

149120

Industria y Comercio
SUPERINTENDENCIA

SUPERINDUSTRIA Y COMERCIO
Radicación : 03088391 00000006 Folios: 18
Fecha (HND): 2006-03-15 10:21:33
Trámite : 811 PET-PATENT 379 FASE NACI 329 COMPLET
Dependencia: 2020 DIVISION DE NUEVAS CREACIONES

FORMULARIO UNICO DE CORRECCIONES Y MODIFICACIONES
2000-10

1

SOLICITUD DE:

☐ Corrección de Error Material

☒ Modificación a una Solicitud

2

SOLICITANTE

Nombre: SANOFI-AVENTIS
DEUTSCHLAND GMBH
Dirección: Brüningstrasse 50
Teléfono: _____ Fax: _____
E-Mail: _____
Domicilio: FRANKFURT AM MAIN, ALEMANIA

IDENTIFICACIÓN

C.C. ☐ NIT ☐
C.E. ☐ Otro ☐
Número _____

3

REPRESENTANTE
O APODERADO

Nombre: LUIS PATIÑO LEYVA
Dirección: Cra. 11ª No.94-78. Oficina 308
Bogotá, D.C., Colombia.
Teléfono: 6161948 Fax: 6163976
E-Mail: _____

IDENTIFICACIÓN

C.C. ☒ NIT ☐
C.E. ☐ Otro ☒
Número 2.930.616 TP 2698

4

Numero de Expediente: 03 088391

+

5

Descripción de la corrección o modificación solicitada: Que se tenga en cuenta el cambio de nombre de la sociedad AVENTIS PHARMA DEUTSCHLAND GMBH, domiciliada en Frankfurt am Main, Alemania, por el de SANOFI-AVENTIS DEUTSCHLAND GMBH, domiciliada en Frankfurt am Main, Alemania, en relación con la solicitud de patente referente a: DERIVADOS DE MERCAPTOACETILAMIDA, PROCEDIMIENTO PARA SU PREPARACIÓN Y SU USO. En consecuencia, el trámite de esta solicitud de patente se debe continuar a nombre de la sociedad SANOFI-AVENTIS DEUTSCHLAND GMBH.

6

Comprobante de pago No. 06 - 17,490

Fecha: Marzo 6 de 2006

7

Anexos:

- ☒ Comprobante de pago de la tasa
☒ El poder con que obro. Se encuentra en el Expediente No. 05 096625.
☒ Los documentos de cambio de nombre respectivos.

8

NOMBRE: LUIS PATIÑO LEYVA

FIRMA: 

C.C. 2.930.616 Bogotá T.P. 2698

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

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~~120~~

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

MIT : 800176089-2

RECIBO OFICIAL DE CAJA : 06 - 17,490
FECHA : MARZO 6 DE 2006

SUPERINDUSTRIA Y COMERCIO

Radicacion : 83866391 00000006 Folios: 10
Fecha (AEB): 2006-03-15 10:21:33
Tramite : 011 PCT-PATENT 379 FASE NACT 329 COMPLET
Dependencia: 8020 DIVISION DE NUEVAS CREACIONES

***** CONSIGNACION *****

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PAGO	Vr. PAGO
GUSTAVO HOLLMAN	CONSIGNACION	BANCO POPULAR	050-00110-6	48485284	28/02/2006	6,555,000.00

***** CONCEPTO *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-03	CAMBIO DE MODALIDAD Y MODIFICA	
		12 MARCAS Y LENAS COMERCIALES	95,000.
		TOTAL :	95,000.

SON: NOVENTA Y CINCO MIL PESOS

Pf. 55126

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No. _____

->Dieser Ausdruck wird nicht unterschrieben und gilt als beglaubigte Abschrift<-

1	2	3	4	5	6	7
1	2	3	4	5	6	7
1				Fricker, Rudolf, Frankfurt am Main, *01.08.1908 Meyer, Moritz, Bad Soden am Taunus, *13.11.1908 Dr. Knuth, Viktor, Pfullen, *08.04.1881 Chappel, Alex, Bad Soden am Taunus, *24.02.1949 Dr. Müller, Michael, Griesheim-Pfeffenberg, *16.03.1903 Dr. Hentschel, Mrs. Hedwig, *14.01.1895 Dr. Wirth, Udo, Rheinfelden, *25.08.1909 Dr. Lipp, Robert, Rheinfelden, *28.08.1909 Lippel, Ida, Koblitz, *25.11.1908 Dr. Rupp, Wilhelm, Koblitz am Main, *12.08.1903 Hofel, Augustus, Bad Soden am Taunus, *08.07.1889 Dr. Wein, Elmar-Michael, Niederhausen, *28.08.1894 Koch, Peter, Pfullen, Starnberg, *18.01.1902 Ruppel, Otto, Lohr, *08.07.1892 Dietrich, Adolf, Bad Soden am Taunus, *13.08.1908 Dr. Frensch, Moritz, Hünfelden-Waldenhausen, *18.08.1904 Dr. Otto, Alfred, Bad Soden am Taunus, *24.01.1904 Hessing, Udo, Frankfurt am Main, *18.08.1909 Dr. Jensch, Robert, Frankfurt am Main, *23.08.1906 Dr. Hans, Rainer, Koblitz, *23.08.1904 Ruppel, Moritz, Lohr, *22.07.1897 Dr. Ruppel, Moritz, Frankfurt am Main, *23.08.1904 Ruppel, Werner, Rheinfelden (Pfeffenberg), *18.10.1881 Walt, Gustav, Griesheim-Pfeffenberg, *14.04.1909 Hahn, Carl-Friedrich, Koblitz, *24.08.1901 Schmitt, Michael, Koblitz, *18.12.1909 Kornmann, Mathias, Eppenheim, *08.08.1904 Dr. Behr, Peter, Koblitz, *24.04.1881 Cassenberg, Oliver, Frankfurt am Main, *28.05.1908 Wiese, Christian, Tübingen, *15.08.1881 Pohl, Hans, Berlin, *24.12.1884		
2				Fricker, Rudolf Dr. Müller, Michael Gesellschafter gemeinsam mit einem Geschäftsführer oder einem anderen Prokuristen: Dr. Ruppel, Alfred, Koblitz, *22.01.1908 Dr. Kötter, Jürgen, Koblitz, *18.08.1903		
3						

El Notario . . . del Círculo de
Seguridad Pública . . . se está foto-
grafiando y certificando de su
autenticidad el contenido de este
documento . . .
13.10.2006
GILBERTO CASTRO CASTRO
NOTARIO
122

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->Dieser Ausdruck wird nicht unterschrieben und gilt als beglaubigte Abschrift<-

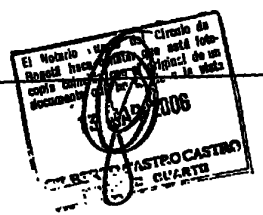
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Nummer der Eintragung	a) Firma b) Sitz, Niederlassung, Zweigstellenansagen c) Gegenstand des Unternehmens	Grund- oder Stammkapital	a) Allgemeine Vertretungsorgane b) Vorstand, Leitungsorgane, geschäftsführende Organe, persönlich haftende Geschäftsführer, Geschäftsführer, Vertretungsberechtigte und besondere Vertretungsbefugnisse	Prokura	a) Rechtsform, Register, Führung oder Geschäftsführung b) Sonstige Rechtsverhältnisse	a) Tag der Eintragung b) Bemerkungen
1	2	3	4	5	6	7
				Gesamtprokura gleichweise mit einem Geschäftsführer oder einem anderen Prokuristen: Bleibner, Lf, Wiesbaden, "08.12.1982		Eintrag-Nr.
4				Prokura erteilt: Dr. Christmann, Friedrich-P. Friedrich am Main. Prokura erteilt: Dr. Otto, Alfred, Paul Götter am Taurus, "24.01.1984 Prokura erteilt: Herr, Stephan, Kollbach, "24.04.1981 Prokura erteilt: Dr. Hans, Thomas, Köln, "29.11.1984 Gesamtprokura gleichweise mit einem Geschäftsführer oder einem anderen Prokuristen: Dr. Herrlich, Hans Thomas, Kollbach, "25.10.1981		28.01.2008 Eintrag-Nr.
5				Gesamtprokura gleichweise mit einem Geschäftsführer oder einem anderen Prokuristen: Dr. Prokura, Heinrich, Jass, Neuburg, "18.07.1981 Prok, Klaus, Berlin, "23.04.1988 Herr, Michael, Frankfurt am Main, "03.05.1971 Dr. Kohl, Thomas, Hofheim am Taunus, "27.08.1981 Dietrich, Volker, Frankfurt am Main, "26.08.1982 Dr. Baumgarten, Michael, Berlin, "28.07.1988 Dr. Blum, Christian, Berlin, "18.11.1982 Friedmann, Heinrich, München, "11.10.1948 Müller, Hans, Göttingen, "08.02.1989 Mertens, Yvonne, Puchheim, "28.08.1988 Lück, Paul, Berlin, "10.11.1982 Lorenz, Wilhelm, Berlin, "27.07.1982 Kraus, Stephan, Wiesbaden, "18.11.1988 Dr. Hans, Friedrich, Berlin, "23.04.1948 Herr, Christoph, Berlin, "23.12.1988 Dr. Heilmann, Christoph, Frankfurt am Main, "28.12.1988 Herr, Manfred, Berlin, "27.08.1982 Dr. Gräbe, Heinrich, Badmünch, "28.08.1988 Dr. Göttingen, Götter, Michael, Berlin, "21.08.1984 Dietrich, Stephan, Berlin, "23.08.1947 Carst, Jari, Berlin, "23.12.1988		18.02.2008 Eintrag-Nr.

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Nummer der Bekanntgabe	a) Form b) Ort, Hinterlegung, Belegprüfungszeiten c) Gegenstand des Unternehmens	Ort Datum	d) Allgemeine Vertretungsbezeichnung e) Vorstand, Aufsichtsratsvorsitz, geschäftsführende Vorstände, persönlich haftende Geschäftsführer, Geschäftsführer, Vertretungsbevollmächtigte und sonstige Vertretungsbefugte	f) Vertretung g) Bezeichnung des Vertreters	h) Vertretung i) Bezeichnung des Vertreters	j) Tag der Vertretung k) Bezeichnung
1	2	3	4	5	6	7
6				<u>Präsident:</u> Werner, Christian, Tübingen, *14.06.1951. <u>Präsident:</u> Dr. Lutz, Rainer, Göttingen, *28.08.1959		22.02.2008 Bund
7				Gesamtsprache gemeinsam mit einem Geschäftsführer oder einem anderen Prokuristen: Dauke, Volker, Frankfurt am Main, *12.08.1959 Dr. Göttschmann, Oliver, München, *21.08.1954		23.02.2008 Bund j) Vertretung St. Nr. 2 von Jura wegen befristet
8				<u>Präsident:</u> Bauer, Otto, Lüneburg, *08.07.1958		10.04.2008 Ostger-Kol
9				<u>Präsident:</u> Dr. Hans, Peter, Kehlheim, *03.05.1944		11.04.2008 Ostger-Kol
10			<u>Präsident:</u> Göttschmann, Oliver, München, *21.08.1954 Bevollmächtigter: Dr. Wenzel, Jean-Yves, Berlin, *27.06.1951			18.04.2008 Ostger-Kol
11				Gesamtsprache gemeinsam mit einem Geschäftsführer oder einem anderen Prokuristen: Witz, Edgar, Berlin, *09.08.1958 Möhrke, Martin, Berlin, *28.08.1958 Dr. Kruse, Dirk, Bad Homburg v. d. Höhe, *08.01.1959	El Notario - Jefe del Circulo de Seguridad Social - ha visto este original de un documento y lo ha firmado el 18.04.2008 GR. BERTHOLD CASTROCASTRO NOT. P. 10 CUARTO	28.04.2008 Ostger-Kol
12				<u>Präsident:</u> Dr. Bock, Andreas, Bonn, Kehlheim, *28.05.1952		20.06.2008 Ostger-Kol
13				Gesamtsprache gemeinsam mit einem Geschäftsführer oder einem anderen Prokuristen: Schulder, Kai, Mülheim am Main, *13.07.1967 Drees, Thomas, Berlin, *04.08.1955		18.08.2008 Ostger-Kol

13

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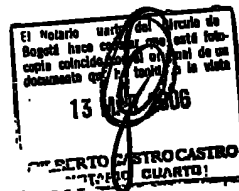
Nr.	Firma a) Name, Rechtsform, Sitz, Geschäftsführer b) Gegenstand des Unternehmens	Stempel oder Signatur	a) Allgemeine Vertretungsbefugnung b) Vorstand, Aufsichtsrat, geschäftsführende Direktoren, persönlich haftende Geschäftsführer, Geschäftsführer, Vertretungsbefugnisse und besondere Vertretungsbefugnisse	Prokura	a) Rechtsform, Beginn, Beendigung oder Geschäftsführervertrag b) Sonstige Rechtsverhältnisse	a) Tag der Eintragung b) Bemerkungen
1				Dr. Müller-Joh. Becker, Bad Nauheim am Taunus, *18.04.1895 Dr. Polakow, Regensburg, *14.07.1883		
14	a) Brand-Auerbach Deutsche Geld				a) Die Geschäftsführerverordnung vom 28.07.2008 hat eine Änderung des Geschäftsführervertrages in § 1 Abs. 1 (Firma) beschlossen.	a) 01.08.2008 Firma-Brand b) Änderung nach 180 § Handelsrecht II
15				Prokura erteilt: Dr. Otto, Otto, Wiesbaden		a) 21.08.2008 Lohr
16			M Holtzner Geschäftsführer: Dr. Lechner, Berlin, *28.08.1951 Beauftragt als Geschäftsführer: Dr. Bruns, München, München am Main, *12.08.1953 Beauftragt als Geschäftsführer: Dr. Bruns, Berlin, Kienberg im Taunus, *23.04.1958	Prokura erteilt: Dr. Bruns, München, München am Main, *12.08.1953 Prokura erteilt: Lechner, Berlin, *27.07.1951 Prokura erteilt: Dr. Bruns, Berlin, Kienberg am Main, *23.04.1958 Geschäftsführer genehmigt mit einem Geschäftsführer oder einem anderen Prokuristen: Roth, Peter, Bad Nauheim v. d. Höhe, *06.07.1959 Glockner, Volker Georg, München, *18.04.1949 Dr. Jansen, Regensburg, *28.08.1959 Dr. Lechner, Berlin, *28.08.1951 Meyerhoff, Stephan, Berlin, *01.04.1974 Dr. Paul, Frankfurt, *28.04.1957		a) 21.08.2008 Lohr
17			M Geschäftsführer: Kohl, Dieter, Mainz, *28.11.1944	Prokura erteilt: Schäfers, Dieter, Wiesbaden, Bad Nauheim am Taunus, *18.07.1958 Prokura erteilt: Dr. Kerschke, Lin. Olfen, *14.01.1959 Prokura erteilt: Dr. Frensch, Marburg, Hünfeld-Waldschmidt, *18.08.1945		a) 15.10.2008 Diago-Kohl

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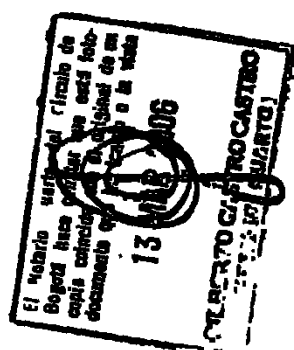
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127 → Dieser Ausdruck wird nicht unterschrieben und gilt als beglaubigte Abschrift.						
1 Name der Abtragung	2 a) Firma b) Sitz, Niederlassung, Zweigstellenansagen c) Gegenstand des Unternehmens	3 Grund- oder Stammkapital	4 a) Allgemeine Vertretungsorgane b) Vorstand, Leitungsorgane, geschäftsführende Direktoren, parallelisch leitende Geschäftsführer, Geschäftsführer, Vertretungsberechtigte und besondere Vertretungsbefugnisse	5 Prokura	6 a) Rechtsform, Register, Bilanzierung oder Gesellschaftsvertrag b) Sonstige Rechtsverhältnisse	7 a) Tag der Abtragung b) Bemerkungen

Frankfurt am Main, 11.10.2005
Der Ausdruck bezeugt den Inhalt des Handelsregisters
Unterzeichnet der Geschäftsstelle



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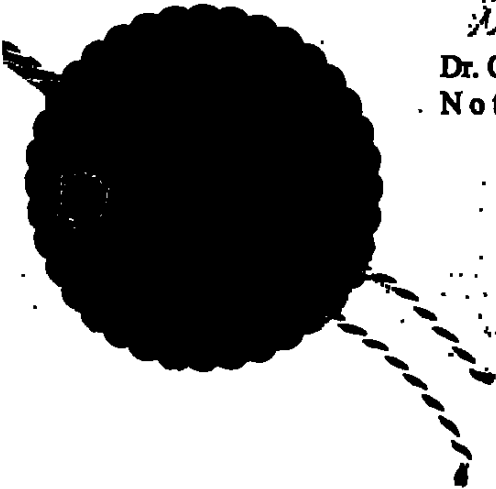
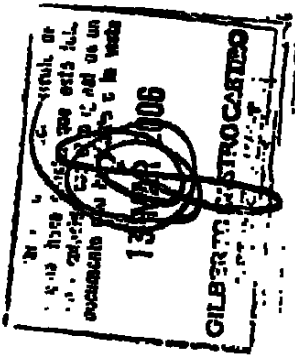
128
129

Die wörtliche Übereinstimmung der vorstehenden Abschrift mit der mir vorliegenden beglaubigten Abschrift beglaube ich hiermit. Die Abschrift besteht aus 7 Blättern.

I herewith certify that the foregoing copy is a true copy of the certified copy which has been presented to me. The copy consists of 7 sheets.

Frankfurt am Main, 21. Oktober 2005

Frankfurt am Main, 21 October, 2005



Dr. Oleg de Lousanoff
Notar



APOSTILLE

(Convention de la Haye du 5 octobre 1961)

- 1. Land: Bundesrepublik Deutschland
Diese öffentliche Urkunde
- 2. ist unterschrieben von Dr. de Lousanoff
- 3. in seiner Eigenschaft als amtlich bestellter Notar
- 4. sie ist versehen mit dem Siegel/Stempel des(der) Notars

Bestätigt

- 5. in Frankfurt/Main
- 6. am 26.10.05
- 7. durch den Herrn Präsidenten des Landgerichts
- 8. unter Nr. 91 Ea A 8468
- 9. Siegel/Stempel
- 10. Unterschrift



Frank
I.V. Frank

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Registro Comercial B

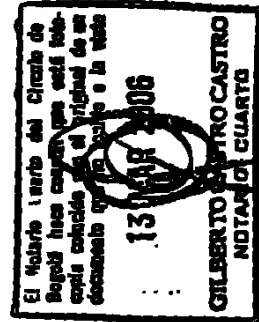
Juzgado Municipal de Frankfurt am Main

Número de la compañía: HRS 40661

Esta impresión no se firma y es válida como copia autenticada

Impresión Oficial

Copia del 11.10.2005 9:39



Entrada No. 1:

Razón social: Aventis Pharma Deutschland GmbH

Domicilio: Frankfurt am Main

Objeto de la empresa:

- a) la producción de productos farmacéuticos en Alemania;
- b) el mercadeo y la venta de productos farmacéuticos;
- c) el desarrollo de productos farmacéuticos y la investigación en este campo

Capital social o nominal: 5.201.000,00 EUROS

Reglamentación general de representación:

La sociedad tiene por lo menos dos gerentes.

La sociedad es representada por dos gerentes o por un gerente conjuntamente con un apoderado.

Gerentes:

Dr. Meier, Heinz-Werner, Matemático Diplomado, Mannheim

Kohl, Dieter, Ingeniero Económico Diplomado, Idstein

Dr. Wess, Günther, Químico Diplomado, Erlensee

Dr. Lehnert, Rudolf, Mainz, *28.02.1951

Zündorf, Peter, Colonia, *10.12.1956

Apoderados:

Poder colectivo conjuntamente con un gerente o con otro apoderado:

Bender, Stefan, Eppstein, *02.09.1960

Walter, Ralf, Langen (Hessen), *26.12.1957

Dr. Götter, Dieter, Wiesbaden

Dambacher, Erich, Niedernhausen

Raimann, Axel, Kelkheim,

Dr. Schmiedel, Rainer, Kelkheim

Dr. Christiansen, Christian-P, Frankfurt am Main

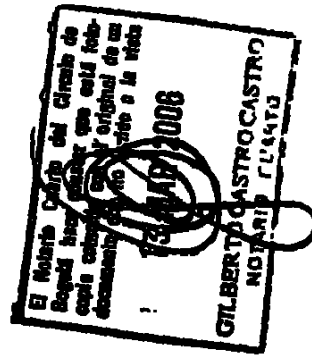
Dr. Fleischmann, Klaus, Eschborn

Dr. Richard, Frank, Krinberg im Taunus,

Preislinger, Richard, Hofheim am Taunus

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Bergmann, Jürgen, Großkrotzenburg
 Schäfer, Manfred, Flörsheim am Main,
 Willems, Arnold, Bad Camberg
 Arnold, Kurt Jakob, Niederdorffelden
 Dr. Kramer, Werner, Mainz,
 Dr. Rösner, Manfred, Eppstein
 Prf. Schölken, Bernward, Kelkheim
 Senft, Mario, Kelkheim
 Szymoniak, Roland, Kelkheim
 Fuchs, Brigitte, Hofheim am Taunus
 Dr. Kirschbaum, Bernd, Mainz, Prof.
 Dr. Selbert, Gerhard, Darmstadt



Dr. Mohr, Roland, Burghaun

Dr. Müller, Werner, Gensingen

Eigenherr, Ekkhard, Kelkheim, *25.07.1952

Dr. Jakobi, Markus, Bad Homburg v.d.Höhe, *23.02.1962

Naumann, Christoph, Königstein im Taunus, *06.05.1955

Dr. Aretz, Werner, Königstein im Taunus, *22.09.1951

Dr. Högn, Thomas, Colonia, *03.11.1944

Dr. Stilz, Hans-Ulrich, Frankfurt am Main, *15.03.1963

Stoppler, Hanfried, Niedernhausen, *04.01.1961

Dr. Milschmann, Manfred Heinrich, *Hofheim am Taunus, *01.12.1949

Dr. Busch, Andreas Eugen, Kelkheim, *26.08.1963

Brinkmann, Stefan Wolfgang, Bad Soden Am Taunus, *10.07.1966

Bieke, Jürgen, Liederbach, *23.06.1954

Dwerhagen, Jost, Frankfurt am Main, *24.11.1946

Dra. Löw, Anita, Nürnberg, *19.03.1953

Marloff, Claudia, Frankfurt am Main, *15.08.1969

Flecher, Renate, Frankfurt am Main, *01.05.1966

Mörler, Manfred, Bad Soden am Taunus, *13.11.1958

Dr. Keuth, Volker, Pulheim, *06.04.1961

Chapell, Alan, Bad Soden am Taunus, *24.02.1949

Dr. Köhler, Michael, Gründau-Rothenbergen, *16.03.1963

Dr. Karkoschka, Urs, Stuttgart, *14.01.1965

Dr. Wirth, Uwe, Kleinostheim, *25.09.1959

Dr. Laux, Reiner, Großholbach, *28.08.1960

Ulrich, Dirck, Kelkheim, *26.11.1966

Dr. Braun, Matthias, Hochheim am Main, *12.08.1963

Heinl, Angelika, Bad Soden am Taunus, *08.07.1965

Dr. Wein, Elmar-Michael, Niedernhausen, *28.09.1954

Koch, Peter, Pulheim, Stommeln, *15.01.1962

Breault, Giles, Lörrach, *05.07.1956

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Denizet, Alain, Bad Soden am Taunus, *13.08.1960

Dr. Foersch, Manfred, Hünstteten-Wallrabenstein, *15.09.1945

Dr. Götz, Jürgen, Bad Soden am Taunus, *04.01.1964

Herzog, Ute, Frankfurt am Main, *16.08.1968

Dr. Jamin, Rainer, Frankfurt am Main, *23.05.1949

Dr. Konz, Elmar, Kelkheim, *03.03.1944

Krauß, Manuel, Liederbach, *27.07.1967

Dr. Siewert, Martin, Frankfurt am Main, *23.04.1958

Rauh, Werner, Seligenstadt (Hessen), *15.10.1951

Welt, Gabriele, Gau-Bischofsheim, *14.04.1956

Klein, Dorothea, Kelkheim, *24.04.1961

Schmitt, Michael, Buddenheim, *18.12.1960

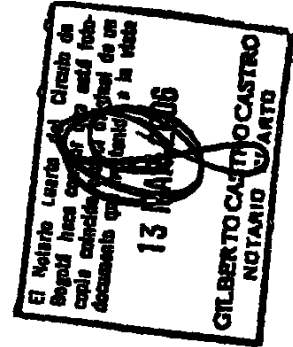
Kammerer, Matthias, Eppstein, *09.09.1966

Dr. Schuster, Peter, Sulzbach, *24.04.1951

Coenenberg, Oliver, Frankfurt am Main, *26.05.1968

Wiese, Carsten, Taunusstein, *16.02.1961

Patel, Meera, Berlin, 24.12.1964



Condiciones legales:

a) Sociedad con responsabilidad limitada.

Contrato de sociedad del 30.10.1995 modificado por última vez el 08.07.2003

b) Entre la sociedad y la compañía Aventis Pharma Holding GmbH (anteriormente llamada Hoechst Marion Roussel Aktiengesellschaft) domiciliada en Frankfurt am Main como empresa dominante se celebró un Contrato de Dominación y Extracción de Ganancias el 15.12.1998, el cual fue aprobado por la asamblea de socios mediante resolución el 15.12.1998.

La sociedad tiene un consejo de vigilancia.

Fecha de la entrada y firma: 16.12.2004 Drescher

Observaciones:

Fecha de la primera entrada: 14.11.1995

Esta hoja ha sido redactada de nuevo para su continuación mediante procesamiento por medios electrónicos y reemplaza la hoja de registro llevada hasta el presente.

Entrada No. 2:

Apoderados: Ha caducado el poder de Dr. Mohr, Roland, Burghaun

Poder colectivo conjuntamente con un gerente o con otro apoderado:

Dr. Enhnen, Alfons, Büttelborn, *22.01.1958

Dr. Kutter, Jürgen, Kelkheim, *18.05.1953

Fecha de la entrada y firma: 20.12.2004 Dinges-Król

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133**Entrada No. 3:**

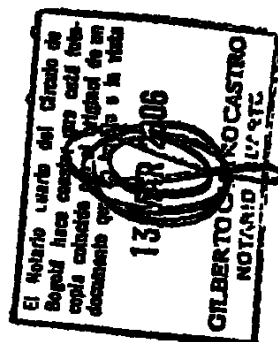
Poder colectivo conjuntamente con un gerente o con otro apoderado:

Bialojahn, Ulf, Wiesbaden, *09.12.1962

Fecha de la entrada y firma: 01.05.2005 Dinges-Kröl

Entrada No. 4:

Apoderados:

Han caducado los poderes de:Dr. Christianse, Chistian-P, Frankfurt am MainDr. Götz, Jürgen, Bad Soden am Taunus, *04.01.1964Klein, Dorothea, Kelkheim, *24.04.1961Dr. Högn, Thomas, Colonia, *03.11.1944

Poder colectivo conjuntamente con un gerente o con otro apoderado:

Dr. Hemrich, Hans Thomas, Kelkheim, *25.10.1961

Fecha de la entrada: 28.01.2005 Dinges-Kröl

Entrada No. 5:

Apoderados:

Poder colectivo conjuntamente con un gerente o con otro apoderado:

Dr. Riederer, Heinrich Jacob, Neubiberg, *18.07.1951

Koch, Klaus, Berlin, *23.04.1958

Henn, Miriam, Frankfurt am Main, *03.05.1971

Dr. Kahl, Thomas, Hofheim am Taunus, *27.06.1961

Dewitz, Volker, Frankfurt am Main, *09.09.1950

Dr. Suermondt, Matthias, Berlin, *26.07.1960

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Luck, Fred, Berlin, *10.11.1962

Lange, Wilfried, Berlin, *27.07.1952

Kress, Stephen, Kleinmachnow, *15.11.1956

Dr. Hundt, Ferdinand, *23.04.1949

Hirtz, Christophe, Berlin, *03.12.1965

Dr. Heinemann, Christoph, Frankfurt am Main, *28.12.1969

Haser, Manfred, Berlin, *27.09.1962

Dr. Greive, Heinrich, Sulzbach, *05.06.1958

Dr. Golombowski-Daffner, Sidonie, Echting, *21.09.1964

Döppler, Stephen, Berlin, *23.08.1947

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Fecha de la entrada: 18.02.2005 Dinges-Kröl

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134**Entrada No. 6:****Apoderados:**Poder caducado: Wiese, Carsten, Taunusstein, *16.02.1961Poder caducado: Dr. Laux, Reiner, *28.08.1960

Fecha de la entrada: 22.02.2005 Berend

Entrada No. 7:**Apoderados:**

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Dewitz, Volker, Frankfurt am Main, *03.09.1950

Dr. Golombowki-Daffner, Sidonie, *21.09.1964

Fecha de la entrada: 8.02.2005 Berend

Observaciones:

La entrada No. 5 ha sido oficialmente corregida.

Entrada No. 8:**Poderes:**Poder caducado: Brault, Gilles, Lörrach, *05.07.1956

Fecha de la entrada: 04.05.2005 Dinges-Król

Entrada No. 9:**Apoderados:**Poder caducado: Dr. Konz, Elmar, Kelkheim, *03.03.1944

Fecha de la entrada: 11.04.2005 Dinges-Król

Entrada No. 10:**Gerentes:**Ha dejado de ser gerente: Zündorf, Peter, Colonia, *10.12.1956

Nombrado gerente: Dr. Wessely, Jean-Yves, Berlín, *27.05.1951

Fecha de la entrada: 18.04.2005 Dinges-Król

Entrada No. 11:**Apoderados:**

Poder colectivo conjuntamente con un gerente o con otro apoderado:

Wirz, Edgar, Berlín, *09.08.1965

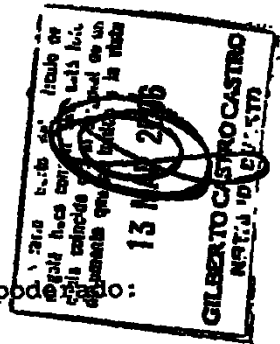
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Dr. Kruse, Dirk, Bad Homburg v.d.H., 06.01.1958

Fecha de la entrada: 28.04.2005 Dinges-Król

Entrada No. 12:**Apoderados:**Poder caducado: Busch, Andreas Eugen, Kelkheim, *26.08.1963

Fecha de la entrada: 30.05.2005 Dinges-Król



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Entrada No. 13:**Apoderados:**

Poder colectivo conjuntamente con un gerente o con otro apoderado:

Schröder, Kai, Mühlheim am Main, *13.07.1967

Dasse, Thomas, Berlin, *04.08.1968

Dra. Müller-Jakic, Barbara, Bad Soden am Taunus, *02.09.1965

Dra. Rußwurm, Regine, Alsbach-Hähnlein, *14.07.1953

Fecha de la entrada: 16.06.2005 Dinges-Król

Entrada No. 14:

Razón social: Sanofi-Aventis Deutschland GmbH

Contrato de sociedad:

La asamblea de socios del 28.07.2005 resolvió cambiar el Artículo 1 del contrato de sociedad (razón social)

Fecha de la entrada: 01.09.2005 Frink-Zinnhardt

Observaciones:

Inscripción Hoja 160 siguientes Volumen especial III

Entrada No. 15:**Apoderados:**

Poder caducado: Dr. Götte, Dieter, Wiesbaden

Fecha de la entrada: 21.09.2005 Leifert

Entrada No. 16:**Gerentes:**

Ha dejado de ser gerente: Dr. Lehnert, Rudolf, Mainz, *28.02.1951

Ha sido nombrado gerente: Braun, Matthias, Hochheim am Main,
*12.08.1963

Ha sido nombrado gerente: Dr. Siewert, Martin, Kronberg im Taunus,
*23.04.1958

Poderes:

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Dr. Braun, Matthias, Hochheim am Main, *12.08.1963

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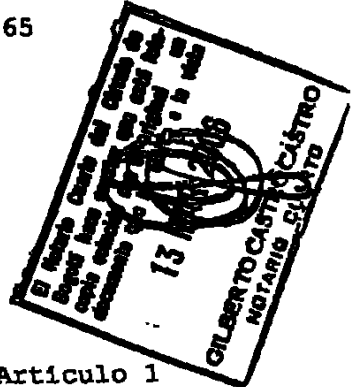
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Bach, Flavia, Bad Homburg, v.d.H., *06.07.1969

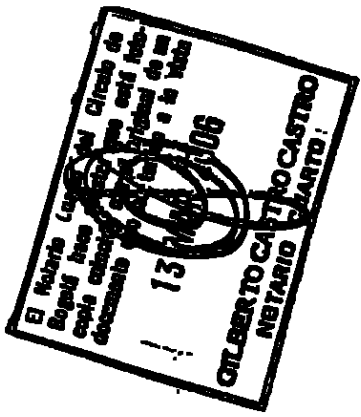
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DIVISION DE NUEVAS CREACIONES

RADICACIÓN EXPEDIENTE No. 03- 88391

EL EXTRACTO DE LA PRESENTE SOLICITUD DE PATENTE DE INVENCION

- PCT, FUE PUBLICADO EN LA GACETA DE PROPIEDAD INDUSTRIAL No 553,

DE FECHA 30 DE JUNIO DE 2005, EL TERMINO HABIL SEÑALADO POR LA

LEY EXPIRA EL 27 DE SEPTIEMBRE DE 2005.

NOTA: Dentro del plazo de los seis (6) meses siguientes a partir de la fecha de publicación en la gaceta de Propiedad Industrial, deberá solicitar y cancelar el examen de patentabilidad so pena de que la solicitud caiga en abandono, de acuerdo con lo establecido en el Artículo 44 de la Decisión 486/2000.

SE PRESENTARON OPOSICIONES POR PARTE DE TERCEROS.

SI

NO **X**

United States Patent [15]

Flynn et al.

US005430145A

[11] Patent Number: 5,430,145

[45] Date of Patent: Jul. 4, 1995

[54] MERCAPTOACETYLAMIDE DERIVATIVES
USEFUL AS INHIBITORS OF
ENKEPHALINASE AND ACE

[75] Inventors: Gary A. Flynn, Philippe Bay, Alan M. Wardlaw, Douglas W. Beight, Shanjun M. Mohit, Eugene L. Green, all of Cincinnati; Timothy P. Burkholder, Fairfield, Ohio; Edward D. Danga, Midland, Mich.; John F. French, Cincinnati, Ohio

[73] Assignee: Merrell Dow Pharmaceuticals Inc., Cincinnati, Ohio

[21] Appl. No.: 149,572

[22] Filed: Nov. 9, 1993

Related U.S. Application Data

[63] Continuation-in-part of Ser. No. 75,981, Jan. 11, 1993, abandoned, which is a continuation-in-part of Ser. No. 861,600, Apr. 3, 1992, abandoned, which is a continuation-in-part of Ser. No. 735,496, Jul. 25, 1991, abandoned, which is a continuation-in-part of Ser. No. 600,052, Oct. 18, 1990, abandoned.

[51] Int. Cl.⁶ A61K 31/35; C07D 223/16; C07D 487/04; C07D 513/04; C07D 498/04

[52] U.S. Cl. 540/321; 540/322

[58] Field of Search 540/322, 321

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Primary Examiner—Robert T. Bond
Attorney, Agent, or Firm—Charlotte L. Barony

[57] ABSTRACT

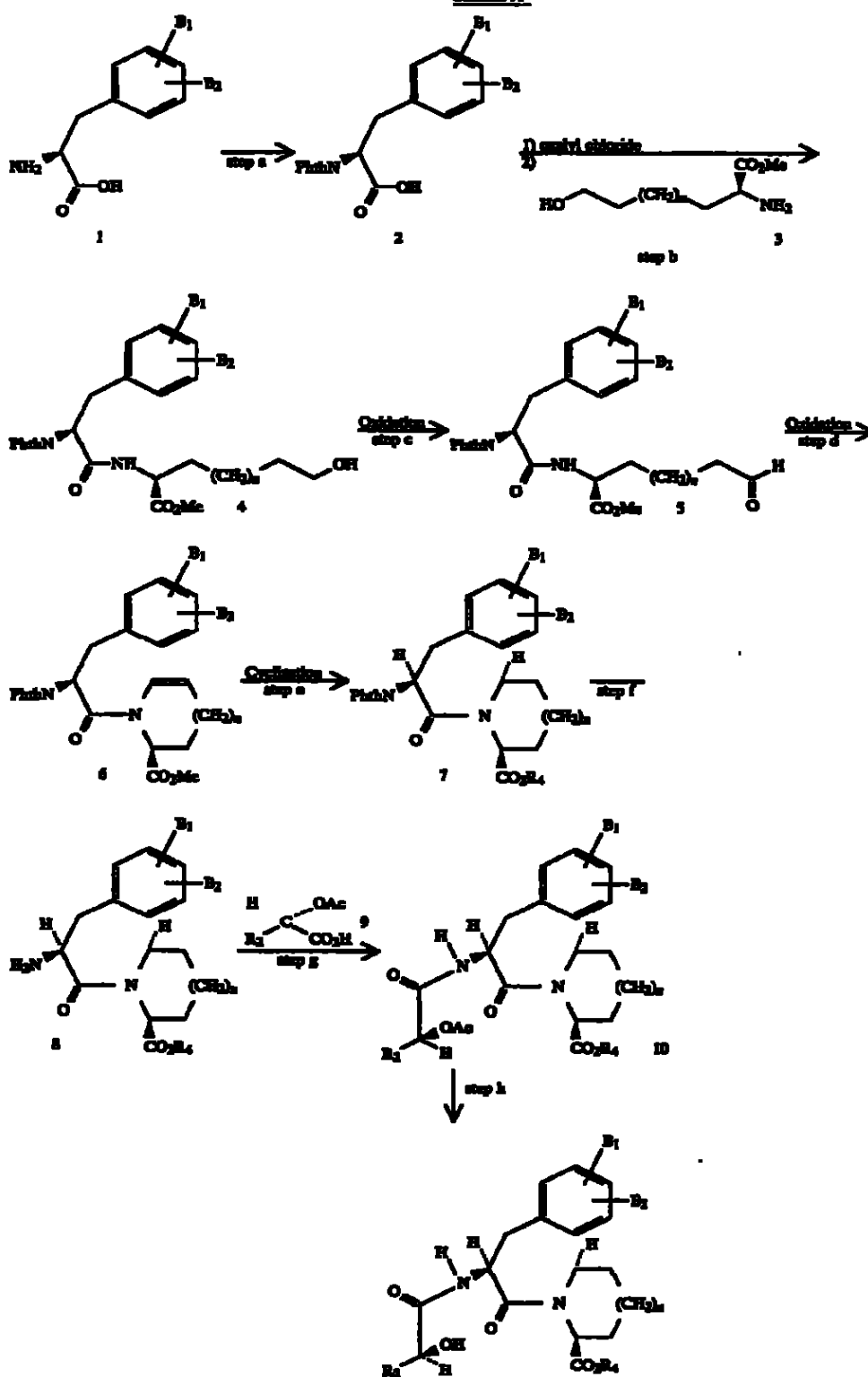
The present invention relates to certain novel mercaptoacetylamide derivatives useful as inhibitors of enkephalinase and of ACE.

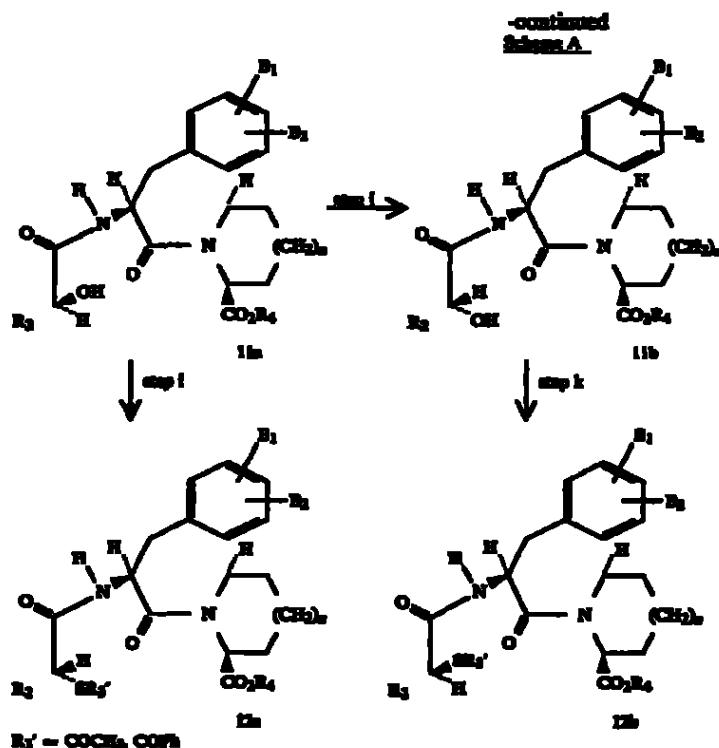
27 Claims, No Drawings

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Scheme A



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In step a, the appropriate phthalimide blocked (S)-phenylalanine derivative of structure 2 can be prepared by reacting the appropriate (S)-phenylalanine derivative of structure 1 with phthalic anhydride in a suitable aprotic solvent, such as dimethylformamide.

In step b, the appropriate phthalimide blocked (S)-phenylalanine derivative of structure 2 can be converted to the corresponding acid chloride, then reacted with the appropriate amino acid methyl ester of structure 3 in a coupling reaction. For example, the appropriate phthalimide blocked (S)-phenylalanine derivative of structure 2 can be reacted with osyl chloride in a suitable aprotic solvent, such as methylene chloride. The resulting acid chloride can then be coupled with the appropriate amino acid methyl ester of structure 3 using *N*-methylmorpholine in a suitable aprotic solvent, such as dimethylformamide, to give the appropriate 1-oxo-3-phenylpropyl-amino acid methyl ester derivative of structure 4.

In step c, the hydroxymethylene functionality of the appropriate 1-oxo-3-phenylpropyl-amino acid methyl ester derivative of structure 4 can be oxidized to the appropriate aldehyde of structure 5 by oxidation techniques well known and appreciated in the art. For example, the hydroxymethylene functionality of the appropriate 1-oxo-3-phenylpropyl-amino acid methyl ester derivative of structure 4 can be oxidized to the appropriate aldehyde of structure 5 by means of a Swern oxidation using osyl chloride and dimethylsulfoxide in a suitable aprotic solvent, such as methylene chloride.

In step d, the appropriate aldehyde of structure 5 can be cyclized to the appropriate enamine of structure 6 by acid catalysis. For example, the appropriate aldehyde of structure 5 can be cyclized to the appropriate enamine

of structure 6 by treatment with trifluoroacetic acid in a suitable aprotic solvent, such as methylene chloride.

In step e, the appropriate enamine of structure 6 can be converted to the corresponding tricyclic compound of structure 7 by an acid catalyzed Friedel-Crafts reaction. For example, the appropriate enamine of structure 6 can be converted to the corresponding tricyclic compound of structure 7 by treatment with a mixture of trifluoroacetic sulfonic acid and trifluoroacetic anhydride in a suitable aprotic solvent, such as methylene chloride.

In step f, the phthalimide protecting group of the appropriate tricyclic compound of structure 7 can be removed using techniques and procedures well known in the art. For example, the phthalimide protecting group of the appropriate tricyclic compound of structure 7 can be removed using hydrazine monohydrate in a suitable protic solvent such as methanol, to give the corresponding amino compound of structure 8.

In step g, the appropriate (S)-acetate compound of structure 10 can be prepared by reacting the appropriate amino compound of structure 8 with the appropriate S-acetate of structure 9. For example, the appropriate amino compound of structure 8 can be reacted with the appropriate (S)-acetate compound of structure 9 in the presence of a coupling reagent such as EEDQ (1-ethoxycarbonyl-3-ethoxy-1,2-dihydroquinoline), DCC (1,3-dicyclohexylcarbodiimide), or diethylazodicarboxylate in a suitable aprotic solvent, such as methylene chloride to give the appropriate (S)-acetate compound of structure 10.

Alternatively, the appropriate (S)-acetate compound of structure 10 can be prepared by reacting the appropriate amino compound of structure 8 with a preformed S-acetate activated ester. For example, the appropriate

amino compound of structure 8 can be reacted with the appropriate preformed (S)-acetate activated ester to give the appropriate (S)-acetoxy compound of structure 10. Examples of suitable activated esters are N-hydroxy-succinimide, isobutylchloroformate, N-ethoxycarbo-
 xyl-2-ethoxy-1,3-dihydroquinoline (BEDQ), 1,1'-car-
 bonylbifluoride, 1-(3-dimethylaminopropyl)-3-ethyl
 carbodiimide and the like

In step h, the (S)-acetate functionality of the appropriate amide compound of structure 10 can be hydro-
 lyzed to the corresponding (S)-alcohol of structure 11a
 with a base, such as lithium hydroxide in a suitable
 solvent mixture, such as tetrahydrofuran and ethanol.

In step i, the (S)-alcohol functionality of the appropri-
 ate amide compound of structure 11a can be converted
 to the corresponding (R)-thioacetate or (R)-thiobenzo-
 ate of structure 12a. For example, the appropriate (S)-
 alcohol of structure 11a can be treated with thioacetic
 acid in a Mitsunobu reaction using triphenylphosphine
 and DIAD (diisopropylazodicarboxylate) in a suitable
 aprotic solvent, such as tetrahydrofuran.

In step j, the (S)-alcohol functionality of the appropri-
 ate amide compound of structure 11a can be converted
 to the corresponding (R)-alcohol of structure 11b. For
 example, the appropriate (S)-alcohol of structure 11a
 can be treated with acetic acid in a Mitsunobu reaction
 using triphenylphosphine and DIAD in a suitable
 aprotic solvent, such as tetrahydrofuran. The resulting
 (R)-acetate can then be hydrolyzed with a base, such as
 lithium hydroxide.

In step k, the (R)-alcohol functionality of the appropri-
 ate amide compound of structure 11b can be con-
 verted to the corresponding (S)-thioacetate or (S)-thio-
 benzoate of structure 12b. For example, the appropri-
 ate (R)-alcohol of structure 11b can be treated with
 thioacetic acid in a Mitsunobu reaction using triphenyl-
 phosphine and DIAD in a suitable aprotic solvent, such
 as tetrahydrofuran.

As summarized in Table 1, the R₃ and R₄ groups on
 the compounds of structures 12a and 12b can be manip-
 ulated using techniques and procedures well known and
 appreciated by one of ordinary skill in the art to give the
 corresponding compounds of structures 13a-18a and
 13b-18b.

For example, the diphenylmethyl ester functionality
 of the appropriate compound of structure 12a can be re-
 moved using trifluoroacetic acid to give the appropri-
 ate carboxylic acid compound of structure 13a. Simi-
 larly, the diphenylmethyl ester functionality of the ap-
 propriate compound of structure 12b can be removed
 using trifluoroacetic acid to give the carboxylic acid
 compound of structure 13b.

The (R)-thioacetate or (R)-thiobenzoate functionality
 of the appropriate compound of structure 13a can be re-
 moved with lithium hydroxide in a suitable solvent
 mixture such as tetrahydrofuran and ethanol to give the
 appropriate (R)-thio compound of structure 14a. Simi-
 larly, the (S)-thioacetate or (S)-thiobenzoate function-
 ality of the appropriate compound of structure 13b can be
 removed with lithium hydroxide in a suitable solvent
 mixture such as tetrahydrofuran and ethanol to give the
 appropriate (S)-thio compound of structure 14b.

Alternatively, the carboxylic acid functionality of the
 appropriate compound of structure 13a can be re-esteri-
 fied using techniques and procedures well known and
 appreciated in the art. For example, a compound of
 structure 15a can be prepared by treating the carboxylic
 acid compound of structure 13a with the appropriate

alkyl halide in a suitable aprotic solvent, such as dimeth-
 ylformamide along with a non-nucleophilic base, such
 as cesium carbonate. Similarly, the carboxylic acid
 functionality of the appropriate compound of structure
 13b can be esterified to the appropriate ester compound
 of structure 15b as described above for 15a.

The (R)-thioacetate or (R)-thiobenzoate functionali-
 ties of the appropriate compounds of structure 15a can
 be hydrolyzed to the corresponding (R)-thiol com-
 pounds of structure 16a with ammonia in a suitable
 protic solvent, such as methanol. Similarly, the (S)-thio-
 acetate or (S)-thiobenzoate functionalities of the ap-
 propriate compounds of structure 15b can be hydro-
 lyzed to the corresponding (S)-thiol compounds of
 structure 16b.

The thiol functionality of the appropriate compound
 of structure 14a can be alkylated using techniques and
 procedures well known and appreciated in the art. For
 example, a compound of structure 17a can be prepared
 by treating the thiol compound of structure 14a with the
 appropriate with chloromethyl pivalate in a suitable
 aprotic solvent, such as dimethylformamide along with
 a non-nucleophilic base, such as cesium carbonate. Simi-
 larly, the thiol functionality of the appropriate com-
 pound of structure 14b can be alkylated to the appropri-
 ate pivalate compound of structure 17b as described
 above for 17a.

The thiol functionality of the appropriate compound
 of structure 16a can be alkylated using techniques and
 procedures well known and appreciated in the art. For
 example, a compound of structure 18a can be prepared
 by treating the thiol compound of structure 16a with the
 appropriate with chloromethyl pivalate as described
 above for the conversion of 14a to 17a. Similarly, the
 thiol functionality of the appropriate compound of
 structure 16b can be alkylated to the appropriate piva-
 late compound of structure 18b as described above for
 18a.

TABLE 1
MANIPULATION OF R₃ AND R₄

Compound	R ₃	R ₄
12a and 12b	COCH ₃ or COPh	H
14a and 14b	H	H
15a and 15b	COCH ₃ or COPh	C ₂ -C ₄ alkyl, Ar-Y, -CH ₂ OCOC(CH ₃) ₃
16a and 16b	H	C ₂ -C ₄ alkyl, Ar-Y, diphenylmethyl, -CH ₂ OCOC(CH ₃) ₃
17a and 17b	-CH ₂ OCOC(CH ₃) ₃	H
18a and 18b	-CH ₂ OCOC(CH ₃) ₃	C ₂ -C ₄ alkyl, Ar-Y, diphenylmethyl, -CH ₂ OCOC(CH ₃) ₃

Although the general procedures outlined in Scheme
 A show the preparation of the compounds of Formula I
 wherein A₁ is (S)-COOR₄ and A₂ is hydrogen, the com-
 pounds of Formula I wherein A₁ is (R)-COOR₄ and A₂
 is hydrogen may be prepared by analogous procedures
 by substituting an appropriate (R)-amino acid methyl
 ester for the (S)-amino acid methyl ester of structure 3
 in step b.

Starting materials for use in the general synthetic
 procedures outlined in Scheme A are readily available
 to one of ordinary skill in the art. For example, certain
 (R)- and (S)-carboxy acetate or benzoate starting mate-

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rials of structure 9 can be prepared by stereoselective reduction of the corresponding pyruvate compounds with alpine boranes as described in *J. Org. Chem.* 47, 1606 (1982), *J. Org. Chem.* 49, 1316 (1984), and *J. Am. Chem. Soc.* 106, 1531 (1984), followed by treating the resulting alcohol with acetic anhydride or benzoic anhydride to give the corresponding (R)- or (S)-carboxy acetate or benzoate compounds of structure 9.

Alternatively, certain tricyclic compounds of structure 7 may be prepared as described in European Patent Application of Flynn and Beight, Application #34333A EP (Jan. 11, 1987).

The following examples present typical syntheses as described in Scheme A. These examples are understood to be illustrative only and are not intended to limit the scope of the present invention in any way. As used herein, the following terms have the indicated meanings: "g" refers to grams; "mmol" refers to millimoles; "mL" refers to milliliters; "bp" refers to boiling point; "°C" refers to degrees Celsius; "mm Hg" refers to millimeters of mercury; "μL" refers to microliters; "μg" refers to micrograms; and "μM" refers to micromolar.

EXAMPLE 1

Preparation of [4S-[4a, 7a(R*), 12b(S)]-7-[(1-Oxo-2(R)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12-b-octahydro-6-oxopyrido[2,1-a][2]benzoxepine-4-carboxylic acid, diphenylmethyl ester

Step a: N-phthaloyl-(S)-phenylalanine (2)

Mix phthalic anhydride (1.82kg, 12.3mole), (S)-phenylalanine (1.84kg, 11.1 mole) and anhydrous dimethylformamide (2.26L). Stir at 115°-120° C. for 2 hours under a nitrogen atmosphere. Pour into rapidly stirring water (32.6L) and cool overnight at 0° C. Filter, wash with cold water (2×2L) and air dry. Dissolve in a mixture of 9A ethanol (8.05L) and water (8.05L) and heat at reflux temperature. Gravity filter, cool to ambient temperature and refrigerate overnight at about 0° C. Filter the crystallized product, wash with cold 50:50 9A ethanol/water (2×2L) and air dry to yield 2.96kg (90.3%) of the title compound; mp 177°-179° C.

Step b: (S)-N-[2-(1,3-Dihydro-1,3-dioxo-2H-isindol-2-yl)-1-oxo-3-phenylpropyl]-6-hydroxy-(S)-norleucine, methyl ester

Mix N-phthaloyl-(S)-phenylalanine (2) (30.2g, 0.17mole), methylene chloride (680mL) and dimethylformamide (0.5mL) under a nitrogen atmosphere. Add oxalyl chloride (17.7mL, 0.2mole) over about 5 minutes with stirring. Stir at ambient temperature for 3 hours and evaporate the solvent in vacuo to leave N-phthaloyl-(S)-phenylalanine, acid chloride as a solid (34.3g, 101.9%).

Mix 6-hydroxy-(S)-norleucine, methyl ester, hydrochloride salt (33.5g, 0.1mole) and dimethylformamide (201mL), cool to about 0° C. and place under nitrogen atmosphere. Add by dropwise addition, N-methylmorpholine (51mL, 0.46mole) with cooling so that the pot temperature stays at 0°-5° C. Stir at 0°-5° C. for an additional 10 minutes, then add a solution of N-phthaloyl-(S)-phenylalanine, acid chloride (33.5g, 0.17mole) in methylene chloride (270mL) over 30 minutes with cooling so that the temperature stays at 0°-5° C. Remove the cooling bath and stir at room temperature for 18 hours.

Evaporate the methylene chloride in vacuo and dilute the remaining residue with ethyl acetate (800mL). Extract the resulting mixture with water (800mL), sepa-

rate the organic layer and extract with 1N hydrochloric acid (270mL), followed by water (3×500mL). Dry the organic layer (MgSO₄), filter and evaporate in vacuo to yield crude product (76g, 98%). Dissolve the crude product in hot toluene (223.5mL), cool to room temperature, then cool overnight at about 0° C. Filter the crystallized product, wash with cold toluene and air dry to yield 56.6g (76%) of the title compound; mp 128°-130° C.

Step c: 2-(1,3-Dihydro-1,3-dioxo-2H-isindol-2-yl)-1-oxo-3-phenylpropyl-6-oxo-(S)-norleucine, methyl ester

Mix oxalyl chloride (80mL, 0.92mole) and methylene chloride (2L) and place under nitrogen atmosphere. Cool below -50° C. and add a solution of dimethyl sulfoxide (63.4mL, 0.92mole) in methylene chloride (425mL). Stir for 15 minutes and add a solution of (S)-N-[2-(1,3-dihydro-1,3-dioxo-2H-isindol-2-yl)-1-oxo-3-phenylpropyl]-6-hydroxy-(S)-norleucine, methyl ester (200g, 0.456mole) in methylene chloride (800mL) over about 45 minutes, keeping the pot temperature below -50° C. for 30 minutes. Add triethylamine (420mL, 3.01mole) over 30 minutes. Stir while warming to 0° C. over 1.25 hours. Transfer the reaction mixture to a 12-liter flask. Stir and cool while adding a solution of OXONE (potassium peroxymonosulfate) (566g) in water (6.74L) at such a rate that the pot temperature stays below 15° C. Stir for 5 minutes, separate the organic layer and extract the aqueous layer with methylene chloride (1L). Combine the organic phases, dry (MgSO₄) and filter to yield the title compound as a solution.

Step d: [3-(R*,R*)]-N-[2-(1,3-Dihydro-1,3-dioxo-2H-isindol-2-yl)-1-oxo-3-phenylpropyl]-1,2,3,4-tetrahydro-3-pyridinecarboxylic acid, methyl ester

Transfer the solution of 2-(1,3-dihydro-1,3-dioxo-2H-isindol-2-yl)-1-oxo-3-phenylpropyl-6-oxo-(S)-norleucine, methyl ester in methylene chloride (volume about 4.5L) to a 12-liter flask and place under nitrogen atmosphere. Stir and add trifluoroacetic acid (440mL, 5.71mole) in one portion. Stir the resulting mixture at room temperature for one hour, then rapidly cool to about 0° C. Add a solution of sodium hydride (240g, 6.0mole) in water (3.4L) in a slow stream to the vigorously stirred mixture at such a rate that the pot temperature stays at about 0° C. Separate the organic phase and extract the aqueous phase with methylene chloride (1L). Combine the organic phases and dry (MgSO₄). Filter and remove the solvent in vacuo to leave a residue (282g, 137%).

Dissolve the above residue in diethyl ether (1L) and wash with water (5×500mL). Evaporate the organic phase in vacuo to leave a residue of 228g. Dilute the residue with methylene chloride (200mL) and purify by silica gel chromatography (methylene chloride) to yield a viscous residue of 225g.

Dilute the above residue with diethyl ether (230mL) and allow to stand at room temperature for 24 hours. Filter the solid, wash with diethyl ether, and air dry to yield 123.2g; mp 140°-142.5° C. Recrystallize (methylene chloride (125mL)/isopropanol (615mL)) by boiling off the solvent until the pot temperature reaches 75° C. and allowing the resulting sample to stand at room temperature for 24 hours. Filter, wash with cold isopropanol and air dry to yield 101.5g of the title compound; mp 144°-146° C.

Evaporate the filtrate from the 101.5g in vacuo to yield 24g. Recrystallize (isopropanol) to yield an additional 3.5g of the title compound.

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Evaporate the filtrate from the 123.2g in vacuo to leave 62g of oil. Purify by silica gel chromatography (25% ethyl acetate/75% hexane), collecting 21-500mL fractions. Combine fractions 9-20 and evaporate in vacuo to yield 35g of a viscous oil. Recrystallize three times (isopropanol/3mL/g) to yield an additional 11.9g of the title compound; mp 142.5°-144.5° C. Total yield of useful material: 116.9g (61.3%).

Step e: [4S-(4a, 7a(R⁺), 12b(S))]-7-[(1,3-Dihydro-1,3-dioxo-2H-isindol-2-yl)]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester

Mix trifluoromethane sulfonic acid (300g, 3.33mole) and trifluoroacetic anhydride (74.8mL, 0.33mole) and place under nitrogen atmosphere. Stir and add a solution of [8-(R⁺, R⁺)]-N-[2-(1,3-dihydro-1,3-dioxo-2H-isindol-2-yl)]-1-oxo-3-phenylpropyl]-1,2,3,4-tetrahydro-2-pyridinecarboxylic acid, methyl ester (200g, 0.48mole) in methylene chloride (1L) with cooling at such a rate as to keep the pot temperature below 35° C. Stir at ambient temperature for 2 days. Pour into vigorously stirring ice water (3L) and stir for 30 minutes. Extract with ethyl acetate (3×1L), combine the organic phases and wash with water (3×500mL). Evaporate in vacuo to a residue. Dissolve the residue in ethyl acetate (4L) and extract with $\frac{1}{2}$ saturated potassium hydrogen carbonate (1L), then $\frac{1}{2}$ saturated potassium hydrogen carbonate (7×1L). Combine the aqueous extracts and dilute with ethyl acetate (2L). Stir the resulting mixture and cool to 5°-10° C. Adjust to pH 2 using concentrated hydrochloric acid (about 750mL).

Separate the organic phase and extract the aqueous phase with ethyl acetate (3×1L). Combine the ethyl acetate extracts, wash with water (3×1L), then saturated sodium chloride (0.8L), and dry (MgSO₄). Filter and wash with ethyl acetate (3×200mL). Evaporate in vacuo to leave (188.3g, 101.5%) [4S-(4a, 7a(R⁺), 12b(S))]-7-[(1,3-dihydro-1,3-dioxo-2H-isindol-2-yl)]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid as a colorless foam.

Dissolve [4S-(4a, 7a(R⁺), 12b(S))]-7-[(1,3-dihydro-1,3-dioxo-2H-isindol-2-yl)]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid (113.9g, 0.28mole) in methylene chloride (1.2L) and dry over anhydrous MgSO₄ (60g). Filter and wash with methylene chloride (3×200mL). Evaporate in vacuo to a residue. Dissolve the residue in anhydrous dimethylformamide (860mL) and place under nitrogen atmosphere. Add calcium carbonate (98.9g, 0.3mole) in one portion. Stir for 45 minutes at ambient temperature. Add bromodiphenylmethane (164.8g, 0.67mole). Stir the resulting mixture at ambient temperature for 18 hours. Quench the reaction with ethyl acetate (2.46L) and water (630mL). Separate the organic phase and wash with water (7×625mL), $\frac{1}{2}$ saturated potassium hydrogen carbonate (625mL), water (625mL), and saturated sodium chloride (625mL). Dry (MgSO₄), filter and evaporate in vacuo to yield 214.4g of an oil. Extract the combined aqueous washings with ethyl acetate (3×500mL), wash with water (4×300mL) and dry (MgSO₄). Filter and evaporate in vacuo to yield an additional 20.2g of an oil.

Dissolve the crude product (234.6g) in methylene chloride (200mL) and plug filter through 213g of silica gel, eluting with methylene chloride (2L). Boil off the solvent and replace with hexane (3L), with the pot temperature reaching a maximum of 65° C. Cool to ambient temperature, decant off the precipitated oil and

crystallize (9A ethanol) to yield 96.6g (60%) of the title compound; mp 153°-155° C.

Step f: [4S-(4a, 7a(R⁺), 12b(S))]-7-(Amino)-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester

Mix [4S-(4a, 7a(R⁺), 12b(S))]-7-[(1,3-dihydro-1,3-dioxo-2H-isindol-2-yl)]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester (170.9g, 0.3mole), hydrazine monohydrate (34.4g, 0.68mole) and methanol (3.4L) under nitrogen atmosphere. Heat at reflux for 5 hours. Cool to ambient temperature and filter to remove phthaloyl hydrazide. Evaporate the filtrate in vacuo to a residue and slurry in chloroform (800mL). Remove insoluble phthaloyl hydrazide by filtration and wash with chloroform (4×210mL). Wash the filtrate with water (4×425mL), dry (MgSO₄), and filter. Evaporate the filtrate to a solid residue of the title compound weighing 142g (107.7%).

Step g: [4S-(4a, 7a(R⁺), 12b(S))]-7-[(1-Oxo-2(S)-acetyloxy-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester

Mix (S)-3-phenylacetic acid (11.17g, 67.2mmol) and sulfuric acid (0.3mL of a 10% solution in acetic acid). Add acetic anhydride (6.34mL, 67.2mmol) over 10 minutes. Warm to 90° C. with stirring for 45 minutes. Allow to cool, pour into diethyl ether and wash with water three times. Separate the organic phase, dry (MgSO₄) and concentrate in vacuo to yield 13.16g (94%) (S)-3-phenyl-2-acetyloxypropionic acid as a white oil.

Mix (S)-3-phenyl-2-acetyloxypropionic acid (3.6g, 17mmol) and [4S-(4a, 7a(R⁺), 12b(S))]-7-(amino)-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester (7.6g, 17mmol) in methylene chloride (50mL). Add EEDQ (4.3g, 17mmol). Stir for 18 hours at ambient temperature under argon atmosphere. Extract with 2N hydrochloric acid, separate the organic phase, wash with water, then with saturated sodium hydrogen carbonate. Dry (MgSO₄) and concentrate in vacuo to yield an off-white foam. Purify by silica gel chromatography (30%, then 40%, then 50% ethyl acetate/hexane) to yield 8.5g (78%) of the title compound.

Step h: [4S-(4a, 7a(R⁺), 12b(S))]-7-[(1-Oxo-2(S)-hydroxy-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester

Dissolve [4S-(4a, 7a(R⁺), 12b(S))]-7-[(1-oxo-2(S)-acetyloxy-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester (11.0g, 17.4mmol) in ethanol (75mL) and tetrahydrofuran (40mL) and add lithium hydroxide (22mL of a 1M solution, 22mmol). Stir the reaction mixture for 2 hours. Remove the solvent in vacuo at 35° C. and partition the residue between ethyl acetate and 1N hydrochloric acid. Separate the organic phase, dry (MgSO₄), and concentrate in vacuo. Purify by silica gel chromatography (1:1/tetrahydrofuran:hexane) to yield 9.6g (94%) of the title compound.

Anal. Calcd for C₃₇H₃₈N₂O₇: C, 73.49; H, 6.16; N, 4.76;

Found: C, 73.30; H, 6.44; N, 4.54.

Step i: [4S-(4a, 7a(R⁺), 12b(S))]-7-[(1-Oxo-2(R)-acetyloxy-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzazepine-4-carboxylic acid, diphenylmethyl ester

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Mix DIAD (3.4g, 16.3mmol), triphenylphosphine (4.28g, 16.3mmol) and anhydrous tetrahydrofuran (200mL). Cool to 0° C. and stir for 30 minutes under nitrogen atmosphere. Add a solution of the [4S-[4a, 7a(R¹), 12b(S)]-7-[(1-oxo-2(S)-hydroxy-3-phenylpropyl)-amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzoxepine-4-carboxylic acid, diphenylmethyl ester (9.6g, 16.3mmol) and thioacetic acid (1.73mL, 24.5mmol) in anhydrous tetrahydrofuran (200mL). Stir at 0° C. for 30 minutes, then allow to warm to ambient temperature. Remove the volatiles in vacuo and purify by silica gel chromatography (1L each of 20%, 30%, 40% then 50% tetrahydrofuran/hexane) to yield 3.127g (49%) of the title compound.

EXAMPLE 2

Preparation of [4S-[4a, 7a(R¹), 12b(S)]-7-[(1-oxo-2(R)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzoxepine-4-carboxylic acid

Mix [4S-[4a, 7a(R¹), 12b(S)]-7-[(1-oxo-2(R)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzoxepine-4-carboxylic acid, diphenylmethyl ester (3.125g, 4.83mmol), sodium (5g) and trifluoroacetic acid (30mL). Stir for 2 hours at ambient temperature under nitrogen atmosphere. Remove the volatiles in vacuo and purify by silica gel chromatography (1400mL 30% tetrahydrofuran/hexane with 5% acetic acid added, then 1000mL 40% tetrahydrofuran/hexane with 5% acetic acid added) to yield a viscous foam. Dissolve the foam in a minimal amount of methylene chloride and dilute with hexane until cloudy. Allow to stand overnight at -30° C., filter the resulting white solid and dry at 36° C. under high vacuum to yield 2.079g (89.53%) of the title compound.

EXAMPLE 3

Preparation of [4S-[4a, 7a(R¹), 12b(S)]-7-[(1-oxo-2(R)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzoxepine-4-carboxylic acid

Dissolve [4S-[4a, 7a(R¹), 12b(S)]-7-[(1-oxo-2(R)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzoxepine-4-carboxylic acid (2.079g, 4.33mmol) in tetrahydrofuran (10mL). Add to a solution of lithium hydroxide (20mL of a 1N solution, 20mmol) in methanol (80mL, deoxygenated by bubbling with nitrogen for 10 minutes). Stir the cloudy solution for 40 minutes. Acidify and dilute the water until cloudy. Remove 10mL of volatile solvent under high vacuum then dilute the mixture to 25mL with water. Stir the mixture for 10 minutes, filter under a blanket of nitrogen, and partially azeotrope dry under nitrogen atmosphere. Dry the solid overnight under high vacuum, then for 18 hours at 35° C. under high vacuum, 24 hours at 40° C., then 64 hours at 50° C. at 10 mm Hg.

In a second run, dissolve [4S-[4a, 7a(R¹), 12b(S)]-7-[(1-oxo-2(R)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzoxepine-4-carboxylic acid (2.819g, 3.87mmol) in tetrahydrofuran (deoxygenated). Add to a degassed solution of lithium hydroxide (27mL of a 1N solution, 27mmol) in methanol (80mL). Stir at ambient temperature under nitrogen atmosphere for 45 minutes. Acidify with hydrochloric acid (15mL of a 2N solution), dilute with water to 230mL and stir for 15 minutes. Collect the solid by filtration under a blanket of nitrogen and wash

with water. Dry for 2 hours at ambient temperature under high vacuum, then for 18 hours at 40° C. under high vacuum, then for 64 hours at 56° C. Combine materials for both runs to yield 3.935g (88.5%) of the title compound.

EXAMPLE 4

Preparation of [4S-[4a, 7a(R¹), 12b(S)]-7-[(1-oxo-2(R)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzoxepine-4-carboxylic acid, benzyl ester

Dissolve [4S-[4a, 7a(R¹), 12b(S)]-7-[(1-oxo-2(R)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzoxepine-4-carboxylic acid (2.06g, 4.33mmol) in methylene chloride (25mL) and dry over anhydrous MgSO₄. Filter and wash with methylene chloride (3x200mL). Evaporate in vacuo to a residue. Dissolve the residue in anhydrous dimethylformamide (25mL) and place under nitrogen atmosphere. Add cesium carbonate (1.65g, 5.0mmol) in one portion. Stir for 45 minutes at ambient temperature. Add benzyl bromide (550mg, 5.0mmol). Stir the resulting mixture at ambient temperature for 18 hours. Quench the reaction with ethyl acetate (50mL) and water (50mL). Separate the organic phase and wash with water (7x50mL), 1 saturated potassium hydrogen carbonate (50mL), water (50mL), and saturated sodium chloride (50mL). Dry (MgSO₄), filter and evaporate in vacuo to yield the title compound.

EXAMPLE 5

Preparation of [4S-[4a, 7a(R¹), 12b(S)]-7-[(1-oxo-2(R)-thio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzoxepine-4-carboxylic acid, benzyl ester

Stir [4S-[4a, 7a(R¹), 12b(S)]-7-[(1-oxo-2(R)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzoxepine-4-carboxylic acid, benzyl ester (2.28g, 4mmol) and saturated methanolic ammonia at ambient temperature until hydrolysis is complete. Evaporate the solvent in vacuo and purify by silica gel chromatography to give the title compound.

EXAMPLE 6

Preparation of [4S-[4a, 7a(R¹), 12b(S)]-7-[(1-oxo-2(S)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxo-pyrido[2,1-a][2]benzoxepine-4-carboxylic acid, diphenylmethyl ester

Step 1: [4S-[4a, 7a(R¹), 12b(S)]-7-[(1-oxo-2(R)-hydroxy-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzoxepine-4-carboxylic acid, diphenylmethyl ester

Dissolve [4S-[4a, 7a(R¹), 12b(S)]-7-[(1-oxo-2(S)-hydroxy-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzoxepine-4-carboxylic acid, diphenylmethyl ester (59mg, 0.1mmol), triphenylphosphine (39mg, 0.15mmol) and acetic acid (0.7 μ L, 0.15mmol) in anhydrous tetrahydrofuran (3mL). Treat with DIAD (32mg, 0.15mmol) at 0° C. Stir for 5 minutes at 0° C., then allow to stir at ambient temperature for 45 minutes. Remove the volatiles in vacuo and purify the residue by silica gel chromatography (3:1/hexane:tetrahydrofuran) to yield 67mg (106%) [4S-[4a, 7a(R¹), 12b(S)]-7-[(1-oxo-2(R)-acetylthio-3-phenylpropyl)amino]-1,2,3,4,6,7,8,12b-octahydro-6-oxopyrido[2,1-a][2]benzoxepine-4-carboxylic acid, diphenylmethyl ester.



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

Application number: 94817788.2

Int. Cl.⁴: A61K 31/47, A61K 31/55,
A61K 37/02

Date of filing: 10.06.94

International application number:
PCT/JP94/00947

International publication number:
WO 94/28801 (22.12.94 94/28)

Priority: 11.06.93 JP 140946/93
14.06.93 JP 141841/93
06.07.93 JP 166892/93
28.10.93 JP 270229/93
28.10.93 JP 282830/93
08.11.93 JP 300807/93
16.11.93 JP 308577/93
17.12.93 JP 317885/93
08.02.94 JP 34300/94
08.02.94 JP 34301/94
07.03.94 JP 35511/94
07.03.94 JP 35512/94

Date of publication of application:
13.09.98 Bulletin 96/37

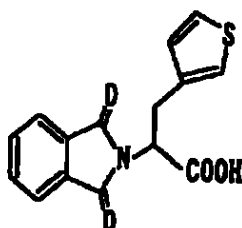
Designated Contracting States:
AT BE CH DE DK ES FR GB GR IE IT LI LU NL
PT SE

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147Synthesis Example B-42-(1,3-Dihydro-1,3-dioxo-2H-isoindol-2-yl)-3-(3-thienyl)propanoic acid

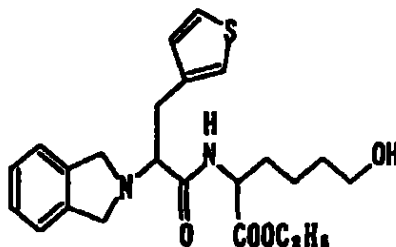
58.0 g (288.6 mmol) of DL-3-(3-thienyl)alanine was reacted in the same manner as that of the Synthesis Example B-1. Thus, 68.4 g of the title compound was obtained as pale yellow crystals (yield 84%).

MASS m/e (FAB); 302(MH⁺)

m.p.: 162–165 °C

¹H-NMR (400 MHz, CDCl₃, Me₄Si);

3.65(1H, dd, J=4.8, 15.0Hz) 3.72(1H, dd, J=11.8, 15.0Hz) 5.21(1H, dd, J=4.8, 11.8Hz) 6.91-6.93(1H, m) 6.97(1H, m like brs) 7.18(1H, dd, J=3.2, 4.8Hz) 7.68-7.72(2H, m) 7.78-7.81(2H, m)

Synthesis Example B-5N-[2-(1,3-dihydro-1,3-dioxo-2H-isoindol-2-yl)-3-(3-thienyl)propanoyl]-6-hydroxynorleucine ethyl ester

23.0 g (108.7 mmol) of 6-hydroxy-DL-norleucine ethyl ester hydrochloride and 32.74 g (108.7 mmol) of the compound obtained in the Synthesis Example B-4 were reacted in the same manner as that of the Synthesis Example B-2. Thus, 25.8 g of the title compound was obtained as pale yellow crystals (yield 52%).

MASS m/e (FAB); 458(MH⁺)

m.p.: 80–85 °C

¹H-NMR (400 MHz, CDCl₃, Me₄Si);

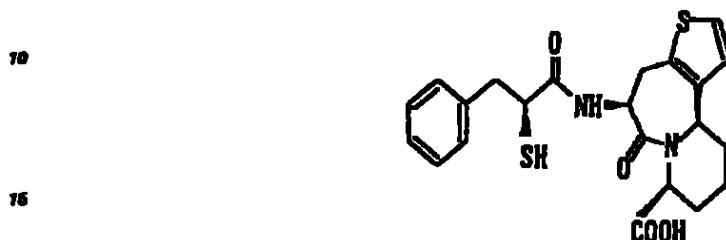
1.23-1.30(3H, m) 1.31-1.98(6H, m) 3.54-3.87(4H, m) 4.08-4.24(2H, m) 4.58-4.88(1H, m) 5.11-5.17(1H, m) 6.68-6.77(total 1H, each brd) 6.83-7.01(2H, m) 7.17-7.22(1H, m) 7.70-7.74(2H, m) 7.78-7.84(2H, m)

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7.50(1H, brd)

Example B-3

- [5S-[5 α ,8 α (R),11 α ,8]]-5-[(8)-2-Mercapto-1-oxo-3-phenylpropyl]amino]-6-oxo-4,5,8,9,10,11,11a-octahydropyrido[1,2-a]thieno[3,2-c]azepine-8-carboxylic acid



- 20 To 163 mg (0.32 mmol) of the compound obtained in the Example B-2 was added 12.7 ml of degassed methanol. Further, 3.6 ml of degassed 1 N sodium hydroxide was added thereto. The mixture thus obtained was stirred at 40 °C. Seven hours thereafter, it was cooled to 0 °C. To the reaction mixture was added 5.7 ml of 2 N hydrochloric acid. Then, the mixture was concentrated to a certain extent under reduced pressure. The crystals precipitated by adding a small amount of water thereto were collected by filtration
- 25 and dried over phosphorus pentoxide under reduced pressure. Thus, 82 mg of a mixture of the title compound with its epimer at a ratio of 4 : 3 was obtained (yield 80%).

¹H-NMR (400 MHz, CDCl₃, Me₄Si):

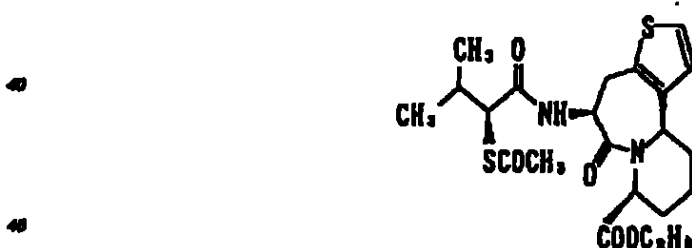
1.83-2.43(6H, m) 2.54-4.30(5H, m) 5.16 and 5.24(total 1H, each m) 5.31 and 5.40(total 1H, each m) 5.82 and 5.79(total 1H, each m) 6.73-6.78(total 1H, m) 6.80-7.04(total 1H, m) 7.19-7.91(total 6H, m)

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Example B-4

- Ethyl [5S-[5 α ,8 α (R),11 α ,8]]-5-[(8)-2-acetylthio-3-methyl-1-oxobutyl]amino]-6-oxo-4,5,8,9,10,11,11a-octahydropyrido[1,2-a]thieno[3,2-c]azepine-8-carboxylate

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- 50 170 ml (0.55 mmol) of the compound obtained in the Example B-1 and (8)-2-acetylthio-3-methyl-butanolic acid (107 mg, 0.61 mmol) were reacted in the same manner as that of Example B-2. Thus, 203 mg of a stereoisomeric mixture of the title compound with its epimer was obtained (yield 79%).

¹H-NMR (400 MHz, CDCl₃, Me₄Si):

- 55 0.86 and 0.88(total 3H, each t, each J=7.2Hz) 1.00 and 1.01(total 3H, each d, each J=6.8Hz) 1.06 and 1.08(total 3H, each d, each J=6.4Hz) 1.58-2.24(total 5H, m) 2.32-2.48(total 2H, m) 2.40 and 2.42(total 3H, each s) 2.84-2.88(total 1H, m) 3.49-3.58(total 1H, m) 3.69-3.88(total 3H, m) 5.23-5.29(total 2H, m) 5.58-5.69(total 1H, m) 6.78(total 1H, m) 7.04(total 1H, m) 7.32-7.58(total 1H, m)

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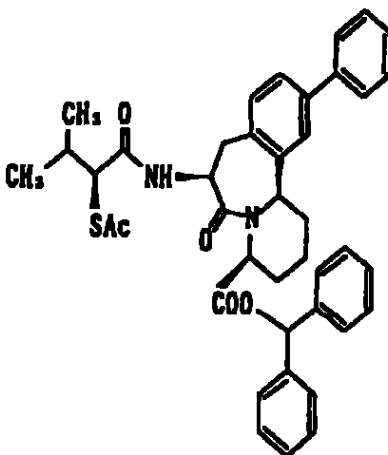
white crystals (0.37 g, yield 86%).

• ¹H-NMR (400 MHz, CDCl₃):

7.51(1H, d, J=7Hz), 7.43(2H, d, J=8Hz), 7.38(2H, t, J=8Hz), 7.28(2H, m), 7.08(2H, d, J=8Hz),
6.98(1H, d, J=8Hz), 6.78(2H, d, J=8Hz), 5.67(1H, quint, J=8Hz), 5.42(1H, m), 5.13(1H, d like,
J=8Hz), 3.73(3H, s), 3.60(2H, m), 3.14(1H, dd, J=14, 7Hz), 3.03(1H, dd, J=14, 7Hz), 2.78(1H, dd,
J=17, 12Hz), 2.47(1H, m), 2.28(1H, m), 1.97(1H, d, J=8Hz), 2.00-1.83(4H, m)

Example E-8

10 Diphenylmethyl [4S-[4a,7a(R),12bS]]-7-[(S)-2-acetylthio-3-methylbutyrylamino]-6-oxo-11-phenyl-1,2,3,4,6,7,8,12b-octahydropyrido[2,1-a][2]benzazepine-4-carboxylate



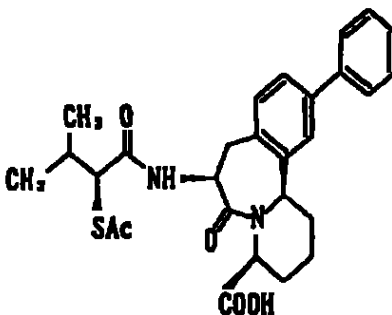
In the same manner as that of Example E-2 and starting with diphenylmethyl [4S-[4a,7a(R),12bS]]-7-amino-6-oxo-11-phenyl-1,2,3,4,6,7,8,12b-octahydropyrido[2,1-a][2]benzazepine-4-carboxylate (0.4 g, 0.774 mmol) obtained in the Example E-1 and (S)-2-acetylthio-3-methylbutanoic acid (0.136 g, 0.774 mmol), the
35 title compound was obtained as a colorless amorphous product (0.38 g, yield 89%).

• ¹H-NMR (400 MHz, CDCl₃):

7.54-6.92(17H, m), 6.68(1H, d, J=8Hz), 6.28(1H, s), 5.85(1H, quint, J=8Hz), 5.48-5.40(2H, m),
4.00(1H, d, J=7Hz), 3.42(1H, dd, J=18, 8Hz), 2.80-2.37(7H, m), 2.02(1H, m), 1.88-1.72(3H, m), 1.08-
40 (3H, d, J=7Hz), 1.04(3H, d, J=7Hz)

Example E-9

45 [4S-[4a,7a(R),12bS]]-7-[(2S)-2-Acetylthio-3-methylbutyrylamino]-6-oxo-11-phenyl-1,2,3,4,6,7,8,12b-octahydropyrido[2,1-a][2]benzazepine-4-carboxylic acid



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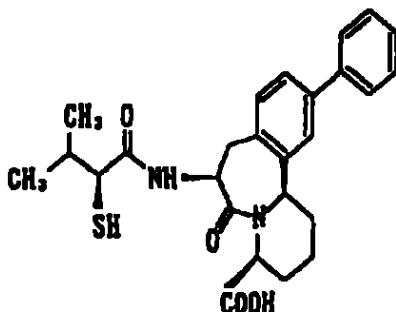
In the same manner as that of Example E-4 and starting with diphenylmethyl [4S-(4a,7a(R),12b(S))-7-(S)-2-acetylthio-3-methylbutyrylamino]-6-oxo-11-phenyl-1,2,3,4,6,7,8,12b-octahydropyrido[2,1-a][2]benzazepine-4-carboxylate (0.36 g, 0.533 mmol) obtained in the Example E-8, the title compound was obtained as a colorless amorphous product (0.157 g, yield 58%).

¹H-NMR (400 MHz, CDCl₃):

7.55-7.28(8H, m), 7.03(1H, brs), 5.88(1H, quint, J=8Hz), 5.48(1H, m), 3.97(1H, d, J=7Hz), 3.51(1H, m), 2.88-2.82(2H, m), 2.58-2.20(7H, m), 2.00-1.80(4H, m), 1.05(3H, d, J=7Hz), 1.01(3H, d, J=7Hz)

Example E-10

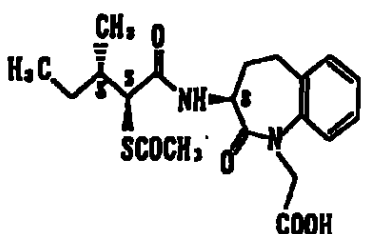
[4S-(4a,7a(R),12b(S))-7-(S)-2-Mercapto-3-methylbutyrylamino]-6-oxo-11-phenyl-1,2,3,4,6,7,8,12b-octahydropyrido[2,1-a][2]benzazepine-4-carboxylic acid



[4S-(4a,7a(R),12b(S))-7-(S)-2-acetylthio-3-methylbutyrylamino]-6-oxo-11-phenyl-1,2,3,4,6,7,8,12b-octahydropyrido[2,1-a][2]benzazepine-4-carboxylic acid (0.147 g, 0.289 mmol) obtained in the Example E-9 was dissolved in degassed ethanol (5 ml). To this solution was added a 1.0 N aqueous solution of lithium hydroxide (0.9 ml). The mixture was stirred under a nitrogen atmosphere at room temperature for 1 hour. The reaction mixture was acidified by adding a 1.0 N aqueous solution of hydrochloric acid under cooling with ice and stirring, followed by extraction with dichloromethane. The organic phase was washed with a saturated aqueous sodium chloride and dried over anhydrous magnesium sulfate. After distilling off the solvent of the organic phase, the obtained residue was crystallized from dichloromethane-hexane. Further, the mother liquor was evaporated to dryness and then treated with isopropyl ether-hexane. Thus, 0.103 g (yield 78%) of the title compound was obtained.

¹H-NMR (400 MHz, CDCl₃):

7.88(1H, d, J=7Hz), 7.51(2H, d, J=8Hz), 7.44(2H, d, J=8Hz), 7.39-7.33(3H, m), 7.08(1H, d, J=8Hz), 6.73(1H, quint, J=8Hz), 5.53(1H, m), 5.28(1H, m), 3.81(1H, dd, J=17, 8Hz), 3.18(1H, dd, J=8, 7Hz), 2.83(1H, dd, J=17, 13Hz), 2.60-2.22(3H, m), 2.08-1.70(4H, m), 1.05(3H, d, J=7Hz)

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151Example 147(3S)-[[(2S,3S)-2-Acetylthio-3-methyl-1-oxopentyl]amino]-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one

0.547 g (1.5 mmol) of (S)-1-carboxymethyl-3-[[[(2S,3S)-3-methyl-1-oxo-2-thiopentyl]amino]-2,3,4,5-tetrahydro-1H-[1]benzazepin-2-one obtained in the Example C-11 and 0.168 ml (1.650 mmol) of acetic anhydride were dissolved in 7 ml of acetonitrile. The obtained solution was dropped into a solution of 0.075 g (0.577 mmol) of cobalt (II) chloride in 10 ml of acetonitrile. After the mixture thus obtained was stirred for 2 hours, it was concentrated under reduced pressure, and water was added thereto, followed by extraction with ethyl acetate. The organic phase was washed with a saturated aqueous sodium chloride, dried over anhydrous magnesium sulfate and then concentrated under reduced pressure. Thus, 0.43 g of the title compound was obtained as a colorless amorphous product.

¹H-NMR (400 MHz, CDCl₃):

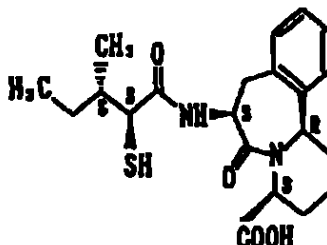
7.30-7.08(5H, m) 4.78(1H, d, J=17Hz) 4.48(1H, dt, J=11, 7Hz) 4.38(1H, d, J=17Hz) 3.88(1H, d, J=7Hz) 3.30(1H, m) 2.70-2.60(2H, m) 2.35(3H, s) 2.02-1.82(2H, m) 1.53(1H, m) 1.11(1H, m) 0.83(3H, d, J=7Hz) 0.84(3H, t, J=7Hz)

Examples 148 to 152

In accordance with the processes of the above Examples 101 to 108, compounds of Examples 148 to 152 were obtained.

Example 148

[4S-[4a,7a(R'),12b(R)]]-7-[[[(2S,3S)-3-Methyl-1-oxo-2-thiopentyl]amino]-8-oxo-1,2,3,4,8,7,8,12b-octahydropyrido[2,1-a][2]benzazepine-4-carboxylic acid



¹H-NMR (400 MHz, CD₃OD):

7.88(2H, d, J=8Hz) 7.17-7.05(3H, m) 7.02(1H, d, J=8Hz) 5.88(1H, quart, J=8Hz) 5.48(1H, brd, J=8Hz) 5.20(1H, m) 3.52(1H, dd, J=17, 6Hz) 3.21(1H, dd, J=8, 7 Hz) 2.80(1H, dd, J=17, 13Hz) 2.80(1H, m) 2.35(1H, m) 1.82-2.03(2H, m) 1.82(1H, d, J=8Hz) 1.27(1H, m) 1.02(3H, d, J=7Hz) 0.83(3H, t, J=7Hz)

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**SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
DIVISIÓN DE NUEVAS CREACIONES**

2020/
Bogotá, D.C.,

**Doctor
Luis Patiño Leyva
Apoderado
AVENTIS PHARMA
DEUTSCHLAND GMBH**

Oficio N° 5806

REFERENCIA	Radicación	03 88391
	Trámite	002
	Evento	001
	Actuación	430
	Folios	008

Como resultado del examen de patentabilidad de la solicitud de patente de invención N° 03 88391, realizado según el artículo 45 de la decisión 486 de la comisión de la Comunidad Andina, se notifica:

1. DOCUMENTOS ESTUDIADOS:

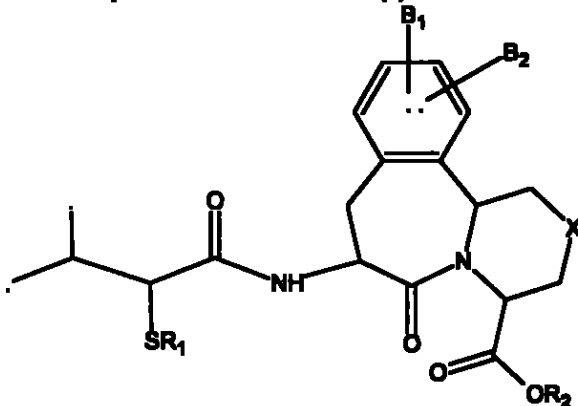
- El petitorio de la solicitud nacional en donde se hace mención a los documentos de prioridad reivindicados US60/283,305 de fecha 12/04/2001 y GB0119305.1 de 08/08/2001.
- La solicitud internacional que corresponde a CAPITULO II y el petitorio PCT que se encuentra en los folios 9 a 27.
- El reporte de búsqueda internacional en los folios 28 a 30.
- La traducción de la solicitud Internacional que consta de un resumen y un capítulo descriptivo y se encuentra en los folios 31 a 46.
- Los ejemplos que ilustran la invención en los folios 47 a 55.
- El capítulo reivindicatorio conformado por las cláusulas 1 a 20 tal como fue presentado en la solicitud original en fase internacional que se encuentra en los folios 56 a 61.
- El dibujo que acompaña la invención y se encuentra en los folios 62.
- El reporte del examen preliminar internacional que consta de 2 páginas que se encuentra en los folios 63 a 67 junto con su traducción correspondiente.
- El petitorio de la solicitud PCT que se encuentra en los folios 68 a 75.
- El primer examen de forma realizado a la solicitud en fase nacional de oficio No. 10377, que se encuentra en el folio 78.
- El memorial de fecha 26/03/2004 mediante el cual se allega la copia del documento de cesión que se encuentra en los folios 81 a 114.
- La solicitud de examen de patentabilidad junto con el pago de la tasa correspondiente, allegada mediante memorial de fecha 08/11/2005, que se encuentra en los folios 116 a 117.
- El documento mediante el cual se informa la sustitución de poder de los folios 118 a 136, allegado en el memorial de fecha 15/03/2006.

2. OBJETO DE LA INVENCION:

La solicitud hace referencia a un **"Derivados de mercaptoacetilamida, procedimiento para su preparación y su uso"**

- **Reivindicaciones 1 a 13:**

Se reivindica un compuesto de fórmula (I):



En particular se reclama protección para el compuesto:

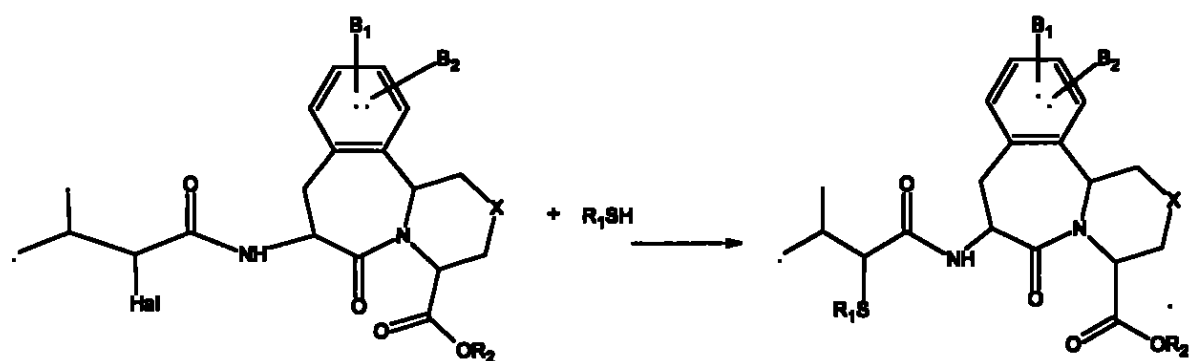
Éster difenilmetílico de ácido [4S-[4 α ,7 α (S),12b β]]-7-[[2(R)-acetiltio-3-metil-1-oxobutil]amino]-1,2,3,4,6,7,8,12b-octahidro-6-oxo-pirido[2,1a][2]benzazepina-4-carboxílico

Éster difenilmetílico de ácido [4S-[4 α ,7 α (S),12b β]]-7-[[2(S)-acetiltio-3-metil-1-oxobutil]amino]-1,2,3,4,6,7,8,12b-octahidro-6-oxo-pirido[2,1a][2]benzazepina-4-carboxílico

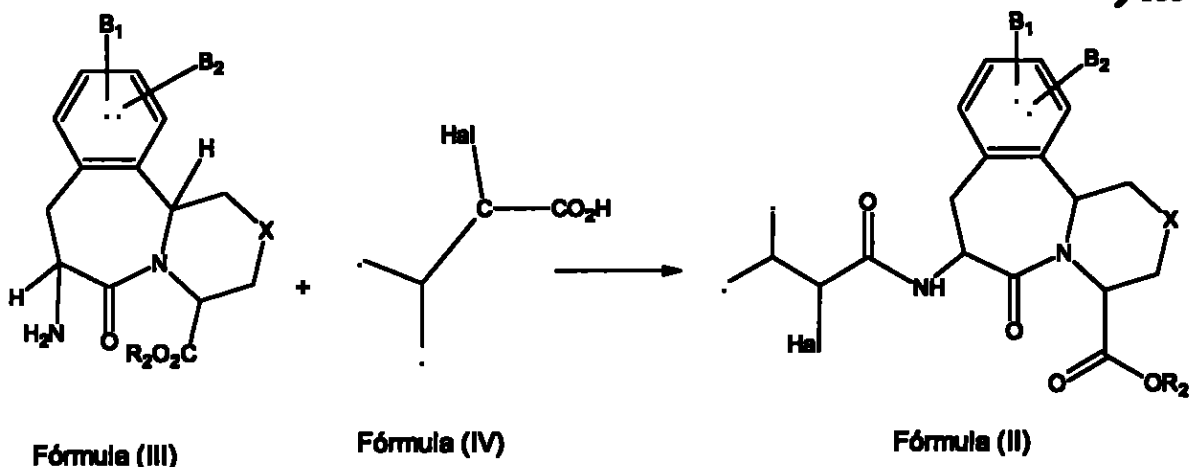
Entre otros...

- **Reivindicaciones 14 y 15:**

Se reivindica un procedimiento para la preparación de un compuesto de fórmula (I) que comprende la fase de hacer reaccionar un compuesto de fórmula (II) con un compuesto de fórmula R_1SH en presencia de una base.



Además se reivindica el procedimiento para la preparación de un compuesto de fórmula (I) que consiste en hacer reaccionar un compuesto de fórmula (III) con un compuesto de fórmula (IV).



• **Reivindicaciones 16 a 18:**

Se reivindica un método para tratar un estado de enfermedad cardiovascular, que comprende administrar a un paciente que necesita tratamiento para el mismo, una cantidad inhibidora terapéuticamente efectiva de enzima convertidora de angiotensina y endopeptidasa neutra, de un compuesto según la reivindicación 1.

En particular se reivindica el método en el que el estado de enfermedad es hipertensión, insuficiencia cardíaca congestiva.

• **Reivindicaciones 19 y 20:**

Se reivindica una composición farmacéutica que comprende uno o más compuestos como se definieron en la reivindicación 1 y un vehículo farmacéuticamente aceptable.

Y se reivindica el método para la preparación de una composición farmacéutica, que comprende la fase de combinar uno o más de los compuestos como se definieron en la reivindicación 1 con un vehículo farmacéuticamente aceptable.

Una vez catalogada la invención ésta se clasificó en la sección: **A 61 K ³¹/08** de la **Clasificación Internacional de Patentes**.

3. CLARIDAD DE LA SOLICITUD:

El artículo 30 de la Decisión 486 contempla que *"Las reivindicaciones definirán la materia que se desea proteger mediante la patente. Deben ser claras y concisas y estar enteramente sustentadas por la descripción"*.

Esta Dependencia se permite señalar que las cláusulas de procedimiento 14 y 15 no contemplan las condiciones físico-químicas necesarias para la obtención de los compuestos de interés y si se tiene en cuenta que las mismas son determinantes en la caracterización y definición de la secuencia lógica de etapas que permite llegar a sintetizar los compuestos que responden a la fórmula (I), tal como se establece en los ejemplos descritos en los folios 47 a 48, es necesario que se haga claridad en torno a este aspecto de la invención.

4. EXCEPCIONES A LA PATENTABILIDAD:

El artículo 20 de la norma Andina en su literal (d) establece: *"No serán patentables:*

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d) Los métodos terapéuticos o quirúrgicos para el tratamiento humano o animal, así como los métodos de diagnóstico aplicados a los seres humanos o a animales."

En atención al artículo 20 de la norma andina se recomienda al interesado eliminar del alcance de su invención las cláusulas relativas al método fármaco terapéutico para el tratamiento de la hipertensión y la insuficiencia cardíaca congestiva basado en la actividad de los compuestos de fórmula (I).

5. DETERMINACIÓN DEL ESTADO DE LA TÉCNICA:

Consultadas las fuentes de información con que cuenta este despacho, se encontraron los siguientes documentos, anteriores a la fecha de presentación de la solicitud en estudio - 12.04.2001-, relacionados con la materia técnica reivindicada:

Nº	Documento	Título	Fecha de Publicación
D1	US5430145	"Mercaptoacetylamlde derivatives useful as inhibitors of enkephalinase and ace"	04/07/1995
D2	EP0671172	"Aminoacid derivative"	13/09/1995

Anterioridades D1 y D2 en los folios 138 a 150.

6. EVALUACIÓN DE LOS REQUISITOS DE PATENTABILIDAD:

El artículo 14 de la decisión 486 de la comisión de la comunidad andina establece que: *"Los países miembros otorgarán patentes para las invenciones, sean de producto o de procedimiento, en todos los campos de la tecnología, siempre que sean nuevas, tengan nivel inventivo y sean susceptibles de aplicación industrial"*

En cumplimiento del artículo 14 de la decisión 486 de la comisión de la comunidad andina, se procedió a evaluar los requisitos de novedad, nivel inventivo y aplicación industrial con el fin de establecer la patentabilidad de la invención reivindicada en la solicitud en estudio.

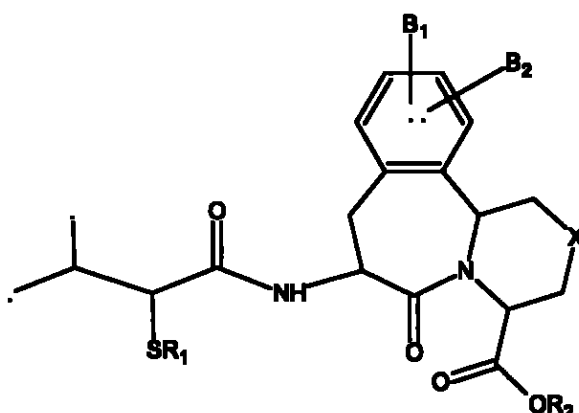
6.1 Evaluación de la NOVEDAD:

El artículo 16 de la decisión 486 dispone: *"Una invención se considerará nueva cuando no está comprendida en el estado de la técnica."*

El estado de la técnica comprenderá todo lo que haya sido accesible al público por una descripción escrita u oral, utilización, comercialización o cualquier otro medio antes de la fecha de presentación de la solicitud de patente o, en su caso, de la prioridad reconocida.

Sólo para el efecto de la determinación de la novedad, también se considerará dentro del estado de la técnica, el contenido de una solicitud de patente en trámite ante la oficina nacional competente, cuya fecha de presentación o de prioridad fuese anterior a la fecha de presentación o de prioridad de la solicitud de patente que se estuviese examinando, siempre que dicho contenido esté incluido en la solicitud de fecha anterior cuando ella se publique o hubiese transcurrido el plazo previsto en el artículo 40".

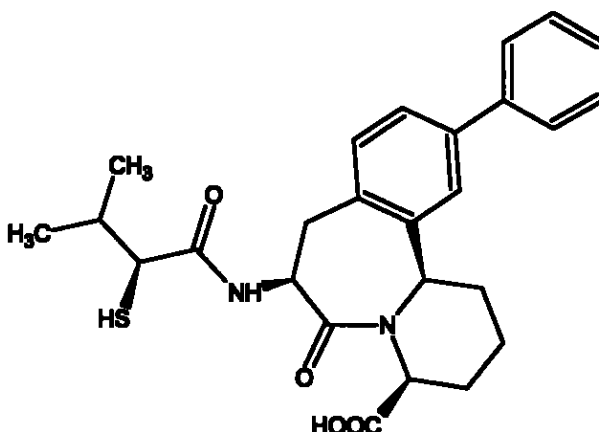
La materia reclamada por la solicitud hace referencia a compuestos de fórmula (I) que presentan la siguiente estructura química:



Para el que:

- o Los radicales B_1 y B_2 pueden formar conjuntamente con los átomos de carbono adyacentes un anillo de benceno.
- o R_2 puede ser un átomo de H
- o R_1 puede ser un átomo de H

Homologando de esta manera las características que presenta la molécula revelada por la anterioridad D2 en su ejemplo E-10 – folio 149 -:



En consecuencia, siendo que existe identidad entre las características esenciales reivindicadas para la fórmula (I) y el ejemplo citado por la anterioridad D2, se encuentra que existe afectación del requisito de NOVEDAD.

6. 2 Evaluación de NIVEL INVENTIVO:

El artículo 18 de la norma Andina establece: *"Se considerará que una invención tiene nivel inventivo, si para una persona del oficio normalmente versada en la materia técnica correspondiente, esa invención no hubiese resultado obvia ni se hubiese derivado de manera evidente del estado de la técnica".*

La anterioridad D1 por su parte revela compuestos de tipo:

- o Difenil-metil éster del ácido [4S-[4 α ,7 α (R*), 12b β]]-7-[(1-oxo-2(R)-acetiltio-3-fenilpropil)amino]-1,2,3,4,6,7,8,12-b-octahidro-6-oxopirido[2,1-a][2]benzazepina-4-carboxílico

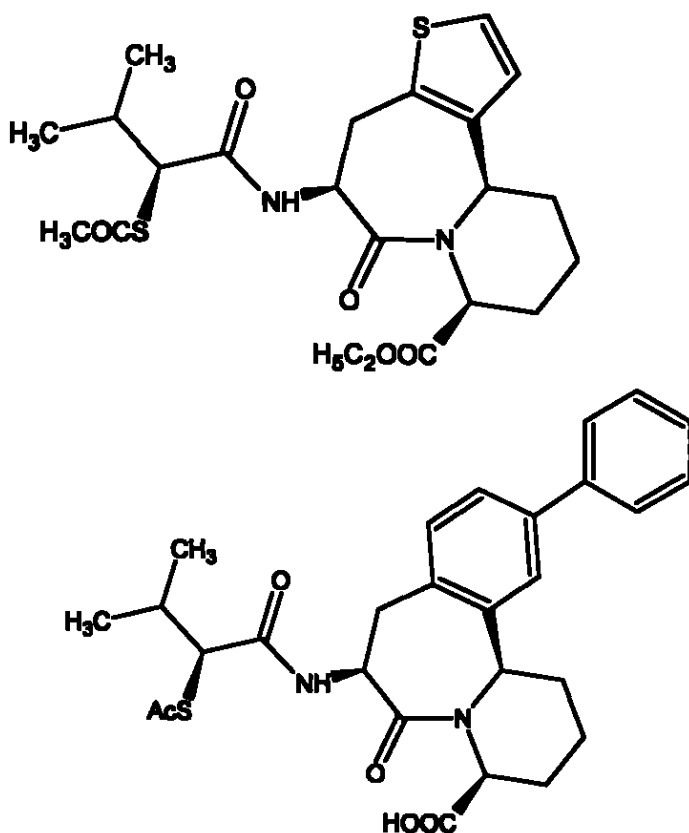
Que al compararse estructuralmente con los compuestos reclamados por la solicitud en estudio, dentro de los que se encuentran:

Éster difenilmetílico de ácido [4S-[4 α ,7 α (S),12b β]]-7-[[2(R)-acetiltio-3-metil-1-oxobutí]amino]-1,2,3,4,6,7,8,12b-octahidro-6-oxo-pirido[2,1a][2]benzazepina-4-carboxílico

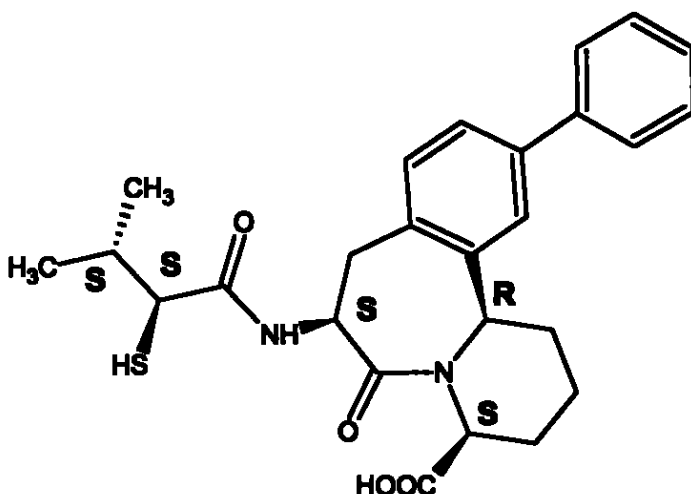
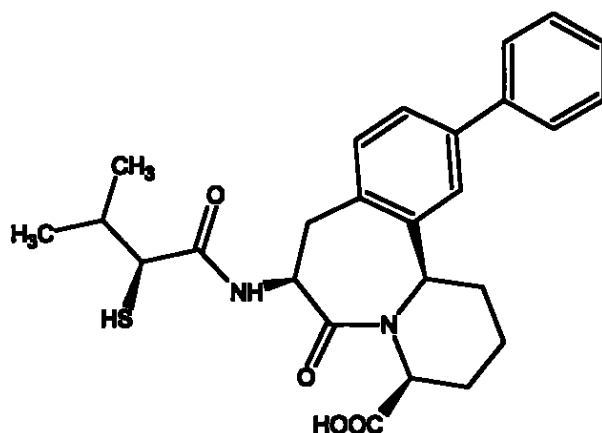
- Éster difenilmetílico de ácido [4S-[4 α ,7 α (S),12b β]]-7-[[2(S)-acetiltio-3-metil-1-oxobutí]amino]-1,2,3,4,6,7,8,12b-octahidro-6-oxo-pirido[2,1a][2]benzazepina-4-carboxílico

Evidencian la derivación evidente del estado del arte de los compuestos reclamados, dado que presentan el mismo núcleo estructural de pirido-benzazepina y sustituciones en análogas en posiciones idénticas a las que se determinan en la fórmula estructural (I) reclamada. Si bien es cierto los compuestos no son idénticos, la anterioridad D1 ya señalaba la estructura básica junto con sustituciones químicamente más complejas que las reclamadas por la solicitud en comento y por ello se considera que no existe un verdadero salto cualitativo en la regla técnica en torno al diseño de derivados de mercaptoacetilamida con núcleo de pirido-benzazepina.

Y si se combinan las enseñanzas del documento D1 con las reveladas por la anterioridad D2 (que afecta el requisito de novedad de la solicitud), se hace aún más palpable que la materia reclamada se deriva evidentemente del estado del arte, porque en la anterioridad D2, se revelan por ejemplo, compuestos de fórmula estructural como las que a continuación se presentan y que definitivamente son análogos estructurales de los compuestos que reclama la solicitud.



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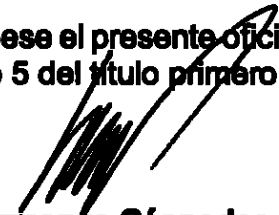


En conclusión los requisitos de patentabilidad de la presente solicitud se encuentran afectados así:

N°	Documento	Reivindicaciones afectadas	Requisito que afecta
D1	US5430145	1 a 20	Nivel Inventivo
D2	EP0671172	1 a 20	Novedad

En cumplimiento del artículo 45 de la Decisión 486 de la Comisión de la Comunidad Andina, se le indica que debe dar respuesta dentro del término de sesenta días contados a partir de la fecha de la notificación de la presente comunicación. En caso de no dar respuesta al presente requerimiento, o si a pesar de la respuesta subsistieran los impedimentos para la concesión, se denegará la patente.

Notifíquese el presente oficio conforme a lo dispuesto en el numeral 5.2, literal e), del capítulo 5 del título primero de la Circular Única N° 10 de 2001.


Alix Carmenza Céspedes de Vergel
Jefe de la División de Nuevas Creaciones

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El anterior requerimiento fue notificado por fijación en lista, de fecha 17 DE JULIO 2007

CONCEPTO TÉCNICO Número 0706	EXAMINADOR TÉCNICO Código 202044
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EXAMEN TÉCNICO DE F NDO			
Nº Radicación	03-88391 Solicitud PCT Cap II	Fecha de presentación	03/10/2003
Nº Prioridad	US60/283,305 GB0119305	Fecha de Prioridad	12/04/2001 08/08/2001

Palabras clave	Mercaptoacetil-amida	Pirido[2,1-a]-benzazepina
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CLASIFICACIONES INTERNACIONALES DE BÚSQUEDA
A61K31/55

DOCUMENTOS CORRESPONDIENTES EN OTROS PAISES	
Patente Original	WO02083671

BASES DE DATOS CONSULTADAS	
ESPACENET	EPOLINE

INFORMES DE EXÁMENES EN OTRAS OFICINAS		
Oficina	Fecha	Reivindicaciones
EPO		

ANTERIORIDADES ENCONTRADAS		
Documento	Relevancia	Relvindicaciones afectadas
US5430145	Nivel Inventivo	1 a 20
EP0671172	Novedad	1 a 20

LITERATURA NO PATENTES		
Documento no Patentes	Relevancia	Relv. Afectadas

Observaciones	
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Fecha del examen	02/05/2007

Requerir 46