acid;
2,*N*-Bis-cyclohexylmethyl-3-oxo-butyramide;
2-Cyclohexylmethyl-*N*-(2-methoxy-benzyl)-3-oxo-butyramide;
20 2-Cyclohexylmethyl-*N*-(1-phenyl-ethyl)-malonamic acid;
N-Benzyl-2-cyclohexylmethyl-*N*-methyl-malonamic acid;
2-Cyclohexylmethyl-*N*-(3-nitro-benzyl)-3-oxo-butyramide;
2-Cyclohexylmethyl-*N*-(4-methoxy-benzyl)-malonamic acid;
N-(3-Carbamoyl-phenyl)-2-cyclohexylmethyl-malonamic acid;
25 2-Cyclohexylmethyl-*N*-pyridin-3-ylmethyl-malonamic acid;
N-(4-Carbamoyl-phenyl)-2-cyclohexylmethyl-malonamic acid;
2-Cyclohexylmethyl-*N*-(tetrahydro-furan-2-ylmethyl)-malonamic acid;
2-Cyclohexylmethyl-3-(3,4-dihydro-2*H*-quinolin-1-yl)-3-oxo-propionic acid;
N-*tert*-Butyl-2-cyclohexylmethyl-*N*-methyl-malonamic acid;
30 2-Cyclohexylmethyl-*N*-methyl-*N*-propyl-malonamic acid;
N-Butyl-2-cyclohexylmethyl-*N*-methyl-malonamic acid;

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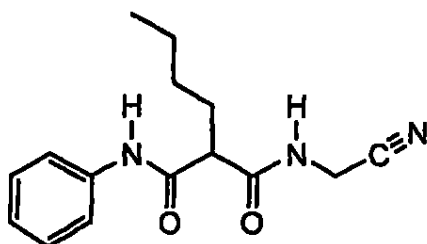
2-Cyclohexylmethyl-*N,N*-dimethyl-malonamic acid;
(*R*)-2-Benzylcarbamoyl-4-phenylsulfanyl-butyrac acid; and
4-Benzenesulfonyl-2-benzylcarbamoyl-butyrac acid;

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EXAMPLE 1

2-butyl-*N*-cyanomethyl-*N'*-phenylmalonamide

(Compound 1)

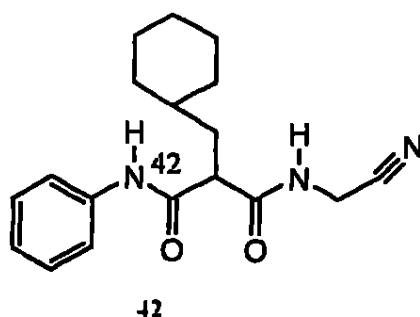


- 10 A solution comprised of 2-Phenylcarbamoyl-hexanoic acid (188g, 0.8mmol), prepared as in Reference 1, in DMF (5.0mL) was treated with PyBOP® (425 0.8mmol), aminoacetonitrile bisulfate (140mg, 0.9 mmol) and triethylamine (600μL, 4.3mmol). The mixture was stirred for 3 hours and then partitioned between water (20 mL) and ethyl acetate (50 mL). The organic layer was separated and washed with 1 M saturated sodium bicarbonate solution, 1 M hydrochloric acid solution and water, dried (MgSO₄) and concentrated. Product was purified from the residue by flash column on silica gel (60°A) with 50% ethyl acetate in hexane to provide 2-butyl-*N*-cyanomethyl-*N'*-phenylmalonamide (125 mg, 57% yield). . ¹H NMR: (DMSO) 10.01 (s, 1H), 7.59 (d, J=8Hz, 2H), 7.31 (t, J=7Hz, 2H), 7.06 (t, J=7Hz, 1H), 4.13 (d, J=6Hz, 2H), 3.32 (t, J=8Hz, 1H), 1.80 (m, 2H), 1.25 (m, 4H), 0.86 (t, J=7Hz, 3H). MS: m/e 273.9.
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EXAMPLE 2

N-Cyanomethyl-2-cyclohexylmethyl-*N'*-phenyl-malonamide

(Compound 2);



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A solution comprised of 2-Cyclohexylmethyl-*N*-phenyl-malonamic acid (350 mg, 1.2 mmol), prepared as in Reference 2, EDCI (250 mg, 1.3 mmol), HOBt hydrate (199 mg, 1.3 mmol), amino acetonitrile bisulfate (200 mg, 1.3 mmol) and *N*-methylmorpholine (0.30 ml, 2.7 mmol) in *N,N*-dimethylpyrrolidinone (5 ml) was stirred at ambient temperature for 15 hours. The reaction mixture was poured into cold 1*N* HCl and extracted with ethylacetate. The organic phase was washed with aqueous saturated sodium bicarbonate and then brine (50 ml each) dried over magnesium sulfate and evaporated. The residue was purified by radial chromatography using 50% ethylacetate/hexane as eluent to provide

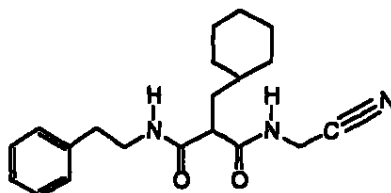
10 *N*-Cyanomethyl-2-cyclohexylmethyl-*N'*-phenyl-malonamide (179 mg, 48% yield). ¹H NMR: (DMSO) 10.01 (s, 1H), 8.47 (t, *J*=5Hz, 1H), 7.59 (d, *J*=7Hz, 2H), 7.31 (t, *J*=8Hz, 2H), 7.07 (t, *J*=7Hz, 1H), 4.13 (d, *J*=5Hz, 2H), 3.47 (t, *J*=7Hz, 1H), 1.6 (m, 7H), 1.1 (m, 4H), 0.9 (m, 2H). MS: *m/e* 313.2.

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EXAMPLE 3

N-cyanomethyl-2-cyclohexylmethyl-*N'*-phenethylmalonamide

(Compound 3)



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A solution comprised of 2-Cyclohexylmethyl-*N*-phenethyl-malonic acid (138 mg, 0.46 mmol), prepared as in Reference 3, EDCI (115 mg, 0.60 mmol), HOBt hydrate (92 mg, 0.60 mmol), *N*-methylmorpholine (0.115 ml, 1.38 mmol) in *N,N*-dimethyl pyrrolidimone (4 ml) was stirred at ambient temperature for 10 min. Aminoacetonitrile

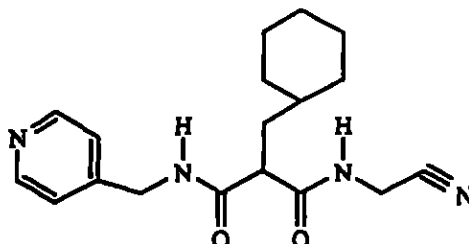
25 bisulfate (106 mg, 0.69 mmol) was added. The reaction mixture was stirred at ambient temperature for 2 hours, then poured into cold 1*N* HCl and extracted twice with ethylacetate (50 ml each). The organic phase was washed with aqueous sodium bicarbonate and then brine (50 ml each), dried over magnesium sulfate and evaporated.

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The residue was purified by radial chromatography using 50% ethylacetate/hexane as eluent to provide *N*-cyanomethyl-2-cyclohexylmethyl-*N'*-phenethylmalonamide (56 mg, 36% yield). ¹H NMR: (DMSO) 8.38 (t, J=5Hz, 1H), 7.98 (t, J=6Hz, 1H), 7.25 (m, 5H), 4.10 (d, J=6Hz, 2H), 3.2 (m, 3H), 2.71 (t, J=7Hz, 2H), 1.6 (m, 7H), 1.1 (m, 4H), 0.85 (m, 2H). MS: m/e 342.10.

EXAMPLE 4

N-cyanomethyl-2-cyclohexylmethyl-*N'*-pyrid-4-ylmethylmalonamide
(Compound 4)



10

A solution comprised of 2-Cyclohexylmethyl-*N*-pyridin-4-ylmethyl-malonic acid (41 mg, 0.14 mmol), prepared as in Reference 4, was coupled to aminoacetonitrile as described in Example 3 to provide *N*-cyanomethyl-2-cyclohexylmethyl-*N'*-pyrid-4-ylmethylmalonamide (13 mg, 28% yield). ¹H NMR: (DMSO) 8.5 (m, 4H), 7.20 (d, J=6Hz, 2H), 4.3 (m, 2H), 4.13 (d, J=5Hz, 2H), 3.3 (m, 1H), 1.6 (m, 7H), 1.1 (m, 4H), 0.83 (m, 2H). MS: m/e 329.08.

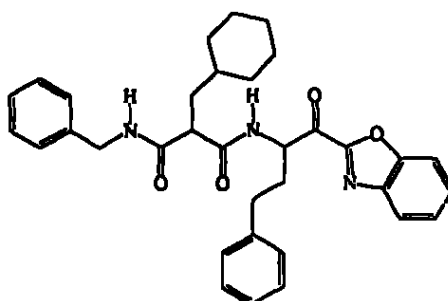
15

EXAMPLE 5

N-[1-(1-Benzooxazol-2-yl-methanoyl)-3-phenyl-propyl]-*N'*-benzyl-2-cyclohexylmethyl-malonamide
(Compound 5)

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A mixture of *N*-benzyl-2-cyclohexylmethyl-malonamic acid (200mg, 0.69mmol), HOBt (159mg, 1.04mmol), EDC (146mg, 0.76mmol), 2-amino-1-benzooxazol-2-yl-4-phenyl-butan-1-one (195mg, 0.69mmol), dichloromethane (3mL) and triethylamine (106μL, 0.76mmol) was allowed to stir 2 hour. The product was extracted into ethyl acetate (60mL) and washed with two 15mL portions of 1N HCl, and two 15mL portions of saturated NaHSO₃, dried over MgSO₄ and concentrated. Ethyl acetate (5mL) was added and a white precipitate formed and was collected to give *N*-[1-(1-benzooxazol-2-yl-1-hydroxy-methyl)-3-phenyl-propyl]-*N'*-benzyl-2-cyclohexylmethyl-malonamide (81mg, 0.12mmol, 21% yield).

N-[1-(1-Benzooxazol-2-yl-1-hydroxy-methyl)-3-phenyl-propyl]-*N'*-benzyl-2-cyclohexylmethyl-malonamide (70mg, 0.126mmol) was dissolved in 0.6mL dichloromethane and treated with Dess Martin periodinane (107mg, 0.253mmol). The mixture was stirred for 2 hours, then 8mL of 0.26M Na₂S₂O₃ in saturated NaHSO₃ was added and the mixture was extracted with two 15mL portions of ethyl acetate and washed with two 4mL portions of saturated NaHSO₃. The organic layer was dried over MgSO₄ and concentrated. The product was recrystallized from ethyl acetate and hexane to give *N*-[1-(1-Benzooxazol-2-yl-methanoyl)-3-phenyl-propyl]-*N'*-benzyl-2-cyclohexylmethyl-malonamide (40mg, 0.072mmol, 57% yield); ¹H NMR: (DMSO) 7.88 (m, 1H), 7.68-7.40 (m, 3H), 7.35-7.10 (m, 10H), 6.90 (m, 1H), 5.65 (m, 1H), 4.43 (d, J=5.7Hz, 2H), 3.25 (m, 1H), 2.74 (t, J=8.0Hz, 1H), 2.46 (m, 1H), 2.17 (m, 1H), 1.77 (t, J=7.4Hz, 1H), 1.64 (m, 7H), 1.22 (m, 4H), 0.87 (m, 2H); MS: (M⁺+1) 552.8; 551.68.

The following compounds of Formula I were provided by proceeding as in the above Examples:

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N-cyanomethyl-N'-cyclohexyl-2-cyclohexylmethylmalonamide (Compound 6); ¹H NMR(DMSO): 8.31 (t, J=6Hz, 1H), 7.82 (d, J=8Hz, 1H), 4.10 (d, J=8Hz, 2H), 3.52 (m, 1H), 3.20 (t, J=7Hz, 1H), 1.6 (m, 12H), 1.1 (m, 9H), 0.83 (m, 2H); MS (m/e) = 320.11;

N-benzyl-N'-cyanomethyl-2-cyclohexylmethylmalonamide (Compound 7); ¹H NMR(DMSO): 8.45 (m, 2H), 7.3 (m, 5H), 4.33 (dd, J=6,15Hz, 1H), 4.23 (dd, J=6,15Hz, 1H), 4.12 (d, 2H), 3.3 (m, 1H), 1.6 (m, 7H), 1.1 (m, 4H), 0.85 (m, 2H); MS (m/e) = 328.15, M.Wt. = 327.43;

N-cyanomethyl-2-cyclohexylmethyl-N'-(4-phenoxyphenyl)malonamide (Compound 8); ¹H NMR(DMSO): 10.1 (s, 1H), 8.50 (t, J=5Hz, 1H), 7.61 (d, J=7Hz, 2H), 7.37 (t, J=7Hz, 2H), 7.11 (t, J=7Hz, 1H), 7.0 (m, 4H), 4.14 (d, J=5Hz, 2H), 3.47 (t, J=7Hz, 1H), 1.7 (m, 7H), 1.1 (m, 4H), 0.92 (m, 2H); MS (m/e) = 406.10, M.Wt. = 405.49;

N-cyanomethyl-2-cyclohexylmethyl-N'-(3-phenylpropyl)malonamide (Compound 9); ¹H NMR(DMSO): 8.38 (t, J=6Hz, 1H), 8.00 (t, J=6Hz, 1H), 7.2 (m, 5H), 4.10 (d, J=5Hz, 2H), 3.23 (t, J=7Hz, 1H), 3.1 (m, 2H), 2.5 (m, 2H), 1.6 (m, 9H), 1.1 (m, 4H), 0.85 (m, 2H); MS (m/e) = 356.02;

N-cyanomethyl-2-cyclohexylmethyl-3-morpholin-4-yl-3-oxopropionamide (Compound 10); ¹H NMR(DMSO): 8.54 (t, J=4Hz, 1H), 4.12 (d, J=5Hz, 2H), 3.5 (m, 8H), 1.65 (m, 8H), 1.15 (m, 4H), 0.85 (m, 2H); MS (m/e) = 308.05;

N-cyanomethyl-2-cyclohexylmethyl-N'-naphth-1-ylmethylmalonamide (Compound 11); ¹H NMR(DMSO): 8.53 (t, J=5Hz, 1H), 8.43 (t, J=6Hz, 1H), 8.04 (m, 1H), 7.94 (m, 1H), 7.86 (d, J=8Hz, 1H), 7.5 (m, 4H), 4.85 (dd, J=6,15Hz, 1H), 4.65 (dd, J=5,15Hz, 1H), 4.12 (d, J=3Hz, 2H), 3.3 (m, 1H), 1.6 (m, 8H), 1.0 (m, 5H); MS (m/e) = 378.18, M.Wt. 377.18;

N-cyanomethyl-2-cyclohexylmethyl-N'-pyrid-3-ylmalonamide (Compound 12); ¹H NMR(DMSO): 10.24 (s, 1H), 8.75 (s, 1H), 8.54 (t, J=5Hz, 1H), 8.29 (d, J=5Hz, 1H), 8.04 (d, J=7Hz, 1H), 7.36 (m, 1H), 4.13 (d, J=5Hz, 2H), 3.49 (t, J=7Hz, 1H), 1.7 (m, 7H), 1.1 (m, 4H), 0.9 (m, 2H); MS (m/e) = 314.91;

N-cyanomethyl-2-cyclohexylmethyl-N',N'-diisobutylmalonamide (Compound 13); ¹H NMR(DMSO): 8.50 (t, J=4Hz, 1H), 4.09 (m, 2H), 3.63 (t, J=7Hz, 1H), 3.2 (m, 2H), 3.05 (m, 2H), 1.9 (m, 2H), 1.6 (m, 7H), 1.1 (m, 4H), 0.8 (m, 14H); MS (m/e) = 350.08, M.Wt. 349.51;

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- N*-cyanomethyl-2-cyclohexylmethyl-*N,N*-diisopropylmalonamide (Compound 14);
¹H NMR(DMSO): 8.45 (t, J=5Hz, 1H), 4.1 (m, 3H), 3.55 (t, J=7Hz, 1H), 3.46 (m, 1H), 1.6 (m, 7H), 1.27 (d, J=7Hz, 6H), 1.11 (m, 10H), 0.85 (m, 2H); MS (m/e) = 321.99, M.Wt. 321.24;
- 5 *N*-cyanomethyl-2-cyclohexylmethyl-*N'*-(6-methoxypyrid-3-yl)malonamide
(Compound 15); ¹H NMR(DMSO): 10.04 (s, 1H), 8.50 (t, J=5Hz, 1H), 8.35 (s, 1H), 7.88 (d, J=9Hz, 1H), 6.80 (d, J=9Hz, 1H), 4.13 (m, 2H), 3.81 (s, 3H), 3.44 (t, J=8Hz, 1H), 1.7 (m, 7H), 1.1 (m, 4H), 0.91 (m, 2H); MS (m/e) = 345.01, M.Wt. 344.18;
- 10 *N*-cyanomethyl-2-cyclohexylmethyl-*N'*-(2-thien-2-ylethyl)malonamide (Compound 16); ¹H NMR(DMSO): 8.40 (t, J=5Hz, 1H), 8.07 (t, J=5Hz, 1H), 7.33 (d, J=5Hz, 1H), 6.95 (m, 1H), 6.87 (m, 1H), 4.10 (d, J=5Hz, 2H), 3.3 (m, 3H), 3.21 (t, J=7Hz, 2H), 1.6 (m, 7H), 1.1 (m, 4H), 0.85 (m, 2H); MS (m/e) = 348.09, M.Wt. 347.48;
- 15 *N*-cyanomethyl-2-cyclohexylmethyl-*N'*-(3-phenoxyphenyl)malonamide
(Compound 17); ¹H NMR(DMSO): 10.1 (s, 1H), 8.45 (t, J=5Hz, 1H), 7.41 (t, J=8Hz, 2H), 7.33 (m, 3H), 7.16 (t, J=7Hz, 1H), 7.03 (d, J=8Hz, 2H), 6.73 (m, 1H), 4.1 (m, 2H), 3.42 (t, J=7Hz, 1H), 1.6 (m, 7H), 1.1 (m, 4H), 0.85 (m, 2H); MS (m/e) = 406.04, M.Wt. 405.49;
- 20 *N*-cyanomethyl-2-cyclohexylmethyl-*N'*-(4-nitrobenzyl)malonamide (Compound 18); ¹H NMR(DMSO): 8.61 (t, J=6Hz, 1H), 8.53 (t, J=6Hz, 1H), 8.17 (d, J=9Hz, 2H), 7.47 (d, J=9Hz, 2H), 4.41 (d, J=6Hz, 2H), 4.14 (d, J=6Hz, 2H), 3.3 (m, 1H), 1.6 (m, 7H), 1.1 (m, 4H), 0.87 (m, 2H); MS (m/e) = 373.02, M.Wt. 372.42;
- 25 *N,N*-biscyanomethyl-2-cyclohexylmethylmalonamide (Compound 19); ¹H NMR(DMSO): 8.59 (t, J=5Hz, 2H), 4.14 (d, J=6Hz, 4H), 3.28 (t, J=8Hz, 1H), 1.6 (m, 7H), 1.1 (m, 4H), 0.86 (m, 2H); MS (m/e) = 276.99, M.Wt. 276.34;
- 30 *N*-cyanomethyl-2-cyclohexylmethyl-*N'*-(5,6,7,8-tetrahydronaphth-1-yl)malonamide
(Compound 20); ¹H NMR(DMSO): 9.28 (s, 1H), 8.57 (t, J=6Hz, 1H), 7.21 (d, J=8Hz, 1H), 7.05 (t, J=8Hz, 1H), 6.90 (d, J=7Hz, 1H), 4.16 (d, J=6Hz, 2H), 3.49 (t, J=7Hz, 1H), 2.7 (m, 2H), 2.5 (m, 2H), 1.7 (m, 11H), 1.1 (m, 4H), 0.91 (m, 2H); MS (m/e) = 368.04, M.Wt. 367.48;
- 30 *N*-cyanomethyl-2-cyclohexylmethyl-*N'*-(2-pyrid-2-ylethyl)malonamide
(Compound 21); ¹H NMR(DMSO): 8.49 (m, 1H), 8.40 (t, J=6Hz, 1H), 8.00 (t, J=5Hz, 1H), 7.68 (dt, J=2,8Hz, 1H), 7.2 (m, 2H), 4.09 (d, J=6Hz, 2H), 3.42 (m, 2H), 3.17 (t, J=8Hz,

1H), 2.85 (t, J=7Hz, 2H), 1.6 (m, 7H), 1.07 (m, 4H), 0.83 (m, 2H); MS (m/e) = 343.04, M.Wt. 342.44;

N-cyanomethyl-2-cyclohexylmethyl-3-(2,3-dihydroindol-1-yl)-3-oxopropionamide
(Compound 22); ¹H NMR(DMSO): 8.73 (t, J=5Hz, 1H), 8.06 (d, J=8Hz, 1H), 7.24 (d, J=7Hz, 1H), 7.15 (t, J=7Hz, 1H), 7.00 (t, J=7Hz, 1H), 4.15 (d, J=5Hz, 2H), 4.1 (m, 2H),
5 3.66 (t, J=7Hz, 1H), 3.14 (m, 2H), 1.6 (m, 7H), 1.1 (m, 4H), 0.91 (m, 2H); MS (m/e) = 340.07, M.Wt. 339.19;

N-cyanomethyl-2-cyclohexylmethyl-3-(3,4-dihydro-1H-isoquinolin-2-yl)-3-oxopropionamide (Compound 23); ¹H NMR(DMSO): 8.64(t, J=5Hz, 1H), 7.15 (s, 4H),
10 4.65 (m, 2H), 4.11 (t, J=6Hz, 2H), 3.77 (m, 2H), 2.8 (m, 2H), 1.7 (m, 7H), 1.1 (m, 4H), 0.89 (m, 2H), 3.54 (m, 1H); MS (m/e) = 354.05, M.Wt. 353.46;

N-cyanomethyl-2-N'-biscyclohexylmethylmalonamide (Compound 24); ¹H NMR(DMSO): 8.34 (t, J=5Hz, 1H), 7.93 (t, J=5Hz, 1H), 4.09 (d, J=6Hz, 2H), 3.23 (dd, J=7.9Hz, 1H), 3.0 (m, 1H), 2.8 (m, 1H), 1.6 (m, 12H), 1.4 (m, 1H), 1.1 (m, 7H), 0.86 (m,
15 4H); MS (m/e) = 334.00, M.Wt. 333.47;

N-cyanomethyl-2-cyclohexylmethyl-N'-(2-methoxybenzyl)malonamide
(Compound 25); ¹H NMR(DMSO): 8.44 (t, J=5Hz, 1H), 8.27 (t, J=6Hz, 1H), 7.24 (dt, J=2.7Hz, 1H), 7.10 (dd, J=2.7Hz, 1H), 6.96 (d, J=7Hz, 1H), 6.88 (dt, J=7.1Hz, 1H), 4.30
20 (dd, J=6.16Hz, 1H), 4.20 (dd, J=5.16Hz, 1H), 4.12 (d, J=6Hz, 2H), 3.79 (s, 3H), 3.3 (m, 1H), 1.6 (m, 7H), 1.1 (m, 4H), 0.85 (m, 2H); MS (m/e) = 358.03, M.Wt. 357.45;

N-cyanomethyl-2-cyclohexylmethyl-N'-(1-phenylethyl)malonamide (Compound 26); ¹H NMR(DMSO): 8.25 (m, 1H), 7.4 (m, 5H), 4.02 (m, 2H), 3.18 (s, 3H), 3.25 (m, 1H), 1.6 (m, 7H), 1.1 (m, 4H), 0.7 (m, 2H); MS (m/e) = 328.08, M.Wt. 327.42;

N-benzyl-N'-cyanomethyl-2-cyclohexylmethyl-N-methylmalonamide (Compound 27); ¹H NMR(DMSO): 8.62 (m, 1H), 7.3 (m, 5H), 4.5 (m, 2H), 4.13 (d, J=6Hz, 2H), 3.7 (m, 1H), 2.93 (s, 3H), 1.6 (m, 7H), 1.1 (m, 4H), 0.88 (m, 2H); MS (m/e) = 342.09, M.Wt. 341.45;

N-cyanomethyl-2-cyclohexylmethyl-N'-(3-nitrobenzyl)malonamide (Compound 28); ¹H NMR(DMSO): 8.6 (t, 1H), 8.5 (t, 1H), 8.1 (m, 2H), 7.6 (m, 2H), 4.1 (m, 2H), 1.6
30 (m, 7H), 1.1 (m, 4H), 0.8 (m, 2H); MS (m/e) = 373.07, M.Wt. 372.42;

N-cyanomethyl-2-cyclohexylmethyl-N'-(4-methoxybenzyl)malonamide

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(Compound 29); ¹H NMR(DMSO): 8.42 (t, J=5Hz, 1H), 8.38 (t, J=6Hz, 1H), 7.14 (d, J=9Hz, 2H), 6.86 (d, J=9Hz, 2H), 4.25 (dd, J=6,15Hz, 1H), 4.15 (dd, J=7,16Hz, 1H), 3.71 (s, 3H), 3.27 (t, J=8Hz, 1H), 1.6 (m, 7H), 1.1 (m, 4H), 0.84 (m, 2H), 4.11 (d, J=6Hz, 2H); MS (m/e) = 356.97, M.Wt. 357.45;

5 *N*-(3-carbamoylphenyl)-*N'*-cyanomethyl-2-cyclohexylmethylmalonamide

(Compound 30); ¹H NMR(DMSO): 10.14 (s, 1H), 8.48 (t, 1H), 8.03 (s, 1H), 7.75 (d, 1H), 7.54 (d, 1H), 7.35 (m, 2H), 4.12 (d, 2H), 3.4 (t, 1H), 1.6 (m, 7H), 1.1 (m, 4H), 0.9 (m, 2H), 3.29 (s, 3H); MS (m/e) = 357.11, M.Wt. 356.42;

10 *N*-cyanomethyl-2-cyclohexylmethyl-*N'*-pyrid-3-ylmethylmalonamide (Compound 31); ¹H NMR(DMSO): 8.4 (m, 4H), 7.55 (d, 1H), 7.25 (dd, 1H), 4.28 (dd, 1H), 4.18 (dd, 1H), 4.05 (d, 2H), 3.2 (m, 1H), 1.6 (m, 7H), 1.01 (m, 4H), 0.78 (m, 2H); MS (m/e) = 329.03, M.Wt. 328.41;

15 *N*-(4-carbamoylphenyl)-*N'*-cyanomethyl-2-cyclohexylmethylmalonamide (Compound 32); ¹H NMR(DMSO): 10.22 (s, 2H), 8.50 (t, J=6Hz, 1H), 7.83 (d, J=9Hz 2H), 7.64 (d, J=9Hz, 2H), 7.52 (s, 1H), 4.13 (d, J=6Hz, 2H), 3.48 (t, J=7Hz, 1H), 1.7 (m, 7H), 1.1 (m, 4H), 0.9 (m, 2H); MS (m/e) = 357.04, M.Wt. 356.42;

20 *N*-cyanomethyl-2-cyclohexylmethyl-*N'*-tetrahydrofuran-2-ylmethylmalonamide (Compound 33); ¹H NMR(DMSO): 8.38 (t, J=5Hz, 1H), 7.98 (t, J=4Hz, 1H), 4.10 (d, J=6Hz 2H), 3.8 (m, 2H), 3.6 (m, 1H), 3.2 (m, 4H), 1.8 (m, 3H), 1.6 (m, 7H), 1.1 (m, 4H), 0.85 (m, 2H); MS (m/e) = 322.02, M.Wt. 321.41;

25 *N*-cyanomethyl-2-cyclohexylmethyl-3-(3,4-dihydro-2*H*-quinolin-1-yl)-3-oxopropionamide (Compound 34); ¹H NMR(DMSO): 8.5 (m, 1H), 7.35 (m, 1H), 7.2 (m, 4H), 4.1 (m, 2H), 3.82 (dd, 1H), 2.78 (t, 1H), 2.72 (t, 1H), 2.59 (m, 1H), 1.8 (m, 2H), 1.5 (m, 7H), 1.0 (m, 4H), 0.7 (m, 2H); MS (m/e) = 354.02, M.Wt. 353.46;

30 *N*-tert-butyl-*N'*-cyanomethyl-2-cyclohexylmethyl-*N*-methylmalonamide (Compound 35); ¹H NMR(DMSO): 8.41 (t, J=5Hz, 1H), 4.09 (d, J=5Hz, 1H), 3.56 (t, J=7Hz, 1H), 2.86 (s, 3H), 1.6 (m, 7H), 1.31 (s, 9H), 1.1 (m, 4H), 0.8 (m, 2H); MS (m/e) = 308.04, M.Wt. 307.43;

35 *N*-cyanomethyl-2-cyclohexylmethyl-*N'*-methyl-*N'*-propylmalonamide (Compound 36); ¹H NMR(DMSO): 8.5 (m, 1H), 4.10 (m, 2H), 3.60 (t, J=7Hz, 1H), 3.2 (m, 2H), 2.96 (s, 3H), 1.65 (m, 7H), 1.45 (m, 2H), 1.1 (m, 4H), 0.8 (m, 5H); MS (m/e) = 294.02, M.Wt.

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293.40;

N-butyl-*N'*-cyanomethyl-2-cyclohexylmethyl-*N*-methylmalonamide (Compound 37); ¹H NMR(DMSO): 8.5 (m, 1H), 4.10 (d, J=5Hz, 2H), 3.60 (t, 1H), 3.3 (m, 2H), 2.95 (s, 3H), 1.6 (m, 7H), 1.4 (m, 2H), 1.1 (m, 6H), 0.8 (m, 5H); MS (m/e) = 308.01, M.Wt. 307.43;

N-cyanomethyl-2-cyclohexylmethyl-*N,N'*-dimethylmalonamide (Compound 38); ¹H NMR(DMSO): 8.55 (t, J=5Hz, 1H), 4.11 (d, J=7Hz, 2H), 3.62 (t, J=8Hz, 1H), 2.99 (s, 3H), 2.81 (s, 3H), 1.6 (m, 7H), 1.1 (m, 4H), 0.85 (m, 2H); MS (m/e) = 266.01, M.Wt. 265.18;

10 *N*-benzyl-*N'*-cyanomethyl-2-(2-phenylsulfonyl-ethyl)malonamide (Compound 39); ¹H NMR(DMSO): 8.56 (t, J=6Hz, 1H), 8.49 (t, J=6Hz, 1H), 7.3 (m, 10H), 4.29 (d, J=6Hz, 2H), 4.14 (d, J=6Hz, 2H), 3.40 (t, J=7Hz, 1H), 2.86 (t, J=8Hz, 2H), 2.05 (m, 2H); MS (m/e) = 368.02, M.Wt. 367.14; and

15 2-(2-phenylsulfonyl-ethyl)-*N*-benzyl-*N'*-cyanomethylmalonamide (Compound 40); ¹H NMR(DMSO): 8.56 (t, J=6Hz, 1H), 8.43 (t, J=6Hz, 1H), 7.86 (d, J=7Hz, 2H), 7.79 (t, J=5Hz, 1H), 7.68 (t, J=8Hz, 2H), 7.25 (m, 5H), 4.26 (d, J=6Hz, 2H), 4.13 (d, J=6Hz, 2H), 3.36 (m, 1H), 3.19 (m, 2H), 2.00 (m, 2H); MS (m/e) = 400.04, M.Wt. 399.47;

20 2-(2-Benzenesulfonyl-ethyl)-*N*-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-pentyl]-*N'*-benzyl-malonamide (Compound 41) ¹H NMR(DMSO): 8.56 (d, J=6Hz, 1H), 8.2 (m, 1H), 8.0-7.5 (m, 9H), 7.3-7.1 (m, 5H), 5.3 (m, 1H), 4.24 (t, J=6Hz, 2H), 3.41 (t, J=7Hz, 1H), 3.18 (m, 2H), 1.96 (m, 3H), 1.67 (m, 1H), 1.30 (m, 4H), 0.82 (m, 3H); MS (m/e) = 576.27, M.Wt. 575.21; and

25 *N,N*-Bis-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-propyl]-2-cyclohexylmethyl-malonamide (Compound 42) ¹H NMR(DMSO): 8.41 (d, J=6Hz, 2H), 8.00 (d, J=8Hz, 2H), 7.89 (d, J=8Hz, 2H), 7.65 (t, J=7Hz, 2H), 7.53 (t, J=8Hz, 2H), 5.19 (m, 2H), 3.42 (t, J=8Hz, 1H), 1.98 (m, 2H), 1.74 (m, 2H), 1.52 (m, 7H), 0.94 (m, 10H), 0.77 (m, 2H); MS (m/e) = 572.26, M.Wt. 573.4.

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EXAMPLE 6

Cathepsin S Assay

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Solutions of test compounds in varying concentrations were prepared in 10 μ L of dimethyl sulfoxide (DMSO) and then diluted into assay buffer (40 μ L, comprising: MES, 50 mM (pH 6.5); EDTA, 2.5 mM; and NaCl, 100 mM). Human cathepsin S (0.158 pMoles in 25 μ L of assay buffer) was added to the dilutions. The assay solutions were mixed for 5-10 seconds on a shaker plate, covered and incubated for 30 minutes at ambient temperature. Z-Val-Val-Arg-AMC (9 nMoles in 25 μ L of assay buffer) was added to the assay solutions and hydrolysis was followed spectrophotometrically at (λ 460 nm) for 5 minutes. Apparent inhibition constants (K_i) were calculated from the enzyme progress curves using standard mathematical models.

EXAMPLE 7

Cathepsin B Assay

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Solutions of test compounds in varying concentrations were prepared in 10 μ L of dimethyl sulfoxide (DMSO) and then diluted into assay buffer (40 μ L, comprising: *N,N*-bis(2-hydroxyethyl)-2-aminoethanesulfonic acid (BES), 50 mM (pH 6); polyoxyethylenesorbitan monolaurate, 0.05%; and dithiothreitol (DTT), 2.5 mM). Human cathepsin B (0.025 pMoles in 25 μ L of assay buffer) was added to the dilutions. The assay solutions were mixed for 5-10 seconds on a shaker plate, covered and incubated for 30 minutes at ambient temperature. Z-FR-AMC (20 nMoles in 25 μ L of assay buffer) was added to the assay solutions and hydrolysis was followed spectrophotometrically at (λ 460 nm) for 5 minutes. Apparent inhibition constants (K_i) were calculated from the enzyme progress curves using standard mathematical models.

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EXAMPLE 8

Cathepsin K Assay

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Solutions of test compounds in varying concentrations were prepared in 10 μ L of

dimethyl sulfoxide (DMSO) and then diluted into assay buffer (40 μ L, comprising: MES, 50 mM (pH 5.5); EDTA, 2.5 mM; and DTT, 2.5 mM). Human cathepsin K (0.0906 pMoles in 25 μ L of assay buffer) was added to the dilutions. The assay solutions were mixed for 5-10 seconds on a shaker plate, covered and incubated for 30 minutes at ambient temperature. Z-Phe-Arg-AMC (4 nMoles in 25 μ L of assay buffer) was added to the assay solutions and hydrolysis was followed spectrophotometrically at (λ 460 nm) for 5 minutes. Apparent inhibition constants (K_i) were calculated from the enzyme progress curves using standard mathematical models.

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EXAMPLE 9

Cathepsin L Assay

Solutions of test compounds in varying concentrations were prepared in 10 μ L of dimethyl sulfoxide (DMSO) and then diluted into assay buffer (40 μ L, comprising: MES, 50 mM (pH 5.5); EDTA, 2.5 mM; and DTT, 2.5 mM). Human cathepsin L (0.05 pMoles in 25 μ L of assay buffer) was added to the dilutions. The assay solutions were mixed for 5-10 seconds on a shaker plate, covered and incubated for 30 minutes at ambient temperature. Z-Phe-Arg-AMC (1 nMoles in 25 μ L of assay buffer) was added to the assay solutions and hydrolysis was followed spectrophotometrically at (λ 460 nm) for 5 minutes. Apparent inhibition constants (K_i) were calculated from the enzyme progress curves using standard mathematical models.

Compounds of the invention were tested according to the above-described assays for protease inhibition and observed to exhibit selective cathepsin S inhibitory activity. For example, the compounds of the invention were found to inhibit cathepsin S protease activity at concentrations that are least 50 fold less than those concentrations required to produce an equiactive inhibition of cathepsin K protease activity. The apparent inhibition constants (K_i) for compounds of the invention, against Cathepsin S, were in the range from about 10^{-10} M to about 10^{-7} M.

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EXAMPLE 10

Representative Pharmaceutical Formulations Containing a Compound of
Formula I

5 ORAL FORMULATION

	Compound of Formula I	10-100 mg
	Citric Acid Monohydrate	105 mg
	Sodium Hydroxide	18 mg
	Flavoring	
10	Water	q.s. to 100 mL

INTRAVENOUS FORMULATION

	Compound of Formula I	0.1-10 mg
	Dextrose Monohydrate	q.s. to make isotonic
15	Citric Acid Monohydrate	1.05 mg
	Sodium Hydroxide	0.18 mg
	Water for Injection	q.s. to 1.0 mL

TABLET FORMULATION

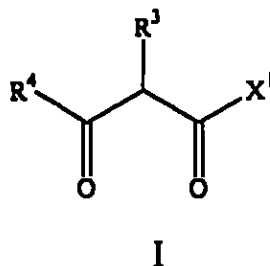
20	Compound of Formula I	1%
	Microcrystalline Cellulose	73%
	Stearic Acid	25%
	Colloidal Silica	1%.

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WE CLAIM:

1. A compound of Formula I:



- 5 in which:

X^1 is $-\text{NHC}(\text{R}^1)(\text{R}^2)\text{X}^2$ or $-\text{NHX}^2$;

- X^2 is cyano, $-\text{C}(\text{R}^7)(\text{R}^8)\text{X}^3$, $-\text{C}(\text{R}^7)(\text{R}^8)\text{CF}_3$, $-\text{C}(\text{R}^7)(\text{R}^8)\text{CF}_2\text{CF}_2\text{R}^9$, $-\text{CH}=\text{CHS}(\text{O})_2\text{R}^5$,
 $-\text{C}(\text{O})\text{CF}_2\text{C}(\text{O})\text{NR}^5\text{R}^5$, $-\text{C}(\text{O})\text{C}(\text{O})\text{NR}^5\text{R}^6$, $-\text{C}(\text{O})\text{C}(\text{O})\text{OR}^5$, $-\text{C}(\text{O})\text{CH}_2\text{OR}^5$,
 $-\text{C}(\text{O})\text{CH}_2\text{N}(\text{R}^6)\text{SO}_2\text{R}^5$ or $-\text{C}(\text{O})\text{C}(\text{O})\text{R}^5$; wherein R^5 is (C_{1-4}) alkyl, (C_{5-10}) aryl (C_{6-6}) alkyl or
 10 (C_{5-10}) heteroaryl (C_{6-6}) alkyl; R^6 is hydrogen or (C_{1-4}) alkyl; R^7 is hydrogen or (C_{1-4}) alkyl and
 R^8 is hydroxy or R^7 and R^8 together form oxo; R^9 is hydrogen, halo, (C_{1-4}) alkyl,
 (C_{5-10}) aryl (C_{6-6}) alkyl or (C_{5-10}) heteroaryl (C_{6-6}) alkyl;

- X^3 comprises a heteromonocyclic ring containing 4 to 6 ring member atoms or a
 fused heterobicyclic ring system containing 8 to 14 ring member atoms and any
 15 carbocyclic ketone, iminoketone or thioketone derivative thereof;

- wherein within R^5 , X^2 or X^3 any alicyclic or aromatic ring system may be
 substituted further by 1 to 5 radicals independently selected from (C_{1-4}) alkyl,
 (C_{1-4}) alkylidene, cyano, halo, halo-substituted (C_{1-4}) alkyl, nitro, $-\text{X}^4\text{NR}^{12}\text{R}^{12}$,
 $-\text{X}^4\text{NR}^{12}\text{C}(\text{O})\text{R}^{12}$, $-\text{X}^4\text{NR}^{12}\text{C}(\text{O})\text{OR}^{12}$, $-\text{X}^4\text{NR}^{12}\text{C}(\text{O})\text{NR}^{12}\text{R}^{12}$, $-\text{X}^4\text{NR}^{12}\text{C}(\text{NR}^{12})\text{NR}^{12}\text{R}^{12}$,
 20 $-\text{X}^4\text{OR}^{12}$, $-\text{X}^4\text{SR}^{12}$, $-\text{X}^4\text{C}(\text{O})\text{OR}^{12}$, $-\text{X}^4\text{C}(\text{O})\text{R}^{12}$, $-\text{X}^4\text{OC}(\text{O})\text{R}^{12}$, $-\text{X}^4\text{C}(\text{O})\text{NR}^{12}\text{R}^{12}$,
 $-\text{X}^4\text{S}(\text{O})_2\text{NR}^{12}\text{R}^{12}$, $-\text{X}^4\text{NR}^{12}\text{S}(\text{O})_2\text{R}^{12}$, $-\text{X}^4\text{P}(\text{O})(\text{OR}^{12})\text{OR}^{12}$, $-\text{X}^4\text{OP}(\text{O})(\text{OR}^{12})\text{OR}^{12}$,
 $-\text{X}^4\text{NR}^{12}\text{C}(\text{O})\text{R}^{13}$, $-\text{X}^4\text{S}(\text{O})\text{R}^{13}$ and $-\text{X}^4\text{S}(\text{O})_2\text{R}^{13}$ and/or 1 radical selected from $-\text{R}^{14}$, $-\text{X}^4\text{OR}^{14}$,
 $-\text{X}^4\text{SR}^{14}$, $-\text{X}^4\text{S}(\text{O})\text{R}^{14}$, $-\text{X}^4\text{S}(\text{O})_2\text{R}^{14}$, $-\text{X}^4\text{C}(\text{O})\text{R}^{14}$, $-\text{X}^4\text{C}(\text{O})\text{OR}^{14}$, $-\text{X}^4\text{OC}(\text{O})\text{R}^{14}$, $-\text{X}^4\text{NR}^{14}\text{R}^{12}$,
 $-\text{X}^4\text{NR}^{12}\text{C}(\text{O})\text{R}^{14}$, $-\text{X}^4\text{NR}^{12}\text{C}(\text{O})\text{OR}^{14}$, $-\text{X}^4\text{C}(\text{O})\text{NR}^{12}\text{R}^{12}$, $-\text{X}^4\text{S}(\text{O})_2\text{NR}^{14}\text{R}^{12}$, $-\text{X}^4\text{NR}^{12}\text{S}(\text{O})_2\text{R}^{14}$,
 25 $-\text{X}^4\text{NR}^{12}\text{C}(\text{O})\text{NR}^{14}\text{R}^{12}$ and $-\text{X}^4\text{NR}^{12}\text{C}(\text{NR}^{12})\text{NR}^{14}\text{R}^{12}$, wherein X^4 is a bond or (C_{1-6}) alkyl; R^{12}
 at each occurrence independently is hydrogen, (C_{1-6}) alkyl or halo-substituted (C_{1-6}) alkyl; R^{13}
 is (C_{1-6}) alkyl or halo-substituted (C_{1-6}) alkyl; and R^{14} is (C_{2-10}) cycloalkyl (C_{6-6}) alkyl,

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hetero(C₃₋₁₀)cycloalkyl(C₀₋₃)alkyl, (C₆₋₁₀)aryl(C₀₋₆)alkyl, hetero(C₃₋₁₀)aryl(C₀₋₆)alkyl, (C₃₋₁₀)bicycloaryl(C₀₋₆)alkyl or hetero(C₄₋₁₀)bicycloaryl(C₀₋₆)alkyl;

- \ R¹ is hydrogen, halo or (C₁₋₆)alkyl and R² is selected from a group consisting of hydrogen, cyano, halo, -X⁴NR¹²R¹², -X⁴NR¹²C(O)R¹², -X⁴NR¹²C(O)OR¹²,
 5 -X⁴NR¹²C(O)NR¹²R¹², -X⁴NR¹²C(NR¹²)NR¹²R¹², -X⁴OR¹², -X⁴SR¹², -X⁴C(O)OR¹²,
 -X⁴C(O)R¹², -X⁴OC(O)R¹², -X⁴C(O)NR¹²R¹², -X⁴S(O)₂NR¹²R¹², -X⁴NR¹²S(O)₂R¹²,
 -X⁴P(O)(OR¹²)OR¹², -X⁴OP(O)(OR¹²)OR¹², -X⁴NR¹²C(O)R¹³, -X⁴S(O)R¹³, -X⁴S(O)₂R¹³,
 -R¹⁴, -X⁴OR¹⁴, -X⁴SR¹⁴, -X⁴S(O)R¹⁴, -X⁴S(O)₂R¹⁴, -X⁴C(O)R¹⁴, -X⁴C(O)OR¹⁴, -X⁴OC(O)R¹⁴,
 -X⁴NR¹⁴R¹², -X⁴NR¹²C(O)R¹⁴, -X⁴NR¹²C(O)OR¹⁴, -X⁴C(O)NR¹²R¹², -X⁴S(O)₂NR¹⁴R¹²,
 10 -X⁴NR¹²S(O)₂R¹⁴, -X⁴NR¹²C(O)NR¹⁴R¹² and -X⁴NR¹²C(NR¹²)NR¹⁴R¹², wherein X⁴, R¹², R¹³
 and R¹⁴ are as defined above; or R¹ and R² taken together with the carbon atom to which
 both R¹ and R² are attached form (C₃₋₆)cycloalkylene or (C₃₋₆)heterocycloalkylene; wherein
 within said R² any heteroaryl, aryl, cycloalkyl, heterocycloalkyl, cycloalkylene or
 heterocycloalkylene is optionally substituted with 1 to 3 radicals independently selected
 15 from (C₁₋₆)alkyl, (C₁₋₆)alkylidene, cyano, halo, halo-substituted(C₁₋₆)alkyl, nitro,
 -X⁴NR¹²R¹², -X⁴NR¹²C(O)R¹², -X⁴NR¹²C(O)OR¹², -X⁴NR¹²C(O)NR¹²R¹²,
 -X⁴NR¹²C(NR¹²)NR¹²R¹², -X⁴OR¹², -X⁴SR¹², -X⁴C(O)OR¹², -X⁴C(O)R¹², -X⁴OC(O)R¹²,
 -X⁴C(O)NR¹²R¹², -X⁴S(O)₂NR¹²R¹², -X⁴NR¹²S(O)₂R¹², -X⁴P(O)(OR¹²)OR¹²,
 -X⁴OP(O)(OR¹²)OR¹², -X⁴NR¹²C(O)R¹³, -X⁴S(O)R¹³, -X⁴S(O)₂R¹³ and -X⁴C(O)R¹³, wherein
 20 X⁴, R¹² and R¹³ are as defined above;

- R³ is -C(R⁶)(R⁶)X³, wherein R⁶ is as defined above and X³ is selected from
 -X⁴NR¹²R¹², -X⁴NR¹²C(O)R¹², -X⁴NR¹²C(O)OR¹², -X⁴NR¹²C(O)NR¹²R¹²,
 -X⁴NR¹²C(NR¹²)NR¹²R¹², -X⁴OR¹², -X⁴SR¹², -X⁴C(O)OR¹², -X⁴C(O)R¹², -X⁴OC(O)R¹²,
 -X⁴R¹², -X⁴C(O)NR¹²R¹², -X⁴S(O)₂NR¹²R¹², -X⁴NR¹²S(O)₂R¹², -X⁴P(O)(OR¹²)OR¹²,
 25 -X⁴OP(O)(OR¹²)OR¹², -X⁴C(O)R¹³, -X⁴NR¹²C(O)R¹³, -X⁴S(O)R¹³ and -X⁴S(O)₂R¹³, -R¹⁴,
 -X⁴OR¹⁴, -X⁴SR¹⁴, -X⁴S(O)R¹⁴, -X⁴S(O)₂R¹⁴, -X⁴C(O)R¹⁴, -X⁴C(O)OR¹⁴, -X⁴OC(O)R¹⁴,
 -X⁴NR¹⁴R¹², -X⁴NR¹²C(O)R¹⁴, -X⁴NR¹²C(O)OR¹⁴, -X⁴C(O)NR¹⁴R¹², -X⁴S(O)₂NR¹⁴R¹²,
 -X⁴NR¹²S(O)₂R¹⁴, -X⁴NR¹²C(O)NR¹⁴R¹² and -X⁴NR¹²C(NR¹²)NR¹⁴R¹² wherein X⁴, R¹², R¹³
 and R¹⁴ are as defined above;

- 30 R⁴ is -NR⁶R⁶, -NR⁶R¹⁴, -NR⁶R¹⁵ or -NR⁶X⁵C(O)R¹⁴ wherein R⁶, X⁵ and R¹⁴ are
 as described above and R¹⁵ is hydrogen, -(C₁₋₆)alkyl or -X⁵OR⁶ wherein X⁵ is as described

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above; or R⁶ and R¹⁵ together with the nitrogen atom to which R⁶ and R¹⁵ are attached form hetero(C₃₋₁₀)cycloalkyl, hetero(C₃₋₁₀)aryl or hetero(C₃₋₁₀)bicycloaryl;

wherein within R³ and R⁴ any alicyclic or aromatic ring system may be substituted further by 1-5 radicals independently selected from (C₁₋₆)alkyl, (C₁₋₆)alkylidene, cyano, halo, halo-substituted(C₁₋₆)alkyl, nitro, -X⁴NR¹²R¹², -X⁴NR¹²C(O)R¹², -X⁴NR¹²C(O)OR¹², -X⁴NR¹²C(O)NR¹²R¹², -X⁴NR¹²C(NR¹²)NR¹²R¹², -X⁴OR¹², -X⁴SR¹², -X⁴C(O)OR¹², -X⁴C(O)R¹², -X⁴OC(O)R¹², -X⁴C(O)NR¹²R¹², -X⁴S(O)₂NR¹²R¹², -X⁴NR¹²S(O)₂R¹², -X⁴P(O)(OR¹²)OR¹², -X⁴OP(O)(OR¹²)OR¹², -X⁴NR¹²C(O)R¹², -X⁴S(O)R¹², -X⁴C(O)R¹² and -X⁴S(O)₂R¹² and/or 1 radical selected from -R¹⁴, -X⁴OR¹⁴, -X⁴SR¹⁴, -X⁴S(O)R¹⁴, -X⁴S(O)₂R¹⁴, -X⁴C(O)R¹⁴, -X⁴C(O)OR¹⁴, -X⁴OC(O)R¹⁴, -X⁴NR¹⁴R¹², -X⁴NR¹²C(O)R¹⁴, -X⁴NR¹²C(O)OR¹⁴, -X⁴C(O)NR¹⁴R¹², -X⁴S(O)₂NR¹⁴R¹², -X⁴NR¹²S(O)₂R¹⁴, -X⁴NR¹²C(O)NR¹⁴R¹² and -X⁴NR¹²C(NR¹²)NR¹⁴R¹²; and within R³ and R⁴ any aliphatic moiety may be substituted further by 1-5 radicals independently selected from cyano, halo, nitro, -NR¹²R¹², -NR¹²C(O)R¹², -NR¹²C(O)OR¹², -NR¹²C(O)NR¹²R¹², -NR¹²C(NR¹²)NR¹²R¹², -OR¹², -SR¹², -C(O)OR¹², -C(O)R¹², -OC(O)R¹², -C(O)NR¹²R¹², -S(O)₂NR¹²R¹², -NR¹²S(O)₂R¹², -P(O)(OR¹²)OR¹², -OP(O)(OR¹²)OR¹², -NR¹²C(O)R¹², -S(O)R¹² and -S(O)₂R¹²; wherein X⁴, R¹², R¹³ and R¹⁴ are as described above;

with the proviso that only one bicyclic ring structure is present within R³ or R⁴; and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such compounds and the N-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

2. The compound of Claim 1 in which:

25 X¹ is -NHC(R¹)(R²)X² or -NHX²;

X² is cyano, -C(O)X³, -C(O)CF₃, -C(O)CF₂CF₂R⁹, -CH=CHS(O)₂R⁵, -C(O)CF₂C(O)NR⁵R⁵, -C(O)C(O)NR⁵R⁶, -C(O)C(O)OR⁵, -C(O)CH₂OR⁵, -C(O)CH₂N(R⁶)SO₂R⁵ or -C(O)C(O)R⁵; wherein R⁵ and R⁶ are as described above;

30 X³ comprises a heteromonocyclic ring containing 4 to 6 ring member atoms or a fused heterobicyclic ring system containing 8 to 14 ring member atoms and any carbocyclic ketone, iminoketone or thioketone derivative thereof;

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wherein within R^5 , X^2 or X^3 any alicyclic or aromatic ring system may be substituted further by 1 to 5 radicals independently selected from (C_{1-6}) alkyl or $-X^4OC(O)R^{12}$ and/or 1 radical selected from $-R^{14}$, $-X^4C(O)R^{14}$ or $-X^4OC(O)R^{14}$;

wherein X^4 , R^{12} and R^{14} are as described above; -

- 5 R^1 is hydrogen or (C_{1-6}) alkyl and R^2 is hydrogen, $-X^4OR^{12}$, (C_{5-10}) heteroaryl (C_{0-6}) alkyl, (C_{5-10}) aryl (C_{0-6}) alkyl, (C_{5-10}) cycloalkyl (C_{0-6}) alkyl, (C_{5-10}) heterocycloalkyl (C_{0-6}) alkyl or (C_{1-6}) alkyl; or R^1 and R^2 taken together with the carbon atom to which both R^1 and R^2 are attached form (C_{3-4}) cycloalkylene or (C_{3-4}) heterocycloalkylene; wherein within said R^2 any heteroaryl, aryl, cycloalkyl, heterocycloalkyl, cycloalkylene or heterocycloalkylene is optionally substituted with 1 to 10 3 radicals independently selected from (C_{1-6}) alkyl and hydroxy;

R^3 is $-CH_2X^5$, wherein X^5 at each occurrence independently is selected from $-X^4SR^{12}$, $-X^4C(O)NR^{12}R^{12}$, $-X^4S(O)_2R^{12}$, $-X^4C(O)R^{12}$, $-X^4SR^{14}$, $-R^{14}$, $-X^4S(O)_2R^{14}$, $-X^4R^{12}$, $-X^4C(O)R^{14}$, $-X^4C(O)NR^{14}R^{12}$, wherein X^4 , R^{12} , R^{13} and R^{14} are as defined above;

- 15 R^4 is $-NR^6R^6$, $-NR^6R^{14}$, $-NR^6R^{13}$ or $-NR^6X^5C(O)R^{14}$ wherein R^6 , X^5 and R^{14} are as described above and R^{13} is hydrogen, (C_{1-6}) alkyl or $-X^5OR^6$ wherein X^5 is as described above; or R^6 and R^{13} together with the nitrogen atom to which R^6 and R^{13} are attached form hetero (C_{3-10}) cycloalkyl, hetero (C_{5-10}) aryl or hetero (C_{1-10}) bicycloaryl;

- wherein within R^3 and R^4 any alicyclic or aromatic ring system may be substituted further by 1-5 radicals independently selected from (C_{1-6}) alkyl, cyano, halo, nitro, halo-substituted (C_{1-6}) alkyl, $-X^4OR^{12}$, $-X^4C(O)OR^{12}$, $-X^4C(O)R^{12}$, $-X^4C(O)NR^{12}R^{12}$, $-X^4NR^{12}S(O)_2R^{12}$ and/or 1 radical selected from $-R^{14}$, $-X^4OR^{14}$ and $-X^4C(O)NR^{14}R^{12}$; within R^3 and R^4 any aliphatic moiety may be substituted further by 1-5 radicals independently selected from cyano; wherein X^4 , R^{12} , R^{13} and R^{14} are as described above; with the proviso 20 that only one bicyclic ring structure is present within R^3 or R^4 ; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such compounds and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.

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3. The compound of Claim 2 in which:

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X^1 is $-NHC(R^1)(R^2)X^2$ or $-NHX^2$;

X^2 is cyano, $-C(O)X^3$, $-CF_3$, $-CF_2CF_3$, (E)-2-benzenesulfonyl-vinyl, 2-dimethylcarbamoyl-2,2-difluoro-acetyl, 1-benzylcarbamoyl-methanoyl, 1-benzyloxy(oxalyl), 2-benzyloxy-acetyl, 2-benzenesulfonylamino-ethanoyl or
5 2-oxo-2-phenyl-ethanoyl;

X^3 is 1*H*-benzoimidazol-2-yl, pyrimidin-2-yl, benzoxazol-2-yl, benzothiazol-2-yl, pyridazin-3-yl, 3-phenyl-[1,2,4]oxadiazol-5-yl, 3-ethyl-[1,2,4]oxadiazol-5-yl, 2-methyl-4-oxo-tetrahydro-furan-3-yl, 2-ethyl-4-oxo-tetrahydro-furan-3-yl, 4-oxo-1-(1-phenyl-methanoyl)-pyrrolidin-3-yl or (S)-2-Acetoxy-4-oxo-azetidin-3-yl;

10 R^1 is hydrogen or methyl and R^2 is hydrogen, methoxymethyl, (C_{1-4}) alkyl, phenethyl, thiophen-2-yl or 5-methyl-furan-2-yl, or (ii) R^1 and R^2 taken together with the carbon atom to which both R^1 and R^2 are attached form cyclopropylene, tetrahydro-pyran-4-ylene or methyl-piperidin-4-ylene.

- 15 4. The compound of claim 3 in which R^3 is selected from thiophene-2-sulfonylmethyl, 3-chloro-2-fluoro-phenylmethanesulfonylmethyl, benzenesulfonylmethyl, phenylmethanesulfonylmethyl, 2-(1,1-difluoro-methoxy)-phenylmethanesulfonylmethyl, 2-benzenesulfonyl-ethyl, 2-(pyridine-2-sulfonyl)-ethyl, 2-(pyridine-4-sulfonyl)-ethyl,
20 2-phenylmethanesulfonyl-ethyl, oxy-pyridin-2-ylmethanesulfonylmethyl, prop-2-ene-1-sulfonylmethyl, 4-methoxy-phenylmethanesulfonylmethyl, *p*-tolylmethanesulfonylmethyl, 4-chloro-phenylmethanesulfonylmethyl, *o*-tolylmethanesulfonylmethyl, 3,5-dimethyl-phenylmethanesulfonylmethyl, 4-trifluoromethyl-phenylmethanesulfonylmethyl,
25 4-trifluoromethoxy-phenylmethanesulfonylmethyl, 2-bromo-phenylmethanesulfonylmethyl, pyridin-2-ylmethanesulfonylmethyl, pyridin-3-ylmethanesulfonylmethyl, pyridin-4-ylmethanesulfonylmethyl, naphthalen-2-ylmethanesulfonylmethyl, 3-methyl-phenylmethanesulfonylmethyl, 3-trifluoromethyl-phenylmethanesulfonylmethyl,
30 3-trifluoromethoxy-phenylmethanesulfonylmethyl, 4-fluoro-2-trifluoromethoxy-phenylmethanesulfonylmethyl,

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- 2-fluoro-6-trifluoromethyl-phenylmethanesulfonylmethyl,
3-chloro-phenylmethanesulfonylmethyl, 2-fluoro-phenylmethanesulfonylmethyl,
2-trifluoro-phenylmethanesulfonylmethyl, 2-cyano-phenylmethanesulfonylmethyl,
4-*tert*-butyl-phenylmethanesulfonylmethyl,
5 2-fluoro-3-methyl-phenylmethanesulfonylmethyl,
3-fluoro-phenylmethanesulfonylmethyl, 4-fluoro-phenylmethanesulfonylmethyl,
2-chloro-phenylmethanesulfonylmethyl,
2,5-difluoro-phenylmethanesulfonylmethyl,
2,6-difluoro-phenylmethanesulfonylmethyl,
10 2,5-dichloro-phenylmethanesulfonylmethyl,
3,4-dichloro-phenylmethanesulfonylmethyl,
2-(1,1-difluoro-methoxy)-phenylmethanesulfonylmethyl,
2-cyano-phenylmethanesulfonylmethyl, 3-cyano-phenylmethanesulfonylmethyl,
2-trifluoromethoxy-phenylmethanesulfonylmethyl,
15 2,3-difluoro-phenylmethanesulfonylmethyl,
2,5-difluoro-phenylmethanesulfonylmethyl, biphenyl-2-ylmethanesulfonylmethyl,
cyclohexylmethyl, 3-fluoro-phenylmethanesulfonylmethyl,
3,4-difluoro-phenylmethanesulfonylmethyl,
2,4-difluoro-phenylmethanesulfonylmethyl,
20 2,4,6-trifluoro-phenylmethanesulfonylmethyl,
2,4,5-trifluoro-phenylmethanesulfonylmethyl,
2,3,4-trifluoro-phenylmethanesulfonylmethyl,
2,3,5-trifluoro-phenylmethanesulfonylmethyl,
2,5,6-trifluoro-phenylmethanesulfonylmethyl,
25 2-chloro-5-trifluoromethylphenylmethanesulfonylmethyl,
2-methyl-propane-1-sulfonyl,
2-fluoro-3-trifluoromethylphenylmethanesulfonylmethyl,
2-fluoro-4-trifluoromethylphenylmethanesulfonylmethyl,
2-fluoro-5-trifluoromethylphenylmethanesulfonylmethyl,
30 4-fluoro-3-trifluoromethylphenylmethanesulfonylmethyl,
2-methoxy-phenylmethanesulfonylmethyl, 3,5

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bis-trifluoromethyl-phenylmethanesulfonylmethyl,
4-difluoromethoxy-phenylmethanesulfonylmethyl,
2-difluoromethoxy-phenylmethanesulfonylmethyl,
3-difluoromethoxy-phenylmethanesulfonylmethyl,
5 2,6-dichloro-phenylmethanesulfonylmethyl, biphenyl-4-ylmethanesulfonylmethyl,
3,5-dimethyl-isoxazol-4-ylmethanesulfonylmethyl,
5-chloro-thiophen-2-ylmethanesulfonylmethyl,
2-[4-(1,1-Difluoro-methoxy)-benzenesulfonyl]-ethyl,
2-[2-(1,1-Difluoro-methoxy)-benzenesulfonyl]-ethyl,
10 2-[3-(1,1-Difluoro-methoxy)-benzenesulfonyl]-ethyl,
2-(4-trifluoromethoxy-benzenesulfonyl)-ethyl,
2-(3-trifluoromethoxy-benzenesulfonyl)-ethyl,
2-(2-trifluoromethoxy-benzenesulfonyl)-ethyl,
(cyanomethyl-methyl-carbamoyl)-methyl, butyl, biphenyl-3-ylmethyl,
15 2-oxo-2-pyrrolidin-1-yl-ethyl, 2-benzenesulfonyl-ethyl, isobutylsulfanylmethyl,
2-phenylsulfanyl-ethyl, cyclohexylmethanesulfonylmethyl,
2-cyclohexyl-ethanesulfonyl, benzyl, naphthalen-2-yl, benzylsulfanylmethyl,
2-trifluoromethyl-benzylsulfanylmethyl, 5-bromo-thiophen-2-ylmethyl
phenylsulfanyl-ethyl and cyclopropylmethanesulfonylmethyl.

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5. The compound of claim 4 in which R⁴ is selected from phenylamino, benzylamino,
4-phenoxy-phenylamino, phenethylamino, 3-phenyl-propylamino, morpholin-4-yl,
cyclohexylamino, naphthalen-1-ylmethyl-amino, pyridin-3-ylamino, 6-methoxy-
pyridin-3-ylamino, diisobutylamino, 4-nitro-benzylamino, 2-thiophen-2-yl-
ethylamino, 3-phenoxy-phenylamino, cyanomethyl-amino, (pyridin-3-ylmethyl)-
25 amino, 5,6,7,8-tetrahydro-naphthalen-1-ylamino, 2-pyridin-2-yl-ethylamino, 2,3-
dihydro-indol-1-yl, 3,4-dihydro-1H-isoquinolin-2-yl, cyclohexylmethyl-amino, 2-
methoxy-benzylamino, 1-phenyl-ethylamino, (pyridin-4-ylmethyl)-amino, benzyl-
methyl-amino, 3-nitro-benzylamino, 4-methoxy-phenylamino, 3-carbamoyl-
30 phenylamino, 4-carbamoyl-phenylamino, (tetrahydro-furan-2-ylmethyl)-amino,
3,4-dihydro-2H-quinolin-1-yl, dimethylamino, butylmethylamino,

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diisopropylamino, propylmethylamino, 1-(benzooxazole-2-carbonyl)-propylamino and isobutylmethylamino.

6. The compound of claim 5 selected from the group consisting of:
- 5 cyanomethyl-*N*-phenyl-malonamide; *N*-Cyanomethyl-2-cyclohexylmethyl-*N*-phenyl-malonamide; *N*-Cyanomethyl-2-cyclohexylmethyl-*N*-phenethyl-malonamide; *N*-Cyanomethyl-2-cyclohexylmethyl-*N*-pyridin-4-ylmethyl-malonamide; *N*-[1-(Benzooxazole-2-carbonyl)-3-phenyl-propyl]-*N*-benzyl-2-cyclohexylmethyl-malonamide; *N*-Cyanomethyl-*N*-cyclohexyl-2-cyclohexylmethyl-malonamide; *N*-Benzyl-*N*-cyanomethyl-2-cyclohexylmethyl-malonamide; *N*-Cyanomethyl-2-cyclohexylmethyl-*N*-(4-phenoxy-phenyl)-malonamide; *N*-Cyanomethyl-2-cyclohexylmethyl-*N*-(3-phenyl-propyl)-malonamide; *N*-Cyanomethyl-2-cyclohexylmethyl-3-morpholin-4-yl-3-oxo-propionamide; *N*-Cyanomethyl-2-cyclohexylmethyl-*N*-naphthalen-1-ylmethyl-malonamide; *N*-Cyanomethyl-2-cyclohexylmethyl-*N*-pyridin-3-yl-malonamide; *N*-Cyanomethyl-2-cyclohexylmethyl-*N,N*-diisobutyl-malonamide; *N*-Cyanomethyl-2-cyclohexylmethyl-*N,N*-diisopropyl-malonamide; *N*-Cyanomethyl-2-cyclohexylmethyl-*N*-(6-methoxy-pyridin-3-yl)-malonamide; *N*-Cyanomethyl-2-cyclohexylmethyl-*N*-(2-thiophen-2-yl-ethyl)-malonamide; *N*-Cyanomethyl-2-cyclohexylmethyl-*N*-(3-phenoxy-phenyl)-malonamide; *N*-Cyanomethyl-2-cyclohexylmethyl-*N*-(4-nitro-benzyl)-malonamide; *N,N*-Bis-cyanomethyl-2-cyclohexylmethyl-malonamide; *N*-Cyanomethyl-2-cyclohexylmethyl-*N*-(5,6,7,8-tetrahydro-naphthalen-1-yl)-malonamide; *N*-Cyanomethyl-2-cyclohexylmethyl-*N*-(2-pyridin-2-yl-ethyl)-malonamide; *N*-Cyanomethyl-2-cyclohexylmethyl-3-(2,3-dihydro-indol-1-yl)-3-oxo-propionamide; *N*-Cyanomethyl-2-cyclohexylmethyl-3-(3,4-dihydro-1H-isoquinolin-2-yl)-3-oxo-propionamide; *N*-Cyanomethyl-2,*N*-bis-cyclohexylmethyl-malonamide; *N*-Cyanomethyl-2-cyclohexylmethyl-*N*-(2-methoxy-benzyl)-malonamide; *N*-Cyanomethyl-2-cyclohexylmethyl-*N*-(1-phenyl-ethyl)-malonamide; *N*-Benzyl-*N*-cyanomethyl-2-cyclohexylmethyl-*N*-methyl-malonamide; *N*-Cyanomethyl-2-cyclohexylmethyl-*N*-(3-nitro-benzyl)-malonamide; *N*-Cyanomethyl-2-cyclohexylmethyl-*N*-(4-methoxy-benzyl)-
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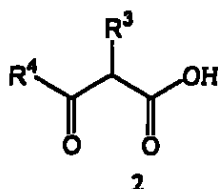
- malonamide; *N*-(3-Carbamoyl-phenyl)-*N'*-cyanomethyl-2-cyclohexylmethyl-malonamide; *N*-Cyanomethyl-2-cyclohexylmethyl-*N'*-pyridin-3-ylmethyl-malonamide; *N*-(4-carbamoylphenyl)-*N'*-cyanomethyl-2-cyclohexylmethylmalonamide; *N*-cyanomethyl-2-cyclohexylmethyl-*N'*-tetrahydrofuran-2-ylmethylmalonamide; *N*-cyanomethyl-2-cyclohexylmethyl-3-(3,4-dihydro-2*H*-quinolin-1-yl)-3-oxopropionamide; *N*-*tert*-butyl-*N'*-cyanomethyl-2-cyclohexylmethyl-*N*-methylmalonamide; *N*-cyanomethyl-2-cyclohexylmethyl-*N'*-methyl-*N'*-propylmalonamide; *N*-butyl-*N'*-cyanomethyl-2-cyclohexylmethyl-*N*-methylmalonamide; *N*-cyanomethyl-2-cyclohexylmethyl-*N,N'*-dimethylmalonamide; *N*-benzyl-*N'*-cyanomethyl-2-(2-phenylsulfanylethyl)malonamide; 2-(2-phenylsulfonylethyl)-*N*-benzyl-*N'*-cyanomethylmalonamide; 2-(2-benzenesulfonyl-ethyl)-*N*-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-pentyl]-*N'*-benzyl-malonamide; *N,N'*-bis-[(*S*)-1-(1-benzooxazol-2-yl-methanoyl)-propyl]-2-cyclohexylmethyl-malonamide; and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof; and the pharmaceutically acceptable salts and solvates of such compounds and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.
7. A pharmaceutical composition comprising a therapeutically effective amount of a compound of Claim 1 in combination with a pharmaceutically acceptable excipient.
8. A method for treating a disease in an animal in which inhibition of Cathepsin S can prevent, inhibit or ameliorate the pathology and/or symptomology of the disease, which method comprises administering to the animal a therapeutically effective amount of compound of Claim 1 or a *N*-oxide derivative or individual isomer or mixture of isomers thereof; or a pharmaceutically acceptable salt or solvate of such compounds and the *N*-oxide derivatives, prodrug derivatives, protected derivatives, individual isomers and mixtures of isomers thereof.
9. The use of a compound of Claim 1 in the manufacture of a medicament for treating

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a disease in an animal in which Cathepsin S activity contributes to the pathology and/or symptomology of the disease.

10. A process for preparing a compound of Formula I:

5 (A) reacting a compound of Formula 2:



with a compound of formula $\text{NH}_2\text{CR}^1\text{R}^2\text{X}^3$, in which R^1 , R^2 , R^3 , R^4 and X^3 are as defined in the Summary of the Invention for Formula I; or

10 (B) reacting a compound of Formula 2 with a compound of Formula NH_2X^3 , in which R^3 , R^4 and X^3 are as described in the Summary of the Invention for Formula I; and

(C) optionally converting a compound of Formula I into a pharmaceutically acceptable salt;

(D) optionally converting a salt form of a compound of Formula I to non-salt form;

15 (E) optionally converting an unoxidized form of a compound of Formula I into a pharmaceutically acceptable *N*-oxide;

(F) optionally converting an *N*-oxide form of a compound of Formula I to its unoxidized form;

20 (G) optionally resolving an individual isomer of a compound of Formula I from a mixture of isomers;

(H) optionally converting a non-derivatized compound of Formula I into a pharmaceutically prodrug derivative; and

(I) optionally converting a prodrug derivative of a compound of Formula I to its non-derivatized form.

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REQUISITOS NECESARIOS PARA PRESENTAR TRAMITE

Indicacion : 001.265 0000000
Fecha (AMB) : 2004-12-04 13:15:14
Tramite : 001 (01-PATENTE) 379 (154-001) 001 (PATENTE)
Dependencia : 2024 DIVISION DE MARCAS Y DISEÑOS

	USUARIO	RADICADOR
PATENTE DE INVENCION	()	()
- Indicación de que se solicita la concesión de una patente.	()	()
- Datos de identificación del solicitante o de la persona que se presenta la solicitud.	()	()
- Descripción de la invención.	()	()
- Dibujos de ser estos pertinentes.	()	()
- Comprobante de Pago de las tasas establecidas.	()	()

COMPLETA () INCOMPLETA ()

DISEÑO INDUSTRIAL ()		
- Indicación de que se solicita el registro de Diseño Industrial	()	()
- Datos de identificación del solicitante o de la persona que presenta la solicitud.	()	()
- Representación gráfica 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: 

Fecha:



2020
Bogotá, D.C.,

Doctora:
Dña María Rodríguez D'Aleman
Apoderada
Axys Pharmaceuticals

Oficio N°
01704

ASUNTO:	Radicación N°	03-113296
	Solicitud Internacional	PCT/US02/17922
	Fecha inicio fase nacional	04/01/2004
	Trámite	011
	Evento	379
	Actuación	430
	Folios	001

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

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

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

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo quinto del título primero de la Circular Única N° 10 de 2001.


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

El anterior requerimiento fue notificado por fijación en lista de fecha 13 FEB. 2004.