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E. S. D.

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO



No. 04-002808-00008-0000

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Act 444 RESPUESTAREQUE Folios: 33

Trámite : 011 Evento : 379 Actuación : 444

Referencia : Expediente No. 04002808
Asunto : REGISTRO - PATENTE PCT DERIVADOS DE
DIAMINA, PROCESOS PARA PRODUCIR LOS
DERIVADOS DE DIAMINA Y FUNGICIDAS QUE
CONTIENEN LOS DERIVADOS DE DIAMINA COMO
INGREDIENTE ACTIVO
Solicitante : MITSUI CHEMICALS, INC.
Clase : A01N 047/012, C07C 269/004, C07C 271/020, C07D
213/081, C07D 275/003, C07D 307/068, C07D 333/040, C07D 405/012,
C07D 409/012

1. Yo, Emilio FERRERO, obrando como apoderado del solicitante en el asunto antes identificado, me refiero al Oficio No. 851 notificado por fijación en lista del 25 de enero de 2008, y atentamente presento junto con este escrito los siguientes artículos:

▪ COPIA DE RESULTADOS DE EXÁMENES DE PATENTABILIDAD EFECTUADOS:

o EP No. 02749 320.4

- Reporte de búsqueda parcial Europea con EP0648740A1
- Acción Oficial de Agosto 28, 2007.
- No se ha realizado un resultado final del examen de la solicitud Europea, por lo que todavía se encuentra pendiente.

o Solicitud US 10/483956

Se adjunta la primera página de US 7,312,245 B2, la cual fue otorgada en Diciembre 25, 2007.



P.B.5818 - Patentaan 2
2280 HV Rijswijk (ZH)
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Directorate General 1

Direction générale 1

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02 AUG 2006

MEWBURN ELLIS LLP

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Date

02.08.06

Reference
IS/FP6200125

Application No./Patent No.
02749320.4 - 2103 PCT/JP0207319

Applicant/Proprietor
Mitsui Chemicals, Inc.

COMMUNICATION

The European Patent Office herewith transmits as an enclosure the supplementary European search report under Article 157(2)(a) EPC for the above-mentioned European patent application.

If applicable, copies of the documents cited in the European search report are attached.

☒ Additional set(s) of copies of the documents cited in the European search report is (are) enclosed as well.

ASD

Refund of the search fee

If applicable under Article 10 Rules relating to fees, a separate communication from the Receiving Section on the refund of the search fee will be sent later.





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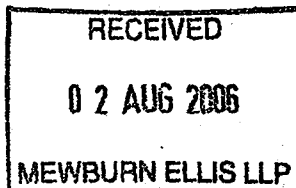
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European Patent
Office

**SUPPLEMENTARY
PARTIAL EUROPEAN SEARCH REPORT**

Application Number

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

EP 02 74 9320

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
A	EP 0 648 740 A (KUMIAI CHEMICAL INDUSTRY) 19 April 1995 (1995-04-19) * the whole document *	1-15	INV. C07C271/20 C07C271/52 C07C269/04 C07C269/06 A01N47/12 C07D213/81 C07D275/03 C07D333/40 C07D213/82 C07D307/68 C07D409/12
			TECHNICAL FIELDS SEARCHED (IPC)
			C07C C07D A01N
The supplementary search report has been based on the last set of claims valid and available at the start of the search.			
INCOMPLETE SEARCH			
The Search Division considers that the present application, or some or all of its claims, does/do not comply with the EPC to such an extent that a meaningful search into the state of the art cannot be carried out, or can only be carried out partially, for the following claims:			
Claims searched completely :			
Claims searched incompletely :			
Claims not searched :			
Reason for the limitation of the search: see sheet C			
Place of search The Hague		Date of completion of the search 25 July 2006	Examiner Beslier, L
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document		T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document	

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EPO FORM 1503 03.02 (P04C20)



European Patent
Office

**SUPPLEMENTARY
PARTIAL EUROPEAN SEARCH REPORT**

Application Number

which under Rule 45 of the European Patent Convention shall be considered, for the purposes of subsequent proceedings, as the European search report

EP 02 74 9320

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373

DOCUMENTS CONSIDERED TO BE RELEVANT			
Category	Citation of document with indication, where appropriate, of relevant passages	Relevant to claim	CLASSIFICATION OF THE APPLICATION (IPC)
A	EP 0 648 740 A (KUMIAI CHEMICAL INDUSTRY) 19 April 1995 (1995-04-19) * the whole document *	1-15	INV. C07C271/20 C07C271/52 C07C269/04 C07C269/06 A01N47/12 C07D213/81 C07D275/03 C07D333/40 C07D213/82 C07D307/68 C07D409/12
			TECHNICAL FIELDS SEARCHED (IPC)
			C07C C07D A01N
The supplementary search report has been based on the last set of claims valid and available at the start of the search.			
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The Search Division considers that the present application, or some or all of its claims, does/do not comply with the EPC to such an extent that a meaningful search into the state of the art cannot be carried out, or can only be carried out partially, for the following claims:			
Claims searched completely :			
Claims searched incompletely :			
Claims not searched :			
Reason for the limitation of the search:			
see sheet C			
Place of search		Date of completion of the search	Examiner
The Hague		25 July 2006	Beslier, L
CATEGORY OF CITED DOCUMENTS			
X : particularly relevant if taken alone Y : particularly relevant if combined with another document of the same category A : technological background O : non-written disclosure P : intermediate document			
T : theory or principle underlying the invention E : earlier patent document, but published on, or after the filing date D : document cited in the application L : document cited for other reasons & : member of the same patent family, corresponding document			

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EPO FORM 1503 03.82 (P44C20)

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European Patent
Office

INCOMPLETE SEARCH
SHEET C

Application Number
EP 02 74 9320

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Claim(s) searched incompletely:
1-15

Reason for the limitation of the search:

The present claims 1-15 relate to an extremely large number of possible compounds. Support and disclosure in the sense of Article 84 and 83 EPC is to be found however for only a very small proportion of the compounds claimed, see the examples. The non-compliance with the substantive provisions is to such an extent, that a meaningful search of the whole claimed subject-matter of the claim could not be carried out (Rule 45 EPC and Guidelines B-VIII, 3). The extent of the search was consequently limited.

The search of claims 1-15 was restricted to those claimed compounds which appear to be supported and a generalisation of their structural formulae, see the examples.

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EP 02 74 9320

25-07-2006

Patent document cited in search report	Publication date	Patent family member(s)	Publication date
EP 0648740	A	19-04-1995	BR 9405281 A 31-08-1999
			CN 1108863 A 20-09-1995
			DE 69406083 D1 13-11-1997
			DE 69406083 T2 26-02-1998
			WO 9425432 A1 10-11-1994
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			US 5574064 A 12-11-1996

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Europäisches Patentamt
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Office européen des brevets



Publication number: **0 648 740 A1**

(12)

EUROPEAN PATENT APPLICATION
published in accordance with Art.
158(3) EPC

(21) Application number: 94914561.9

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(87) International publication number:
WO 94/25432 (10.11.94 94/25)

(51) Int. Cl.⁶: **C07C 271/22, C07C 271/32,
C07C 271/54, C07C 317/14,
C07C 327/20, C07D 213/28,
C07D 239/32, C07D 307/04,
C07D 307/40, C07D 307/77,
C07D 333/14**

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19.04.95 Bulletin 95/16

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EP 0 648 740 A1

(54) AMINO ACID AMIDE DERIVATIVE, AGROHORTICULTURAL BACTERICIDE, AND PRODUCTION
PROCESS.

(57) An amino acid amide derivative represented by general formula (I) and an agrohorticultural bactericide

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an alkylene oxide group,
an aralkyl group (optionally having at least one same or different substituent selected from the group consisting of a methyl group, a cyano group, and a nitro group),
a phenyl group (optionally having at least one same or different substituent selected from the group

consisting of a halogen atom,
a lower alkyl group which may be substituted with a same or different halogen atom,
a lower alkoxy group which may be substituted with a same or different halogen atom,
a cyano group, and
a nitro group), or
a heterocyclic group,

R² represents an ethyl group, an *n*-propyl group, an isopropyl group, an isobutyl group, a *sec*-butyl group, a *tert*-butyl group, an alkenyl group, a cycloalkyl group, a phenyl group (optionally having at least one substituent of halogen atom),

R³ represents a hydrogen atom or a lower alkyl group,

R⁴ represents a hydrogen atom, a lower alkyl group, or a cyano group,

R⁵, R⁶, and R⁷ independently represent a hydrogen atom or a lower alkyl group,

R⁸ represents a hydrogen atom, a lower alkyl group, an aralkyl group, a phenyl group, an alkoxy carbonyl group, or a cyano group,

Z¹ and Z² independently represent an oxygen atom or a sulfur atom,

Z³ represents

an oxygen atom,

a sulfur atom,

a group N-R¹⁰ (wherein R¹⁰ represents a hydrogen atom, a methyl group, a methylcarbonyl group, a phenylcarbonyl group, a methoxycarbonyl group, or a methoxymethyl group),

a sulfinyl group,

a sulfonyl group,

a group COO,

a group CONR¹¹ (wherein R¹¹ represents a hydrogen atom or a lower alkyl group),

Q represents

a phenyl group [optionally having at least one same or different substituent selected from the group consisting of

a halogen atom,

a lower alkyl group which may be substituted with at least one same or different halogen atom,

a lower alkoxy group which may be substituted with a same or different halogen atom,

a cyano group,

a nitro group,

a lower alkoxy carbonyl group,

a methylsulfonyl group,

a methylsulfinyl group,

a methylthio group which may be substituted with a halogen atom,

a dimethylamino group,

a phenylsulfonyl group,

an acyl group, and

a phenyl group],

an alkylene oxide group,

a heterocyclic group (optionally having a substituent selected from the group consisting of a halogen atom, an alkyl group, a trifluoromethyl group, and a nitro group), or

a condensed heterocyclic group optionally having a substituent selected from the group consisting of a halogen atom and a nitro group,

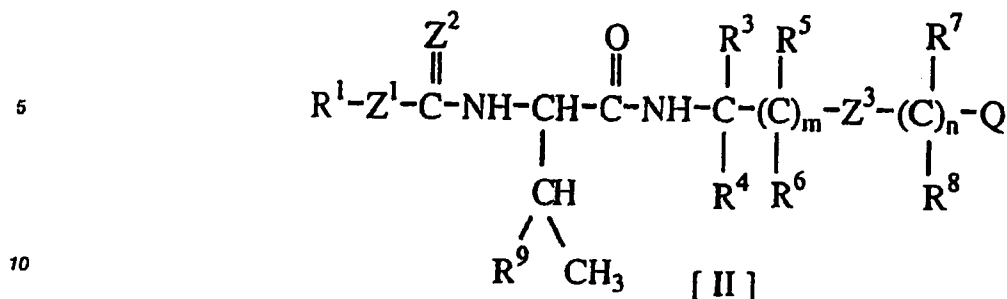
m represents an integer from 0 to 2, and

n represents 0 or 1.

2. An amino-acid amide derivative as recited in claim 1, which is represented by the formula:

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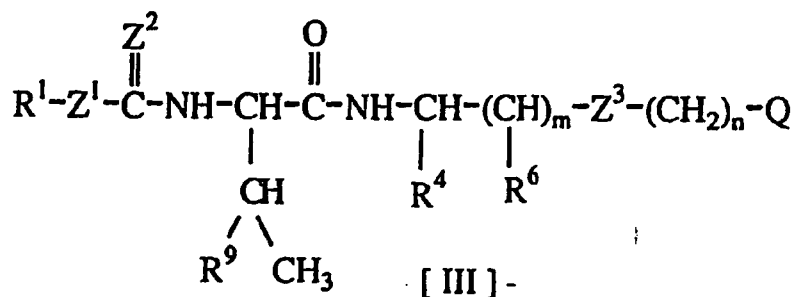


wherein R¹ represents
 a lower alkyl group (optionally having at least one same or different substituent selected from the group consisting of a halogen atom and an alkoxy group),
 a lower alkenyl group,
 a lower alkynyl group,
 a cycloalkyl group (optionally having at least one substituent of methyl group),
 a cycloalkenyl group,
 an alkylene oxide group,
 an aralkyl group (optionally having at least one same or different substituent selected from the group consisting of a methyl group, a cyano group, and a nitro group),
 a phenyl group (optionally having at least one same or different substituent selected from the group consisting of a halogen atom, a methyl group, a methoxy group, a cyano group, a trifluoromethyl group, a trifluoromethoxy group, and a nitro group),
 or a heterocyclic group,
 R³ represents a hydrogen atom or a lower alkyl group,
 R⁴ represents a hydrogen atom, a lower alkyl group, or a cyano group,
 R⁵, R⁶, and R⁷ independently represent a hydrogen atom or a lower alkyl group,
 R⁸ represents a hydrogen atom, a lower alkyl group, an aralkyl group, a phenyl group, an alkoxy carbonyl group, or a cyano group,
 R⁹ represents a hydrogen atom, a methyl group or an ethyl group,
 Z¹ and Z² independently represent an oxygen atom or a sulfur atom,
 Z³ represents an oxygen atom, a sulfur atom, a group N-R¹⁰ (wherein R¹⁰ represents a hydrogen atom, a methyl group, a methylcarbonyl group, a phenylcarbonyl group, a methoxycarbonyl group, or a methoxymethyl group), a sulfinyl group, or a sulfonyl group,
 Q represents
 a phenyl group [optionally having at least one same or different substituent selected from the group consisting of
 a halogen atom,
 a lower alkyl group which may be substituted with at least one halogen atom,
 a lower alkoxy group which may be substituted with at least one halogen atom,
 a cyano group,
 a nitro group,
 a lower alkoxy carbonyl group,
 a methylsulfonyl group,
 a methylsulfinyl group,
 a methylthio group which may be substituted with a halogen atom,
 a dimethylamino group,
 a phenylsulfonyl group,
 an acyl group, and
 a phenyl group],
 a heterocyclic group (optionally having a substituent selected from the group consisting of a halogen atom and a nitro group), or
 a condensed heterocyclic group (optionally having a substituent selected from the group consisting of a halogen atom and a nitro group),
 m represents an integer from 0 to 2, and

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n represents 0 or 1.

3. An amino-acid amide derivative as recited in Claim 1, which is represented by the formula:



wherein R¹ represents a C₁ - C₆ alkyl group (optionally having at least one same or different substituent selected from the group consisting of a halogen atom and an alkoxy group), a C₂ - C₆ alkenyl group, a C₂ - C₆ alkynyl group, a C₃ - C₈ cycloalkyl group (optionally having at least one substituent of methyl group), a C₂ - C₈ alkylene oxide group, a C₇ - C₈ aralkyl group (optionally having at least one substituent of methyl group), or a phenyl group (optionally having at least one same or different substituent selected from the group consisting of a halogen atom, a methyl group, a methoxy group, a trifluoromethyl group, a trifluoromethoxy group, and a nitro group),

R⁴ represents a hydrogen atom, a C₁ - C₃ alkyl group, or a cyano group,

R⁶ represents a hydrogen atom or a C₁ - C₃ alkyl group,

R⁹ represents a hydrogen atom, a methyl group, or an ethyl group,

Z¹ and Z² independently represent an oxygen atom or a sulfur atom,

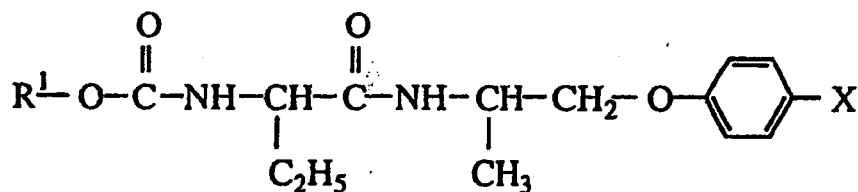
Z³ represents an oxygen atom, a sulfur atom, a group N-R¹⁰ (wherein R¹⁰ represents a hydrogen atom, a methyl group, a methylcarbonyl group, or a phenylcarbonyl group), a sulfinyl group, or a sulfonyl group,

Q represents a phenyl group [optionally having at least one same or different substituent selected from the group consisting of a halogen atom, a C₁ - C₃ alkyl group which may be substituted with at least one same or different halogen atom, a C₁ - C₃ alkoxy group which may be substituted with a same or different halogen atom, a cyano group, a nitro group, a methylsulfonyl group, a methylsulfinyl group, and a methylthio group], a pyrimidinyl group, or a pyridyl group which may be substituted with a halogen atom,

m represents 1 or 2, and

n represents 0 or 1.

4. An amino-acid amide derivative as recited in Claim 1, which is represented by the formula:



[IV]

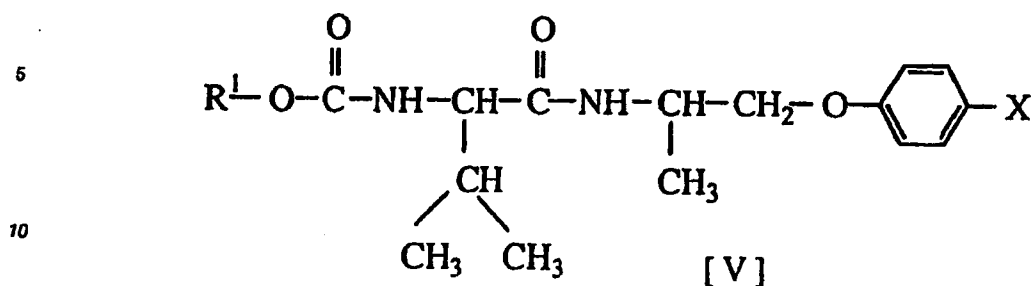
wherein R¹ represents an isopropyl group, a *tert*-butyl group, a cyclopentyl group, or a phenyl group (optionally having at least one same or different substituent selected from the group consisting of a halogen atom, a methyl group, a methoxy group, and a nitro group), and

X represents a halogen atom, a cyano group, or a nitro group.

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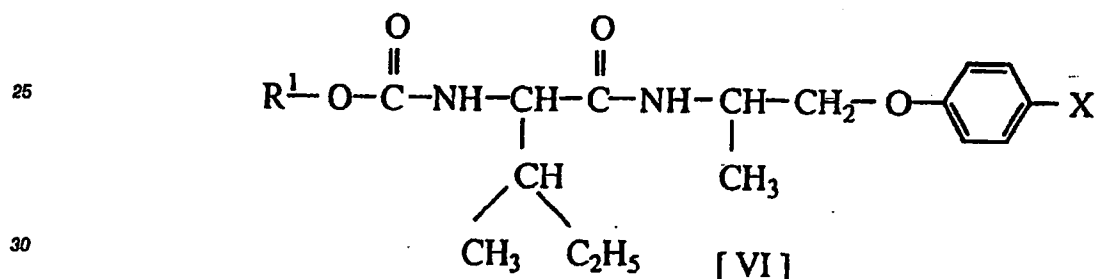
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5. An amino-acid amide derivative as recited in Claim 1, which is represented by the formula:



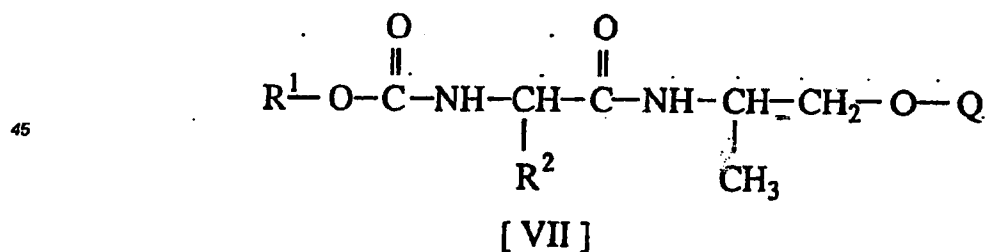
wherein R¹ represents an isopropyl group, a *tert*-butyl group, a cyclopentyl group, a cyclohexyl group which may be substituted with a methyl group, or a phenyl group (optionally having at least one same or different substituent selected from the group consisting of a halogen atom, a methyl group, a methoxy group, a trifluoromethyl group, a trifluoromethoxy group, and a nitro group), and X represents a halogen atom, a cyano group, or a nitro group.

6. An amino-acid amide derivative as recited in Claim 1, which is represented by the formula:



wherein R¹ represents an isopropyl group, a *tert*-butyl group, a cyclopentyl group, or a phenyl group (optionally having at least one same or different substituent selected from the group consisting of a halogen atom, a methyl group, a methoxy group, and a nitro group), and X represents a halogen atom, a cyano group, or a nitro group.

7. An amino-acid amide derivative as recited in Claim 1, which is represented by the formula:



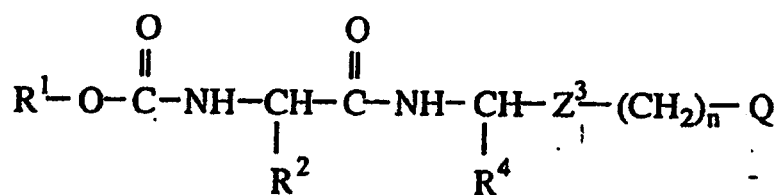
wherein R¹ represents a C₁ ~ C₆ alkyl group (optionally having at least one substituent cyano group), a C₃ ~ C₈ cycloalkyl group (optionally having at least one substituent halogen atom), a C₄ ~ C₈ cycloalkyl C₁ ~ C₃ alkyl group, a benzyl group or a phenyl group (optionally having at least one same or different substituent selected from the group consisting of a halogen atom and a difluoromethoxy group),

R² represents an *n*-propyl group, an isopropyl group, an isobutyl group, a *tert*-butyl group, an isopropenyl group, a C₃ ~ C₈ cycloalkyl group, or a phenyl group (optionally having at least one

substituent halogen atom), and

Q represents a phenyl group (optionally having at least one substituent cyano group), a pyridyl group (optionally having at least one substituent of a same or different halogen atom or trifluoromethyl group), or a pyrimidinyl group (optionally having at least one same or different substituent of a halogen atom or C₁ - C₃ alkyl group).

8. An amino-acid amide derivative as recited in Claim 1, which is represented by the formula:



[VIII]

wherein R¹ represents a C₁ - C₆ alkyl group, a C₃ - C₈ cycloalkyl group, or a phenyl group (optionally having at least one substituent halogen atom),

R² represents an ethyl group, an isopropyl group, or a *sec*-butyl group,

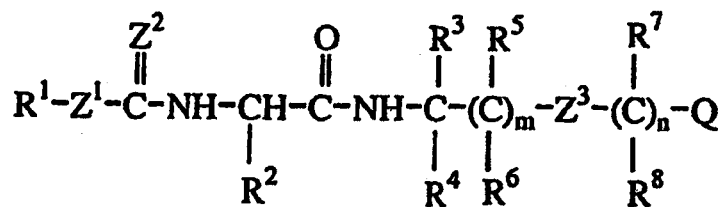
R⁴ represents a hydrogen atom or a C₁ - C₃ alkyl group,

Z³ represents a group COO, a group CONR¹² (wherein R¹² represents a hydrogen atom or a C₁ - C₃ alkyl group),

Q represents a phenyl group (optionally having at least one same or different substituent selected from the group consisting of a halogen atom, a C₁ - C₃ alkyl group, a C₁ - C₃ alkoxy group, and a cyano group), and

n represents 0 or 1.

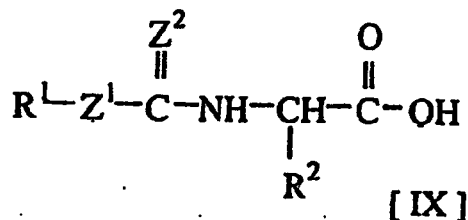
9. A process for preparing an amino-acid amide derivative represented by the formula:



[I]

wherein R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, Z¹, Z², Z³, Q, m, and n have the same meanings as defined in Claim 1,

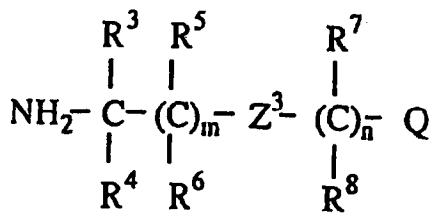
comprising the step of: reacting a compound represented by the formula:



wherein R¹, R², Z¹, and Z² have the same meanings as defined in Claim 1, with a compound represented by the formula:

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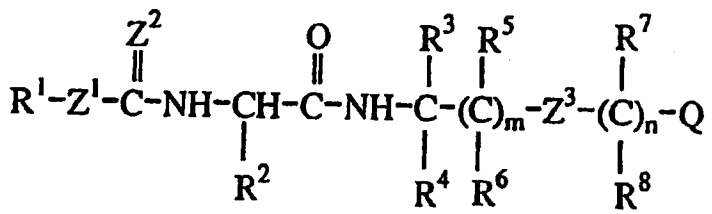
[X]

wherein R³, R⁴, R⁵, R⁶, R⁷, R⁸, Z³, Q, m, and n have the same meanings as defined in Claim 1.

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10. A process for preparing an amino-acid amide derivative represented by the formula:

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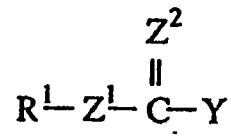
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[I]

wherein R¹, R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, Z¹, Z², Z³, Q, m, and n have the same meanings as defined in Claim 1,

comprising the step of: reacting a compound represented by the formula:

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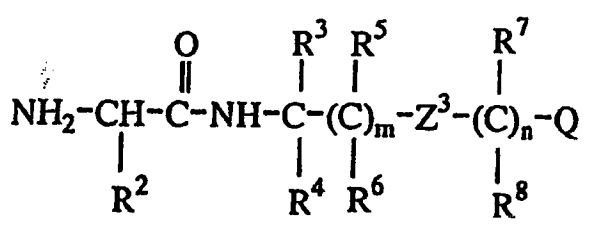
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[XI]

wherein Y represents a halogen atom, a 4,6-dimethylpyrimidinylthio group, a group R¹OC(O)O-, or a group -ON=C(CN)Ph (wherein Ph represents a phenyl group), and R¹, Z¹, and Z² have the same meanings as defined in Claim 1,

with a compound represented by the formula:

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[XII]

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wherein R², R³, R⁴, R⁵, R⁶, R⁷, R⁸, Z³, Q, m, and n have the same meanings as defined in Claim 1.

11. An agricultural or horticultural fungicidal composition which includes an effective amount of an amino-acid amide derivative as recited in Claim 1.

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INTERNATIONAL SEARCH REPORT

International application No.

PCT/JP94/00708

A. CLASSIFICATION OF SUBJECT MATTER

Int. Cl⁵ C07C271/22, 271/32, 271/54, 317/14, 327/20, C07D213/28, 239/32, 307/04, 307/40, 307/77, 333/14, 333/50, A01N47/12
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)

Int. Cl⁵ C07C271/22, 271/32, 271/54, 271/06, 327/20, 317/14, C07D213/28, 239/32, 307/04, 307/40, 307/77, 333/14, 333/50,

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)

CAS ONLINE

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JP, A, 4-338372 (Bayer AG.), November 25, 1992 (25. 11. 92), Pages 1 to 3 & EP, A2, 496,239	1-11
A	JP, A, 4-283554 (Bayer AG.), October 8, 1992 (08. 10. 92), Pages 1 to 3 & EP, A1, 485,794	1-11
A	JP, A, 4-308507 (American Cyanamid Co.), October 30, 1992 (30. 10. 92), Pages 1 to 3 & EP, A1, 493,683	1-11
A	JP, A, 4-230653 (Bayer AG.), August 19, 1992 (19. 08. 92), Pages 1 to 2 & EP, A, 477,639	1-11
A	JP, A, 4-230652 (Bayer AG.), August 19, 1992 (19. 08. 92), Pages 1 to 2 & EP, A1, 550,788	1-11

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

☐ See patent family annex.

* Special categories of cited documents:

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

"E" earlier document but published on or after the international filing date

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

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

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

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

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

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

"Z" document member of the same patent family

Date of the actual completion of the international search

July 7, 1994 (07. 07. 94)

Date of mailing of the international search report

July 26, 1994 (26. 07. 94)

Name and mailing address of the ISA/

Japanese Patent Office

Authorized officer

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FAX +49 89 2399-4465

Europäisches
Patentamt

Generaldirektion 2

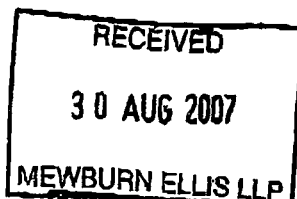
European
Patent Office

Directorate General 2

Office européen
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Direction Générale 2

Stuart, Ian Alexander
Mewburn Ellis LLP
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23 Kingsway
London WC2B 6HP
ROYAUME-UNI



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Telephone numbers: Branch at The Hague

Primary Examiner (substantive examination) +31 70 340-9518

Formalities Officer / Assistent (Formalities and other matters) +31 70 340-1948

Application No. 02 749 320.4 - 127P 1.	Ref. IS/FP6200125	Date 28.08.2007
Applicant Mitsui Chemicals, Inc.		

Communication pursuant to Article 96(2) EPC

The examination of the above-identified application has revealed that it does not meet the requirements of the European Patent Convention for the reasons enclosed herewith. If the deficiencies indicated are not rectified the application may be refused pursuant to Article 97(1) EPC.

You are invited to file your observations and insofar as the deficiencies are such as to be rectifiable, to correct the indicated deficiencies within a period

of 4 months

from the notification of this communication, this period being computed in accordance with Rules 78(2) and 83(2) and (4) EPC.

One set of amendments to the description, claims and drawings is to be filed within the said period on separate sheets (Rule 36(1) EPC).

Failure to comply with this invitation in due time will result in the application being deemed to be withdrawn (Article 96(3) EPC).



Duval, Eric
Primary Examiner
for the Examining Division

Enclosure(s): 4 page/s reasons (Form 2906)

**Bescheld/Protokoll (Anlage)****Communication/Minutes (Annex)****Notification/Procès-verbal (Annexe)**

Datum
Date 28.08.2007
Date

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Sheet 1
Feuille

Anmelde-Nr.:
Application No.: 02 749 320.4
Demande n°:

1. The examination is being carried out on the following application documents:

Description, Pages

1, 5-82 as originally filed
2-4 as annexed to the Int. Prel. Examination Report

Claims, Numbers

2(part), 3-15 as originally filed
1, 2(part) as annexed to the Int. Prel. Examination Report

2. Reference is made to the following documents; the numbering will be adhered to in the rest of the procedure:

- D1: WO 01 46124 A1 (for convenience, see the equivalent document US2004/0009982 in English)
D2: KYNE GRAHAM M. ET AL.: 'Enantioselective amino acid recognition using acyclic thiourea receptors' JOURNAL OF THE CHEMICAL SOCIETY, PERKIN TRANSACTIONS 1 no. 11, 2001, pages 1258 - 1263, XP002957636
D3: WO 01 05783 A1
D4: WO 02 40483 A1 (for convenience, see the equivalent document EP-1340757 in English)
D5: EP-A-0 648 740 (KUMIAI CHEMICAL INDUSTRY) 19 April 1995 (1995-04-19)

3. The amendments annexed to the Int. Prel. Examination Report introduce subject-matter which extends beyond the content of the application as filed, contrary to Article 123(2) EPC. The amendments concerned are the following:

A proviso has been introduced in claims 1 and 2, removing from the claimed subject-matter the compounds of formula (1) where R1 is tert-butyl. This proviso does not appear to be present in the application as originally filed; a basis for said amendment was furthermore not indicated by the applicant.

The introduction of said proviso cannot be considered to be validly based on the prior art documents either, for the following reason:

A disclaimer may be allowable in order to restore novelty by delimiting a claim against an accidental anticipation under Article 54(2) EPC; it should however not remove more



Bescheld/Protokoll (Anlage)

Communication/Minutes (Annex)

Notification/Procès-verbal (Annexe)

Datum
Date
Date

28.08.2007

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2

Anmelde-Nr.:
Application No.:
Demande n°:

02 749 320.4

than is necessary to restore novelty (see G1/03). In the present case, although some isolated compounds corresponding to formula (1) where R1=tert-butyl are known from the prior art, disclaiming all the compounds of formula (1) where R1=tert-butyl leads to the exclusion of a large number of compounds which are presumably not part of the state of the art.

The disclaimer introduced in claim 1 and 2, and the corresponding modifications on pages 2-4 of the description, are therefore unallowable under Article 123(2).

4. Clarity

The application does not meet the requirements of Article 84 EPC, because claims 1-5 are not clear.

Claim 1 contains a proviso removing from the claimed subject-matter compounds "where R3, R4, R5 and R6 all represent a hydrogen atom or where any one of R3, R4, R5 and R6 represents a methyl group which may be substituted and the others represent a hydrogen atom". In this respect, the description (cf. pages 57-62) shows a large number of compounds corresponding to formula (1) of claim 1, where R4-R6=H and R3 is iso-propyl of iso-butyl, i.e. a methyl substituted with alkyls. Thus said examples are excluded from the scope of claim 1 by said proviso, and do not fall within the scope of any other claim.

This contradiction between the claims and the description renders the claims unclear.

5. Novelty

The present application does not meet the requirements of Article 52(1) EPC, because the subject-matter of claims 1-4 and 9-11 is not new in the sense of Article 54(1) and (2) EPC.

5.1 Document D1 discloses (cf. compounds 8-19, table 1) compounds corresponding to formula (1) where R1=alkyl, R2=R3=R4=R7=H, R5=R6=Me, R8 is a substituted aryl, and their use as insecticides. D1 thus anticipates claims 1-4, as well as claims 9 (the functional definition "a fungicide" does not confer novelty here, since the ability to be a fungicide stems from the structure of the compounds) and 11 (cf. D1, production process 2).

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Beschuld/Protokoll (Anlage)

Communication/Minutes (Annex)

Notification/Procès-verbal (Annexe)

Datum
Date 28.08.2007
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Anmelde-Nr.:
Application No.: 02 749 320.4
Demande n°:

5.2 As a result of the lack of clarity of the proviso (see 4. above), the subject-matter of claims 1-4, 9 and 10 cannot be clearly distinguished from the compounds and processes disclosed in documents D2 (cf. page 1259, compound 9) and D3 (cf. compound 42, page 40).

5.2 The PCT application D4 published on 23.05.2002 claims the priority date of 16.11.2000. It has been supplied to the European Patent Office in one of its official languages and the national fee provided for in Article 22, paragraph 1 or Article 39, paragraph 1 of the Co-operation Treaty has been paid. The requirements of Article 158(2) EPC are thus fulfilled.

Its content as filed is therefore considered as comprised in the state of the art relevant to the question of novelty, pursuant to Article 54(3) and (4) EPC. This earlier application shows (cf. reference example 61, intermediates 3-7) compounds which, for the reason explained above (see 4.), cannot be distinguished from formula (1).

Thus, D4 is prejudicial to the novelty of the subject-matter of claims 1-4, 9 and 11 of the present application insofar as the same Contracting States are designated.

5.3 Owing to the fact that the International and European searches could not be completed over the whole scope of the claims, a further search, at a later stage of the proceedings, is likely to retrieve more documents relevant to the issue of novelty.

6. Inventive step

The present application does not meet the requirements of Article 52(1) EPC, because the subject-matter of claims 1-15 does not involve an inventive step in the sense of Article 56 EPC.

The groups R1-R8 in formula (1) of claim 1, as well as the groups R9, R10, R15 and R16 of formula (9) of claim 5, are defined as being optionally substituted by any substituent. As a result of this unlimited optional substitution, the scope of claims 1 and 5 is broadened to such an extent that it encompasses compounds which could not solve the technical problem underlying the application, i.e. the provision of fungicides. Non-limiting terms as cited above may include:

- groups which are structurally so remote from those of the examples that the activity



Bescheld/Protokoll (Anlage)

Communication/Minutes (Annex)

Notification/Procès-verbal (Annexe)

Datum
Date 28.08.2007
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Sheet 4
FeuilleAnmelde-Nr.:
Application No.: 02 749 320.4
Demande n°:

of the resulting molecules could not be predicted within the limits of qualitative structure-activity relationships studies.

- groups which may impart toxic or herbicidal properties to the resulting molecules, thus making its use as an insecticide impossible.

Thus claim 1 does not meet the requirement of article 56 EPC that the technical problem should be solved over the whole scope of the claim.

7. The following deficiencies are additionally noted:

To meet the requirements of Rule 27(1)(b) EPC, the document D5 should be identified in the description and the relevant background art disclosed therein should be briefly discussed.

8. The applicant is invited to file new claims which take account of the above comments.

In order to facilitate the examination of the conformity of the amended application with the requirements of Article 123(2) EPC, the applicant should clearly identify the amendments carried out, irrespective of whether they concern amendments by addition, replacement or deletion, and to indicate the passages of the application as filed on which these amendments are based (see Guidelines E-II, 1).

If the applicant regards it as appropriate these indications could be submitted in handwritten form on a copy of the relevant parts of the application as filed.



US007312245B2

332

(12) **United States Patent**
Chiba et al.

(10) **Patent No.:** **US 7,312,245 B2**
(45) **Date of Patent:** **Dec. 25, 2007**

(54) **DIAMINE DERIVATIVES, PROCESS FOR PRODUCING THE DIAMINE DERIVATIVES, AND FUNGICIDES CONTAINING THE DIAMINE DERIVATIVES AS AN ACTIVE INGREDIENT**

2003/0229092 A1 12/2003 Ohimeyer et al.
2004/0009982 A1 1/2004 Tohnishi et al.

FOREIGN PATENT DOCUMENTS

(75) **Inventors:** Yutaka Chiba, Mobara (JP); Hidenori Daido, Mobara (JP); Tomohisa Akase, Minato-ku (JP); Hirozumi Matsuno, Minato-ku (JP); Junro Kishi, Minato-ku (JP)

EP	0 648 740 A1	4/1995
WO	99/41231 A1	8/1999
WO	01/05783	1/2001
WO	01/46124	6/2001
WO	01/46152	6/2001
WO	WO 01/46152 A1 *	6/2001
WO	02/40483	5/2002

(73) **Assignee:** Mitsui Chemical, Inc., Tokyo (JP)

(*) **Notice:** Subject to any disclaimer, the term of this patent is extended or adjusted under 35 U.S.C. 154(b) by 502 days.

OTHER PUBLICATIONS

Kyne et al, "Enantioselective amino acid recognition using acyclic thiourea receptors", *Journal of the Chemical Society, Perkin Trans I*, No. 11, pp. 1258-1263 (2001), published by The Royal Society of Chemistry.

* cited by examiner

Primary Examiner—Paul A. Zucker
(74) **Attorney, Agent, or Firm**—Buchanan Ingersoll & Rooney PC

(21) **Appl. No.:** 10/483,956

(22) **PCT Filed:** Jul. 18, 2002

(86) **PCT No.:** PCT/JP02/07319

§ 371 (c)(1),
(2), (4) **Date:** Jan. 16, 2004

(87) **PCT Pub. No.:** WO03/008372

PCT Pub. Date: Jan. 30, 2003

(65) **Prior Publication Data**

US 2005/0075512 A1 Apr. 7, 2005

(30) **Foreign Application Priority Data**

Jul. 18, 2001 (JP) 2001-218387

(51) **Int. Cl.**

A61K 31/235 (2006.01)
C07C 229/00 (2006.01)
C07C 271/00 (2006.01)

(52) **U.S. Cl.** 514/533; 560/19; 560/32

(58) **Field of Classification Search** None
See application file for complete search history.

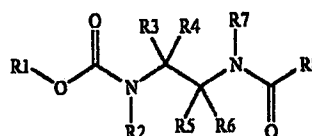
(56) **References Cited**

U.S. PATENT DOCUMENTS

6,358,960 B1 3/2002 Senokuchi et al.

(57) **ABSTRACT**

A fungicide can be provided by using, as an active ingredient, a diamine derivative of the following general formula (1):



wherein

R1 to R7 represent a specific substituent such as an alkyl group with 1 to 6 carbon atoms, and R8 represents an aryl group, which may be substituted or a heteroaryl group, which may be substituted.

17 Claims, No Drawings

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(19) 日本国特許庁 (J P) (12) 公開特許公報 (A) (11) 特許出願公開番号
特開2003-96046
(P2003-96046A)
(43) 公開日 平成15年4月3日 (2003.4.3)

(51) Int. Cl. ⁷	識別記号	F I	テームコード (参考)
C 0 7 C 271/20	Z C C	C 0 7 C 271/20	Z C C 4 C 0 2 3
A 0 1 N 47/12		A 0 1 N 47/12	Z 4 C 0 3 3
C 0 7 C 269/06		C 0 7 C 269/06	4 C 0 3 7
271/52		271/52	4 C 0 5 5
315/04		315/04	4 C 0 6 3

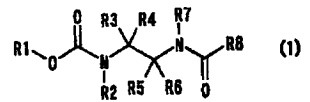
審査請求 有 請求項の数15 O L (全 58 頁) 最終頁に続く

(21) 出願番号	特願2002-210199 (P2002-210199)	(71) 出願人	000005887 三井化学株式会社 東京都千代田区霞が関三丁目2番5号
(22) 出願日	平成14年7月18日 (2002.7.18)	(72) 発明者	千葉 豊 千葉県茂原市東郷1144 三井化学株式会社 内
(31) 優先権主張番号	特願2001-218387 (P2001-218387)	(72) 発明者	大同 英則 千葉県茂原市東郷1144 三井化学株式会社 内
(32) 優先日	平成13年7月18日 (2001.7.18)	(74) 代理人	100088328 弁理士 金田 暢之 (外2名)
(33) 優先権主張国	日本 (J P)		

最終頁に続く

(54) 【発明の名称】 ジアミン誘導体、その製造方法およびそれらを有効成分とする殺菌剤

(57) 【要約】
【課題】 イネいもち病に対し優れた防除効果を示すと
ともに有用作物に対し何ら害を及ぼさない殺菌剤を提供
する。
【解決手段】 式 (1)
【化1】



(R1~R7は炭素数1~6のアルキル基等の特定の置換基を表し、R8は置換されていてもよいアリール基または置換されていてもよいヘテロアリール基を表す。) で表されるジアミン誘導体とその製造法および該化合物を有効成分として含有する殺菌剤。

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Datos bibliográficos	Descripción	Reivindicaciones	Documento original	Situación Jurídica de INPADOC
Número de patente:	JP2003096046			
Fecha de publicación:	2003-04-03			
Inventor:	CHIBA YUTAKA; DAIDO HIDENORI; AKESE TOMOHISA; MATSUNO HIROMI; KISHI JUNRO			
Solicitante:	MITSUI CHEMICALS INC			
Clasificación:				
- Internacional:	C07D333/16; A01N47/12; C07C269/06; C07C271/20; C07C271/52; C07C315/04; C07C317/18; C07C319/20; C07C323/12; C07D213/81; C07D277/20; C07D277/56; C07D307/12; C07D307/42; C07D307/68; C07D333/38; C07D405/12; C07D409/12; C07D333/00; A01N47/10; C07C269/00; C07C271/00; C07C315/00; C07C317/00; C07C319/00; C07C323/00; C07D213/00; C07D277/00; C07D307/00; C07D405/00; C07D409/00; (IPC1-7): C07C271/20; A01N47/12; C07C269/06; C07C271/52; C07C315/04; C07C317/18; C07C319/20; C07C323/12; C07D213/81; C07D277/56; C07D307/12; C07D307/42; C07D307/68; C07D333/16; C07D333/38; C07D405/12; C07D409/12			
- europea:				
Número de solicitud:	JP20020210199 20020718			
Número(s) de prioridad:	JP20020210199 20020718; JP20010218387 20010718			
Visualizar la familia de patentes de INPADOC				
View forward citations				
Resumen de JP2003096046				
PROBLEM TO BE SOLVED: To provide a germicide which increasingly protects rice plants from rice blast and does not cause any damages to useful crops. SOLUTION: A diamine derivative represented by formula (1) (wherein, R1 to R7 are each a specific substituent such as a 1-6C alkyl group and so on and R8 is an aryl group or heteroaryl group both of which may be substituted), a production method therefor and the germicide which contains the derivative as the active ingredient.				
Datos suministrados desde la base de datos esp@cenet - Worldwide				

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PERKIN

Enantioselective amino acid recognition using acyclic thiourea receptors

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^b Departamento de Química Orgánica, Universidad Autónoma de Madrid, Cantoblanco, E-28049, Madrid, Spain

Received (in Cambridge, UK) 9th March 2001, Accepted 25th April 2001

First published as an Advance Article on the web 11th May 2001

A series of acyclic thiourea derivatives, designed to create a cleft with four hydrogen bond donors suitable for carboxylate recognition, have been prepared, and their ability to bind to *N*-protected amino acid carboxylate salts has been investigated. The crystal structure of one of the thioureas has been determined showing that it forms a hydrogen bonded centrosymmetric dimer in the solid-state, in a conformation appropriate for the desired binding of carboxylates. The thioureas show good discrimination between different amino acids and those thioureas incorporating chiral moieties show moderate enantioselectivity for a range of amino acid derivatives.

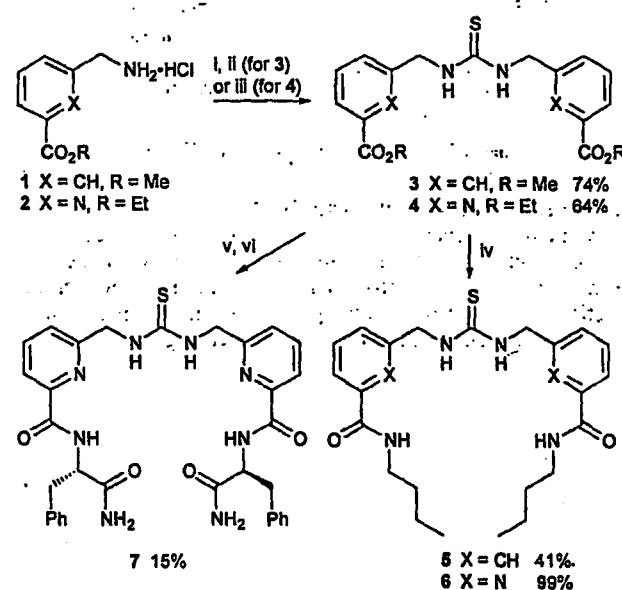
Introduction

Enantioselective recognition remains a major challenge for host-guest chemists.¹ The ability to discriminate between enantiomers, using synthetic receptors, would, for example, allow separation of racemates by selective transport across a membrane.² We, and others, have previously utilised thioureas as a binding site for the carboxylate functionality,³ and incorporation of thioureas into macrocyclic structures has produced selective receptors for carboxylate derivatives such as amino acids.⁴ Such receptors are, however, structurally rather complex and demanding to synthesise. In an effort to produce simpler enantioselective receptors for carboxylate derivatives we have now prepared a series of acyclic thioureas and have examined their ability to bind a range of amino acids.⁵ In these novel receptors the thiourea functionality is linked to aryl amides to provide additional hydrogen bonds to the carboxylate moiety and it was anticipated that the formation of a well defined set of four hydrogen bonds around the carboxylate, binding to both the *syn* and *anti* lone pairs of the carboxylate,⁶ should also serve to create a cleft which, when chiral building blocks are incorporated, might discriminate effectively between enantiomeric guests (Fig. 1). The use of pyridyl amides might further help to preorganise the chiral cleft since the desired U-shaped conformation may be stabilised by weak hydrogen bonding of the amide and thiourea hydrogens to the pyridyl nitrogen.⁷ In order to test this hypothesis we prepared the achiral receptors 5 and 6. We also prepared two chiral pyridyl receptors 7 and 15, the former incorporating a primary amide, derived from phenylalanine, to provide further hydrogen bonding functionality, and the latter incorporating an electron

deficient aromatic amide to provide aromatic interactions with guests with aromatic sidechains.

Results and discussion

The thiourea receptors 5–7 were readily prepared (Scheme 1)



Scheme 1 Reagents and conditions: (i) CSCl_2 , K_2CO_3 , H_2O , CH_2Cl_2 ; (ii) 1, Et₃N; (iii) CS_2 , DCC, DMAP; (iv) $n\text{BuNH}_2$; (v) LiOH, dioxane, H_2O ; (vi) DPPA, (2*S*)-2-amino-3-phenylpropanamide.

by coupling of amino esters 1 or 2 to give the corresponding thiourea esters 3 and 4, which could be converted directly to the butyl amides 5 and 6, or, in the case of 4, hydrolysed to the corresponding diacid, and coupled with (2*S*)-2-amino-3-phenylpropanamide to give 7. Receptor 15 was prepared from the protected diamine 8, derived from *L*-phenylalanine.⁸ Treatment of 8 with hydrazine and coupling of the resulting amine with *p*-nitrobenzoyl chloride gave amide 9. Removal of the Boc-protecting group, and coupling with acid chloride 12 gave 13. Removal of the phthalimide group with hydrazine, and coupling of the resulting amine with acid chloride 12 gave 15.

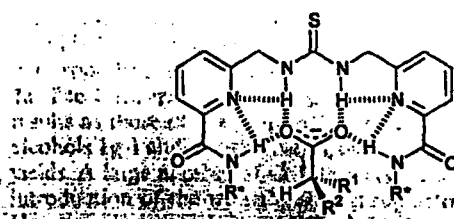


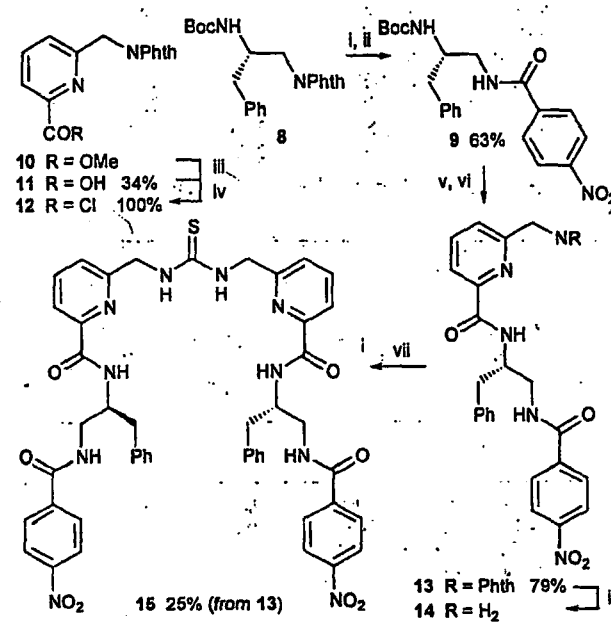
Fig. 1 Proposed binding of carboxylates by a bispyridylthiourea. R¹ represents a chiral group.

Table 1 Hydrogen bonds for thiourea 6 [Å and °]

D-H...A ^a	d(D-H)	d(H...A)	d(D...A)	∠(DHA)
N(1)-H(1N)...O(2)#1	0.86(2)	2.24(2)	2.978(2)	144.3(18)
N(4)-HN4...O(2)#1	0.85(2)	2.09(2)	2.897(2)	157.5(19)
N(3)-HN3...O(2)#1	0.86(2)	2.34(2)	3.089(2)	145.9(19)

^a Symmetry transformations used to generate equivalent atoms: #1 -x + 2, -y + 1, -z + 1.

conversion of the resulting amine 14 to the isothiocyanate and coupling with a further equivalent of the amine, gave the desired thiourea 15 (Scheme 2).



Phth = phthaloyl

Scheme 2 Reagents and conditions: (i) H_2NNH_2 , EtOH; (ii) $p\text{-NO}_2\text{C}_6\text{H}_4\text{COCl}$, Et_3N , DMAP; (iii) TMSCl, NaI, CH_3CN ; (iv) SOCl_2 ; (v) TFA, CH_2Cl_2 ; (vi) 12, DMAP; (vii) CS_2 , DCC, DMAP, then further addition of 14.

We were able to obtain a crystal structure⁹ of the achiral pyridyl receptor 6 which revealed that it forms a centrosymmetric dimer in the solid-state, with one amide carbonyl forming a triple hydrogen bond motif (Table 1) with both of the thiourea NH's and one amide NH of the other monomer unit (Fig. 2). The molecule adopts a folded conformation such that the three NH groups point inwards to an essentially planar cavity, into which the carbonyl of the second molecule can dock. Two of the pyridine rings experience intermolecular π - π stacking interactions with their centroids separated by 3.968 Å and the angle between the least squares planes being only 0.03°. Thus the crystal structure reveals, in part, the desired hydrogen bond arrangement required for carboxylate recognition depicted in Fig. 1. Dilution studies with NMR samples of all the thioureas, however, showed that the dimerisation observed in the solid state is not occurring to any significant extent in solution. Furthermore, in neat CDCl_3 , the signals of the NH's for the pyridyl receptors 6 and 7 are considerably more downfield in comparison to those for receptor 5, consistent with the notion that there are weak hydrogen bonds between the pyridyl nitrogen and the NH's in the former case (Fig. 1). Addition of 10% (by volume) CD_3SOCD_3 to these samples leads to significant downfield shifts for the signals for both the amide and thiourea NH's of receptor 5, but only a small downfield shift for the amide NH of the pyridyl receptor 6, and an upfield shift for the thiourea NH of this compound (Fig. 3).

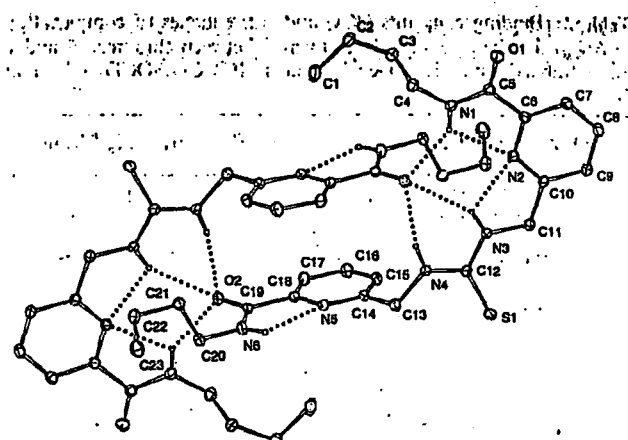


Fig. 2 Thermal ellipsoid plot (30% probability level) of 6 showing the hydrogen bonded centrosymmetric dimer.

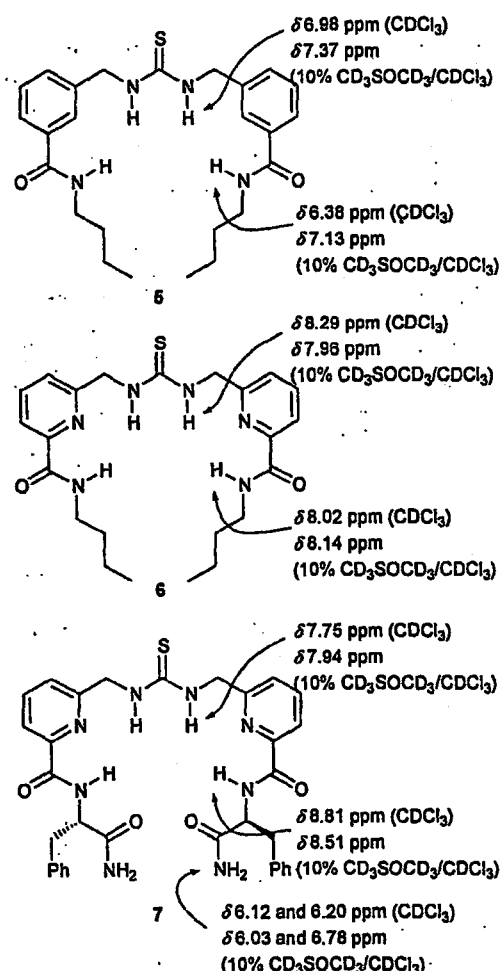


Fig. 3 Comparison of the NMR shifts for the NH signals of thioureas 5-7 in CDCl_3 and 10% $\text{CD}_3\text{SOCD}_3\text{-CDCl}_3$.

Similarly for the chiral pyridyl receptor 7, addition of 10% (by volume) CD_3SOCD_3 to a sample in CDCl_3 gives just a small downfield shift for the thiourea NH signal and an upfield shift for the secondary amide NH signal, all of which is consistent with the notion that in the case of the pyridyl receptors 6 and 7 there is substantial intramolecular hydrogen bonding.

The benzo compound 5 proved to be rather insoluble in deuteriochloroform and binding studies with this compound were carried out in 10% $\text{CD}_3\text{SOCD}_3\text{-CDCl}_3$ as solvent, whereas the pyridyl compounds were sufficiently soluble to allow studies also in neat CDCl_3 . Initially we compared the

Table 2 Binding constants (K_{eq}) and free energies of complexation ($-\Delta G_{\text{eq}}$) for the 1:1 complexes formed between thioureas 5 and 6 and tetrabutylammonium phenylacetate, in 10% $\text{CD}_3\text{SOCD}_2\text{-CDCl}_3$ at 20 °C.

Receptor	Substrate	$K_{\text{eq}}/\text{M}^{-1}$	$-\Delta G_{\text{eq}}/\text{kJ mol}^{-1}$
5	$\text{PhCH}_2\text{CO}_2^- \text{NBu}_4^+$	740	16.1
6	$\text{PhCH}_2\text{CO}_2^- \text{NBu}_4^+$	420	14.7

^a Errors were estimated as <10%. ^b Errors were estimated as <0.2 kJ mol⁻¹.

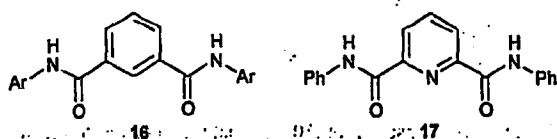


Fig. 4 Crabtree's anion receptors.

binding properties of the achiral receptors 5 and 6. Using NMR titration experiments, monitoring the shift of both the NH and ArH signals of the receptors, we obtained binding constants for both 5 and 6 with the tetrabutylammonium salt of phenylacetic acid in 10% $\text{CD}_3\text{SOCD}_2\text{-CDCl}_3$ (Table 2).¹⁰ For both receptors, binding with phenylacetic acid carboxylate leads to significant downfield shifts of the signals for both the urea NH (~2 ppm for 5, >3 ppm for 6) and amide NH (~1 ppm for 5, ~0.5 ppm for 6), indicating hydrogen bond formation, and smaller shifts (~0.2 ppm) of signals for the aromatic protons. The two binding constants are similar although binding with the pyridyl receptor 6 is slightly weaker. Thus the pyridyl receptor 6 may be more preorganised for binding as desired, but absolute binding of a carboxylate anion may be disfavoured by electrostatic repulsion between the anion and the pyridine nitrogen lone-pair—as suggested by Crabtree's studies on binding of various anions with related receptors 16 and 17 (Fig. 4).¹¹

Binding studies with the chiral pyridyl receptor 7 and a range of amino acid derivatives, as the tetrabutylammonium salts, in neat CDCl_3 , were carried out and the results are presented in Table 3. The receptor is strongly selective for different amino acids (e.g. >30 : 1 selectivity for $N\text{-Ac-L-Trp-CO}_2^-$ over $N\text{-Ac-L-Ser-CO}_2^-$), but in general the receptor shows only moderate enantioselectivity with a general preference for L-amino acids and a highest enantioselectivity for $N\text{-Ac-Gln-CO}_2^-$ (L : D ≈ 2 : 1). Binding constants were also highest for amino acids with sidechains incorporating hydrogen bonding functionality ($N\text{-Ac-Gln-CO}_2^-$) or an electron rich aromatic sidechain ($N\text{-Ac-Trp-CO}_2^-$). The corresponding $N\text{-Boc}$ derivatives gave reduced binding constants, but gave better enantioselectivity in the case of $N\text{-Boc-Trp-CO}_2^-$. For all substrates tested, binding resulted in significant downfield shifts of the NH signals from the thiourea (1.6–2.1 ppm), the secondary amide (0.3–0.7 ppm) and for one of the primary amide protons (1.2–1.5 ppm), and an upfield shift (0.3–0.7 ppm) of the other primary amide proton. This suggests that binding of the amino acids involves hydrogen bonds to the thiourea, secondary amide and one of the primary amide NH's, but also involves breaking of an intramolecular hydrogen bond to the other primary amide NH. Conversely, binding of the tryptophan derivatives led to a significant upfield shift for the indole NH signal (>1 ppm) presumably reflecting the breaking of an intramolecular hydrogen bond between the indole NH and the carboxylate on binding, and similarly binding of the glutamine and asparagine derivatives led to upfield shifts for one of the primary amide NH's in each case. As well as showing modest enantioselectivity in binding amino acid derivatives, the receptors can be used as chiral shift

Table 3 Binding constants (K_{eq}) and free energies of complexation ($-\Delta G_{\text{eq}}$) for the 1:1 complexes formed between thiourea 7 and tetrabutylammonium salts of various amino acid derivatives, in CDCl_3 at 20 °C.

Entry	Substrate	$K_{\text{eq}}/\text{M}^{-1}$	$-\Delta G_{\text{eq}}/\text{kJ mol}^{-1}$
1	$N\text{-Ac-L-Ala-CO}_2^- \text{NBu}_4^+$	3450	19.8
2	$N\text{-Ac-D-Ala-CO}_2^- \text{NBu}_4^+$	2520	19.1
3	$N\text{-Ac-L-Phe-CO}_2^- \text{NBu}_4^+$	4770	20.6
4	$N\text{-Ac-D-Phe-CO}_2^- \text{NBu}_4^+$	2990	19.5
5	$N\text{-Ac-L-Asn-CO}_2^- \text{NBu}_4^+$	1690	18.1
6	$N\text{-Ac-D-Asn-CO}_2^- \text{NBu}_4^+$	800	16.3
7	$N\text{-Ac-L-Gln-CO}_2^- \text{NBu}_4^+$	9000	22.2
8	$N\text{-Ac-D-Gln-CO}_2^- \text{NBu}_4^+$	4520	20.5
9	$N\text{-Boc-L-Gln-CO}_2^- \text{NBu}_4^+$	1190	17.3
10	$N\text{-Boc-D-Gln-CO}_2^- \text{NBu}_4^+$	810	16.3
11	$N\text{-Ac-L-Ser-CO}_2^- \text{NBu}_4^+$	380	14.5
12	$N\text{-Ac-D-Ser-CO}_2^- \text{NBu}_4^+$	480	15.0
13	$N\text{-Ac-L-Trp-CO}_2^- \text{NBu}_4^+$	12400	23.0
14	$N\text{-Ac-D-Trp-CO}_2^- \text{NBu}_4^+$	14800	23.4
15	$N\text{-Boc-L-Trp-CO}_2^- \text{NBu}_4^+$	3140	19.6
16	$N\text{-Boc-D-Trp-CO}_2^- \text{NBu}_4^+$	2225	18.8

^a Errors were estimated as <10%. ^b Errors were estimated as <0.2 kJ mol⁻¹.

Table 4 Binding constants (K_{eq}) and free energies of complexation ($-\Delta G_{\text{eq}}$) for the 1:1 complexes formed between thiourea 15 and tetrabutylammonium salts of various amino acid derivatives, in CDCl_3 at 20 °C.

Entry	Substrate	$K_{\text{eq}}/\text{M}^{-1}$	$-\Delta G_{\text{eq}}/\text{kJ mol}^{-1}$
1	$N\text{-Boc-L-Trp-CO}_2^- \text{NBu}_4^+$	1925	18.4
2	$N\text{-Boc-D-Trp-CO}_2^- \text{NBu}_4^+$	3785	20.1
3	$(R)\text{-Naproxen-CO}_2^- \text{NBu}_4^+$	1570	17.9
4	$(S)\text{-Naproxen-CO}_2^- \text{NBu}_4^+$	1870	18.4

^a Errors were estimated as <10%. ^b Errors were estimated as <0.2 kJ mol⁻¹.

reagents. Thus, for example, we prepared a CDCl_3 solution of receptor 6 with the tetrabutylammonium salt of racemic $N\text{-Ac-Phe}$, which leads to two cleanly resolved signals for the NCOCH_3 group of the two resulting diastereomeric complexes at 1.86 and 1.88 ppm.

Thiourea 15 showed similar downfield shifts for the thiourea NH (~2 ppm), pyridyl amide NH (~0.5 ppm) and nitrobenzamide NH (~1.1 ppm) on titration with the enantiomers of $N\text{-Boc-Trp}$, and the receptor now showed a modest selectivity for the D-enantiomer (Table 4). A probable contribution to the binding from aromatic interactions is evidenced by downfield shifts (~0.2 ppm) of the signals for both aromatic protons from the p -nitrobenzamide on complexation. The receptor also bound the enantiomers of naproxen (as the tetrabutylammonium salts), with associated shifts (~0.2 ppm) for the signals for the protons from the p -nitrobenzamide, but was unable to discriminate effectively between the enantiomers.

In summary we have prepared a series of simple acyclic thiourea receptors which are both sidechain selective and moderately enantioselective for a range of amino acid derivatives. Despite the modest enantioselectivity observed the receptors are simple to prepare, and evidence from the NMR binding studies does suggest that the tweezer receptors do indeed wrap around the substrates as desired using a combination of several hydrogen bonding interactions. These results indicate that more selective receptors may result from the introduction of suitable functionality for more specific interactions with the sidechain functionality of the amino acid guests.)

Experimental. and 1535; m/z (ES)⁺ 455.4 (M + H)⁺ (Found: C, 63.98; H, 7.59; N, 11.74. C₂₃H₂₄N₄O₂S.MeOH requires C, 64.17; H, 7.87; N, 11.51%).

General procedures

All reactions requiring anhydrous conditions were conducted in flame dried glassware under a static, inert atmosphere unless otherwise stated. CH₂Cl₂ was distilled from calcium hydride, and petrol was distilled and the fraction boiling between 40 and 60 °C was used. All other solvents were of commercial grade and were used without further purification. Thin layer chromatography was performed on plastic backed sheets (Camlab) coated with silica gel (SiO₂: 0.25 mm). Flash column chromatography was performed on Sorbil C₆₀, 40–60 mesh silica.

Infra-red spectra were recorded on a Perkin-Elmer 1600 series FT-IR spectrometer. Proton NMR spectra were obtained at 270 MHz on a JEOL GX 270, at 300 MHz on a Bruker AC 300, and at 360 MHz on a Bruker Aspect 3000 spectrometer. Spectra were referenced with respect to the residual solvent peak for the deuterated solvent concerned. ¹³C NMR spectra were obtained at 75 MHz on a Bruker AC 300 and at 100 MHz on a Bruker DPX 400. COSY spectra and ¹H–¹³C correlation spectra were performed on a Bruker AC 300. Mass spectra were obtained on a VG analytical 70-250-SE normal geometry double focusing mass spectrometer or on a Micromass Platform quadrupole mass analyser with an electrospray ion source.

Methyl 3-((((3-(methoxycarbonyl)benzyl)amino)thiocarbonyl)amino)methyl)benzoate 3

Based on a procedure originally reported by Anslyn,¹² a suspension of amine hydrochloride 1 (0.84 g, 4.17 mmol) in CH₂Cl₂ (15 mL) was added dropwise to a vigorously stirred mixture of potassium carbonate (1.14 g, 8.34 mmol) in water (45 mL) and thiophosgene (0.73 mL, 9.52 mmol) in CH₂Cl₂ (45 mL). The mixture was stirred at rt for 1 hour then heated at reflux for 12 hours. After cooling to rt the organic layer was separated, dried (MgSO₄), filtered and concentrated *in vacuo* to give crude isothiocyanate as an orange oil which was used in the next step without further purification. Amine 1 (0.65 g, 3.24 mmol) was added to a stirred solution of the isothiocyanate (0.67 g, 3.31 mmol) and triethylamine (1.32 mL, 9.72 mmol) in CH₂Cl₂ (30 mL). The mixture was heated at reflux for 12 hours and after allowing to cool to rt was washed with 2.0 M HCl (3 × 20 mL), dried (MgSO₄) and the solvent removed *in vacuo* to give thiourea 3 as an orange viscous oil (1.15 g, 74%); R_f 0.47 (ethyl acetate); δ_H (300 MHz, CDCl₃) 3.83 (6H, s, CH₃), 4.70 (4H, d, *J* 5, ArCH₂), 6.74 (2H, br s, NH), 7.32 (2H, t, *J* 8, ArH), 7.45 (2H, d, *J* 8, ArH), 7.83 (2H, s, ArH), 7.84 (2H, d, *J* 8, ArH); δ_C (75.5 MHz, CDCl₃) 48.2, 52.4, 128.7, 129.0, 129.1, 130.6, 132.4, 137.9, 167.1, 182.9; m/z (ES)⁺ 373.5 (M + H)⁺, 395.5 (M – Na)⁺ HRMS: found 372.1223. C₁₉H₂₁N₂O₄S (M + H)⁺ requires 373.1222.

N-1-Butyl-3-((((3-(butylamino)carbonyl)benzyl)amino)thiocarbonyl)amino)methyl)benzamide 5

Diester 3 (50 mg, 0.13 mmol) was dissolved in butylamine (5 mL) and heated at reflux for 12 hours. After cooling to rt the excess butylamine was removed *in vacuo* to yield a white solid which was purified by crystallisation (ethyl acetate–methanol) to give thiourea 5 as colourless crystals (25 mg, 41%); mp 88–90 °C (ethyl acetate–methanol); R_f 0.47 (ethyl acetate); δ_H (300 MHz, CDCl₃) 0.94 (6H, t, *J* 7, CH₃), 1.37 (4H, sextet, *J* 7, CH₂CH₂CH₃), 1.55 (4H, quintet, *J* 7, CH₂), 3.32 (4H, q, *J* 7, CH₂NHCO), 4.7 (4H, d, *J* 5, CH₂NHCS), 6.38 (2H, br s, NHCS), 6.98 (2H, br s, NHCO), 7.32 (2H, d, *J* 8, ArH), 7.40 (2H, d, *J* 8, ArH), 7.53 (2H, d, *J* 8, ArH), 7.54 (2H, s, ArH); δ_C (100 MHz, [(CD₃)₂SO–CDCl₃, 10:90 v/v]) 11.5, 18.1, 29.4, 37.8, 45.8, 124.0, 124.1, 126.7, 128.5, 133.0, 136.7, 166.8, 182.4; ν_{max} /cm^{–1} (neat) 3285, 3225, 3060, 2960, 2930, 2865, 1635, 1585

and 1535; m/z (ES)⁺ 455.4 (M + H)⁺ (Found: C, 63.98; H, 7.59; N, 11.74. C₂₃H₂₄N₄O₂S.MeOH requires C, 64.17; H, 7.87; N, 11.51%).

Ethyl 6-((((6-(ethoxycarbonyl)-2-pyridyl)methyl)amino)thiocarbonyl)amino)methyl)pyridine-2-carboxylate 4

Based on a procedure originally reported by Anslyn,¹² DMAP (0.57 g, 4.70 mmol) was added to a suspension of amine hydrochloride salt 2 (0.41 g, 1.88 mmol), DCC (0.19 g, 0.94 mmol) and carbon disulfide (0.40 mL, 6.58 mmol) in dry, CHCl₃ (10 mL) at –10 °C. The solution was stirred at rt for 1 hour then heated at reflux for 12 hours. The solvent was removed *in vacuo* and the resultant orange oil was purified by flash column chromatography, eluting with ethyl acetate–petroleum ether (70:30 to 100:0 v/v) to give thiourea 4 as a yellow solid (0.25 g, 64%); mp 103–104 °C (ethyl acetate–petroleum ether); R_f 0.44 (ethyl acetate); δ_H (300 MHz, CDCl₃) 1.45 (6H, t, *J* 7, CH₃), 4.49 (4H, q, *J* 7, CH₂CH₃), 5.02 (4H, br s, CH₂N), 7.50 (2H, d, *J* 8, pyrH), 7.83 (2H, t, *J* 8, pyrH), 8.02 (2H, d, *J* 8, pyrH), 8.56 (2H, br s, NH); δ_C (75.5 MHz, CDCl₃) 14.4, 49.5, 62.2, 124.0, 125.7, 138.0, 147.2, 157.4, 165.1, 183.3; ν_{max} /cm^{–1} (neat) 3545, 3300, 1705, and 1530; m/z (ES)⁺ 403.0 (M + H)⁺, 424.9 (M + Na)⁺ (Found: C, 56.69; H, 5.68; N, 13.63. C₁₉H₂₂N₄O₄S requires C, 56.70; H, 5.51; N, 13.92%).

N-1-Butyl-6-((((6-(butylamino)carbonyl)-2-pyridyl)methyl)amino)thiocarbonyl)amino)methyl)pyridine-2-carboxamide 6

Diester 4 (26 mg, 65 μ mol) was dissolved in butylamine (4 mL) and the solution was heated at reflux for 12 hours. The excess butylamine was removed *in vacuo* and the resultant yellow solid was recrystallised from ethyl acetate–petroleum ether to give thiourea 6 as colourless crystals (32 mg, 100%); mp 95–96 °C (ethyl acetate–petroleum ether); R_f 0.31 (ethyl acetate); δ_H (300 MHz, CDCl₃) 0.80 (6H, t, *J* 7, CH₃), 1.21 (4H, sextet, *J* 7, CH₂CH₃), 1.44 (4H, quintet, *J* 7, CH₂CH₂CH₃), 3.26 (4H, q, *J* 7, CH₂CH₂N), 4.98 (4H, s, CH₂NHC–S), 7.48 (2H, d, *J* 8, pyrH), 7.77 (2H, t, *J* 8, pyrH), 7.96 (2H, d, *J* 8, pyrH), 8.02 (2H, br s, NH), 8.29 (2H, br s, NH); δ_C (75.5 MHz, CDCl₃) 13.8, 20.3, 31.8, 39.6, 49.5, 121.3, 125.2, 138.8, 149.0, 155.9, 164.1; ν_{max} /cm^{–1} (neat) 3360, 3300, 2950, 2860, 2360, 1670, 1640, 1570, and 1530; m/z (ES)⁺ 457.4 (M + H)⁺, 479.5 (M + Na)⁺; HRMS (FAB): found 457.2384. C₂₃H₃₃N₆O₂S requires 457.2386. An X-ray crystal structure was obtained (see text).

N-[(1S)-2-Amino-1-benzyl-2-oxoethyl]-6-((((6-(((1S)-2-amino-1-benzyl-2-oxoethyl)amino)carbonyl)-2-pyridyl)methyl)amino)thiocarbonyl)amino)methyl)pyridine-2-carboxamide 7

LiOH (20.1 mL of a 1 M soln, 20.1 mmol) was added to diester 4 (0.81 g, 2.01 mmol) in 1,4-dioxane (23 mL) and the mixture was stirred for 1 hour. KHSO₄ (20.1 mL of a 1 M soln, 20.1 mmol) was added and the water was removed *in vacuo* and by azeotroping with acetonitrile (20 mL). Methanol (5 mL) was added to the resultant solid, the insoluble material was removed by filtration and the excess methanol was removed *in vacuo* to yield the diacid as a pale yellow solid (0.70 g, 100%) which was used in the next reaction without further purification. Diphenylphosphoryl azide (DPPA) (0.42 mL, 1.92 mmol) followed by triethylamine (0.53 mL, 3.83 mmol) were added to a stirred mixture of the diacid (0.30 g, 0.87 mmol) and (2S)-2-amino-3-phenylpropanamide (0.31 g, 1.92 mmol) in DMF (0.5 mL) at 0 °C. The mixture was stirred at 0 °C for 2 hours and at rt for 2 days. The solvent was removed *in vacuo* and the crude oil was suspended in CH₂Cl₂ (15 mL), washed with water (15 mL), dried (MgSO₄) and concentrated *in vacuo* to give an oil which was purified by flash column chromatography eluting with methanol–CH₂Cl₂ (1:99 to 10:90 v/v) to give thiourea 7 as a white solid (84 mg, 15%); mp 126–128 °C (ethanol–water);

R_f 0.43 [methanol- CH_2Cl_2 (10 : 90 v/v)]; $[\alpha]_D^{20} +36.0^\circ$ (c 1 in CH_2Cl_2); δ_H (300 MHz, CDCl_3) 3.12 (2H, dd, J 7, 14, $\text{CH}_A\text{H}_B\text{Ph}$), 3.17 (2H, dd, J 7, 14, $\text{CH}_A\text{H}_B\text{Ph}$), 4.87 (2H, apparent q, J 7, CONHCH), 4.99 (4H, m, CSNHCH₂), 6.34 (2H, br s, NH_AH_B), 6.47 (2H, br s, NH_AH_B), 7.15–7.25 (10H, m, ArH), 7.43 (2H, d, J 8, ArH), 7.74 (2H, t, J 8, pyrH), 7.91 (2H, d, J 8, pyrH), 8.00 (2H, br s, CSNH), 8.80 (2H, d, J 8, CONHCH); δ_C (75.5 MHz, CDCl_3) 39.4, 50.0, 55.6, 121.5, 125.9, 127.8, 129.4, 130.2, 130.4, 138.0, 139.3, 149.6, 158.6, 165.8 and 175.69; $\nu_{\text{max}}/\text{cm}^{-1}$ 2395, 2360, 1660, 1650 and 1515; m/z (ES^+) 639.6 ($M + H$), 661.6 ($M + Na$), 677.5 ($M + K$); HRMS (FAB): found 661.2311. $\text{C}_{33}\text{H}_{34}\text{N}_8\text{O}_4\text{NaS}$ requires 661.2321.

6-[(1,3-Dioxo-2,3-dihydro-1H-isoindol-2-yl)methyl]pyridine-2-carboxylic acid 11

Based on a procedure originally reported by Olah,¹³ chlorotrimethylsilane (16.6 mL, 0.13 mol) was added to a solution of ester 10¹⁴ (10.1 g, 32.7 mmol) and sodium iodide (19.6 g, 0.13 mol) in acetonitrile (50 mL) at 0 °C. The reaction mixture was allowed to warm to rt and heated at reflux for 4 days. After allowing to cool to rt, water (200 mL) was added, the reaction mixture was diluted with CH_2Cl_2 (100 mL) and was washed successively with water (100 mL) followed by aqueous sodium thiosulfate (150 mL). The organic phase was extracted with saturated sodium hydrogen carbonate (50 mL) and the aqueous phase acidified to pH 3 using 2.0 M HCl. The acidic solution was extracted with methanol- CH_2Cl_2 [3×150 mL (5 : 95 v/v)], dried (MgSO_4) and the solvent removed *in vacuo* to give acid 11 as a white solid (3.12 g, 34%); mp 219–221 °C (from methanol- CHCl_3); R_f 0.21 [methanol- CH_2Cl_2 (10 : 90 v/v)]; δ_H (400 MHz, $[(\text{CD}_3)_2\text{SO}-\text{CDCl}_3$, 10 : 90 v/v]) 5.03 (2H, s, PhthNCH₂), 7.33 (1H, dd, J 1, 8, pyrH), 7.73 (2H, dd, J 3, 5, ArH), 7.77 (1H, t, J 8, pyrH), 7.82 (2H, dd, J 3, 5, ArH), 7.96 (1H, dd, J 1, 8, pyrH); δ_C (100 MHz, CD_3OD) 42.5, 123.1, 123.2, 123.7, 131.5, 134.0, 137.8, 147.6, 155.5, 165.7, 167.5; $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3360, 1750, 1705, 1600 and 1420 (Found: C, 64.07; H, 3.55; N, 9.95. $\text{C}_{15}\text{H}_{10}\text{N}_2\text{O}_4$ requires C, 63.83; H, 3.57; N, 9.92%).

tert-Butyl-N-[(1S)-1-benzyl-2-[(4-nitrobenzoyl)amino]ethyl]-carbamate 9

Hydrazine hydrate (90 μL , 1.88 mmol) was added to a solution of phthalimide 8⁹ (0.48 g, 1.26 mmol) in ethanol (25 mL) and the mixture heated at reflux for 6 hours. After cooling to rt the insoluble material was removed by filtration and the excess solvent removed *in vacuo* to give the amine as a pale yellow solid, which was suspended in dry CH_2Cl_2 (20 mL). 4-Nitrobenzoyl chloride (0.52 g, 2.82 mmol) followed by triethylamine (0.39 mL, 2.82 mmol) and DMAP (50 mg, 0.41 mmol) were added. After stirring at rt for 12 hours solvent was removed *in vacuo* and the crude material was purified by flash column chromatography eluting with ethyl acetate-petroleum ether (30 : 70 v/v) to give amide 9 as a white solid (0.31 g, 63%); mp 184–186 °C (ethyl acetate); R_f 0.5 [ethyl acetate-petroleum ether (30 : 70 v/v)]; δ_H (300 MHz, $[(\text{CD}_3)_2\text{SO}-\text{CDCl}_3$, 10 : 90 v/v]) 1.29 (9H, s, $\text{C}(\text{CH}_3)_3$), 2.69 (1H, dd, J 9, 14, $\text{CH}_A\text{H}_B\text{Ph}$), 2.80 (1H, dd, J 6, 14, $\text{CH}_A\text{H}_B\text{Ph}$), 3.38–3.33 (2H, m, CH_2N), 3.93 (1H, dt, J 6, 9, CHCH_2), 6.81 (1H, d, J 9, NHCH), 7.31–7.16 (5H, m, ArH), 8.07 (2H, d, J 9, ArH), 8.32 (2H, d, J 9, ArH), 8.80 (1H, t, J 5, NHCH₂); δ_C (100 MHz, $\text{DMSO}-d_6$) 26.5, 36.1, 42.0, 49.7, 75.8, 121.7, 124.2, 126.3, 127.1, 127.4, 137.2, 138.6, 147.2, 153.6, 163.2; $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3350, 1690, 1644, 1550 and 1525; m/z (ES^+) 400.4 ($M + H$)⁺ (Found: C, 63.28; H, 6.62; N, 10.44. $\text{C}_{21}\text{H}_{25}\text{N}_3\text{O}_5$ requires C, 63.15; H, 6.31; N, 10.52%).

N-[(1S)-1-Benzyl-2-[(4-nitrobenzoyl)amino]ethyl]-6-[(1,3-dioxo-2,3-dihydro-1H-isoindol-2-yl)methyl]pyridine-2-carboxamide 13
TFA- CH_2Cl_2 [5 mL (50 : 50 v/v)] was added to a solution of protected amine 9 (0.21 g, 0.53 mmol) in CH_2Cl_2 (10 mL) at

0 °C and the mixture was stirred for 12 hours at rt. The solvent was removed *in vacuo* and the resulting oil was triturated with ether (2 $\times$ 10 mL) to give the amine TFA salt as a pale yellow oil. Acid 11 (0.19 g, 0.68 mmol) was heated at reflux in thionyl chloride (2 mL) for 8 hours then cooled and stirred at rt for 12 hours. The excess thionyl chloride was removed *in vacuo* to give acid chloride 12 as a white solid, which was dissolved in dry DMF (5 mL) and added dropwise to a solution of amine TFA salt and DMAP (70 mg, 0.57 mmol) in DMF and the mixture was stirred at rt for 2 days. Solvent was removed *in vacuo* and the brown residue was purified by filtration through a pad of silica gel, eluting with ethyl acetate, to give amide 13 as a white solid (0.23 g, 79%); R_f 0.59 (ethyl acetate); mp 174–176 °C (CHCl_3 -hexane); $[\alpha]_D^{20} -11.3^\circ$ (c 1 in CH_2Cl_2); δ_H (400 MHz, CDCl_3) 2.78 (1H, dd, J 8, 15, $\text{CH}_A\text{H}_B\text{Ph}$), 2.82 (1H, dd, J 7, 15, $\text{CH}_A\text{H}_B\text{Ph}$), 3.38 (1H, ddd, J 3, 4, 14, NHCH_2CH_2), 3.63 (1H, ddd, J 5, 10, 14, NHCH_2CH_2), 4.37 (1H, m, NHCHCH_2), 4.97 (2H, s, CH_2Phth), 7.11–7.25 (5H, m, ArH), 7.40 (2H, d, J 8, pyrH), 7.72 (2H, dd, J 3, 5, ArH), 7.76 (1H, t, J 8, pyrH), 7.84 (2H, dd, J 3, 5, ArH), 7.86–7.90 (3H, m, ArH and NHCH_2CH_2), 7.96 (1H, d, J 8, pyrH), 8.12 (1H, d, J 8, NHCHCH_2), 8.17 (2H, d, J 9, ArH); δ_C (100 MHz, CDCl_3) 39.3, 43.0, 47.3, 51.5, 121.6, 124.0, 124.1, 125.3, 127.5, 128.7, 129.5, 129.3, 132.4, 134.9, 136.9, 139.0, 140.1, 149.0, 149.9, 154.7, 165.7, 166.1, 168.4; $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3350, 2360, 1685, 1644, 1600 and 1550; m/z (ES^+) 564.3 ($M + H$)⁺. HRMS: found 564.1879. $\text{C}_{31}\text{H}_{26}\text{N}_6\text{O}_6$ ($M + H$)⁺ requires 564.1883.

N-2-[(1S)-1-Benzyl-2-[(4-nitrobenzoyl)amino]ethyl]-6-[(6-[(1S)-1-benzyl-2-[(4-nitrobenzoyl)amino]ethyl)amino]-carbonyl]-2-pyridyl)methyl]amino]thiocarbonyl]amino)-methyl]-2-pyridinecarboxamide 15

Hydrazine hydrate (17 μL , 0.35 mmol) was added to a solution of phthalimide 13 (0.20 g, 0.35 mmol) in ethanol (5 mL) and the mixture heated at reflux for 12 hours. The insoluble material was removed by filtration and the filtrate concentrated *in vacuo* to give amine 14 as a yellow residue which was used in the next step without further purification. Carbon disulfide (74 μL , 1.21 mmol) was added to a solution of the amine (75 mg, 1.73 μmol), DCC (36 mg, 174 μmol) and DMAP (43 mg, 0.35 mmol) in dry CH_2Cl_2 (2 mL) at -10 °C and the mixture was stirred for 1 hour. After warming to rt the excess solvent and carbon disulfide were removed *in vacuo*. The resultant orange oil was dissolved in dry CH_2Cl_2 (2 mL) and further amine 14 (75 mg, 1.73 μmol) was added. After stirring at rt for 5 days the solvent was removed *in vacuo* and the brown residue was purified by flash column chromatography eluting with methanol- CH_2Cl_2 (1 : 99 to 10 : 90 v/v) to give thiourea 15 as a pale yellow solid (60 mg, 25%); R_f 0.59 (ethyl acetate); $[\alpha]_D^{20} +36.0^\circ$ (c 2 in CH_2Cl_2); δ_H (400 MHz, CDCl_3) 2.90 (1H, dd, J 8, 14, $\text{CH}_A\text{H}_B\text{Ph}$), 3.22 (1H, dd, J 6, 14, $\text{CH}_A\text{H}_B\text{Ph}$), 3.58 (1H, dd, J 3, 14, $\text{CH}_A\text{H}_B\text{NH}$), 3.80 (1H, dd, J 10, 14, $\text{CH}_A\text{H}_B\text{NH}$), 4.51 (2H, m, CHCH_2Ph), 5.02 (2H, d, J 17, $\text{CH}_A\text{H}_B\text{NHCS}$), 5.10 (2H, d, J 17, $\text{CH}_A\text{H}_B\text{NHCS}$), 7.22–7.35 (10H, m, ArH), 7.56 (2H, d, J 8, pyrH), 7.73 (2H, br s, CH_2NHCO), 7.83 (4H, d, J 9, ArH), 7.89 (2H, t, J 8, pyrH), 8.07 (2H, d, J 8, pyrH), 8.11 (4H, d, J 8.5, ArH), 8.44 (2H, br m, NHCS), 8.89 (2H, d, J 5, NHCH); δ_C (100 MHz, CDCl_3) 37.3, 42.7, 47.2, 51.0, 120.0, 122.3, 123.9, 125.5, 126.7, 127.4, 127.7, 135.5, 137.7, 146.4, 148.1, 154.1, 162.6, 165.9, 182.3; $\nu_{\text{max}}/\text{cm}^{-1}$ (neat) 3285, 1650, 1595 and 1518; m/z (ES^+) 910.4 ($M + H$)⁺ (Found: C, 62.38; H, 5.10; N, 15.46. $\text{C}_{47}\text{H}_{44}\text{N}_{10}\text{O}_8\text{S}$ -MeOH requires C, 62.10; H, 4.88; N, 15.41%).

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followed by epoxide hydride-catalyzed hydrolysis to give epoxidation to yield the 1,2- and 3,4-epoxide (4 and 5) liver esterase, occurs via monooxygenase (CYP-4B0-catalyzed) P450 series to contain a gold to form a metabolite in animal tissues. Phenanthrene 3 is the principal member of the

to the inability of the more widely used heterocyclic enzymes (e.g. *S. aureus* α -glucosidase) to cleave such substrates (e.g. toluene dioxygenase (TDO) and