Industria y Comercio

SUPERINTENDENCIA

Organización CSA Ltda

NOV 26

Delegatura de Propiedad Industrial

División de Nuevas Creciones

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO INVENTARIO

PCT

SOLICITUD

PATENTE DE INVENCIÓN

21. **EXPEDIENTE No.** 07-136830

54. **TÍTULO** DERIVADO DE AMINA CICLICA CON GRUPO ALQUILO SUSTITUIDO

51. **CLASIFICACIÓN INTERNACIONAL** C07D 211/072, 401/06; A61K 31/5377, 31/445, 31/541; A61P 7/02.

71. **SOLICITANTE** DAIICHI SANKYO COMPANY, LIMITED

DOMICILIO TOKIO, JAPON

74. **APODERADO** EMILIO FERRERO

C.C 438.019 de Usaquén

22. **BOGOTÁ, D. C.,** 381

(FORMA P-10)

Industria y Comercio
SUPERINTENDENCIA

[redacted]

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 07-136830- -00000-0000
Fecha: 2007-12-27 18:02:02 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 674

FORMULARIO UNICO DE SOLICITUD DE PATENTE PCT ENTRADA EN FASE NACIONAL

1 SOLICITUD DE:

☒ Patente de Invención. ☐ Patente de Modelo de Utilidad.
☒ Capítulo I. ☐ Capítulo II.

2 SOLICITANTE (71)

Nombre: **DAIICHI SANKYO COMPANY, LIMITED.**
sociedad constituida y existente bajo las leyes de Japón.

Dirección: 3-5-1 Nihonbashi-honcho, Chuo-ku, Tokyo 103-8426, Japón

Domicilio: Tokyo, Japón

IDENTIFICACIÓN
C.C. ☐ NIT ☐
C.E. ☐ Otro ☐
Cual ____
Número ____

3 REPRESENTANTE O APODERADO

Nombre: EMILIO FERRERO
Dirección: Carrera 4ª. No. 72-35
Teléfono: 347 36 11
Fax: 211 86 50
E-mail: clientes@cavelier.com
Domicilio: Bogotá, Colombia.

IDENTIFICACIÓN
C.C. ☒ NIT ☐
C.E. ☐ Otro ☐
Cual ____
Número 438.019 T.P 31.929

4 INVENTOR (ES) (72)

1. Tomio KIMURA
c/o Diichi Sankyo Company, Limited, 1-2-58, Hiromachi, Shinagawa-ku, Tokyo 140-8710, Japón

2. Naoki TANAKA
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3. Hiroyuki KOBAYASHI
c/o Diichi Sankyo Company, Limited, 1-2-58, Hiromachi, Shinagawa-ku, Tokyo 140-8710, Japón

4. Atsuhiro SUGIDACHI
c/o Diichi Sankyo Company, Limited, 1-2-58, Hiromachi, Shinagawa-ku, Tokyo 140-8710, Japón

5 PCT (86)

Solicitud Internacional No. PCT/JP2006/310556 Fecha: 26 de mayo de 2006
Publicación Internacional No. WO 2006/126676 A1 Fecha: 30 de noviembre de 2006

6 Título (54)

DERIVADO DE AMINA CÍCLICA CON GRUPO ALQUILO SUSTITUIDO

7 Clasificación Internacional (51) C07D 211/072, 401/06; A61K 31/5377, 31/445 31/541; A61P 7/02.

8 Prioridad SI☒ NO☐

(33) País de Origen	(32) Fecha	(31) Número de Solicitud
JP	27 de mayo de 2005	2005-155009

9 Comprobante de pago No.: 07-104,466 **Fecha:** 26 de diciembre de 2007

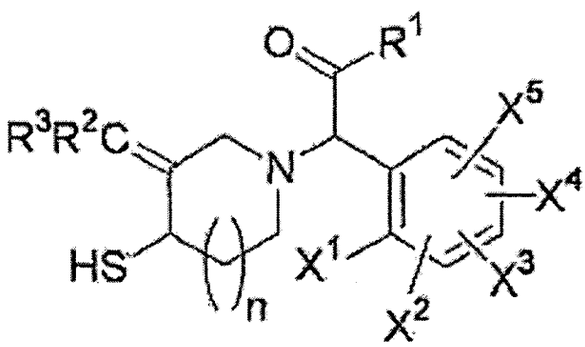
10

Anexos:

- ☒ Comprobante de pago de la tasa de presentación de la solicitud por $ 482.000.oo.
- ☐ Comprobante de pago por reivindicación de prioridad.
- ☒ Documento que acredita la existencia y representación legal cuando el solicitante sea persona jurídica.
- ☒ Poderes, si fuere el caso.
- ☒ Documento de cesión del inventor al solicitante o a su causante.
- ☐ Declaraciones.
- ☒ Copia de la solicitud internacional. (Resumen, descripción, reivindicaciones, dibujos)
- ☒ Traducción de la solicitud internacional al castellano. (Resumen, descripción, reivindicaciones, dibujos)
- ☐ Copia del examen preliminar efectuado por la IPEA.
- ☐ Traducción del examen preliminar efectuado por la IPEA.
- ☐ De ser el caso, copia del contrato de acceso.
- ☐ De ser el caso, documento que acredite la licencia o autorización de uso de conocimientos tradicionales de las comunidades indígenas.
- ☐ De ser el caso, certificado de depósito del material biológico.
- ☒ Arte final 12x12
- ☐ De ser el caso, información sobre otras solicitudes de patente o títulos obtenidos en el extranjero por el mismo titular o su causante, relacionadas parcial o totalmente con la invención de esta solicitud.
- ☒ Otros: VER HOJA DE DOCUMENTOS ANEXOS

11

FIGURA CARACTERÍSTICA



(I)

12 Solicito la concesión de la patente,

NOMBRE: EMILIO FERRERO

FIRMA : _____

C.C. 438.019 de Usaquén T.P. 31.929

AHP

DOCUMENTOS ANEXOS

1. ☒ Publicación Internacional WO 2006/126676 A1

   Descripción:

   Páginas 292 en el idioma original

   Páginas 345 en español

   Reivindicaciones: Número (s) 31

   Figuras: Número (s)

2. ☒ **Forma PCT/ISA/210.** Informe de Búsqueda Internacional.

3. ☒ **Forma PCT/IB/306.** Notificación de la inscripción del cambio de solicitante de la sociedad **SANKYO COMPANY, LIMITED** a **DAIICHI SANKYO COMPANY, LIMITED.**

4. ☒ Extracto de publicación.

NO SE REALIZARON MODIFICACIONES EN LA FASE INTERNACIONAL

2608

CAVELIER
ABOGADOS
EDIFICIO SISKI
CARRERA 4a N° 72-35
BOGOTA, 8 – COLOMBIA

179

Representación y Poder con autenticación notarial y Apostille para patentes, modelos de utilidad, diseños industriales, marcas de fábrica, nombres comerciales, enseñas, nombres de dominio, lemas comerciales, licencias.

Representation and Power-of- Attorney with notarial authentication and Apostille for patents, utility models, industrial designs, trademarks, commercial names, trade emblems, domain names, slogans, licenses.

REPRESENTACION Y PODER

REPRESENTATION AND POWER- OF- ATTORNEY

75869
6113

Yo (nosotros), abajo firmado (s)/I (we), the undersigned

DAIICHI SANKYO COMPANY, LIMITED

domiciliado (s) en/of 3-5-1, Nihonbashi Honcho,

Chuo-ku, Tokyo 103-8426, Japan

por el presente nombramos a EMILIO FERRERO, tpa. 31929; GONZALO PERDOMO, tpa. 831; LUZ CLEMENCIA DE PAEZ, tpa. 23555 y DANIEL PEÑA, tpa. 65620, domiciliados en la Carrera 4ª N° 72-35, Bogotá, Colombia, en obedecimiento a lo dispuesto en el parágrafo 1o del Artículo 543 del Código de Comercio, el primero como principal y los demás como suplentes, en su orden, como mis (nuestros) representantes en todos los asuntos de propiedad industrial con facultad para recibir notificaciones y nombrar apoderados judiciales o extrajudiciales. El primer representante suplente reemplazará al principal en caso de ausencia o impedimento temporal o definitivo de aquél. La misma regla se aplicará cuando el segundo representante suplente haya de reemplazar al primero, o el tercero al segundo. En tales casos, el representante principal, o el primero, o segundo suplente, en su caso, o ambos, declararán su intención de no ejercer la representación mediante declaración autenticada por Notario Público en Colombia, o por Notario u otro Funcionario Público, o Cónsul de Colombia, en el extranjero; y si se tratare de impedimento, con el certificado respectivo. Si alguno de los brados faltare definitivamente, el siguiente tomará su lugar. Cuando cesare la ausencia o impedimento del representante principal, o de su primero o segundo suplentes, en su caso, podrán ejercer la representación, en su orden, uno u otros según el caso, asumiéndola por el solo hecho de ejercerla, cesando en ese momento el ejercicio de la representación por el primero, segundo o tercer suplente en su caso.

Además, confiero (conferimos) poder a los abogados arriba nombrados, para obtener la protección de mi (nuestra) propiedad industrial y contra la competencia desleal, a cuyo efecto autorizo (amos) a los dichos apoderados para que me (nos) representen ante cualesquiera entidades o personas, ejerzan o no jurisdicción, especialmente ante las del orden administrativo, contencioso-administrativo y judicial, así como los tribunales de arbitramento, en todo lo concerniente a los siguientes asuntos: a) Obtención de patentes de invención, modelos de utilidad, y diseños industriales; el registro de marcas de fábrica, colectivas, defensivas, de servicio, lemas comerciales, nombres comerciales, enseñas, nombres de dominio, variedades vegetales y denominaciones de origen; su renovación, traspaso, cambio de nombre o domicilio,

in due compliance with the terms of paragraph 1st. of article 543 of the Commercial Code, do hereby appoint EMILIO FERRERO, tpa. 31929; GONZALO PERDOMO, tpa. 831; LUZ CLEMENCIA DE PAEZ, tpa. 23555 and DANIEL PEÑA, tpa. 65620, domiciled at Carrera 4ª N° 72-35, Bogotá, Colombia, the first as principal and the others as alternates, in the order of their appointment, as our representatives for all industrial property matters with faculty to receive notifications and to appoint attorneys in and out of Court. The first alternate shall replace the principal in case of his absence or of temporal or definitive impediment. The same rule will apply when the second alternate representative is to replace the first one, or when the third is to replace the first or second alternates in their turn, or both of them, second. In such cases, the principal representative, or the first or second alternates in their turn, or both of them, shall state their intention not to act as representatives through a declaration given before a Notary Public in Colombia, or before a Notary or another Public Official or a Colombian Consul abroad; and in case of impediment, the appropriate certificate shall suffice. If any of the appointees were to be definitely absent, the following alternate shall take his place. When the absence or impediment of the principal representative, or of the first or second alternate in their turn ceases, the representation can be taken again in their sequence, by the principal, the first or second alternate depending on case, and the mere fact or its exercise will suffice. The exercise of the representation by the first, second or third alternates in their turn shall end at such time.

COMO NOTARIO SEXTO (6) DEL CIRCULO DE BOGOTA CERTIFICO QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
26 DIC 2007
PABLO [illegible] BRAVO

In addition, we grant a Power of Attorney in favor of the above-named attorneys-at-law so that they may obtain the protection of my (our) industrial property and against the unfair competition, for which purpose I (we) authorize the said attorneys to represent me (us) before any authorities or persons with or without jurisdiction, specially those administrative, administrative contentious and judicial, as well as before Arbitration Court, in all matters concerning the following: a) Obtainment of patents, utility models and industrial designs; the registration of trademarks, collective, defensive and service marks, slogans, commercial names, trade emblems, domain names, vegetal varieties and denominations of origin; its renewal, assignment, change of name or domicile, voluntary cancellation; and the registration of licenses of use of

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cancelación voluntaria; y el registro de licencias de uso de esos derechos; b) Las acciones de competencia desleal, protección del consumidor, oposiciones u observaciones, cancelación administrativa y judicial, nulidad, medidas cautelares, concesión de licencias, la tutela, la protección de secretos industriales, y en general los juicios civiles, penales, administrativos o contencioso-administrativos relacionados con estos derechos; acciones y procesos que promovamos o se nos promuevan. Y para que en todos los asuntos arriba determinados, puedan sustituir este mandato, transigir, conciliar, admitir los hechos del proceso, desistir, cancelar, recibir, renunciar, y ratificar los actos de agentes oficiosos.

the above rights; b) Actions of unfair competition, protection to the consumer, oppositions or observations, administrative or Court cancellation, nullity, infringement, granting of licenses, the action for writ mandamus, the protection of trade secrets, and in general the civil, penal, and administrative suits relating to those rights; actions and suits instituted by me (us) or against me (us). And that in all the above matters they may substitute this Power of Attorney, compromise, conciliate, admit the facts of the case, desist, cancel, receive, resign, and ratify acts done by representatives without a power of attorney.

Dado y firmado hoy/Given and signed this May 11, 2007

en/in Tokyo, Japan

por/by DAIICHI SANKYO COMPANY, LIMITED

By:

Firma Tsutomu Une Signature

Member of the Board and

Senior Executive Officer

COMO NOTARIO SEXTO (E) DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA

26 DIC 2007

PABLO MANRIQUEZ BARAJAS

NOTARIO (E)

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CERTIFICACION NOTARIAL (SOCIEDAD)

El infrascrito Notario Certifica: Que la firma que antecede de _____ es auténtica; que el signatario desempeña actualmente el cargo de _____ de la compañía **DAIICHI SANKYO COMPANY, LIMITED** _____, sociedad que actualmente existe y está organizada de acuerdo a las leyes de Japón _____, que la dirección de dicha compañía es 3-5-1, Nihonbashi Honcho, Chuo-ku, Tokio 103-8426, Japón _____, y que el signatario tiene facultad para otorgar este documento.

Todos los hechos anteriores le constan por haber examinado los documentos respectivos y de todo ello da fe.

Lo y firmado en _____

El _____

NOTARIAL CERTIFICATION (COMPANY)

The undersigned Notary certifies: That the preceding signature of Tsutomu Une _____ is authentic, that the signatory currently acts in the position of Member of the Board and Senior Executive Officer _____ of the company **DAIICHI SANKYO COMPANY, LIMITED** _____, a company currently existing and organized under the laws of Japan _____, that the address is 3-5-1, Nihonbashi Honcho, Chuo-ku, Tokyo 103-8426, Japan _____, and that the signatory has the power to grant this document.

The Notary Public is aware and attests to the above facts upon examination of the corresponding documents.

Given and signed in _____

On _____

El Notario Público - The Notary Public
(Firma-sello) (Signature-seal)

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Country: .....
   This public document
2. has been signed by .....
3. acting in the capacity of .....
4. bears the seal/stamp of .....

Certified

5. at ..... 6. the .....
7. by .....
8. No. .....
9. Seal/stamp 10. Signature

....

COMO NOTARIO SEXTO (E) DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
26 DIC 2007
PABLO MELDE BARAJAS
NOTARIO (E)

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7

NOTARIAL CERTIFICATE Registration No 897

This is to certify that the signature on the foregoing document is genuine and authentic signature of Tsutomu Une, Member of the Board and Senior Executive Officer of DAIICHI SANKYO COMPANY, LIMITED, a corporation existing and organized under the laws of Japan, who has produced sufficient proof of his power to execute the said instrument on behalf of the above-mentioned corporation.

MAY 14 2007

TOKYO LEGAL AFFAIRS BUREAU
NOTARY
1-1, 2CHOME UCHISAIWAICHO
CHIYODA-KU
TOKYO JAPAN

Tadahiko Mitsuda
TADAHIKO MITSUDA
NOTARY

COMO NOTARIO SEXTO (E) DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA

26 DIC 2007

PABLO MERCED BARAJAS
NOTARIO (E)

8

平成１９年登簿第　897　号

認　　証

嘱託人第一三共株式会社取締役采孟の代理人城野喬は、本公証人に対し、嘱託人が別添文書に署名したことを自認している旨陳述した。

よって、これを認証する。

平成１９年　５　月　14　日、本公証人役場において

東京都千代田区内幸町２丁目１番１号

東　京　法　務　局　所　属

公　証　人

Notary

満田忠彦

TADAHIKO MITSUDA

証　　明

上記署名は、東京法務局所属公証人の署名に相違ないものであり、かつ、その押印は、真実のものであることを証明する。

平成１９年　５　月　14　日

東　京　法　務　局　長　　戸田信久

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Country: JAPAN

   This public document

2. has been signed by TADAHIKO MITSUDA
3. acting in the capacity of Notary of the Tokyo Legal Affairs Bureau
4. bears the seal/stamp of TADAHIKO MITSUDA

   Certified

5. at Tokyo
6. MAY 14 2007
7. by the Ministry of Foreign Affairs
8. 07- № 001649
9. Seal/stamp:
10. Signature

Kazutoyo OYABE

For the Minister for Foreign Affairs

COMO NOTARIO SEXTO (E) DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA

26 DIC 2007

PABLO MENDEZ J. RAJAS

NOTARIO (E)

9

Libro de registro 2007 No.897

CERTIFICADO

Takashi Siroco, delegado del solicitante,el Gerente de Saiichi Sankyo Co.Ltd Tsutomu Une, manifesto ante el suscrito que dicho señor reconoce la firma que aparece en el documento adjunto.

Por lo tanto certifico que esta firma es autentica.

Mayo 14, 2007, en el despacho notarial
2-1-1, Uchisaiwai-Cho, Chiyoda-Ku, Tokio.
Notario adscrito al Departamento de Asuntos Juridicos de Tokio
Tadahiko Mitsuda (firma y sello oficial)

MINISTERIO DE RELACIONES EXTERIORES
2007 AGO 21 A 10:47
JEFE DE LEGALIZACIONES
BOGOTA D.C.

CERTIFICACION

Certifico que la firma que aparece arriba es del notario adscrito al Departamento de Asuntos Juridicos de Tokio, y su sello estampado en el documento también es legítimo.

Mayo 14, 2007
Director del Departamento de Asuntos Juridicos de Tokio
Nobuhisa Toda -sello oficial-

NO SE ASUME RESPONSABILIDAD DEL TEXTO
LA FIRMA APARECE EN EL DOCUMENTO DESEMPEÑA FUNCIONES INDICADAS

La presente traduccion oficial se ha efectuado bajo amparo de APOSTILLE No. 001649 del Ministerio de Asuntos Extranjeros del Japon con fecha Mayo 14, 2007, y esta firmado por Kazutoyo Oyabe.

COMO NOTARIO SEXTO (E) DEL CIRCULO DE BOGOTA, DAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA
28 DIC 2007
PABLO MENDEZ BARAJAS
NOTARIO (E)

Traductor Oficial
Japonés - Español
Tsutomu Muramatsu
Resolución No. 909 Mayo 6 1987

TRADUCCIÓN OFICIAL 186/2007 DE UN DOCUMENTO ESCRITO EN INGLÉS Y EN ESPAÑOL DE ACUERDO CON EL CUAL **DAIICHI SANKYO COMPANY LIMITED.**, EMPRESA DOMICILIADA EN 3-5-1, NIHONBASHI HONCHO, CHUO-KU, TOKIO 103-8426, JAPÓN OTORGA PODER A EMILIO FERRERO, TPA 31929, GONZALO PERDOMO, TPA 831; LUZ CLEMENCIA DE PAEZ, TPA 23555 Y A DANIEL PEÑA, TPA 65620.

EXPEDIDO Y FIRMADO HOY 11 DE MAYO DE 2007 EN TOKIO, JAPÓN POR DAIICHI SANKYO COMPANY, LIMITED.

FIRMADO: TSUTOME UNE, MIEMBRO DE LA JUNTA Y EJECUTIVO PRINCIPAL

CERTIFICACIÓN NOTARIAL EN INGLÉS Y EN ESPAÑOL, PARA CERTIFICAR LA COMPARECENCIA DE TSUTOMU UNE, COMO MIEMBRO DE LA JUNTA Y EJECUTIVO PRINCIPAL DE LA EMPRESA DAIICHI SANKYO COMPANY LIMITED, UNA EMPRESA ACTUALMENTE EXISTENTE Y CONSTITUIDA DE ACUERDO CON LAS LEYES DE JAPÓN, CON DOMICILIO EN 3-5-1.NIHONBASI HONCHO, CHUO-KU, TOKIO, 103-8426, JAPÓN.

CERTIFICACIÓN NOTARIAL

REGISTRO 897

Por la presente certifico que la firma en el documento precedente es la firma genuina y auténtica de TSUTOMU UNE, miembro de la junta y ejecutivo principal de DAIICHI SANKYO COMPANY, LIMITED, una sociedad constituida y organizada de acuerdo con las leyes de Japón, que ha presentado prueba suficiente de facultad para firmar dicho documento a nombre de dicha sociedad.

Firmado: Tadahiko Mitsuda, notario

SELLO: OFICINA DE ASUNTOS JURÍDICOS DE TOKIO, NOTARIO. 1-1. 2CHOME UCHISAIWAICHO CHIYODA-KU TOKIO, JAPÓN.

COMO NOTARIO SEXTO (E) DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE HE TENIDO A LA VISTA

PABLO MENDOZA ARAJAS
NOTARIO (E)

APOSTILLA

(CONVENCIÓN DE LA HAYA DEL 5 DE OCTUBRE DE 1961)

1. PAIS: JAPÓN

Este documento público

2. ha sido firmado por TADAHIKO MITSUDA

3. quien actúa en su calidad de notario de la Oficina de asuntos jurídicos de Tokio

4. y lleva el sello/estampilla de TADAHIKO MITSUDA

CERTIFICADO

5. en Tokio, 6. el 14 de mayo de 2007

7. por el Ministerio de Asuntos Exteriores

8. 07-no.001649

9. Sello: MINISTERIO DE ASUNTOS EXTERIORES, JAPÓN

10. Firma: KAZUTOYO OYABE a nombre del Ministro de Asuntos Exteriores.

COLO- 15869-845-001-8

WPCL002G ID 9090

Bogotá, 13 de agosto de 2007.

Eduardo Calado
Eduardo Calado Nogueira
TRADUCTOR OFICIAL
INGLES ESPAÑOL INGLES
Res. 641 Febrero de 1976

MINISTERIO DE RELACIONES EXTERIORES
2007 AGO 21 A 10 47
JEFE DE LEGALIZACIONES
BOGOTA D.C.

645605
Edgar Calado
LA FIRMA APARECE EN EL DOCUMENTO DESEMPEÑA LAS FUNCIONES INDICADAS

NO SE ASUME RESPONSABILIDAD DEL TEXTO

COMO NOTARIO SEXTO (E) DEL CIRCULO DE BOGOTA, HAGO CONSTAR QUE LA FOTOCOPIA COINCIDE CON EL ORIGINAL QUE SE TENIDO A LA VISTA
2 DIC 2007
PABLO MENDEZ BARAJAS
NOTARIO (E)

CAVELIER
ABOGADOS
EDIFICIO SISKI
CARRERA 4a No 72-35
BOGOTA, B COLOMBIA

5534 FP0607 CO

CESION

Yo, (nosotros), abajo firmado(s)

domiciliado(s) en

declaro(amos) bajo juramento ser único(s) y verdadero(s) inventor(es) de la invención:

declaro(amos) asf mismo que cedo(emos) y transfiero(erimos), sin limitación, a favor de la sociedad

constituída y existente de conformidad con las leyes de

domiciliada en

todoa los derechos inherentes a dicha invención y que la citada Compañia queda facultada para solicitar en su nombra la patente correspondiente en la República de Colombia

ASSIGNMENT

I(We), the undersigned
(1) KIMURA, Tomio (2) TANAKA, Naoki (3) KOBAYASHI, Hiroyuki (4) SUGIDACHI, Atsuhiro
of
(1)-(4) c/o DAIICHI SANKYO COMPANY, LIMITED, 2-58, Hiromachi 1-chome, Shinagawa-ku, Tokyo 140-8710, Japan

state(s) under oath to be sole and true inventor(s) of the invention:
"CYCLIC AMINE DERIVATIVE HAVING SUBSTITUTED ALKYL GROUP"

state as well, that assign, without reservations or limitations in favour of
DAIICHI SANKYO COMPANY, LIMITED

a corporation constituted and existing in conformity with the laws of **Japan**

domiciled in **3-5-1, Nihonbashi Honcho, Chuo-ku, Tokyo 103-8426, Japan**

all rights inherent to said invention and that the above mentioned company hereby is enabled to apply, in its name, for the corresponding patent in the Republic of Colombia

Dado y firmado hoy/Given and signed this
en/in **Tokyo, Japan**

Firma

Tomio Kimura
KIMURA, Tomio

Naoki Tanaka
TANAKA, Naoki

Hiroyuki Kobayashi
KOBAYASHI, Hiroyuki

Atsuhiro Sugidachi
SUGIDACHI, Atsuhiro

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WPPODERE-343

NOTARIAL CERTIFICATE Registration No 2456

This is to certify that the signatures on the foregoing document are genuine and authentic signatures of Tomio KIMURA, Naoki TANAKA, Hiroyuki KOBAYASHI and Atsuhiro SUGIDACHI.

NOV 28 2007

TOKYO LEGAL AFFAIRS BUREAU
NOTARY
2-2-2, UCHISAIWAICHO
CHIYODA-KU
TOKYO JAPAN

HIROSHI NAKAJIMA
NOTARY

平成１９年登薄第 2456 号

認　　証

嘱託人木村富美夫、田中直樹、小林宏行及び杉立収寛の代理人城野喬は、本公証人に対し、嘱託人が別添文書に署名したことを自認している旨陳述した。

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平成１９年 11 月 28 日、本公証人役場において

東京都千代田区内幸町２丁目２番２号

東京法務局所属

公証人

Notary

中島治

HIROSHI NAKAJIMA

証　　明

上記署名は、東京法務局所属公証人の署名に相違ないものであり、かつ、その押印は、真実のものであることを証明する。

平成１９年 11 月 28 日

東京法務局長　五十嵐義治

APOSTILLE

(Convention de La Haye du 5 octobre 1961)

1. Country: JAPAN

This public document

2. has been signed by HIROSHI NAKAJIMA
3. acting in the capacity of Notary of the Tokyo Legal Affairs Bureau
4. bears the seal/stamp of HIROSHI NAKAJIMA, NOTARY

Certified

5. at Tokyo
6. NOV 28 2007
7. by the Ministry of Foreign Affairs
8. 07- № 037110
9. Seal/stamp:
10. Signature

MINISTRY OF FOREIGN AFFAIRS JAPAN 外務省

K. Oyabe

Kazutoyo OYABE

For the Minister for Foreign Affairs

TRADUCCIÓN OFICIAL No. 12.24/07b realizada por Diego Vargas, Traductor Oficial, Resolución No. 0001 de 1999 del Ministerio de Justicia y registrado ante el Ministerio de Relaciones Exteriores de Colombia.

A continuación se traducen los sellos y legalizaciones de un documento de cesión mediante el cual (1)KUMURA, Tomio (2) TANAKA, Naoki (3) KOBAYASHI, Hiroyuki (4) SUGIDACHI, Atsuhiro, domiciliados en (1)-(4) c/o DAIICHI SANKYO COMPANY, LIMITED, 2-58, Hiromachi 1-chome, Shinagawa-ku, Tokio 140-8710, Japón, declaran bajo juramento ser únicos y verdaderos inventores de la invención: "*Derivados de amina cíclica con grupo alquilo sustituido*" y declaran así mismo que ceden y transfieren, sin limitación, a favor de **DAIICHI SANKYO COMPANY, LIMITED**, una sociedad constituida y existente de conformidad con las leyes de Japón, domiciliada en 3-5-1, Nihonbashi Honcho, Chuo-ku, Tokio 103-8426, Japón, todos los derechos inherentes a dicha invención y que la citada compañía queda facultada para solicitar en su nombre la patente correspondiente en la República de Colombia.

Dado y firmado en Tokio, Japón.

Firma Ilegible	*Firma Ilegible*
KIMURA, Tomio	TANAKA, Naoki
Firma Ilegible	*Firma Ilegible*
KOBAYASHI, Hiroyuki	SUGIDACHI, Atsuhiro

CERTIFICADO NOTARIAL Registro No.*2456*

El presente es para certificar que las firmas en el anterior documento son las legítimas y auténticas firmas de Tomio KIMURA, Naoki TANAKA, Hiroyuki KOBAYAHSI y Atsuhiro SUGIDACHI.

NOV 28 2007

Firma ilegible

HIROSHI NAKAJIMA

NOTARIO

Sello: Oficina de Asuntos Legales de Tokio
NOTARIO
1-1, 2-Chome Uchisaiwaicho,
Chiyoda-ku,
Tokio, Japón

(Anexo)

TEXTO EN JAPONÉS

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(Convention de La Haye du 5 octubre 1961)

1. País: JAPÓN

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2. ha sido firmado por HIROSHI NAKAJIMA

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5. en Tokio 6. APR 25 2007

7. por el Ministerio de Relaciones Exteriores

8. 07 - **No. 037110**

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TRADUCTOR E INTERPRETE OFICIAL
ESPAÑOL - INGLES – INGLES - ESPAÑOL
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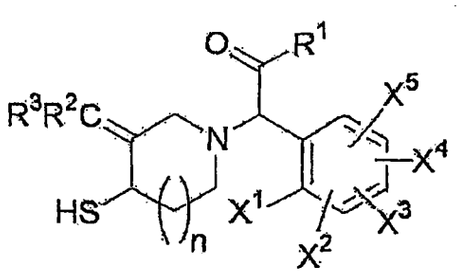
(54) Title: CYCLIC AMINE DERIVATIVE HAVING SUBSTITUTED ALKYL GROUP

(54) 発明の名称: 置換アルキル基を有する環状アミン誘導体



(I)

(57) Abstract: Disclosed is a compound represented by the general formula (I) below, a pharmacologically acceptable salt thereof, or a prodrug thereof. [Chemical formula 1] (I) (In the formula, R^1 represents a hydrogen atom, an optionally substituted C_1-C_6 alkyl group, an optionally substituted C_3-C_6 cycloalkyl group or the like; R^2 represents a hydrogen atom, a halogen atom, a carboxy group, a C_2-C_7 alkoxycarbonyl group, a carbamoyl group, a cyano group, a C_1-C_6 alkyl group, a halogeno C_1-C_6 alkyl group, a C_1-C_6 alkyl group substituted with a heteroaryl group or the like; R^3 represents a substituted C_1-C_6 alkyl group, a heterocyclyl group, or a mono- to penta-substituted heterocyclyl group; X^1, X^2, X^3, X^4 and X^5 independently represent a hydrogen atom, a halogen atom, an amino group, a carboxy group, a carbamoyl group, a cyano group, a nitro group, a C_1-C_6 alkyl group or the like; and n represents an integer of 0-2.)

[続葉有]

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Specification

Cyclic Amine Derivative Having Substituted Alkyl Group

[Technical Field]

The present invention relates to compounds which exhibit activity in the inhibition of platelet aggregation, pharmacologically acceptable salts thereof, and prodrugs thereof.

[Background of the Invention]

Recently, the number of patients with cardiovascular diseases associated with aging of the population and changes of eating habits and lifestyle has risen markedly. Since thrombotic diseases such as cerebral infarction, myocardial infarction and peripheral circulatory disorders have not only high morbidity but also result in poor prognosis and limitation on activities of daily living, patient with these disorders have an undue burden of personal and social disability. It is well known that the direct causes of these diseases are angiostenosis caused by thrombus induced by platelet activation (adhesion to damaged areas of blood vessels, release of physiologically active substances, clot formation, and so on) and ischemia associated with angiostenosis. Thus, antithrombotic agents that inhibit platelet activation play important roles in preventing the occurrence and recurrence of these diseases as well as in their treatment. Furthermore, these agents are considered to become more and more important in the future as the number of patients with thrombotic diseases increases.

Several biological substances related to platelet aggregation, such as adenosine 5'-diphosphate (ADP), thromboxane A_2 (TXA_2), collagen, serotonin (5-hydroxytryptamine, 5-HT) and the like, are known. Moreover, $P2Y_1$ and $P2Y_{12}$

receptors are known as ADP receptors. Some existing antithrombotic agents act by exerting antagonistic action against these receptors. Examples of such antithrombotic agents are ticlopidine and clopidogrel, which have thienopyridine structures.

In addition, compounds as described in Patent Documents 1 and 2 are known as compounds having non-thienopyridine structures and antagonistic action against ADP receptors. However, there are certain problems in that these compounds are chemically unstable or only weakly active.

Patent Document 1: WO98/08811

Patent Document 2: WO99/43648

[Disclosure of the Invention]

[Problems to be Solved by the Invention]

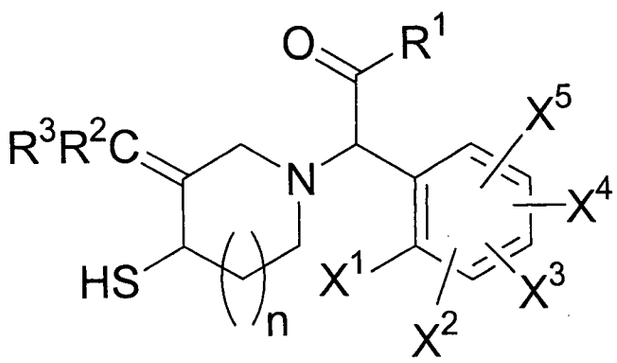
The present inventors, in order to create novel antithrombotic agents, have diligently explored chemically stable compounds having non-thienopyridine structures and activity in the inhibition of platelet aggregation, and found that compounds having the general formula (I) of the present invention, pharmacologically acceptable salts thereof and prodrugs thereof have desirable characteristics, and thus completed the present invention.

The present invention provides compounds having the general formula (I), pharmacologically acceptable salts thereof or prodrugs thereof; pharmaceutical compositions comprising compounds having the general formula (I), pharmacologically acceptable salts thereof or prodrugs thereof, as active ingredients (particularly pharmaceutical compositions for prophylactic or therapeutic agents for diseases related to thrombus or embolus formation); use of the compound having the general formula (I), pharmacologically acceptable salts thereof or prodrugs thereof to manufacture pharmaceutical compositions (particularly pharmaceutical compositions

for prophylactic or therapeutic agents for diseases related to thrombus or embolus formation); use of compounds having the general formula (I), pharmacologically acceptable salts thereof or prodrugs thereof for prophylactic or therapeutic agents for diseases related to thrombus or embolus formation; and prophylactic or therapeutic methods for diseases (particularly diseases related to thrombus or embolus formation) by administration of pharmacologically effective dose of compounds having the general formula (I), pharmacologically acceptable salts thereof or prodrugs thereof to warm-blooded animals (especially humans).

[Means for Solving the Problems]

The present invention relates the compound having the general formula (I) shown below,



(I)

[wherein R^1 represents a hydrogen atom, a C1-C6 alkyl group which may be substituted (said substituent group represents a halogen atom or a C1-C6 alkoxy group), a C3-C6 cycloalkyl group which may be substituted (said substituent group represents a halogen atom or a C1-C6 alkoxy group), a C1-C6 alkoxy group which may be substituted (said substituent group represents a halogen atom or a C1-C6 alkoxy group), or a C6-C10 aryl group which may be substituted (said substituent group represents a halogen atom, a C1-C6 alkyl group, a C1-C6 alkoxy group, a cyano group or a nitro group);

R^2 represents a hydrogen atom, a halogen atom, a carboxy group, a C2-C7 alkoxycarbonyl group, a carbamoyl group, a cyano group, a C1-C6 alkyl group, a halogeno C1-C6 alkyl group, a C1-C6 alkyl group substituted by a heteroaryl group, a C1-C6 alkoxy group, a halogeno C1-C6 alkoxy group, a hydroxy C1-C6 alkyl group, a C2-C12 alkoxyalkyl group, a formyl group, a C2-C7 alkanoyl group, a C4-C7 cycloalkylcarbonyl group, a C2-C7 alkylcarbamoyl group, a di(C1-C6 alkyl)carbamoyl group, a group of formula R^4-CO-CR^5R^6-$(CH_2)_m$- {wherein R^4 represents a hydroxyl group, an amino group, a C1-C6 alkyl group, a C1-C6 alkylamino group, a di(C1-C6 alkyl)amino group, a hydroxyamino group, a C1-C6 alkoxyamino group or a C1-C6 alkoxy group; R^5 and R^6 are the same or different and each represents a hydrogen atom or a C1-C6 alkyl group; and m represents an integer of from 0 to 5}, a group of formula R^7-CO-$(CH_2)_l$-N(R^8)- {wherein R^7 represents a hydroxyl group, an amino group, a C1-C6 alkyl group, a C1-C6 alkylamino group, a di(C1-C6 alkyl)amino group, a hydroxyamino group, a C1-C6 alkoxyamino group or a C1-C6 alkoxy group; R^8 represents a hydrogen atom or a C1-C6 alkyl group; and l represents an integer of from 0 to 5} or a sulfamoyl C1-C6 alkyl group;

R^3 represents a substituted C1-C6 alkyl group {said substituent group represents a C6-C10 aryl group or a C6-C10 aryl group substituted with from 1 to 5 substituents selected from <Substituent group α>; a heterocyclyl group or a heterocyclyl group substituted with from 1 to 5 substituents selected from <Substituent group α> (said heterocyclyl groups may be substituted by from 1 to 4 oxo groups); a heteroaryl group or a heteroaryl group substituted with from 1 to 5 substituents selected from <Substituent group α>; or a substituent selected from <Substituent group β>}, or a heterocyclyl group or a heterocyclyl group substituted with from 1 to 5 substituents selected from <Substituent group α> (said heterocyclyl groups may be substituted by from 1 to 4 oxo groups);

X^1, X^2, X^3, X^4 and X^5 each independently represent a hydrogen atom, a halogen atom, an amino group, a carboxy group, a carbamoyl group, a cyano group, a nitro group, a C1-C6 alkyl group, a halogeno C1-C6 alkyl group, a C1-C6 alkoxy group or a halogeno C1-C6 alkoxy group;

n represents an integer of from 0 to 2,

<Substituent group α> is defined by a halogen atom, an amino group, a carboxy group, a C2-C7 alkoxycarbonyl group, a carbamoyl group, a cyano group, a hydroxyl group, a nitro group, a C1-C6 alkyl group, a halogeno C1-C6 alkyl group, a C1-C6 alkyl group substituted with heteroaryl group(s), a C1-C6 alkoxy group, a halogeno C1-C6 alkoxy group, a hydroxy C1-C6 alkyl group, a C2-C12 alkoxyalkyl group, a formyl group, a C2-C7 alkanoyl group, a C4-C7 cycloalkylcarbonyl group, a C1-C6 alkylamino group, a di(C1-C6 alkyl)amino group, a C2-C7 alkylcarbamoyl group, a di(C1-C6 alkyl)carbamoyl group, a group of formula R^4-CO-CR^5R^6-$(CH_2)_m$- {wherein R^4 represents a hydroxyl group, an amino group, a C1-C6 alkyl group, a C1-C6 alkylamino group, a di(C1-C6 alkyl)amino group, a hydroxyamino group, a C1-C6 alkoxyamino group or a C1-C6 alkoxy group; R^5 and R^6 are the same or different and each represents a hydrogen atom or a C1-C6 alkyl group; and m represents an integer of from 0 to 5} and a sulfamoyl C1-C6 alkyl group; and

<Substituent group β> is defined by a halogen atom, an amino group, a carboxy group, a C2-C7 alkoxycarbonyl group, a carbamoyl group, a cyano group, a hydroxyl group, a nitro group, a C1-C6 alkoxy group, a halogeno C1-C6 alkoxy group, a formyl group, a C2-C7 alkanoyl group, a C4-C7 cycloalkylcarbonyl group, a C1-C6 alkylamino group, a di(C1-C6 alkyl)amino group, a C2-C7 alkylcarbamoyl group, a di(C1-C6 alkyl)carbamoyl group, a hydroxyaminocarbonyl group, a (C1-C6 alkoxy)aminocarbonyl group, a group of formula R^9-CO-$(CH_2)_k$-N(R^{10})- {wherein R^9 represents a hydroxyl group, an amino group, a C1-C6 alkyl group, a C1-C6 alkylamino group, a di(C1-C6 alkyl)amino group, a hydroxyamino group, a C1-C6

alkoxyamino group or a C1-C6 alkoxy group; R^{10} represents a hydrogen atom or a C1-C6 alkyl group; and k represents an integer of from 0 to 5} and a sulfamoyl C1-C6 alkyl group], pharmacologically acceptable salts thereof or prodrugs thereof.

A compound having the general formula (I) shown above, a pharmacologically acceptable salt thereof or a prodrug thereof is preferably

(1) a compound wherein R^1 represents a C1-C6 alkyl group, a halogeno C1-C6 alkyl group, a C3-C6 cycloalkyl group, a halogeno C3-C6 cycloalkyl group or a C1-C6 alkoxy group, pharmacologically acceptable salts thereof or prodrugs thereof;

(2) a compound wherein R^1 represents a C3-C6 cycloalkyl group, a halogeno C3-C6 cycloalkyl group or a C1-C6 alkoxy group, pharmacologically acceptable salts thereof or prodrugs thereof;

(3) a compound wherein R^1 represents a C3-C6 cycloalkyl group or a C1-C6 alkoxy group, pharmacologically acceptable salts thereof or prodrugs thereof;

(4) a compound wherein R^1 represents a cyclopropyl group or a methoxy group, pharmacologically acceptable salts thereof or prodrugs thereof;

(5) a compound wherein R^1 represents a cyclopropyl group, pharmacologically acceptable salts thereof or prodrugs thereof;

(6) a compound wherein R^2 represents a hydrogen atom or a C1-C6 alkyl group, pharmacologically acceptable salts thereof or prodrugs thereof;

(7) a compound wherein R^2 represents a hydrogen atom or a methyl group, pharmacologically acceptable salts thereof or prodrugs thereof;

(8) a compound wherein R^2 represents a hydrogen atom, pharmacologically acceptable salts thereof or prodrugs thereof;

(9) a compound wherein R^3 represents a substituted C1-C6 alkyl group {said substituent group represents a heterocyclyl group or a heterocyclyl group substituted with 1 or 2 substituents selected from <Substituent group α> (said heterocyclyl groups may be substituted by 1 or 2 oxo groups), a heteroaryl group or a heteroaryl

group substituted with 1 or 2 substituents selected from <Substituent group α> or a substituent selected from <Substituent group β>}, or a heterocyclyl group or a heterocyclyl group substituted with 1 or 2 substituents selected from <Substituent group α> (said heterocyclyl groups may be substituted by 1 or 2 oxo groups), pharmacologically acceptable salts thereof or prodrugs thereof;

(10) a compound wherein R^3 represents a substituted C1-C6 alkyl group {said substituent group represents a 4- to 7-membered heterocyclyl group containing at least one nitrogen atom which may be substituted with 1 or 2 substituents selected from <Substituent group α1> (said heterocyclyl group may be substituted by one oxo group), a heteroaryl group containing at least one nitrogen atom which may be substituted with 1 or 2 substituents selected from <Substituent group α1>, a carboxy group, a C2-C7 alkoxycarbonyl group, a cyano group, a hydroxyl group, a C1-C6 alkoxy group or a group of formula R^9-CO-$(CH_2)_k$-N(R^{10})- (wherein R^9 represents a hydroxyl group or a C1-C6 alkoxy group; R^{10} represents a C1-C6 alkyl group; and k represents an integer of from 1 to 5)}, or a 4- to 7-membered heterocyclyl group containing at least one nitrogen atom which may be substituted with one substituent selected from <Substituent group α1> (said heterocyclyl group may be substituted by one oxo group), and

<Substituent group α1> is a group consisting of a carboxy group, a C2-C7 alkoxycarbonyl group and a group of formula R^4-CO-CR^5R^6-$(CH_2)_m$- (wherein R^4 represents a hydroxyl group, an amino group, a C1-C6 alkylamino group, a di(C1-C6 alkyl)amino group, a hydroxyamino group, a C1-C6 alkoxyamino group or a C1-C6 alkoxy group; R^5 and R^6 each represents a hydrogen atom; and m represents an integer of from 0 to 5), pharmacologically acceptable salts thereof or prodrugs thereof;

(11) a compound wherein R^3 represents a substituted C1-C3 alkyl group {said substituent group represents a pyrrolidinyl, piperidinyl, morpholinyl,

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thiomorpholinyl, piperazinyl, pyrazolyl, triazolyl or tetrazolyl group which may be substituted with 1 or 2 substituents selected from <Substituent group α2> (said pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl or piperazinyl group may be substituted by one oxo group), a carboxy group, a C2-C4 alkoxycarbonyl group, a hydroxyl group or a group of formula R^9-CO-$(CH_2)_k$-N(R^{10})- (wherein R^9 represents a hydroxyl group or a C1-C3 alkoxy group; R^{10} represents a C1-C3 alkyl group; and k represents an integer of from 1 to 3)}, or a pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl or piperazinyl group which may be substituted with one substituent selected from <Substituent group α2> (said pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl or piperazinyl group may be substituted by one oxo group), and

<Substituent group α2> is a group consisting of a carboxy group, a C2-C4 alkoxycarbonyl group and a group of formula R^4-CO-CR^5R^6-$(CH_2)_m$- (wherein R^4 represents a hydroxyl group or a C1-C3 alkoxy group, R^5 and R^6 each represents a hydrogen atom, and m represents an integer of from 0 to 2), pharmacologically acceptable salts thereof,or prodrugs thereof;

(12) a compound wherein R^3 represents a substituted methyl or ethyl group {said substituent group represents a pyrrolidinyl, piperidinyl, piperazinyl or pyrazolyl group which may be substituted with 1 or 2 substituents selected from <Substituent group α3> (said pyrrolidinyl, piperidinyl or piperazinyl group may be substituted by one oxo group), a carboxy group or a group of formula R^9-CO-$(CH_2)_k$-N(R^{10})- (wherein R^9 represents a hydroxyl group, a methoxy group or an ethoxy group; R^{10} represents a methyl group, an ethyl group or an isopropyl group; and k represents an integer of from 1 to 3), and

<Substituent group α3> is a group consisting of a carboxy group, a methoxycarbonyl group, an ethoxycarbonyl group, a carboxymethyl group, a methoxycarbonylmethyl group, an ethoxycarbonylmethyl group, a 2-(carboxy)ethyl

group, a 2-(methoxycarbonyl)ethyl group and a 2-(ethoxycarbonyl)ethyl group, pharmacologically acceptable salts thereof or prodrugs thereof;

(13) a compound wherein X^1, X^2, X^3, X^4 and X^5 represent independently a hydrogen atom or a halogen atom, pharmacologically acceptable salts thereof or prodrugs thereof;

(14) a compound wherein X^1 and X^2 represent independently a hydrogen atom or a halogen atom; and X^3, X^4 and X^5 represent a hydrogen atom, pharmacologically acceptable salts thereof or prodrugs thereof;

(15) a compound wherein X^1 represents a halogen atom; and X^2, X^3, X^4 and X^5 represent a hydrogen atom, pharmacologically acceptable salts thereof or prodrugs thereof;

(16) a compound wherein X^1 represents a fluorine atom; and X^2, X^3, X^4 and X^5 represent a hydrogen atom, pharmacologically acceptable salts thereof or prodrugs thereof;

(17) a compound wherein n represents 0 or 1, pharmacologically acceptable salts thereof or prodrugs thereof; and

(18) a compound wherein n represents 1, pharmacologically acceptable salts thereof or prodrugs thereof.

Further, in each group of (1) - (5), (6) - (8), (9) - (12), (13) - (16) and (17) - (18) described above, a more preferable compound is shown as the number increases [the same concept is applied to each group of (19) - (22) described below]. A compound obtained by selecting R^1 from each group of (1) - (5); R^2 from each group of (6) - (8); R^3 from each group of (9) - (12); X^1, X^2, X^3, X^4 and X^5 from each group of (13) - (16); and n from each group of (17) - (18), respectively, followed by arbitrarily combining these selected groups is also preferable, and can be, for example, the following:

(19) a compound wherein R^1 represents a C3-C6 cycloalkyl group or a C1-C6 alkoxy group;

R^2 represents a hydrogen atom or a C1-C6 alkyl group;

R^3 represents a substituted C1-C6 alkyl group {said substituent group represents a heterocyclyl group or a heterocyclyl group substituted with 1 or 2 substituents selected from <Substituent group α> (said heterocyclyl groups may be substituted by 1 or 2 oxo groups), a heteroaryl group or a heteroaryl group substituted with 1 or 2 substituents selected from <Substituent group α>, or a substituent selected from <Substituent group β>}, or a heterocyclyl group or a heterocyclyl group substituted with 1 or 2 substituents selected from <Substituent group α> (said heterocyclyl groups may be substituted by 1 or 2 oxo groups);

X^1 and X^2 represent independently a hydrogen atom or a halogen atom;

X^3, X^4, and X^5 represent a hydrogen atom; and

n is 0 or 1, a pharmacologically acceptable salt thereof, or a prodrug thereof;

(20) a compound wherein R^1 represents a cyclopropyl group or a methoxy group;

R^2 represents a hydrogen atom or a methyl group;

R^3 represents a substituted C1-C6 alkyl group {said substituent group represents a 4- to 7-membered heterocyclyl group containing at least one nitrogen atom which may be substituted with 1 or 2 substituents selected from <Substituent group α1> (said heterocyclyl group may be substituted by one oxo group), a heteroaryl group containing at least one nitrogen atom which may be substituted with 1 or 2 substituents selected from <Substituent group α1>, a carboxy group, a C2-C7 alkoxycarbonyl group, a cyano group, a hydroxyl group, a C1-C6 alkoxy group or a group of formula R^9-CO-$(CH_2)_k$-N(R^{10})- (wherein R^9 represents a hydroxyl group or a C1-C6 alkoxy group; R^{10} represents a C1-C6 alkyl group; and k represents an integer of from 1 to 5)}, or a 4- to 7-membered heterocyclyl group containing at least

one nitrogen atom which may be substituted with one substituent selected from <Substituent group α1> (said heterocyclyl group may be substituted by one oxo group), and

<Substituent group α1> is a group consisting of a carboxy group, a C2-C7 alkoxycarbonyl group, and a group of formula R^4-CO-CR^5R^6-$(CH_2)_m$- (wherein R^4 represents a hydroxyl group, an amino group, a C1-C6 alkylamino group, a di(C1-C6 alkyl)amino group, a hydroxyamino group, a C1-C6 alkoxyamino group or a C1-C6 alkoxy group; R^5 and R^6 each represents a hydrogen atom; and m represents an integer of from 0 to 5);

X^1 represents a halogen atom;

X^2, X^3, X^4 and X^5 represent a hydrogen atom; and

n represents 1, pharmacologically acceptable salts thereof or prodrugs thereof;

(21) a compound wherein R^1 represents a cyclopropyl group;

R^2 represents a hydrogen atom;

R^3 represents a substituted C1-C3 alkyl group {said substituent group represents a pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, pyrazolyl, triazolyl or tetrazolyl group which may be substituted with 1 or 2 substituents selected from <Substituent group α2> (said pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl or piperazinyl group may be substituted by one oxo group), a carboxy group, a C2-C4 alkoxycarbonyl group, a hydroxyl group or a group of formula R^9-CO-$(CH_2)_k$-N(R^{10})- (wherein R^9 represents a hydroxyl group or a C1-C3 alkoxy group; R^{10} represents a C1-C3 alkyl group; and k represents an integer of from 1 to 3)}, or a pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl or piperazinyl group which may be substituted with one substituent selected from <Substituent group α2> (said pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, or piperazinyl group may be substituted by one oxo group), and

<Substituent group α2> is a group consisting of a carboxy group, a C2-C4 alkoxycarbonyl group, and a group of formula R^4-CO-CR^5R^6-$(CH_2)_m$- (wherein R^4 represents a hydroxyl group or a C1-C3 alkoxy group, R^5 and R^6 each represents a hydrogen atom, and m represents an integer of from 0 to 2);

X^1 represents a fluorine atom;

X^2, X^3, X^4 and X^5 represent a hydrogen atom; and

n represents 1, pharmacologically acceptable salts thereof or prodrugs thereof, and

(22) a compound wherein R^1 represents a cyclopropyl group;

R^2 represents a hydrogen atom;

R^3 represents a substituted methyl or ethyl group {said substituent group represents a pyrrolidinyl, piperidinyl, piperazinyl or pyrazolyl group which may be substituted with 1 or 2 substituents selected from <Substituent group α3> (said pyrrolidinyl, piperidinyl or piperazinyl group may be substituted by one oxo group), a carboxy group or a group of formula R^9-CO-$(CH_2)_k$-N(R^{10})- (wherein R^9 represents a hydroxyl group, a methoxy group or an ethoxy group; R^{10} represents a methyl group, an ethyl group or an isopropyl group; and k represents an integer of from 1 to 3), and

<Substituent group α3> is a group consisting of a carboxy group, a methoxycarbonyl group, an ethoxycarbonyl group, a carboxymethyl group, a methoxycarbonylmethyl group, an ethoxycarbonylmethyl group, a 2-(carboxy)ethyl group, a 2-(methoxycarbonyl)ethyl group and a 2-(ethoxycarbonyl)ethyl group;

X^1 represents a fluorine atom;

X^2, X^3, X^4 and X^5 represent a hydrogen atom; and

n represents 1, pharmacologically acceptable salts thereof or prodrugs thereof.

Furthermore, another aspect of the present invention relates to a medicament containing the compound, pharmacologically acceptable salts thereof or prodrugs

thereof described in (1) - (22) above (preferably an antithrombotic agent); use of the compound, pharmacologically acceptable salts thereof or prodrugs thereof to manufacture pharmaceutical compositions; use of the compound, pharmacologically acceptable salts thereof or prodrugs thereof for prophylactic or therapeutic agents for diseases related to thrombus or embolus formation; and prophylactic or therapeutic methods for diseases (particularly diseases related to thrombus or embolus formation) by administration of pharmacologically effective dose of the compound, pharmacologically acceptable salts thereof or prodrugs thereof to a warm-blooded animals (especially humans).

The "C1-C6 alkyl group" in the general formula (I) shown above can be, for example, a straight or branched chain alkyl group having from 1 to 6 carbon atoms such as a methyl, ethyl, propyl, isopropyl, butyl, isobutyl, s-butyl, t-butyl, pentyl, isopentyl, 2-methylbutyl, neopentyl, 1-ethylpropyl, hexyl, 4-methylpentyl, 3-methylpentyl, 2-methylpentyl, 1-methylpentyl, 3,3-dimethylbutyl, 2,2-dimethylbutyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,3-dimethylbutyl or 2-ethylbutyl group, and is preferably a straight or branched chain alkyl group having from 1 to 4 carbon atoms, more preferably a straight or branched chain alkyl group having from 1 to 3 carbon atoms, more preferably a methyl or ethyl group, and most preferably a methyl group.

The "halogen atom" in the general formula (I) shown above can be, for example, a fluorine atom, a chlorine atom, a bromine atom or an iodine atom, and is preferably a fluorine atom or a chlorine atom, and more preferably a fluorine atom.

The "C1-C6 alkoxy group" in the general formula (I) shown above indicates a group wherein said "C1-C6 alkyl group" is bonded to an oxygen atom, and can be, for example, a straight or branched chain alkoxy group having from 1 to 6 carbon atoms such as a methoxy, ethoxy, n-propoxy, isopropoxy, n-butoxy, isobutoxy, s-butoxy, t-butoxy, n-pentyloxy, isopentyloxy, 2-methylbutoxy, neopentyloxy, n-

hexyloxy, 4-methylpentyloxy, 3-methylpentyloxy, 2-methylpentyloxy, 3,3-dimethylbutoxy, 2,2-dimethylbutoxy, 1,1-dimethylbutoxy, 1,2-dimethylbutoxy, 1,3-dimethylbutoxy or 2,3-dimethylbutoxy group, and is preferably a straight or branched chain alkoxy group having from 1 to 4 carbon atoms, more preferably a straight or branched chain alkoxy group having from 1 to 3 carbon atoms, and most preferably a methoxy or ethoxy group.

The "C3-C6 cycloalkyl group" in general formula (I) shown above can be, for example, a 3- to 6-membered saturated cyclic hydrocarbon group such as a cyclopropyl, cyclobutyl, cyclopentyl or cyclohexyl group, and is preferably a cyclopropyl group.

The "C6-C10 aryl group" in general formula (I) shown above can be, for example, an aromatic hydrocarbon group having from 6 to 10 carbon atoms such as phenyl or naphthyl group, and is preferably a phenyl group.

The "C2-C7 alkoxycarbonyl group" in general formula (I) shown above can be, for example, a straight or branched chain alkoxycarbonyl group having from 2 to 7 carbon atoms such as a methoxycarbonyl, ethoxycarbonyl, n-propoxycarbonyl, isopropoxycarbonyl, n-butoxycarbonyl, isobutoxycarbonyl, s-butoxycarbonyl, t-butoxycarbonyl, n-pentyloxycarbonyl, isopentyloxycarbonyl, 2-methylbutoxycarbonyl, neopentyloxycarbonyl, n-hexyloxycarbonyl, 4-methylpentyloxycarbonyl, 3-methylpentyloxycarbonyl, 2-methylpentyloxycarbonyl, 3,3-dimethylbutoxycarbonyl, 2,2-dimethylbutoxycarbonyl, 1,1-dimethylbutoxycarbonyl, 1,2-dimethylbutoxycarbonyl, 1,3-dimethylbutoxycarbonyl or 2,3-dimethylbutoxycarbonyl group, and is preferably a straight or branched chain alkoxycarbonyl group having from 2 to 5 carbon atoms, more preferably a straight or branched chain alkoxycarbonyl group having from 2 to 4 carbon atoms, and further more preferably a methoxycarbonyl or ethoxycarbonyl group.

The "halogeno C1-C6 alkyl group" in general formula (I) shown above indicates a group wherein said "C1-C6 alkyl group" is substituted with halogen atom(s), and can be, for example, a trifluoromethyl, trichloromethyl, difluoromethyl, dichloromethyl, dibromomethyl, fluoromethyl, 2,2,2-trifluoroethyl, 2,2,2-trichloroethyl, 2-bromoethyl, 2-chloroethyl, 2-fluoroethyl, 2-iodoethyl, 3-chloropropyl, 4-fluorobutyl, 6-iodohexyl or 2,2-dibromoethyl group, and is preferably a trifluoromethyl group.

The "heteroaryl group" in general formula (I) shown above can be, for example, a 5- to 7-membered aromatic heterocyclic group containing from 1 to 4 sulfur atom(s), oxygen atom(s) and/or nitrogen atom(s) such as a furyl, thienyl, pyrrolyl, pyrazolyl, imidazolyl, oxazolyl, isoxazolyl, thiazolyl, isothiazolyl, triazolyl, tetrazolyl, thiadiazolyl, oxadiazolyl, pyranyl, pyridyl, pyridazinyl, pyrimidinyl or pyrazinyl group, or an aromatic heterocyclic group fused with other cyclic groups such as an isoindolyl, indolyl, isoquinolyl and quinolyl group, and is preferably a 5- to 7-membered aromatic heterocyclic group containing at least one nitrogen atom, and more preferably a pyrazolyl, triazolyl or tetrazolyl group.

The "halogeno C1-C6 alkoxy group" in general formula (I) shown above indicates a group wherein said "C1-C6 alkoxy group" is substituted with halogen atom(s), and can be, for example, a trifluoromethoxy, trichloromethoxy, difluoromethoxy, dichloromethoxy, dibromomethoxy, fluoromethoxy, 2,2,2-trichloroethoxy, 2,2,2-trifluoroethoxy, 2-bromoethoxy, 2-chloroethoxy, 2-fluoroethoxy or 2,2-dibromoethoxy group, and is preferably a 2-bromoethoxy, 2-chloroethoxy or 2-fluoroethoxy group.

The "hydroxy C1-C6 alkyl group" in general formula (I) shown above indicates a group wherein said "C1-C6 alkyl group" is substituted with hydroxyl group(s), and can be, for example, a hydroxymethyl, 1-hydroxyethyl, 2-hydroxyethyl, 1-hydroxy-2-methylethyl, 2-hydroxy-2-methylethyl, 1-hydroxypropyl, 2-

hydroxypropyl, 3-hydroxypropyl, 1-hydroxybutyl, 2-hydroxybutyl, 3-hydroxybutyl, 4-hydroxybutyl, 5-hydroxypentyl or 6-hydroxyhexyl group, and is preferably a hydroxymethyl, 2-hydroxyethyl or 3-hydroxypropyl group.

The "C2-C12 alkoxyalkyl group" in general formula (I) shown above indicates a group wherein said "C1-C6 alkoxy group" is bonded to said "C1-C6 alkyl group", and can be, for example, a methoxymethyl, ethoxymethyl, n-propoxymethyl, isopropoxymethyl, n-butoxymethyl, isobutoxymethyl, s-butoxymethyl, t-butoxymethyl, n-pentyloxymethyl, isopentyloxymethyl, 2-methylbutoxymethyl, neopentyloxymethyl, n-hexyloxymethyl, 4-methylpentyloxymethyl, 3-methylpentyloxymethyl, 2-methylpentyloxymethyl, 3,3-dimethylbutoxymethyl, 2,2-dimethylbutoxymethyl, 1,1-dimethylbutoxymethyl, 1,2-dimethylbutoxymethyl, 1,3-dimethylbutoxymethyl, 2,3-dimethylbutoxymethyl, 2-methoxyethyl, 2-ethoxyethyl, 2-(n-propoxy)ethyl, 2-(isopropoxy)ethyl, 2-(n-butoxy)ethyl, 2-(isobutoxy)ethyl, 2-(s-butoxy)ethyl, 2-(t-butoxy)ethyl, 2-(n-pentyloxy)ethyl, 2-(isopentyloxy)ethyl, 2-(2-methylbutoxy)ethyl, 2-(neopentyloxy)ethyl, 2-(n-hexyloxy)ethyl, 2-(4-methylpentyloxy)ethyl, 2-(3-methylpentyloxy)ethyl, 2-(2-methylpentyloxy)ethyl, 2-(3,3-dimethylbutoxy)ethyl, 2,2-dimethylbutoxyethyl, 1,1-dimethylbutoxyethyl, 1,2-dimethylbutoxyethyl, 1,3-dimethylbutoxyethyl or 2,3-dimethylbutoxyethyl group, and is preferably a straight or branched chain alkoxyalkyl group having from 2 to 4 carbon atoms, and more preferably a methoxymethyl or methoxyethyl group.

The "C2-C7 alkanoyl group" in the general formula (I) shown above can be, for example, a straight or branched chain alkanoyl group having from 2 to 7 carbon atoms such as an acetyl, propionyl, butyryl, isobutyryl, pentanoyl, pivaloyl, valeryl, isovaleryl, hexanoyl or heptanoyl group, and is preferably a straight or branched chain alkanoyl group having from 2 to 5 carbon atoms, more preferably a straight or branched chain alkanoyl group having from 2 to 4 carbon atoms, and further more preferably an acetyl group.

The "C4-C7 cycloalkylcarbonyl group" in general formula (I) shown above indicates a group wherein said "C3-C6 cycloalkyl group" is bonded to a carbonyl group, and can be, for example, a cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl or cyclohexylcarbonyl group, and is preferably a cyclopropylcarbonyl group.

The "C2-C7 alkylcarbamoyl group" in general formula (I) shown above indicates a group wherein one "C1-C6 alkyl group" is bonded to a carbamoyl group, and can be, for example, a methylcarbamoyl, ethylcarbamoyl, propylcarbamoyl, isopropylcarbamoyl, butylcarbamoyl, isobutylcarbamoyl, s-butylcarbamoyl, t-butylcarbamoyl, pentylcarbamoyl, isopentylcarbamoyl, 2-methylbutylcarbamoyl, neopentylcarbamoyl, 1-ethylpropylcarbamoyl, hexylcarbamoyl, 4-methylpentylcarbamoyl, 3-methylpentylcarbamoyl, 2-methylpentylcarbamoyl, 1-methylpentylcarbamoyl, 3,3-dimethylbutylcarbamoyl, 2,2-dimethylbutylcarbamoyl, 1,1-dimethylbutylcarbamoyl, 1,2-dimethylbutylcarbamoyl, 1,3-dimethylbutylcarbamoyl, 2,3-dimethylbutylcarbamoyl or 2-ethylbutylcarbamoyl group, and is preferably an alkylcarbamoyl group having from 2 to 5 carbon atoms, and more preferably a methylcarbamoyl or ethylcarbamoyl group.

The "di(C1-C6 alkyl)carbamoyl group" in general formula (I) shown above indicates a group wherein a carbamoyl group is disubstituted with two "C1-C6 alkyl groups", and can be, for example, a dimethylcarbamoyl, methylethylcarbamoyl, diethylcarbamoyl, di-n-propylcarbamoyl, diisopropylcarbamoyl, N-(n-propyl)-N-ethylcarbamoyl, di-n-butylcarbamoyl, diisobutylcarbamoyl, di-s-butylcarbamoyl, di-t-butylcarbamoyl, di-n-pentylcarbamoyl, diisopentylcarbamoyl, di-2-methylbutylcarbamoyl, dineopentylcarbamoyl, di-1-ethylpropylcarbamoyl, di-n-hexylcarbamoyl, di-4-methylpentylcarbamoyl, di-3-methylpentylcarbamoyl, di-2-methylpentylcarbamoyl, di-1-methylpentylcarbamoyl, di-3,3-dimethylbutylcarbamoyl, di-2,2-dimethylbutylcarbamoyl, di-1,1-

dimethylbutylcarbamoyl, di-1,2-dimethylbutylcarbamoyl, di-1,3-dimethylbutylcarbamoyl, di-2,3-dimethylbutylcarbamoyl or di-2-ethylbutylcarbamoyl group, and is preferably a dimethylcarbamoyl, methylethylcarbamoyl or diethylcarbamoyl group.

The "C1-C6 alkylamino group" in general formula (I) shown above indicates a group wherein one "C1-C6 alkyl group" is bonded to an amino group, and can be, for example, a straight or branched chain alkylamino group having from 1 to 6 carbon atoms such as methylamino, ethylamino, propylamino, isopropylamino, butylamino, isobutylamino, s-butylamino, t-butylamino, pentylamino, isopentylamino, 2-methylbutylamino, neopentylamino, 1-ethylpropylamino, hexylamino, 4-methylpentylamino, 3-methylpentylamino, 2-methylpentylamino, 1-methylpentylamino, 3,3-dimethylbutylamino, 2,2-dimethylbutylamino, 1,1-dimethylbutylamino, 1,2-dimethylbutylamino, 1,3-dimethylbutylamino, 2,3-dimethylbutylamino or 2-ethylbutylamino group, and is preferably a straight or branched chain alkylamino group having from 1 to 4 carbon atoms, more preferably a straight or branched chain alkylamino group having from 1 to 3 carbon atoms, and further more preferably a methylamino group.

The "di(C1-C6 alkyl)amino group" in general formula (I) shown above indicates a group wherein an amino group is substituted with two "C1-C6 alkyl groups", and can be, for example, a dimethylamino, methylethylamino, diethylamino, di-n-propylamino, diisopropylamino, N-(n-propyl)-N-ethylamino, di-n-butylamino, diisobutylamino, di-s-butylamino, di-t-butylamino, di-n-pentylamino, diisopentylamino, di-2-methylbutylamino, dineopentylamino, di-1-ethylpropylamino, di-n-hexylamino, di-4-methylpentylamino, di-3-methylpentylamino, di-2-methylpentylamino, di-1-methylpentylamino, di-3,3-dimethylbutylamino, di-2,2-dimethylbutylamino, di-1,1-dimethylbutylamino, di-1,2-dimethylbutylamino, di-1,3-

dimethylbutylamino, di-2,3-dimethylbutylamino or di-2-ethylbutylamino group, and is preferably a dimethylamino, methylethylamino or diethylamino group.

The "C1-C6 alkoxyamino group" in general formula (I) shown above indicates a group wherein the oxygen atom of a hydroxyamino group is substituted with said "C1-C6 alkyl group", and can be, for example, a methoxyamino, ethoxyamino, n-propoxyamino, isopropoxyamino, n-butoxyamino, isobutoxyamino, s-butoxyamino, t-butoxyamino, n-pentyloxyamino, isopentyloxyamino, 2-methylbutoxyamino, neopentyloxyamino, n-hexyloxyamino, 4-methylpentyloxyamino, 3-methylpentyloxyamino, 2-methylpentyloxyamino, 3,3-dimethylbutoxyamino, 2,2-dimethylbutoxyamino, 1,1-dimethylbutoxyamino, 1,2-dimethylbutoxyamino, 1,3-dimethylbutoxyamino or 2,3-dimethylbutoxyamino group, and is preferably a straight or branched chain alkoxyamino group having from 1 to 4 carbon atoms, more preferably a straight or branched chain alkoxyamino group having from 1 to 3 carbon atoms, and further more preferably a methoxyamino group.

The "sulfamoyl C1-C6 alkyl group" in general formula (I) shown above indicates a group wherein said "C1-C6 alkyl group" is substituted with sulfamoyl group(s), and can be, for example, a sulfamoylmethyl, 1-sulfamoylethyl, 2-sulfamoylethyl, 1-sulfamoyl-2-methylethyl, 2-sulfamoyl-2-methylethyl, 1-sulfamoylpropyl, 2-sulfamoylpropyl, 3-sulfamoylpropyl, 1-sulfamoylbutyl, 2-sulfamoylbutyl, 3-sulfamoylbutyl, 4-sulfamoylbutyl, 5-sulfamoylpentyl or 6-sulfamoylhexyl group, and is preferably a sulfamoylalkyl group having from 1 to 4 carbon atoms, more preferably a sulfamoylalkyl group having from 1 to 3 carbon atoms, and further more preferably a sulfamoylmethyl, 2-sulfamoylethyl or 3-sulfamoylpropyl group.

The "heterocyclyl group" in general formula (I) shown above can be, for example, a partially or completely reduced 4- to 7-membered heterocyclic group containing from 1 to 3 sulfur atom(s), oxygen atom(s) and/or nitrogen atom(s) such

as a morpholinyl, thiomorpholinyl, azetidinyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrrazolidinyl, pyrrazolinyl, piperidyl, piperazinyl, homopiperazinyl or homopiperidinyl group, and is preferably a 4- to 7-membered heterocyclyl group containing at least one nitrogen atom, more preferably a morpholinyl, thiomorpholinyl, pyrrolidinyl, pyrrolinyl, imidazolidinyl, imidazolinyl, pyrrazolidinyl, pyrrazolinyl, piperidyl or piperazinyl group, and more preferably a pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl or piperazinyl group.

The "heterocyclyl group (said heterocyclyl group may be substituted by from 1 to 4 oxo groups)" in general formula (I) shown above can be oxopiperazinyl or dioxopiperazinyl group, in addition to said "heterocyclyl group"; and is preferably a 2-oxo-1-piperazino, 3-oxo-1-piperazino or 2,5-dioxo-1-piperazino group; and more preferably a 2-oxo-1-piperazino or 3-oxo-1-piperazino group.

The Substituent group α in general formula (I) shown above, is preferably a group consisting of a carboxy group, a C2-C7 alkoxycarbonyl group, and a group of formula R^4-CO-CR^5R^6-$(CH_2)_m$- (wherein R^4 represents a hydroxyl group, an amino group, a C1-C6 alkylamino group, a di(C1-C6 alkyl)amino group, a hydroxyamino group, a C1-C6 alkoxyamino group or a C1-C6 alkoxy group; R^5 and R^6 each represents a hydrogen atom; and m represents an integer of from 0 to 5), more preferably a group consisting of a carboxy group, a C2-C4 alkoxycarbonyl group and a group of formula R^4-CO-CR^5R^6-$(CH_2)_m$- (wherein R^4 represents a hydroxyl group or a C1-C3 alkoxy group; R^5 and R^6 each represents a hydrogen atom; and m represents an integer of from 0 to 2), and further more preferably a group consisting of a carboxy group, a methoxycarbonyl group, an ethoxycarbonyl group, a carboxymethyl group, a methoxycarbonylmethyl group, an ethoxycarbonylmethyl group, a 2-(carboxy)ethyl group, a 2-(methoxycarbonyl)ethyl group and a 2-(ethoxycarbonyl)ethyl group.

The Substituent group β in general formula (I) shown above is preferably a group consisting of a carboxy group, a C2-C7 alkoxycarbonyl group, a cyano group, a hydroxyl group, a C1-C6 alkoxy group and a group of formula R^9-CO-$(CH_2)_k$-N(R^{10})- (wherein R^9 represents a hydroxyl group or a C1-C6 alkoxy group; R^{10} represents a C1-C6 alkyl group; and k represents an integer of from 1 to 5), more preferably a group consisting of a carboxy group, a C2-C4 alkoxycarbonyl group, a hydroxyl group and a group of formula R^9-CO-$(CH_2)_k$-N(R^{10})- (wherein R^9 represents a hydroxyl group or a C1-C3 alkoxy group; R^{10} represents a C1-C3 alkyl group; and k represents an integer of from 1 to 3), and more preferably a group consisting of a carboxy group and a group of formula R^9-CO-$(CH_2)_k$-N(R^{10})- (wherein R^9 represents a hydroxyl group, a methoxy group or an ethoxy group; R^{10} represents a methyl group, an ethyl group or an isopropyl group; and k represents an integer of from 1 to 3).

In the compounds (I) of the present invention, optical isomers due to asymmetric carbon atoms in their structures (including diastereomers) may be present, and additionally, geometrical isomers due to the carbon-carbon double bond may be also present in the same compound. The present invention encompasses all of these isomers.

As some compounds (I) of the present invention have various groups such as a sulfanyl group, a carboxy group, a hydroxyl group or an amino group in their structure, the "prodrug thereof" means a derivative in which any of such groups is modified by an appropriate functional group that can be cleaved by a biological process such as hydrolysis in vivo. In these cases, it can be determined whether the derivative is "an appropriate functional group that can be cleaved by a biological process such as hydrolysis in vivo" or not according to whether the original compound or a pharmacologically acceptable salt thereof can be detected, by administering the derivative to an experimental animal such as a rat or a mouse by an

intravenous injection, subcutaneous injection or oral administration, and measuring a body fluid of the animal thereafter.

When the compounds (I) of the present invention contain a sulfanyl group in their structures, the functional group employed for forming a prodrug thereof is not particularly restricted, and can be, for example, an "aliphatic acyl group", including an alkanoyl group such as a formyl, acetyl, propionyl, butyryl, isobutyryl, pentanoyl, pivaloyl, valeryl, isovaleryl, octanoyl, nonanoyl, decanoyl, 3-methylnonanoyl, 8-methylnonanoyl, 3-ethyloctanoyl, 3,7-dimethyloctanoyl, undecanoyl, dodecanoyl, tridecanoyl, tetradecanoyl, pentadecanoyl, hexadecanoyl, 1-methylpentadecanoyl, 14-methylpentadecanoyl, 13,13-dimethyltetradecanoyl, heptadecanoyl, 15-methylhexadecanoyl, octadecanoyl, 1-methylheptadecanoyl, nonadecanoyl, icosanoyl or henicosanoyl group; an alkylcarbonyl group substituted with a carboxy group such as a succinoyl, glutaroyl or adipoyl group; a carbonyl group substituted with a halogeno lower alkyl group such as a chloroacetyl, dichloroacetyl, trichloroacetyl or trifluoroacetyl group; a saturated cyclic hydrocarbon-carbonyl group such as a cyclopropylcarbonyl, cyclobutylcarbonyl, cyclopentylcarbonyl, cyclohexylcarbonyl, cycloheptylcarbonyl or cyclooctylcarbonyl group; an alkylcarbonyl group substituted with lower alkoxy group(s) such as a methoxyacetyl group; and an unsaturated alkylcarbonyl group such as a (E)-2-methyl-2-butenoyl group (preferably C1-C6 alkanoyl group); a "carbonyloxyalkyl group", including an oxodioxolenylmethyl group such as a (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl or a (5-phenyl-2-oxo-1,3-dioxolen-4-yl)methyl group; an "aromatic acyl group", including an arylcarbonyl group such as a benzoyl, α-naphthoyl, β-naphthoyl, pyridoyl, thienoyl or furoyl group; a halogeno arylcarbonyl group such as a 2-bromobenzoyl or 4-chlorobenzoyl group; an arylcarbonyl group substituted with lower alkyl group(s) such as a 2,4,6-trimethylbenzoyl or 4-toluoyl group; a lower alkoxylated arylcarbonyl group such as a 4-anisoyl group; an arylcarbonyl group

substituted with carboxy group(s) such as a 2-carboxybenzoyl, 3-carboxybenzoyl or 4-carboxybenzoyl group; a nitrated arylcarbonyl group such as a 4-nitrobenzoyl or 2-nitrobenzoyl group; an arylcarbonyl group substituted with lower alkoxycarbonyl group(s) such as a 2-(methoxycarbonyl)benzoyl group; and an arylcarbonyl group substituted with aryl group(s) such as a 4-phenylbenzoyl group (preferably an arylcarbonyl group); an "aralkylcarbonyl group", including a carbonyl group substituted with a lower alkyl group which is substituted with from 1 to 3 aryl groups such as a phenylacetyl, α-naphthylpropionyl, β-naphthylbutyryl, diphenylisobutyryl, triphenylacetyl, α-naphthyldiphenylisobutyryl or 9-anthrylpentanoyl group; and a lower alkylcarbonyl group substituted with from 1 to 3 aryl groups, of which an aryl ring is substituted with lower alkyl group(s), lower alkoxy group(s), nitro group(s), halogen atom(s) or cyano group(s), such as a 4-methylphenylacetyl, 2,4,6-trimethylphenylformyl, 3,4,5-trimethylphenylbutyryl, 4-methoxyphenylisobutyryl, 4-methoxyphenyldiphenylpivaloyl, 2-nitrophenylacetyl, 4-nitrophenylpropionyl, 4-chlorophenylbutyryl, 4-bromophenylacetyl or 4-cyanophenylpentanoyl group; a "tetrahydropyranyl or tetrahydrothiopyranyl group" such as a tetrahydropyran-2-yl, 3-bromotetrahydropyran-2-yl, 4-methoxytetrahydropyran-4-yl, tetrahydrothiopyran-2-yl or 4-methoxytetrahydrothiopyran-4-yl group; a "tetrahydrofuranyl or tetrahydrothiofuranyl group" such as a tetrahydrofuran-2-yl or tetrahydrothiofuran-2-yl group; an "alkoxymethyl group", including a lower alkoxymethyl group such as a methoxymethyl, 1,1-dimethyl-1-methoxymethyl, ethoxymethyl, propoxymethyl, isopropoxymethyl, butoxymethyl or t-butoxymethyl group; a lower alkoxymethyl group substituted with lower alkoxy group(s) such as a 2-methoxyethoxymethyl group; and a halogeno lower alkoxymethyl group such as a 2,2,2-trichloroethoxymethyl or bis(2-chloroethoxy)methyl group; a "substituted ethyl group", including a lower alkoxylated ethyl group such as a 1-ethoxyethyl or 1-(isopropoxy)ethyl group; and a halogenated ethyl group such as a 2,2,2-trichloroethyl

group; an "aralkyl group", including a lower alkyl group substituted with from 1 to 3 aryl groups such as a benzyl, α-naphthylmethyl, β-naphthylmethyl, diphenylmethyl, triphenylmethyl, α-naphthyldiphenylmethyl or 9-anthrylmethyl group; and a lower alkyl group substituted with from 1 to 3 aryl groups, of which an aryl ring is substituted with lower alkyl group(s), lower alkoxy group(s), nitro group(s), halogen atom(s) or cyano group(s), such as a 4-methylbenzyl, 2,4,6-trimethylbenzyl, 3,4,5-trimethylbenzyl, 4-methoxybenzyl, 4-methoxyphenyldiphenylmethyl, 2-nitrobenzyl, 4-nitrobenzyl, 4-chlorobenzyl, 4-bromobenzyl or 4-cyanobenzyl group; an "alkoxycarbonyl group", including a lower alkoxycarbonyl group such as a methoxycarbonyl, ethoxycarbonyl, t-butoxycarbonyl or isobutoxycarbonyl group; and a lower alkoxycarbonyl group substituted with halogen atom(s) or tri-lower alkylsilyl group(s) such as a 2,2,2-trichloroethoxycarbonyl or 2-trimethylsilylethoxycarbonyl group; an "alkenyloxycarbonyl group" such as a vinyloxycarbonyl and allyloxycarbonyl group; an "aralkyloxycarbonyl group", of which an aryl ring may be substituted with 1 or 2 substituents selected from lower alkoxy group(s) or nitro group(s), such as a benzyloxycarbonyl, 4-methoxybenzyloxycarbonyl, 3,4-dimethoxybenzyloxycarbonyl, 2-nitrobenzyloxycarbonyl or 4-nitrobenzyloxycarbonyl group; a straight or branched chain alkylsulfanyl group having from 1 to 6 carbon atoms such as a methylsulfanyl, ethylsulfanyl, n-propylsulfanyl, isopropylsulfanyl, n-butylsulfanyl, isobutylsulfanyl, s-butylsulfanyl, t-butylsulfanyl, n-pentylsulfanyl, isopentylsulfanyl, 2-methylbutylsulfanyl, neopentylsulfanyl, 1-ethylpropylsulfanyl, n-hexylsulfanyl, 4-methylpentylsulfanyl, 3-methylpentylsulfanyl, 2-methylpentylsulfanyl, 1-methylpentylsulfanyl, 3,3-dimethylbutylsulfanyl, 2,2-dimethylbutylsulfanyl, 1,1-dimethylbutylsulfanyl, 1,2-dimethylbutylsulfanyl, 1,3-dimethylbutylsulfanyl, 2,3-dimethylbutylsulfanyl or 2-ethylbutylsulfanyl group; or an "aminoacyl group of an α-amino acid" such as a phenylalanine, and is preferably a group which forms a

pharmacologically acceptable ester such as an "aliphatic acyl group" or an "aromatic acyl group", or "C1-C6 alkylsulfanyl group" such as a methylsulfanyl, ethylsulfanyl, n-propylsulfanyl, isopropylsulfanyl, n-butylsulfanyl, isobutylsulfanyl, s-butylsulfanyl or t-butylsulfanyl group; more preferably a group which forms a pharmacologically acceptable ester; further more preferably a "C1-C6 alkanoyl group" such as a formyl, acetyl, propionyl, butyryl, isobutyryl, pentanoyl or pivaloyl group or an "arylcarbonyl group" such as a benzoyl group; particularly preferably a "C1-C3 alkanoyl group" or a benzoyl group; and most preferably an acetyl group.

When the compounds (I) of the present invention contain a carboxy group in their structures, the functional group employed for forming a prodrug thereof can be, for example, a "lower alkyl groups" such as a methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, s-butyl, tert-butyl, n-pentyl, isopentyl, 2-methylbutyl, neopentyl, 1-ethylpropyl, n-hexyl, 4-methylpentyl, 3-methylpentyl, 2-methylpentyl, 1-methylpentyl, 3,3-dimethylbutyl, 2,2-dimethylbutyl, 1,1-dimethylbutyl, 1,2-dimethylbutyl, 1,3-dimethylbutyl, 2,3-dimethylbutyl or 2-ethylbutyl group (preferably a C1-C6 alkyl group); an "alkoxy lower alkyl group", including a lower alkoxy lower alkyl group such as a methoxymethyl, 1-ethoxyethyl, 1-methyl-1-methoxyethyl, 1-(isopropoxy)ethyl, 2-methoxyethyl, 2-ethoxyethyl, 1,1-dimethyl-1-methoxymethyl, ethoxymethyl, n-propoxymethyl, isopropoxymethyl, n-butoxymethyl or tert-butoxymethyl group; a lower alkoxylated lower alkoxy lower alkyl group such as a 2-methoxyethoxymethyl group; an "aryl"oxy "lower alkyl group" such as a phenoxymethyl group; and a halogenated lower alkoxy lower alkyl group such as a 2,2,2-trichloroethoxymethyl or bis(2-chloroethoxy)methyl group; a "lower alkoxy" carbonyl "lower alkyl group" such as a methoxycarbonylmethyl group; a cyano "lower alkyl group" such as a cyanomethyl or 2-cyanoethyl group; a "lower alkyl" thiomethyl group such as a methylthiomethyl or ethylthiomethyl group; an "aryl" thiomethyl group such as a phenylthiomethyl or naphthylthiomethyl

group; a "lower alkyl" sulfonyl "lower alkyl group", which may be substituted with halogen atom(s), such as a 2-methanesulfonylethyl or 2-trifluoromethanesulfonylethyl group; an "aryl" sulfonyl "lower alkyl group" such as a 2-benzenesulfonylethyl or 2-toluenesulfonylethyl group; an acyloxy "lower alkyl group", including an "aliphatic acyl"oxy "lower alkyl group" such as a formyloxymethyl, acetoxymethyl, propionyloxymethyl, butyryloxymethyl, pivaloyloxymethyl, valeryloxymethyl, isovaleryloxymethyl, hexanoyloxymethyl, 1-formyloxyethyl, 1-acetoxyethyl, 1-propionyloxyethyl, 1-butyryloxyethyl, 1-pivaloyloxyethyl, 1-valeryloxyethyl, 1-isovaleryloxyethyl, 1-hexanoyloxyethyl, 2-formyloxyethyl, 2-acetoxyethyl, 2-propionyloxyethyl, 2-butyryloxyethyl, 2-pivaloyloxyethyl, 2-valeryloxyethyl, 2-isovaleryloxyethyl, 2-hexanoyloxyethyl, 1-formyloxypropyl, 1-acetoxypropyl, 1-propionyloxypropyl, 1-butyryloxypropyl, 1-pivaloyloxypropyl, 1-valeryloxypropyl, 1-isovaleryloxypropyl, 1-hexanoyloxypropyl, 1-acetoxybutyl, 1-propionyloxybutyl, 1-butyryloxybutyl, 1-pivaloyloxybutyl, 1-acetoxypentyl, 1-propionyloxypentyl, 1-butyryloxypentyl, 1-pivaloyloxypentyl or 1-pivaloyloxyhexyl group; a "cycloalkyl" carbonyloxy "lower alkyl group" such as a cyclopentanoyloxymethyl, cyclohexanoyloxymethyl, 1-cyclopentanoyloxyethyl, 1-cyclohexanoyloxyethyl, 1-cyclopentanoyloxypropyl, 1-cyclohexanoyloxypropyl, 1-cyclopentanoyloxybutyl or 1-cyclohexanoyloxybutyl group; and an "aromatic acyl"oxy "lower alkyl group" such as a benzoyloxymethyl group; an "(alkoxycarbonyloxy)alkyl group" such as a methoxycarbonyloxymethyl, ethoxycarbonyloxymethyl, propoxycarbonyloxymethyl, isopropoxycarbonyloxymethyl, butoxycarbonyloxymethyl, isobutoxycarbonyloxymethyl, pentyloxycarbonyloxymethyl, hexyloxycarbonyloxymethyl, cyclohexyloxycarbonyloxymethyl, cyclohexyloxycarbonyloxy(cyclohexyl)methyl, 1-(methoxycarbonyloxy)ethyl, 1-(ethoxycarbonyloxy)ethyl, 1-propoxycarbonyloxyethyl, 1-

(isopropoxycarbonyloxy)ethyl, 1-butoxycarbonyloxyethyl, 1-isobutoxycarbonyloxyethyl, 1-(tert-butoxycarbonyloxy)ethyl, 1-pentyloxycarbonyloxyethyl, 1-hexyloxycarbonyloxyethyl, 1-cyclopentyloxycarbonyloxyethyl, 1-cyclopentyloxycarbonyloxypropyl, 1-cyclohexyloxycarbonyloxypropyl, 1-cyclopentyloxycarbonyloxybutyl, 1-cyclohexyloxycarbonyloxybutyl, 1-(cyclohexyloxycarbonyloxy)ethyl, 1-(ethoxycarbonyloxy)propyl, 2-methoxycarbonyloxyethyl, 2-ethoxycarbonyloxyethyl, 2-propoxycarbonyloxyethyl, 2-isopropoxycarbonyloxyethyl, 2-butoxycarbonyloxyethyl, 2-isobutoxycarbonyloxyethyl, 2-pentyloxycarbonyloxyethyl, 2-hexyloxycarbonyloxyethyl, 1-methoxycarbonyloxypropyl, 1-ethoxycarbonyloxypropyl, 1-propoxycarbonyloxypropyl, 1-isopropoxycarbonyloxypropyl, 1-butoxycarbonyloxypropyl, 1-isobutoxycarbonyloxypropyl, 1-pentyloxycarbonyloxypropyl, 1-hexyloxycarbonyloxypropyl, 1-methoxycarbonyloxybutyl, 1-ethoxycarbonyloxybutyl, 1-propoxycarbonyloxybutyl, 1-isopropoxycarbonyloxybutyl, 1-butoxycarbonyloxybutyl, 1-isobutoxycarbonyloxybutyl, 1-methoxycarbonyloxypentyl, 1-ethoxycarbonyloxypentyl, 1-methoxycarbonyloxyhexyl or 1-ethoxycarbonyloxyhexyl group; a "carbonyloxyalkyl group", including an oxodioxolenylmethyl group such as a (5-phenyl-2-oxo-1,3-dioxolen-4-yl)methyl, [5-(4-methylphenyl)-2-oxo-1,3-dioxolen-4-yl]methyl, [5-(4-methoxyphenyl)-2-oxo-1,3-dioxolen-4-yl]methyl, [5-(4-fluorophenyl)-2-oxo-1,3-dioxolen-4-yl]methyl, [5-(4-chlorophenyl)-2-oxo-1,3-dioxolen-4-yl]methyl, (2-oxo-1,3-dioxolen-4-yl)methyl, (5-methyl-2-oxo-1,3-dioxolen-4-yl)methyl, (5-ethyl-2-oxo-1,3-dioxolen-4-yl)methyl, (5-propyl-2-oxo-1,3-dioxolen-4-yl)methyl, (5-isopropyl-2-oxo-1,3-dioxolen-4-yl)methyl or (5-butyl-2-oxo-1,3-dioxolen-4-yl)methyl group; a "phthalidyl group" such as a phthalidyl, dimethylphthalidyl or dimethoxyphthalidyl group; an "aryl

group" such as a phenyl and indanyl group; a "carboxyalkyl group" such as a carboxymethyl group; or a "residual group forming an amino acid amide" such as a phenylalanine, and is preferably a group which forms pharmacologically acceptable esters such as an "alkyl group", "alkoxyalkyl group", "carbonyloxyalkyl group" or (alkoxycarbonyloxy)alkyl group; more preferably a "C1-C6 alkyl group" such as a methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, s-butyl, tert-butyl, n-pentyl, isopentyl, 2-methylbutyl, neopentyl, 1-ethylpropyl, n-hexyl, 4-methylpentyl, 3-methylpentyl, 2-methylpentyl or 1-methylpentyl; and particularly preferably methyl or ethyl group.

When the compounds (I) of the present invention contain a hydroxyl group in their structures, the functional group employed for forming a prodrug thereof can be, for example, an "aliphatic acyl group", including an alkylcarbonyl group such as a formyl, acetyl, propionyl, butyryl, isobutyryl, pentanoyl, pivaloyl, valeryl, isovaleryl, octanoyl, nonanoyl, decanoyl, 3-methylnonanoyl, 8-methylnonanoyl, 3-ethyloctanoyl, 3,7-dimethyloctanoyl, undecanoyl, dodecanoyl, tridecanoyl, tetradecanoyl, pentadecanoyl, hexadecanoyl, 1-methylpentadecanoyl, 14-methylpentadecanoyl, 13,13-dimethyltetradecanoyl, heptadecanoyl, 15-methylhexadecanoyl, octadecanoyl, 1-methylheptadecanoyl, nonadecanoyl, icosanoyl or henicosanoyl group; a carboxylated alkylcarbonyl group such as a succinoyl, glutaroyl or adipoyl group; a halogeno lower alkylcarbonyl group such as a chloroacetyl, dichloroacetyl, trichloroacetyl or trifluoroacetyl group; a lower alkoxy lower alkylcarbonyl group such as a methoxyacetyl group; and an unsaturated alkylcarbonyl group such as a (E)-2-methyl-2-butenoyl group (preferably a C1-C6 alkanoyl group); an "aromatic acyl group", including an arylcarbonyl group such as a benzoyl, α-naphthoyl or β-naphthoyl group; a halogenoarylcarbonyl group such as a 2-bromobenzoyl or 4-chlorobenzoyl group; a lower alkylated arylcarbonyl group such as a 2,4,6-trimethylbenzoyl or 4-toluoyl group; a lower alkoxylated arylcarbonyl group such as

a 4-anisoyl group; a carboxylated arylcarbonyl group such as a 2-carboxybenzoyl, 3-carboxybenzoyl or 4-carboxybenzoyl group; a nitrated arylcarbonyl group such as a 4-nitrobenzoyl or 2-nitrobenzoyl group; a lower alkoxycarbonylated arylcarbonyl group such as a 2-(methoxycarbonyl)benzoyl group; and an arylated arylcarbonyl group such as a 4-phenylbenzoyl group; a "carbonyloxyalkyl group", including an acyloxyalkyl group such as an ethylcarbonyloxymethyl, pivaloyloxymethyl, dimethylaminoacetyloxymethyl or 1-acetoxyethyl group; a 1-(alkoxycarbonyloxy)alkyl group such as a 1-(methoxycarbonyloxy)ethyl, 1-(ethoxycarbonyloxy)ethyl, ethoxycarbonyloxymethyl, 1-(isopropoxycarbonyloxy)ethyl, 1-(t-butoxycarbonyloxy)ethyl, 1-(ethoxycarbonyloxy)propyl or 1-(cyclohexyloxycarbonyloxy)ethyl group; a phthalidyl group; and an oxodioxolenylmethyl group such as a 4-methyl-oxodioxolenylmethyl, 4-phenyl-oxodioxolenylmethyl or oxodioxolenylmethyl group; a "residual group of a salt of a succinic acid half-ester"; a "residual group of a salt of a phosphoric acid ester"; a "residual group forming an amino acid ester"; a carbamoyl group; a carbamoyl group substituted with 1 or 2 lower alkyl groups; or a "carbonyloxyalkyloxycarbonyl group" such as a pivaloyloxymethyloxycarbonyl group, and is preferably a group which forms a pharmacologically acceptable ester such as an "aliphatic acyl group" or an "aromatic acyl group", more preferably a "C1-C6 alkanoyl group" such as an acetyl, propionyl, butyryl, isobutyryl, pentanoyl or pivaloyl group; and particularly preferably an acetyl group.

When the compounds (I) of the present invention contain an amino group in their structures, the functional group employed for forming a prodrug thereof can be, for example, an aliphatic acyl group, including an alkanoyl group such as a formyl, acetyl, propionyl, butyryl, isobutyryl, pentanoyl, pivaloyl, valeryl, isovaleryl, octanoyl, lauroyl, palmitoyl or stearoyl group; a halogeno lower alkylcarbonyl group such as a chloroacetyl, dichloroacetyl, trichloroacetyl or trifluoroacetyl group; a

lower alkoxy lower alkylcarbonyl group such as a methoxyacetyl group; and an unsaturated alkylcarbonyl group such as a (E)-2-methyl-2-butenoyl group (preferably a C1-C6 alkanoyl group); an aromatic acyl group, including an arylcarbonyl group such as a benzoyl, α-naphthoyl or β-naphthoyl group, a halogenoarylcarbonyl group such as a 2-bromobenzoyl or 4-chlorobenzoyl group, a lower alkylated arylcarbonyl group such as a 2,4,6-trimethylbenzoyl or 4-toluoyl group, a lower alkoxylated arylcarbonyl group such as a 4-anisoyl group, a nitrated arylcarbonyl group such as a 4-nitrobenzoyl or 2-nitrobenzoyl group, a lower alkoxycarbonylated arylcarbonyl group such as a 2-(methoxycarbonyl)benzoyl group, and an arylated arylcarbonyl group such as a 4-phenylbenzoyl group; an alkoxycarbonyl group, including a lower alkoxycarbonyl group such as a methoxycarbonyl, ethoxycarbonyl, t-butoxycarbonyl or isobutoxycarbonyl group, and a lower alkoxycarbonyl group substituted with halogen atom(s) or tri-lower alkylsilyl group(s), such as a 2,2,2-trichloroethoxycarbonyl or 2-trimethylsilylethoxycarbonyl group; an alkenyloxycarbonyl group such as a vinyloxycarbonyl or allyloxycarbonyl group; or an aryloxycarbonyl group, of which an aryl ring may be substituted with 1 or 2 lower alkoxy group(s), nitro group(s) or halogen atom(s), such as a phenoxycarbonyl, 4-methoxyphenoxycarbonyl, 3,4-dimethoxyphenoxycarbonyl, 2-nitrophenoxycarbonyl, 4-nitrophenoxycarbonyl or 4-fluorophenoxycarbonyl group, and is preferably a C1-C6 alkanoyl group.

The "prodrug" of the compounds having the formula (I) is preferably a pharmacologically acceptable ester thereof that are prepared by converting the sulfanyl group, carboxy group or hydroxyl group contained in said compounds, respectively.

The "pharmacologically acceptable salts thereof" mean a salt that is prepared from the compounds (I) of the present invention. Such salt is preferably a metal salt, including an alkali metal salt such as sodium salt, potassium salt or lithium salt, an

alkaline earth metal salt such as calcium salt or magnesium salt, an aluminium salt, an iron salt, a zinc salt, a copper salt, a nickel salt and a cobalt salt; an amine salt, including an inorganic salt such as ammonium salt, and an organic salt such as t-octylamine salt, dibenzylamine salt, morpholine salt, glucosamine salt, phenylglycine alkyl ester salt, ethylenediamine salt, N-methylglucamine salt, guanidine salt, diethylamine salt, triethylamine salt, dicyclohexylamine salt, N,N'-dibenzylethylenediamine salt, chloroprocaine salt, procaine salt, diethanolamine salt, N-benzyl-phenethylamine salt, piperazine salt, tetramethylammonium salt or tris(hydroxymethyl)aminomethane salt; an inorganic acid salt, including a hydrohalogenic acid salt such as hydrofluoride, hydrochloride, hydrobromide or hydroiodide, a nitrate, a perchlorate, a sulfate and a phosphate; an organic acid salt, including a lower alkanesulfonate such as methanesulfonate, trifluoromethanesulfonate or ethanesulfonate, an arylsulfonate such as a benzenesulfonate or p-toluenesulfonate, an acetate, a malate, a fumarate, a succinate, a citrate, a tartrate, an oxalate, a maleate and a trifluoroacetate; or an amino acid salt such as glycine salt, lysine salt, arginine salt, ornithine salt, glutamate or aspartate, and more preferably an inorganic acid salt or an organic acid salt.

Furthermore, the compounds (I) of the present invention can exist as a hydrate or solvate thereof.

The preferred examples of the compounds of general formula (I) can be specifically shown in Tables 1-6, but the scope of the present invention should not be limited to these compounds.

The meaning of the abbreviations in the following Tables is shown below.

Ac: acetyl group,

Me: methyl group,

Et: ethyl group,

iPr: isopropyl group,

1-Pyza: pyrazol-1-yl group,

3-Pyza: pyrazol-3-yl group,

4-Pyza: pyrazol-4-yl group,

5-Pyza: pyrazol-5-yl group,

1-Triz: 1,2,3-triazol-1-yl group,

2-Triz: 1,2,3-triazol-2-yl group,

4-Triz: 1,2,3-triazol-4-yl group,

5-Triz: 1,2,3-triazol-5-yl group,

1-Tez: tetrazol-1-yl group,

2-Tez: tetrazol-2-yl group,

5-Tez: tetrazol-5-yl group,

1-Pyrd: pyrrolidino group,

1-Pip: piperidino group,

4-Pip: piperidin-4-yl group,

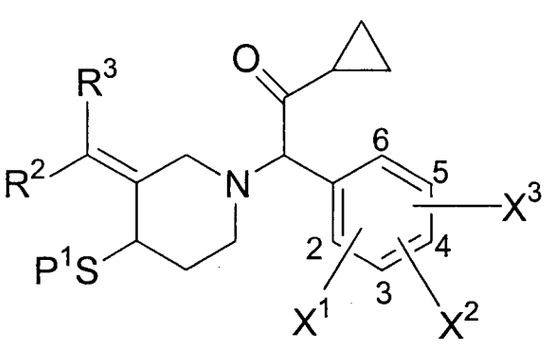
Mor: morpholino group,

Thim: thiomorpholino group,

1-Piz: piperazino group, and

2,5-dioxo-1-Pip: 2,5-dioxo-1-piperidino group.

(Table 1)



Compound No.	P^1	R^2	R^3	X^1	X^2	X^3
1-1	H	H	CH_2-1-Pyza	2-F	H	H

1-2	Ac	H	CH_2-1-Pyza	2-F	H	H
1-3	H	H	CH_2-1-Pyza	2-F	4-F	H
1-4	Ac	H	CH_2-1-Pyza	2-F	4-F	H
1-5	H	H	CH_2-(3-CO_2H-1-Pyza)	2-F	H	H
1-6	Ac	H	CH_2-(3-CO_2H-1-Pyza)	2-F	H	H
1-7	H	H	CH_2-(3-CO_2H-1-Pyza)	2-F	4-F	H
1-8	Ac	H	CH_2-(3-CO_2H-1-Pyza)	2-F	4-F	H
1-9	H	H	CH_2-(3-CO_2Me-1-Pyza)	2-F	H	H
1-10	Ac	H	CH_2-(3-CO_2Me-1-Pyza)	2-F	H	H
1-11	H	H	CH_2-(3-CO_2Me-1-Pyza)	2-F	4-F	H
1-12	Ac	H	CH_2-(3-CO_2Me-1-Pyza)	2-F	4-F	H
1-13	H	H	CH_2-(3-CO_2Et-1-Pyza)	2-F	H	H
1-14	Ac	H	CH_2-(3-CO_2Et-1-Pyza)	2-F	H	H
1-15	H	H	CH_2-(3-CO_2Et-1-Pyza)	2-F	4-F	H
1-16	Ac	H	CH_2-(3-CO_2Et-1-Pyza)	2-F	4-F	H
1-17	H	H	CH_2-(4-CO_2H-1-Pyza)	2-F	H	H
1-18	Ac	H	CH_2-(4-CO_2H-1-Pyza)	2-F	H	H
1-19	H	H	CH_2-(4-CO_2H-1-Pyza)	2-F	4-F	H
1-20	Ac	H	CH_2-(4-CO_2H-1-Pyza)	2-F	4-F	H
1-21	H	H	CH_2-(4-CO_2Me-1-Pyza)	2-F	H	H
1-22	Ac	H	CH_2-(4-CO_2Me-1-Pyza)	2-F	H	H
1-23	H	H	CH_2-(4-CO_2Me-1-Pyza)	2-F	4-F	H
1-24	Ac	H	CH_2-(4-CO_2Me-1-Pyza)	2-F	4-F	H
1-25	H	H	CH_2-(4-CO_2Et-1-Pyza)	2-F	H	H
1-26	Ac	H	CH_2-(4-CO_2Et-1-Pyza)	2-F	H	H
1-27	H	H	CH_2-(4-CO_2Et-1-Pyza)	2-F	4-F	H
1-28	Ac	H	CH_2-(4-CO_2Et-1-Pyza)	2-F	4-F	H
1-29	H	H	CH_2-(5-CO_2H-1-Pyza)	2-F	H	H
1-30	Ac	H	CH_2-(5-CO_2H-1-Pyza)	2-F	H	H
1-31	H	H	CH_2-(5-CO_2H-1-Pyza)	2-F	4-F	H
1-32	Ac	H	CH_2-(5-CO_2H-1-Pyza)	2-F	4-F	H
1-33	H	H	CH_2-(5-CO_2Me-1-Pyza)	2-F	H	H
1-34	Ac	H	CH_2-(5-CO_2Me-1-Pyza)	2-F	H	H
1-35	H	H	CH_2-(5-CO_2Me-1-Pyza)	2-F	4-F	H
1-36	Ac	H	CH_2-(5-CO_2Me-1-Pyza)	2-F	4-F	H
1-37	H	H	CH_2-(5-CO_2Et-1-Pyza)	2-F	H	H
1-38	Ac	H	CH_2-(5-CO_2Et-1-Pyza)	2-F	H	H
1-39	H	H	CH_2-(5-CO_2Et-1-Pyza)	2-F	4-F	H
1-40	Ac	H	CH_2-(5-CO_2Et-1-Pyza)	2-F	4-F	H
1-41	H	H	CH_2-(3-CH_2CO_2H-1-Pyza)	2-F	H	H
1-42	Ac	H	CH_2-(3-CH_2CO_2H-1-Pyza)	2-F	H	H
1-43	H	H	CH_2-(3-CH_2CO_2H-1-Pyza)	2-F	4-F	H
1-44	Ac	H	CH_2-(3-CH_2CO_2H-1-Pyza)	2-F	4-F	H
1-45	H	H	CH_2-(3-CH_2CO_2Me-1-Pyza)	2-F	H	H
1-46	Ac	H	CH_2-(3-CH_2CO_2Me-1-Pyza)	2-F	H	H
1-47	H	H	CH_2-(3-CH_2CO_2Me-1-Pyza)	2-F	4-F	H
1-48	Ac	H	CH_2-(3-CH_2CO_2Me-1-Pyza)	2-F	4-F	H
1-49	H	H	CH_2-(3-CH_2CO_2Et-1-Pyza)	2-F	H	H
1-50	Ac	H	CH_2-(3-CH_2CO_2Et-1-Pyza)	2-F	H	H
1-51	H	H	CH_2-(3-CH_2CO_2Et-1-Pyza)	2-F	4-F	H
1-52	Ac	H	CH_2-(3-CH_2CO_2Et-1-Pyza)	2-F	4-F	H
1-53	H	H	CH_2-(4-CH_2CO_2H-1-Pyza)	2-F	H	H
1-54	Ac	H	CH_2-(4-CH_2CO_2H-1-Pyza)	2-F	H	H
1-55	H	H	CH_2-(4-CH_2CO_2H-1-Pyza)	2-F	4-F	H
1-56	Ac	H	CH_2-(4-CH_2CO_2H-1-Pyza)	2-F	4-F	H
1-57	H	H	CH_2-(4-CH_2CO_2Me-1-Pyza)	2-F	H	H
1-58	Ac	H	CH_2-(4-CH_2CO_2Me-1-Pyza)	2-F	H	H

1-59	H	H	CH_2-(4-CH_2CO_2Me-1-Pyza)	2-F	4-F	H
1-60	Ac	H	CH_2-(4-CH_2CO_2Me-1-Pyza)	2-F	4-F	H
1-61	H	H	CH_2-(4-CH_2CO_2Et-1-Pyza)	2-F	H	H
1-62	Ac	H	CH_2-(4-CH_2CO_2Et-1-Pyza)	2-F	H	H
1-63	H	H	CH_2-(4-CH_2CO_2Et-1-Pyza)	2-F	4-F	H
1-64	Ac	H	CH_2-(4-CH_2CO_2Et-1-Pyza)	2-F	4-F	H
1-65	H	H	CH_2-(5-CH_2CO_2H-1-Pyza)	2-F	H	H
1-66	Ac	H	CH_2-(5-CH_2CO_2H-1-Pyza)	2-F	H	H
1-67	H	H	CH_2-(5-CH_2CO_2H-1-Pyza)	2-F	4-F	H
1-68	Ac	H	CH_2-(5-CH_2CO_2H-1-Pyza)	2-F	4-F	H
1-69	H	H	CH_2-(5-CH_2CO_2Me-1-Pyza)	2-F	H	H
1-70	Ac	H	CH_2-(5-CH_2CO_2Me-1-Pyza)	2-F	H	H
1-71	H	H	CH_2-(5-CH_2CO_2Me-1-Pyza)	2-F	4-F	H
1-72	Ac	H	CH_2-(5-CH_2CO_2Me-1-Pyza)	2-F	4-F	H
1-73	H	H	CH_2-(5-CH_2CO_2Et-1-Pyza)	2-F	H	H
1-74	Ac	H	CH_2-(5-CH_2CO_2Et-1-Pyza)	2-F	H	H
1-75	H	H	CH_2-(5-CH_2CO_2Et-1-Pyza)	2-F	4-F	H
1-76	Ac	H	CH_2-(5-CH_2CO_2Et-1-Pyza)	2-F	4-F	H
1-77	H	H	CH_2-(3-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
1-78	Ac	H	CH_2-(3-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
1-79	H	H	CH_2-(3-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
1-80	Ac	H	CH_2-(3-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
1-81	H	H	CH_2-(3-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
1-82	Ac	H	CH_2-(3-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
1-83	H	H	CH_2-(4-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
1-84	Ac	H	CH_2-(4-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
1-85	H	H	CH_2-(4-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
1-86	Ac	H	CH_2-(4-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
1-87	H	H	CH_2-(4-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
1-88	Ac	H	CH_2-(4-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
1-89	H	H	CH_2-(5-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
1-90	Ac	H	CH_2-(5-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
1-91	H	H	CH_2-(5-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
1-92	Ac	H	CH_2-(5-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
1-93	H	H	CH_2-(5-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
1-94	Ac	H	CH_2-(5-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
1-95	H	H	CH_2-(3-$CH_2CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
1-96	Ac	H	CH_2-(3-$CH_2CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
1-97	H	H	CH_2-(3-$CH_2CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
1-98	Ac	H	CH_2-(3-$CH_2CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
1-99	H	H	CH_2-(3-$CH_2CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
1-100	Ac	H	CH_2-(3-$CH_2CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
1-101	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
1-102	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
1-103	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
1-104	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
1-105	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
1-106	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
1-107	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
1-108	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
1-109	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
1-110	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
1-111	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
1-112	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
1-113	H	H	CH_2CH_2-1-Pyza	2-F	H	H
1-114	Ac	H	CH_2CH_2-1-Pyza	2-F	H	H
1-115	H	H	CH_2CH_2-(3-CO_2H-1-Pyza)	2-F	H	H

1-116	Ac	H	CH_2CH_2-(3-CO_2H-1-Pyza)	2-F	H	H
1-117	H	H	CH_2CH_2-(3-CO_2Me-1-Pyza)	2-F	H	H
1-118	Ac	H	CH_2CH_2-(3-CO_2Me-1-Pyza)	2-F	H	H
1-119	H	H	CH_2CH_2-(3-CO_2Et-1-Pyza)	2-F	H	H
1-120	Ac	H	CH_2CH_2-(3-CO_2Et-1-Pyza)	2-F	H	H
1-121	H	H	CH_2CH_2-(4-CO_2H-1-Pyza)	2-F	H	H
1-122	Ac	H	CH_2CH_2-(4-CO_2H-1-Pyza)	2-F	H	H
1-123	H	H	CH_2CH_2-(4-CO_2Me-1-Pyza)	2-F	H	H
1-124	Ac	H	CH_2CH_2-(4-CO_2Me-1-Pyza)	2-F	H	H
1-125	H	H	CH_2CH_2-(4-CO_2Et-1-Pyza)	2-F	H	H
1-126	Ac	H	CH_2CH_2-(4-CO_2Et-1-Pyza)	2-F	H	H
1-127	H	H	CH_2CH_2-(5-CO_2H-1-Pyza)	2-F	H	H
1-128	Ac	H	CH_2CH_2-(5-CO_2H-1-Pyza)	2-F	H	H
1-129	H	H	CH_2CH_2-(5-CO_2Me-1-Pyza)	2-F	H	H
1-130	Ac	H	CH_2CH_2-(5-CO_2Me-1-Pyza)	2-F	H	H
1-131	H	H	CH_2CH_2-(5-CO_2Et-1-Pyza)	2-F	H	H
1-132	Ac	H	CH_2CH_2-(5-CO_2Et-1-Pyza)	2-F	H	H
1-133	H	H	CH_2CH_2-(3-CH_2CO_2H-1-Pyza)	2-F	H	H
1-134	Ac	H	CH_2CH_2-(3-CH_2CO_2H-1-Pyza)	2-F	H	H
1-135	H	H	CH_2CH_2-(3-CH_2CO_2Me-1-Pyza)	2-F	H	H
1-136	Ac	H	CH_2CH_2-(3-CH_2CO_2Me-1-Pyza)	2-F	H	H
1-137	H	H	CH_2CH_2-(3-CH_2CO_2Et-1-Pyza)	2-F	H	H
1-138	Ac	H	CH_2CH_2-(3-CH_2CO_2Et-1-Pyza)	2-F	H	H
1-139	H	H	CH_2CH_2-(4-CH_2CO_2H-1-Pyza)	2-F	H	H
1-140	Ac	H	CH_2CH_2-(4-CH_2CO_2H-1-Pyza)	2-F	H	H
1-141	H	H	CH_2CH_2-(4-CH_2CO_2Me-1-Pyza)	2-F	H	H
1-142	Ac	H	CH_2CH_2-(4-CH_2CO_2Me-1-Pyza)	2-F	H	H
1-143	H	H	CH_2CH_2-(4-CH_2CO_2Et-1-Pyza)	2-F	H	H
1-144	Ac	H	CH_2CH_2-(4-CH_2CO_2Et-1-Pyza)	2-F	H	H
1-145	H	H	CH_2CH_2-(5-CH_2CO_2H-1-Pyza)	2-F	H	H
1-146	Ac	H	CH_2CH_2-(5-CH_2CO_2H-1-Pyza)	2-F	H	H
1-147	H	H	CH_2CH_2-(5-CH_2CO_2Me-1-Pyza)	2-F	H	H
1-148	Ac	H	CH_2CH_2-(5-CH_2CO_2Me-1-Pyza)	2-F	H	H
1-149	H	H	CH_2CH_2-(5-CH_2CO_2Et-1-Pyza)	2-F	H	H
1-150	Ac	H	CH_2CH_2-(5-CH_2CO_2Et-1-Pyza)	2-F	H	H
1-151	H	H	CH_2CH_2-(3-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
1-152	Ac	H	CH_2CH_2-(3-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
1-153	H	H	CH_2CH_2-(3-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
1-154	Ac	H	CH_2CH_2-(3-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
1-155	H	H	CH_2CH_2-(3-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
1-156	Ac	H	CH_2CH_2-(3-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
1-157	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
1-158	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
1-159	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
1-160	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
1-161	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
1-162	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
1-163	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
1-164	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
1-165	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
1-166	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
1-167	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2Et$-1-Pyza	2-F	H	H
1-168	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
1-169	H	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
1-170	Ac	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
1-171	H	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
1-172	Ac	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H

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1-173	H	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
1-174	Ac	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
1-175	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
1-176	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
1-177	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
1-178	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
1-179	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
1-180	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
1-181	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
1-182	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
1-183	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
1-184	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
1-185	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
1-186	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
1-187	H	H	CH_2-3-Pyza	2-F	H	H
1-188	Ac	H	CH_2-3-Pyza	2-F	H	H
1-189	H	H	CH_2-3-Pyza	2-F	4-F	H
1-190	Ac	H	CH_2-3-Pyza	2-F	4-F	H
1-191	H	H	CH_2-(1-CO_2Me-3-Pyza)	2-F	H	H
1-192	Ac	H	CH_2-(1-CO_2Me-3-Pyza)	2-F	H	H
1-193	H	H	CH_2-(1-CO_2Et-3-Pyza)	2-F	H	H
1-194	Ac	H	CH_2-(1-CO_2Et-3-Pyza)	2-F	H	H
1-195	H	H	CH_2-(4-CO_2H-3-Pyza)	2-F	H	H
1-196	Ac	H	CH_2-(4-CO_2H-3-Pyza)	2-F	H	H
1-197	H	H	CH_2-(4-CO_2Me-3-Pyza)	2-F	H	H
1-198	Ac	H	CH_2-(4-CO_2Me-3-Pyza)	2-F	H	H
1-199	H	H	CH_2-(4-CO_2Et-3-Pyza)	2-F	H	H
1-200	Ac	H	CH_2-(4-CO_2Et-3-Pyza)	2-F	H	H
1-201	H	H	CH_2-(5-CO_2H-3-Pyza)	2-F	H	H
1-202	Ac	H	CH_2-(5-CO_2H-3-Pyza)	2-F	H	H
1-203	H	H	CH_2-(5-CO_2Me-3-Pyza)	2-F	H	H
1-204	Ac	H	CH_2-(5-CO_2Me-3-Pyza)	2-F	H	H
1-205	H	H	CH_2-(5-CO_2Et-3-Pyza)	2-F	H	H
1-206	Ac	H	CH_2-(5-CO_2Et-3-Pyza)	2-F	H	H
1-207	H	H	CH_2-(1-CH_2CO_2H-3-Pyza)	2-F	H	H
1-208	Ac	H	CH_2-(1-CH_2CO_2H-3-Pyza)	2-F	H	H
1-209	H	H	CH_2-(1-CH_2CO_2Me-3-Pyza)	2-F	H	H
1-210	Ac	H	CH_2-(1-CH_2CO_2Me-3-Pyza)	2-F	H	H
1-211	H	H	CH_2-(1-CH_2CO_2Et-3-Pyza)	2-F	H	H
1-212	Ac	H	CH_2-(1-CH_2CO_2Et-3-Pyza)	2-F	H	H
1-213	H	H	CH_2-(4-CH_2CO_2H-3-Pyza)	2-F	H	H
1-214	Ac	H	CH_2-(4-CH_2CO_2H-3-Pyza)	2-F	H	H
1-215	H	H	CH_2-(4-CH_2CO_2Me-3-Pyza)	2-F	H	H
1-216	Ac	H	CH_2-(4-CH_2CO_2Me-3-Pyza)	2-F	H	H
1-217	H	H	CH_2-(4-CH_2CO_2Et-3-Pyza)	2-F	H	H
1-218	Ac	H	CH_2-(4-CH_2CO_2Et-3-Pyza)	2-F	H	H
1-219	H	H	CH_2-(5-CH_2CO_2H-3-Pyza)	2-F	H	H
1-220	Ac	H	CH_2-(5-CH_2CO_2H-3-Pyza)	2-F	H	H
1-221	H	H	CH_2-(5-CH_2CO_2Me-3-Pyza)	2-F	H	H
1-222	Ac	H	CH_2-(5-CH_2CO_2Me-3-Pyza)	2-F	H	H
1-223	H	H	CH_2-(5-CH_2CO_2Et-3-Pyza)	2-F	H	H
1-224	Ac	H	CH_2-(5-CH_2CO_2Et-3-Pyza)	2-F	H	H
1-225	H	H	CH_2-(1-$CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
1-226	Ac	H	CH_2-(1-$CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
1-227	H	H	CH_2-(1-$CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
1-228	Ac	H	CH_2-(1-$CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
1-229	H	H	CH_2-(1-$CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H

1-230	Ac	H	CH_2-(1-$CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
1-231	H	H	CH_2-(4-$CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
1-232	Ac	H	CH_2-(4-$CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
1-233	H	H	CH_2-(4-$CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
1-234	Ac	H	CH_2-(4-$CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
1-235	H	H	CH_2-(4-$CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
1-236	Ac	H	CH_2-(4-$CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
1-237	H	H	CH_2-(5-$CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
1-238	Ac	H	CH_2-(5-$CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
1-239	H	H	CH_2-(5-$CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
1-240	Ac	H	CH_2-(5-$CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
1-241	H	H	CH_2-(5-$CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
1-242	Ac	H	CH_2-(5-$CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
1-245	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
1-246	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
1-247	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
1-248	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
1-249	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
1-250	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
1-251	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
1-252	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
1-253	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
1-254	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
1-255	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
1-256	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
1-257	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
1-258	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
1-259	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
1-260	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
1-261	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
1-262	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
1-263	H	H	CH_2CH_2-3-Pyza	2-F	H	H
1-264	Ac	H	CH_2CH_2-3-Pyza	2-F	H	H
1-265	H	H	CH_2CH_2-3-Pyza	2-F	4-F	H
1-266	Ac	H	CH_2CH_2-3-Pyza	2-F	4-F	H
1-267	H	H	CH_2CH_2-(1-CO_2Me-3-Pyza)	2-F	H	H
1-268	Ac	H	CH_2CH_2-(1-CO_2Me-3-Pyza)	2-F	H	H
1-269	H	H	CH_2CH_2-(1-CO_2Et-3-Pyza)	2-F	H	H
1-270	Ac	H	CH_2CH_2-(1-CO_2Et-3-Pyza)	2-F	H	H
1-271	H	H	CH_2CH_2-(4-CO_2H-3-Pyza)	2-F	H	H
1-272	Ac	H	CH_2CH_2-(4-CO_2H-3-Pyza)	2-F	H	H
1-273	H	H	CH_2CH_2-(4-CO_2Me-3-Pyza)	2-F	H	H
1-274	Ac	H	CH_2CH_2-(4-CO_2Me-3-Pyza)	2-F	H	H
1-275	H	H	CH_2CH_2-(4-CO_2Et-3-Pyza)	2-F	H	H
1-276	Ac	H	CH_2CH_2-(4-CO_2Et-3-Pyza)	2-F	H	H
1-277	H	H	CH_2CH_2-(5-CO_2H-3-Pyza)	2-F	H	H
1-278	Ac	H	CH_2CH_2-(5-CO_2H-3-Pyza)	2-F	H	H
1-279	H	H	CH_2CH_2-(5-CO_2Me-3-Pyza)	2-F	H	H
1-280	Ac	H	CH_2CH_2-(5-CO_2Me-3-Pyza)	2-F	H	H
1-281	H	H	CH_2CH_2-(5-CO_2Et-3-Pyza)	2-F	H	H
1-282	Ac	H	CH_2CH_2-(5-CO_2Et-3-Pyza)	2-F	H	H
1-283	H	H	CH_2CH_2-(1-CH_2CO_2H-3-Pyza)	2-F	H	H
1-284	Ac	H	CH_2CH_2-(1-CH_2CO_2H-3-Pyza)	2-F	H	H
1-285	H	H	CH_2CH_2-(1-CH_2CO_2Me-3-Pyza)	2-F	H	H
1-286	Ac	H	CH_2CH_2-(1-CH_2CO_2Me-3-Pyza)	2-F	H	H
1-287	H	H	CH_2CH_2-(1-CH_2CO_2Et-3-Pyza)	2-F	H	H
1-288	Ac	H	CH_2CH_2-(1-CH_2CO_2Et-3-Pyza)	2-F	H	H

1-289	H	H	CH_2CH_2-(4-CH_2CO_2H-3-Pyza)	2-F	H	H
1-290	Ac	H	CH_2CH_2-(4-CH_2CO_2H-3-Pyza)	2-F	H	H
1-291	H	H	CH_2CH_2-(4-CH_2CO_2Me-3-Pyza)	2-F	H	H
1-292	Ac	H	CH_2CH_2-(4-CH_2CO_2Me-3-Pyza)	2-F	H	H
1-293	H	H	CH_2CH_2-(4-CH_2CO_2Et-3-Pyza)	2-F	H	H
1-294	Ac	H	CH_2CH_2-(4-CH_2CO_2Et-3-Pyza)	2-F	H	H
1-295	H	H	CH_2CH_2-(5-CH_2CO_2H-3-Pyza)	2-F	H	H
1-296	Ac	H	CH_2CH_2-(5-CH_2CO_2H-3-Pyza)	2-F	H	H
1-297	H	H	CH_2CH_2-(5-CH_2CO_2Me-3-Pyza)	2-F	H	H
1-298	Ac	H	CH_2CH_2-(5-CH_2CO_2Me-3-Pyza)	2-F	H	H
1-299	H	H	CH_2CH_2-(5-CH_2CO_2Et-3-Pyza)	2-F	H	H
1-300	Ac	H	CH_2CH_2-(5-CH_2CO_2Et-3-Pyza)	2-F	H	H
1-301	H	H	CH_2CH_2-(1-$CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
1-302	Ac	H	CH_2CH_2-(1-$CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
1-303	H	H	CH_2CH_2-(1-$CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
1-304	Ac	H	CH_2CH_2-(1-$CH_2CH_2CO_2Me$-3-Pyza	2-F	H	H
1-305	H	H	CH_2CH_2-(1-$CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
1-306	Ac	H	CH_2CH_2-(1-$CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
1-307	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
1-308	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
1-309	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
1-310	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-3-Pyza	2-F	H	H
1-311	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
1-312	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
1-313	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
1-314	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
1-315	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
1-316	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
1-317	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
1-318	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
1-319	H	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
1-320	Ac	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
1-321	H	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
1-322	Ac	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
1-323	H	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
1-324	Ac	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
1-325	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
1-326	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
1-327	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
1-328	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
1-329	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
1-330	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
1-331	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
1-332	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
1-333	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
1-334	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
1-335	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
1-336	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
1-337	H	H	CH_2-4-Pyza	2-F	H	H
1-338	Ac	H	CH_2-4-Pyza	2-F	H	H
1-339	H	H	CH_2-4-Pyza	2-F	4-F	H
1-340	Ac	H	CH_2-4-Pyza	2-F	4-F	H
1-341	H	H	CH_2-(1-CO_2Me-4-Pyza)	2-F	H	H
1-342	Ac	H	CH_2-(1-CO_2Me-4-Pyza)	2-F	H	H
1-343	H	H	CH_2-(1-CO_2Et-4-Pyza)	2-F	H	H
1-344	Ac	H	CH_2-(1-CO_2Et-4-Pyza)	2-F	H	H
1-345	H	H	CH_2-(3-CO_2H-4-Pyza)	2-F	H	H

1-346	Ac	H	CH_2-(3-CO_2H-4-Pyza)	2-F	H	H
1-347	H	H	CH_2-(3-CO_2Me-4-Pyza)	2-F	H	H
1-348	Ac	H	CH_2-(3-CO_2Me-4-Pyza)	2-F	H	H
1-349	H	H	CH_2-(3-CO_2Et-4-Pyza)	2-F	H	H
1-350	Ac	H	CH_2-(3-CO_2Et-4-Pyza)	2-F	H	H
1-351	H	H	CH_2-(1-CH_2CO_2H-4-Pyza)	2-F	H	H
1-352	Ac	H	CH_2-(1-CH_2CO_2H-4-Pyza)	2-F	H	H
1-353	H	H	CH_2-(1-CH_2CO_2Me-4-Pyza)	2-F	H	H
1-354	Ac	H	CH_2-(1-CH_2CO_2Me-4-Pyza)	2-F	H	H
1-355	H	H	CH_2-(1-CH_2CO_2Et-4-Pyza)	2-F	H	H
1-356	Ac	H	CH_2-(1-CH_2CO_2Et-4-Pyza)	2-F	H	H
1-357	H	H	CH_2-(3-CH_2CO_2H-4-Pyza)	2-F	H	H
1-358	Ac	H	CH_2-(3-CH_2CO_2H-4-Pyza)	2-F	H	H
1-359	H	H	CH_2-(3-CH_2CO_2Me-4-Pyza)	2-F	H	H
1-360	Ac	H	CH_2-(3-CH_2CO_2Me-4-Pyza)	2-F	H	H
1-361	H	H	CH_2-(3-CH_2CO_2Et-4-Pyza)	2-F	H	H
1-362	Ac	H	CH_2-(3-CH_2CO_2Et-4-Pyza)	2-F	H	H
1-363	H	H	CH_2-(1-$CH_2CH_2CO_2H$-4-Pyza)	2-F	H	H
1-364	Ac	H	CH_2-(1-$CH_2CH_2CO_2H$-4-Pyza)	2-F	H	H
1-365	H	H	CH_2-(1-$CH_2CH_2CO_2Me$-4-Pyza)	2-F	H	H
1-366	Ac	H	CH_2-(1-$CH_2CH_2CO_2Me$-4-Pyza)	2-F	H	H
1-367	H	H	CH_2-(1-$CH_2CH_2CO_2Et$-4-Pyza)	2-F	H	H
1-368	Ac	H	CH_2-(1-$CH_2CH_2CO_2Et$-4-Pyza)	2-F	H	H
1-369	H	H	CH_2-(3-$CH_2CH_2CO_2H$-4-Pyza)	2-F	H	H
1-370	Ac	H	CH_2-(3-$CH_2CH_2CO_2H$-4-Pyza)	2-F	H	H
1-371	H	H	CH_2-(3-$CH_2CH_2CO_2Me$-4-Pyza)	2-F	H	H
1-372	Ac	H	CH_2-(3-$CH_2CH_2CO_2Me$-4-Pyza)	2-F	H	H
1-373	H	H	CH_2-(3-$CH_2CH_2CO_2Et$-4-Pyza)	2-F	H	H
1-374	Ac	H	CH_2-(3-$CH_2CH_2CO_2Et$-4-Pyza)	2-F	H	H
1-375	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2H$-4-Pyza)	2-F	H	H
1-376	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2H$-4-Pyza)	2-F	H	H
1-377	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2Me$-4-Pyza)	2-F	H	H
1-378	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2Me$-4-Pyza)	2-F	H	H
1-379	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2Et$-4-Pyza)	2-F	H	H
1-380	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2Et$-4-Pyza)	2-F	H	H
1-381	H	H	CH_2-(3-$CH_2CH_2CH_2CO_2H$-4-Pyza)	2-F	H	H
1-382	Ac	H	CH_2-(3-$CH_2CH_2CH_2CO_2H$-4-Pyza)	2-F	H	H
1-383	H	H	CH_2-(3-$CH_2CH_2CH_2CO_2Me$-4-Pyza)	2-F	H	H
1-384	Ac	H	CH_2-(3-$CH_2CH_2CH_2CO_2Me$-4-Pyza)	2-F	H	H
1-385	H	H	CH_2-(3-$CH_2CH_2CH_2CO_2Et$-4-Pyza)	2-F	H	H
1-386	Ac	H	CH_2-(3-$CH_2CH_2CH_2CO_2Et$-4-Pyza)	2-F	H	H
1-387	H	H	CH_2CH_2-4-Pyza	2-F	H	H
1-388	Ac	H	CH_2CH_2-4-Pyza	2-F	H	H
1-389	H	H	CH_2CH_2-4-Pyza	2-F	4-F	H
1-390	Ac	H	CH_2CH_2-4-Pyza	2-F	4-F	H
1-391	H	H	CH_2CH_2-(1-CO_2Me-4-Pyza)	2-F	H	H
1-392	Ac	H	CH_2CH_2-(1-CO_2Me-4-Pyza)	2-F	H	H
1-393	H	H	CH_2CH_2-(1-CO_2Et-4-Pyza)	2-F	H	H
1-394	Ac	H	CH_2CH_2-(1-CO_2Et-4-Pyza)	2-F	H	H
1-395	H	H	CH_2CH_2-(3-CO_2H-4-Pyza)	2-F	H	H
1-396	Ac	H	CH_2CH_2-(3-CO_2H-4-Pyza)	2-F	H	H
1-397	H	H	CH_2CH_2-(3-CO_2Me-4-Pyza)	2-F	H	H
1-398	Ac	H	CH_2CH_2-(3-CO_2Me-4-Pyza)	2-F	H	H
1-399	H	H	CH_2CH_2-(3-CO_2Et-4-Pyza)	2-F	H	H
1-400	Ac	H	CH_2CH_2-(3-CO_2Et-4-Pyza)	2-F	H	H
1-401	H	H	CH_2CH_2-(1-CH_2CO_2H-4-Pyza)	2-F	H	H
1-402	Ac	H	CH_2CH_2-(1-CH_2CO_2H-4-Pyza)	2-F	H	H

1-403	H	H	CH_2CH_2-(1-CH_2CO_2Me-4-Pyza)	2-F	H	H
1-404	Ac	H	CH_2CH_2-(1-CH_2CO_2Me-4-Pyza)	2-F	H	H
1-405	H	H	CH_2CH_2-(1-CH_2CO_2Et-4-Pyza)	2-F	H	H
1-406	Ac	H	CH_2CH_2-(1-CH_2CO_2Et-4-Pyza)	2-F	H	H
1-407	H	H	CH_2CH_2-(3-CH_2CO_2H-4-Pyza)	2-F	H	H
1-408	Ac	H	CH_2CH_2-(3-CH_2CO_2H-4-Pyza)	2-F	H	H
1-409	H	H	CH_2CH_2-(3-CH_2CO_2Me-4-Pyza)	2-F	H	H
1-410	Ac	H	CH_2CH_2-(3-CH_2CO_2Me-4-Pyza)	2-F	H	H
1-411	H	H	CH_2CH_2-(3-CH_2CO_2Et-4-Pyza)	2-F	H	H
1-412	Ac	H	CH_2CH_2-(3-CH_2CO_2Et-4-Pyza)	2-F	H	H
1-413	H	H	CH_2CH_2-(1-$CH_2CH_2CO_2H$-4-Pyza)	2-F	H	H
1-414	Ac	H	CH_2CH_2-(1-$CH_2CH_2CO_2H$-4-Pyza)	2-F	H	H
1-415	H	H	CH_2CH_2-(1-$CH_2CH_2CO_2Me$-4-Pyza)	2-F	H	H
1-416	Ac	H	CH_2CH_2-(1-$CH_2CH_2CO_2Me$-4-Pyza)	2-F	H	H
1-417	H	H	CH_2CH_2-(1-$CH_2CH_2CO_2Et$-4-Pyza)	2-F	H	H
1-418	Ac	H	CH_2CH_2-(1-$CH_2CH_2CO_2Et$-4-Pyza)	2-F	H	H
1-419	H	H	CH_2CH_2-(3-$CH_2CH_2CO_2H$-4-Pyza)	2-F	H	H
1-420	Ac	H	CH_2CH_2-(3-$CH_2CH_2CO_2H$-4-Pyza)	2-F	H	H
1-421	H	H	CH_2CH_2-(3-$CH_2CH_2CO_2Me$-4-Pyza)	2-F	H	H
1-422	Ac	H	CH_2CH_2-(3-$CH_2CH_2CO_2Me$-4-Pyza)	2-F	H	H
1-423	H	H	CH_2CH_2-(3-$CH_2CH_2CO_2Et$-4-Pyza)	2-F	H	H
1-424	Ac	H	CH_2CH_2-(3-$CH_2CH_2CO_2Et$-4-Pyza)	2-F	H	H
1-425	H	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2H$-4-Pyza)	2-F	H	H
1-426	Ac	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2H$-4-Pyza)	2-F	H	H
1-427	H	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Me$-4-Pyza)	2-F	H	H
1-428	Ac	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Me$-4-Pyza)	2-F	H	H
1-429	H	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Et$-4-Pyza)	2-F	H	H
1-430	Ac	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Et$-4-Pyza)	2-F	H	H
1-431	H	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2H$-4-Pyza)	2-F	H	H
1-432	Ac	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2H$-4-Pyza)	2-F	H	H
1-433	H	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2Me$-4-Pyza)	2-F	H	H
1-434	Ac	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2Me$-4-Pyza)	2-F	H	H
1-435	H	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2Et$-4-Pyza)	2-F	H	H
1-436	Ac	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2Et$-4-Pyza)	2-F	H	H
1-437	H	H	CH_2-(1-CO_2Me-5-Pyza)	2-F	4-F	H
1-438	Ac	H	CH_2-(1-CO_2Me-5-Pyza)	2-F	4-F	H
1-439	H	H	CH_2-(1-CO_2Me-5-Pyza)	2-F	H	H
1-440	Ac	H	CH_2-(1-CO_2Me-5-Pyza)	2-F	H	H
1-441	H	H	CH_2-(1-CO_2Et-5-Pyza)	2-F	H	H
1-442	Ac	H	CH_2-(1-CO_2Et-5-Pyza)	2-F	H	H
1-443	H	H	CH_2-(1-CH_2CO_2H-5-Pyza)	2-F	H	H
1-444	Ac	H	CH_2-(1-CH_2CO_2H-5-Pyza)	2-F	H	H
1-445	H	H	CH_2-(1-CH_2CO_2Me-5-Pyza)	2-F	H	H
1-446	Ac	H	CH_2-(1-CH_2CO_2Me-5-Pyza)	2-F	H	H
1-447	H	H	CH_2-(1-CH_2CO_2Et-5-Pyza)	2-F	H	H
1-448	Ac	H	CH_2-(1-CH_2CO_2Et-5-Pyza)	2-F	H	H
1-449	H	H	CH_2-(1-$CH_2CH_2CO_2H$-5-Pyza)	2-F	H	H
1-450	Ac	H	CH_2-(1-$CH_2CH_2CO_2H$-5-Pyza)	2-F	H	H
1-451	H	H	CH_2-(1-$CH_2CH_2CO_2Me$-5-Pyza)	2-F	H	H
1-452	Ac	H	CH_2-(1-$CH_2CH_2CO_2Me$-5-Pyza)	2-F	H	H
1-453	H	H	CH_2-(1-$CH_2CH_2CO_2Et$-5-Pyza)	2-F	H	H
1-454	Ac	H	CH_2-(1-$CH_2CH_2CO_2Et$-5-Pyza)	2-F	H	H
1-455	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2H$-5-Pyza)	2-F	H	H
1-456	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2H$-5-Pyza)	2-F	H	H
1-457	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2Me$-5-Pyza)	2-F	H	H
1-458	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2Me$-5-Pyza)	2-F	H	H
1-459	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2Et$-5-Pyza)	2-F	H	H

1-460	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2Et$-5-Pyza)	2-F	H	H
1-461	H	H	CH_2CH_2-(1-CO_2Me-5-Pyza)	2-F	4-F	H
1-462	Ac	H	CH_2CH_2-(1-CO_2Me-5-Pyza)	2-F	4-F	H
1-463	H	H	CH_2CH_2-(1-CO_2Me-5-Pyza)	2-F	H	H
1-464	Ac	H	CH_2CH_2-(1-CO_2Me-5-Pyza)	2-F	H	H
1-465	H	H	CH_2CH_2-(1-CO_2Et-5-Pyza)	2-F	H	H
1-466	Ac	H	CH_2CH_2-(1-CO_2Et-5-Pyza)	2-F	H	H
1-467	H	H	CH_2CH_2-(1-CH_2CO_2H-5-Pyza)	2-F	H	H
1-468	Ac	H	CH_2CH_2-(1-CH_2CO_2H-5-Pyza)	2-F	H	H
1-469	H	H	CH_2CH_2-(1-CH_2CO_2Me-5-Pyza)	2-F	H	H
1-470	Ac	H	CH_2CH_2-(1-CH_2CO_2Me-5-Pyza)	2-F	H	H
1-471	H	H	CH_2CH_2-(1-CH_2CO_2Et-5-Pyza)	2-F	H	H
1-472	Ac	H	CH_2CH_2-(1-CH_2CO_2Et-5-Pyza)	2-F	H	H
1-473	H	H	CH_2CH_2-(1-$CH_2CH_2CO_2H$-5-Pyza)	2-F	H	H
1-474	Ac	H	CH_2CH_2-(1-$CH_2CH_2CO_2H$-5-Pyza)	2-F	H	H
1-475	H	H	CH_2CH_2-(1-$CH_2CH_2CO_2Me$-5-Pyza)	2-F	H	H
1-476	Ac	H	CH_2CH_2-(1-$CH_2CH_2CO_2Me$-5-Pyza)	2-F	H	H
1-477	H	H	CH_2CH_2-(1-$CH_2CH_2CO_2Et$-5-Pyza)	2-F	H	H
1-478	Ac	H	CH_2CH_2-(1-$CH_2CH_2CO_2Et$-5-Pyza)	2-F	H	H
1-479	H	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2H$-5-Pyza)	2-F	H	H
1-480	Ac	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2H$-5-Pyza)	2-F	H	H
1-481	H	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Me$-5-Pyza)	2-F	H	H
1-482	Ac	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Me$-5-Pyza)	2-F	H	H
1-483	H	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Et$-5-Pyza)	2-F	H	H
1-484	Ac	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Et$-5-Pyza)	2-F	H	H
1-485	H	H	CH_2-1-Triz	2-F	H	H
1-486	Ac	H	CH_2-1-Triz	2-F	H	H
1-487	H	H	CH_2-(4-CO_2H-1-Triz)	2-F	H	H
1-488	Ac	H	CH_2-(4-CO_2H-1-Triz)	2-F	H	H
1-489	H	H	CH_2-(4-CO_2Me-1-Triz)	2-F	H	H
1-490	Ac	H	CH_2-(4-CO_2Me-1-Triz)	2-F	H	H
1-491	H	H	CH_2-(4-CO_2Et-1-Triz)	2-F	H	H
1-492	Ac	H	CH_2-(4-CO_2Et-1-Triz)	2-F	H	H
1-493	H	H	CH_2-(5-CO_2H-1-Triz)	2-F	H	H
1-494	Ac	H	CH_2-(5-CO_2H-1-Triz)	2-F	H	H
1-495	H	H	CH_2-(5-CO_2Me-1-Triz)	2-F	H	H
1-496	Ac	H	CH_2-(5-CO_2Me-1-Triz)	2-F	H	H
1-497	H	H	CH_2-(5-CO_2Et-1-Triz)	2-F	H	H
1-498	Ac	H	CH_2-(5-CO_2Et-1-Triz)	2-F	H	H
1-499	H	H	CH_2-(4-CH_2CO_2H-1-Triz)	2-F	H	H
1-500	Ac	H	CH_2-(4-CH_2CO_2H-1-Triz)	2-F	H	H
1-501	H	H	CH_2-(4-CH_2CO_2Me-1-Triz)	2-F	H	H
1-502	Ac	H	CH_2-(4-CH_2CO_2Me-1-Triz)	2-F	H	H
1-503	H	H	CH_2-(4-CH_2CO_2Et-1-Triz)	2-F	H	H
1-504	Ac	H	CH_2-(4-CH_2CO_2Et-1-Triz)	2-F	H	H
1-505	H	H	CH_2-(5-CH_2GO_2H-1-Triz)	2-F	H	H
1-506	Ac	H	CH_2-(5-CH_2CO_2H-1-Triz)	2-F	H	H
1-507	H	H	CH_2-(5-CH_2CO_2Me-1-Triz)	2-F	H	H
1-508	Ac	H	CH_2-(5-CH_2CO_2Me-1-Triz)	2-F	H	H
1-509	H	H	CH_2-(5-CH_2CO_2Et-1-Triz)	2-F	H	H
1-510	Ac	H	CH_2-(5-CH_2CO_2Et-1-Triz)	2-F	H	H
1-511	H	H	CH_2-(4-$CH_2CH_2CO_2H$-1-Triz)	2-F	H	H
1-512	Ac	H	CH_2-(4-$CH_2CH_2CO_2H$-1-Triz)	2-F	H	H
1-513	H	H	CH_2-(4-$CH_2CH_2CO_2Me$-1-Triz)	2-F	H	H
1-514	Ac	H	CH_2-(4-$CH_2CH_2CO_2Me$-1-Triz)	2-F	H	H
1-515	H	H	CH_2-(4-$CH_2CH_2CO_2Et$-1-Triz)	2-F	H	H
1-516	Ac	H	CH_2-(4-$CH_2CH_2CO_2Et$-1-Triz)	2-F	H	H

1-517	H	H	CH_2-(5-$CH_2CH_2CO_2H$-1-Triz)	2-F	H	H
1-518	Ac	H	CH_2-(5-$CH_2CH_2CO_2H$-1-Triz)	2-F	H	H
1-519	H	H	CH_2-(5-$CH_2CH_2CO_2Me$-1-Triz)	2-F	H	H
1-520	Ac	H	CH_2-(5-$CH_2CH_2CO_2Me$-1-Triz)	2-F	H	H
1-521	H	H	CH_2-(5-$CH_2CH_2CO_2Et$-1-Triz)	2-F	H	H
1-522	Ac	H	CH_2-(5-$CH_2CH_2CO_2Et$-1-Triz)	2-F	H	H
1-523	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2H$-1-Triz)	2-F	H	H
1-524	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2H$-1-Triz)	2-F	H	H
1-525	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2Me$-1-Triz)	2-F	H	H
1-526	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2Me$-1-Triz)	2-F	H	H
1-527	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2Et$-1-Triz)	2-F	H	H
1-528	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2Et$-1-Triz)	2-F	H	H
1-529	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2H$-1-Triz)	2-F	H	H
1-530	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2H$-1-Triz)	2-F	H	H
1-531	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2Me$-1-Triz)	2-F	H	H
1-532	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2Me$-1-Triz)	2-F	H	H
1-533	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2Et$-1-Triz)	2-F	H	H
1-534	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2Et$-1-Triz)	2-F	H	H
1-535	H	H	CH_2CH_2-1-Triz	2-F	H	H
1-356[TY1]	Ac	H	CH_2CH_2-1-Triz	2-F	H	H
1-537	H	H	CH_2CH_2-(4-CO_2H-1-Triz)	2-F	H	H
1-538	Ac	H	CH_2CH_2-(4-CO_2H-1-Triz)	2-F	H	H
1-539	H	H	CH_2CH_2-(4-CO_2Me-1-Triz)	2-F	H	H
1-540	Ac	H	CH_2CH_2-(4-CO_2Me-1-Triz)	2-F	H	H
1-541	H	H	CH_2CH_2-(4-CO_2Et-1-Triz)	2-F	H	H
1-542	Ac	H	CH_2CH_2-(4-CO_2Et-1-Triz)	2-F	H	H
1-543	H	H	CH_2CH_2-(5-CO_2H-1-Triz)	2-F	H	H
1-544	Ac	H	CH_2CH_2-(5-CO_2H-1-Triz)	2-F	H	H
1-545	H	H	CH_2CH_2-(5-CO_2Me-1-Triz)	2-F	H	H
1-546	Ac	H	CH_2CH_2-(5-CO_2Me-1-Triz)	2-F	H	H
1-547	H	H	CH_2CH_2-(5-CO_2Et-1-Triz)	2-F	H	H
1-548	Ac	H	CH_2CH_2-(5-CO_2Et-1-Triz)	2-F	H	H
1-549	H	H	CH_2CH_2-(4-CH_2CO_2H-1-Triz)	2-F	H	H
1-550	Ac	H	CH_2CH_2-(4-CH_2CO_2H-1-Triz)	2-F	H	H
1-551	H	H	CH_2CH_2-(4-CH_2CO_2Me-1-Triz)	2-F	H	H
1-552	Ac	H	CH_2CH_2-(4-CH_2CO_2Me-1-Triz)	2-F	H	H
1-553	H	H	CH_2CH_2-(4-CH_2CO_2Et-1-Triz)	2-F	H	H
1-554	Ac	H	CH_2CH_2-(4-CH_2CO_2Et-1-Triz)	2-F	H	H
1-555	H	H	CH_2CH_2-(5-CH_2CO_2H-1-Triz)	2-F	H	H
1-556	Ac	H	CH_2CH_2-(5-CH_2CO_2H-1-Triz)	2-F	H	H
1-557	H	H	CH_2CH_2-(5-CH_2CO_2Me-1-Triz)	2-F	H	H
1-558	Ac	H	CH_2CH_2-(5-CH_2CO_2Me-1-Triz)	2-F	H	H
1-559	H	H	CH_2CH_2-(5-CH_2CO_2Et-1-Triz)	2-F	H	H
1-560	Ac	H	CH_2CH_2-(5-CH_2CO_2Et-1-Triz)	2-F	H	H
1-561	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2H$-1-Triz)	2-F	H	H
1-562	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2H$-1-Triz)	2-F	H	H
1-563	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-1-Triz)	2-F	H	H
1-564	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-1-Triz)	2-F	H	H
1-565	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-1-Triz)	2-F	H	H
1-566	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-1-Triz)	2-F	H	H
1-567	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2H$-1-Triz)	2-F	H	H
1-568	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2H$-1-Triz)	2-F	H	H
1-569	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2Me$-1-Triz)	2-F	H	H
1-570	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2Me$-1-Triz)	2-F	H	H
1-571	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2Et$-1-Triz)	2-F	H	H
1-572	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2Et$-1-Triz)	2-F	H	H
1-573	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2H$-1-Triz)	2-F	H	H

1-574	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2H$-1-Triz)	2-F	H	H
1-575	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Me$-1-Triz)	2-F	H	H
1-576	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Me$-1-Triz)	2-F	H	H
1-577	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Et$-1-Triz)	2-F	H	H
1-578	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Et$-1-Triz)	2-F	H	H
1-579	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2H$-1-Triz)	2-F	H	H
1-580	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2H$-1-Triz)	2-F	H	H
1-581	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Me$-1-Triz)	2-F	H	H
1-582	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Me$-1-Triz)	2-F	H	H
1-583	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Et$-1-Triz)	2-F	H	H
1-584	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Et$-1-Triz)	2-F	H	H
1-585	H	H	CH_2-2-Triz	2-F	H	H
1-586	Ac	H	CH_2-2-Triz	2-F	H	H
1-587	H	H	CH_2-(4-CO_2H-2-Triz)	2-F	H	H
1-588	Ac	H	CH_2-(4-CO_2H-2-Triz)	2-F	H	H
1-589	H	H	CH_2-(4-CO_2Me-2-Triz)	2-F	H	H
1-590	Ac	H	CH_2-(4-CO_2Me-2-Triz)	2-F	H	H
1-591	H	H	CH_2-(4-CO_2Et-2-Triz)	2-F	H	H
1-592	Ac	H	CH_2-(4-CO_2Et-2-Triz)	2-F	H	H
1-593	H	H	CH_2-(4-CH_2CO_2H-2-Triz)	2-F	H	H
1-594	Ac	H	CH_2-(4-CH_2CO_2H-2-Triz)	2-F	H	H
1-595	H	H	CH_2-(4-CH_2CO_2Me-2-Triz)	2-F	H	H
1-596	Ac	H	CH_2-(4-CH_2CO_2Me-2-Triz)	2-F	H	H
1-597	H	H	CH_2-(4-CH_2CO_2Et-2-Triz)	2-F	H	H
1-598	Ac	H	CH_2-(4-CH_2CO_2Et-2-Triz)	2-F	H	H
1-599	H	H	CH_2-(4-$CH_2CH_2CO_2H$-2-Triz)	2-F	H	H
1-600	Ac	H	CH_2-(4-$CH_2CH_2CO_2H$-2-Triz)	2-F	H	H
1-601	H	H	CH_2-(4-$CH_2CH_2CO_2Me$-2-Triz)	2-F	H	H
1-602	Ac	H	CH_2-(4-$CH_2CH_2CO_2Me$-2-Triz)	2-F	H	H
1-603	H	H	CH_2-(4-$CH_2CH_2CO_2Et$-2-Triz)	2-F	H	H
1-604	Ac	H	CH_2-(4-$CH_2CH_2CO_2Et$-2-Triz)	2-F	H	H
1-605	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2H$-2-Triz)	2-F	H	H
1-606	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2H$-2-Triz)	2-F	H	H
1-607	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2Me$-2-Triz)	2-F	H	H
1-608	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2Me$-2-Triz)	2-F	H	H
1-609	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2Et$-2-Triz)	2-F	H	H
1-610	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2Et$-2-Triz)	2-F	H	H
1-611	H	H	CH_2CH_2-2-Triz	2-F	H	H
1-612	Ac	H	CH_2CH_2-2-Triz	2-F	H	H
1-613	H	H	CH_2CH_2-(4-CO_2H-2-Triz)	2-F	H	H
1-614	Ac	H	CH_2CH_2-(4-CO_2H-2-Triz)	2-F	H	H
1-615	H	H	CH_2CH_2-(4-CO_2Me-2-Triz)	2-F	H	H
1-616	Ac	H	CH_2CH_2-(4-CO_2Me-2-Triz)	2-F	H	H
1-617	H	H	CH_2CH_2-(4-CO_2Et-2-Triz)	2-F	H	H
1-618	Ac	H	CH_2CH_2-(4-CO_2Et-2-Triz)	2-F	H	H
1-619	H	H	CH_2CH_2-(4-CH_2CO_2H-2-Triz)	2-F	H	H
1-620	Ac	H	CH_2CH_2-(4-CH_2CO_2H-2-Triz)	2-F	H	H
1-621	H	H	CH_2CH_2-(4-CH_2CO_2Me-2-Triz)	2-F	H	H
1-622	Ac	H	CH_2CH_2-(4-CH_2CO_2Me-2-Triz)	2-F	H	H
1-623	H	H	CH_2CH_2-(4-CH_2CO_2Et-2-Triz)	2-F	H	H
1-624	Ac	H	CH_2CH_2-(4-CH_2CO_2Et-2-Triz)	2-F	H	H
1-625	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2H$-2-Triz)	2-F	H	H
1-626	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2H$-2-Triz)	2-F	H	H
1-627	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-2-Triz)	2-F	H	H
1-628	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-2-Triz)	2-F	H	H
1-629	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-2-Triz)	2-F	H	H
1-630	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-2-Triz)	2-F	H	H

1-631	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2H$-2-Triz)	2-F	H	H
1-632	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2H$-2-Triz)	2-F	H	H
1-633	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Me$-2-Triz)	2-F	H	H
1-634	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Me$-2-Triz)	2-F	H	H
1-635	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Et$-2-Triz)	2-F	H	H
1-636	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Et$-2-Triz)	2-F	H	H
1-637	H	H	CH_2-4-Triz	2-F	H	H
1-638	Ac	H	CH_2-4-Triz	2-F	H	H
1-639	H	H	CH_2-4-Triz	2-F	4-F	H
1-640	Ac	H	CH_2-4-Triz	2-F	4-F	H
1-641	H	H	CH_2-(1-CO_2Me-4-Triz)	2-F	H	H
1-642	Ac	H	CH_2-(1-CO_2Me-4-Triz)	2-F	H	H
1-643	H	H	CH_2-(1-CO_2Et-4-Triz)	2-F	H	H
1-644	Ac	H	CH_2-(1-CO_2Et-4-Triz)	2-F	H	H
1-645	H	H	CH_2-(5-CO_2H-4-Triz)	2-F	H	H
1-646	Ac	H	CH_2-(5-CO_2H-4-Triz)	2-F	H	H
1-647	H	H	CH_2-(5-CO_2Me-4-Triz)	2-F	H	H
1-648	Ac	H	CH_2-(5-CO_2Me-4-Triz)	2-F	H	H
1-649	H	H	CH_2-(5-CO_2Et-4-Triz)	2-F	H	H
1-650	Ac	H	CH_2-(5-CO_2Et-4-Triz)	2-F	H	H
1-651	H	H	CH_2-(1-CH_2CO_2H-4-Triz)	2-F	H	H
1-652	Ac	H	CH_2-(1-CH_2CO_2H-4-Triz)	2-F	H	H
1-653	H	H	CH_2-(1-CH_2CO_2Me-4-Triz)	2-F	H	H
1-654	Ac	H	CH_2-(1-CH_2CO_2Me-4-Triz)	2-F	H	H
1-655	H	H	CH_2-(1-CH_2CO_2Et-4-Triz)	2-F	H	H
1-656	Ac	H	CH_2-(1-CH_2CO_2Et-4-Triz)	2-F	H	H
1-657	H	H	CH_2-(5-CH_2CO_2H-4-Triz)	2-F	H	H
1-658	Ac	H	CH_2-(5-CH_2CO_2H-4-Triz)	2-F	H	H
1-659	H	H	CH_2-(5-CH_2CO_2Me-4-Triz)	2-F	H	H
1-660	Ac	H	CH_2-(5-CH_2CO_2Me-4-Triz)	2-F	H	H
1-661	H	H	CH_2-(5-CH_2CO_2Et-4-Triz)	2-F	H	H
1-662	Ac	H	CH_2-(5-CH_2CO_2Et-4-Triz)	2-F	H	H
1-663	H	H	CH_2-(1-$CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
1-664	Ac	H	CH_2-(1-$CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
1-665	H	H	CH_2-(1-$CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
1-666	Ac	H	CH_2-(1-$CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
1-667	H	H	CH_2-(1-$CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
1-668	Ac	H	CH_2-(1-$CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
1-669	H	H	CH_2-(5-$CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
1-670	Ac	H	CH_2-(5-$CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
1-671	H	H	CH_2-(5-$CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
1-672	Ac	H	CH_2-(5-$CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
1-673	H	H	CH_2-(5-$CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
1-674	Ac	H	CH_2-(5-$CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
1-675	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
1-676	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
1-677	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
1-678	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
1-679	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
1-680	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
1-681	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
1-682	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
1-683	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
1-684	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
1-685	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
1-686	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
1-687	H	H	CH_2CH_2-4-Triz	2-F	H	H

1-688	Ac	H	CH_2CH_2-4-Triz	2-F	H	H
1-689	H	H	CH_2CH_2-4-Triz	2-F	4-F	H
1-690	Ac	H	CH_2CH_2-4-Triz	2-F	4-F	H
1-691	H	H	CH_2CH_2-(1-CO_2Me-4-Triz)	2-F	H	H
1-692	Ac	H	CH_2CH_2-(1-CO_2Me-4-Triz)	2-F	H	H
1-693	H	H	CH_2CH_2-(1-CO_2Et-4-Triz)	2-F	H	H
1-694	Ac	H	CH_2CH_2-(1-CO_2Et-4-Triz)	2-F	H	H
1-695	H	H	CH_2CH_2-(5-CO_2H-4-Triz)	2-F	H	H
1-696	Ac	H	CH_2CH_2-(5-CO_2H-4-Triz)	2-F	H	H
1-697	H	H	CH_2CH_2-(5-CO_2Me-4-Triz)	2-F	H	H
1-698	Ac	H	CH_2CH_2-(5-CO_2Me-4-Triz)	2-F	H	H
1-699	H	H	CH_2CH_2-(5-CO_2Et-4-Triz)	2-F	H	H
1-700	Ac	H	CH_2CH_2-(5-CO_2Et-4-Triz)	2-F	H	H
1-701	H	H	CH_2CH_2-(1-CH_2CO_2H-4-Triz)	2-F	H	H
1-702	Ac	H	CH_2CH_2-(1-CH_2CO_2H-4-Triz)	2-F	H	H
1-703	H	H	CH_2CH_2-(1-CH_2CO_2Me-4-Triz)	2-F	H	H
1-704	Ac	H	CH_2CH_2-(1-CH_2CO_2Me-4-Triz)	2-F	H	H
1-705	H	H	CH_2CH_2-(1-CH_2CO_2Et-4-Triz)	2-F	H	H
1-706	Ac	H	CH_2CH_2-(1-CH_2CO_2Et-4-Triz)	2-F	H	H
1-707	H	H	CH_2CH_2-(5-CH_2CO_2H-4-Triz)	2-F	H	H
1-708	Ac	H	CH_2CH_2-(5-CH_2CO_2H-4-Triz)	2-F	H	H
1-709	H	H	CH_2CH_2-(5-CH_2CO_2Me-4-Triz)	2-F	H	H
1-710	Ac	H	CH_2CH_2-(5-CH_2CO_2Me-4-Triz)	2-F	H	H
1-711	H	H	CH_2CH_2-(5-CH_2CO_2Et-4-Triz)	2-F	H	H
1-712	Ac	H	CH_2CH_2-(5-CH_2CO_2Et-4-Triz)	2-F	H	H
1-713	H	H	CH_2CH_2-(1-$CH_2CH_2CO_2$H-4-Triz)	2-F	H	H
1-714	Ac	H	CH_2CH_2-(1-$CH_2CH_2CO_2$H-4-Triz)	2-F	H	H
1-715	H	H	CH_2CH_2-(1-$CH_2CH_2CO_2$Me-4-Triz)	2-F	H	H
1-716	Ac	H	CH_2CH_2-(1-$CH_2CH_2CO_2$Me-4-Triz)	2-F	H	H
1-717	H	H	CH_2CH_2-(1-$CH_2CH_2CO_2$Et-4-Triz)	2-F	H	H
1-718	Ac	H	CH_2CH_2-(1-$CH_2CH_2CO_2$Et-4-Triz)	2-F	H	H
1-719	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2$H-4-Triz)	2-F	H	H
1-720	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2$H-4-Triz)	2-F	H	H
1-721	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2$Me-4-Triz)	2-F	H	H
1-722	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2$Me-4-Triz)	2-F	H	H
1-723	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2$Et-4-Triz)	2-F	H	H
1-724	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2$Et-4-Triz)	2-F	H	H
1-725	H	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2$H-4-Triz)	2-F	H	H
1-726	Ac	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2$H-4-Triz)	2-F	H	H
1-727	H	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2$Me-4-Triz)	2-F	H	H
1-728	Ac	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2$Me-4-Triz)	2-F	H	H
1-729	H	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2$Et-4-Triz)	2-F	H	H
1-730	Ac	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2$Et-4-Triz)	2-F	H	H
1-731	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2$H-4-Triz)	2-F	H	H
1-732	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2$H-4-Triz)	2-F	H	H
1-733	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2$Me-4-Triz)	2-F	H	H
1-734	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2$Me-4-Triz)	2-F	H	H
1-735	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2$Et-4-Triz)	2-F	H	H
1-736	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2$Et-4-Triz)	2-F	H	H
1-737	H	H	CH_2-(1-CO_2Me-5-Triz)	2-F	4-F	H
1-738	Ac	H	CH_2-(1-CO_2Me-5-Triz)	2-F	4-F	H
1-739	H	H	CH_2-(1-CO_2Me-5-Triz)	2-F	H	H
1-740	Ac	H	CH_2-(1-CO_2Me-5-Triz)	2-F	H	H
1-741	H	H	CH_2-(1-CO_2Et-5-Triz)	2-F	H	H
1-742	Ac	H	CH_2-(1-CO_2Et-5-Triz)	2-F	H	H
1-743	H	H	CH_2-(1-CH_2CO_2H-5-Triz)	2-F	H	H
1-744	Ac	H	CH_2-(1-CH_2CO_2H-5-Triz)	2-F	H	H

1-745	H	H	CH_2-(1-CH_2CO_2Me-5-Triz)	2-F	H	H
1-746	Ac	H	CH_2-(1-CH_2CO_2Me-5-Triz)	2-F	H	H
1-747	H	H	CH_2-(1-CH_2CO_2Et-5-Triz)	2-F	H	H
1-748	Ac	H	CH_2-(1-CH_2CO_2Et-5-Triz)	2-F	H	H
1-749	H	H	CH_2-(1-$CH_2CH_2CO_2H$-5-Triz)	2-F	H	H
1-750	Ac	H	CH_2-(1-$CH_2CH_2CO_2H$-5-Triz)	2-F	H	H
1-751	H	H	CH_2-(1-$CH_2CH_2CO_2Me$-5-Triz)	2-F	H	H
1-752	Ac	H	CH_2-(1-$CH_2CH_2CO_2Me$-5-Triz)	2-F	H	H
1-753	H	H	CH_2-(1-$CH_2CH_2CO_2Et$-5-Triz)	2-F	H	H
1-754	Ac	H	CH_2-(1-$CH_2CH_2CO_2Et$-5-Triz)	2-F	H	H
1-755	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2H$-5-Triz)	2-F	H	H
1-756	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2H$-5-Triz)	2-F	H	H
1-757	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2Me$-5-Triz)	2-F	H	H
1-758	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2Me$-5-Triz)	2-F	H	H
1-759	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2Et$-5-Triz)	2-F	H	H
1-760	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2Et$-5-Triz)	2-F	H	H
1-761	H	H	CH_2-1-Tez	2-F	H	H
1-762	Ac	H	CH_2-1-Tez	2-F	H	H
1-763	H	H	CH_2-(5-CO_2H-1-Tez)	2-F	H	H
1-764	Ac	H	CH_2-(5-CO_2H-1-Tez)	2-F	H	H
1-765	H	H	CH_2-(5-CO_2Me-1-Tez)	2-F	H	H
1-766	Ac	H	CH_2-(5-CO_2Me-1-Tez)	2-F	H	H
1-767	H	H	CH_2-(5-CO_2Et-1-Tez)	2-F	H	H
1-768	Ac	H	CH_2-(5-CO_2Et-1-Tez)	2-F	H	H
1-769	H	H	CH_2-(5-CH_2CO_2H-1-Tez)	2-F	H	H
1-770	Ac	H	CH_2-(5-CH_2CO_2H-1-Tez)	2-F	H	H
1-771	H	H	CH_2-(5-CH_2CO_2Me-1-Tez)	2-F	H	H
1-772	Ac	H	CH_2-(5-CH_2CO_2Me-1-Tez)	2-F	H	H
1-773	H	H	CH_2-(5-CH_2CO_2Et-1-Tez)	2-F	H	H
1-774	Ac	H	CH_2-(5-CH_2CO_2Et-1-Tez)	2-F	H	H
1-775	H	H	CH_2-(5-$CH_2CH_2CO_2H$-1-Tez)	2-F	H	H
1-776	Ac	H	CH_2-(5-$CH_2CH_2CO_2H$-1-Tez)	2-F	H	H
1-777	H	H	CH_2-(5-$CH_2CH_2CO_2Me$-1-Tez)	2-F	H	H
1-778	Ac	H	CH_2-(5-$CH_2CH_2CO_2Me$-1-Tez)	2-F	H	H
1-779	H	H	CH_2-(5-$CH_2CH_2CO_2Et$-1-Tez)	2-F	H	H
1-780	Ac	H	CH_2-(5-$CH_2CH_2CO_2Et$-1-Tez)	2-F	H	H
1-781	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2H$-1-Tez)	2-F	H	H
1-782	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2H$-1-Tez)	2-F	H	H
1-783	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2Me$-1-Tez)	2-F	H	H
1-784	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2Me$-1-Tez)	2-F	H	H
1-785	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2Et$-1-Tez)	2-F	H	H
1-786	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2Et$-1-Tez)	2-F	H	H
1-787	H	H	CH_2CH_2-1-Tez	2-F	H	H
1-788	Ac	H	CH_2CH_2-1-Tez	2-F	H	H
1-789	H	H	CH_2CH_2-(5-CO_2H-1-Tez)	2-F	H	H
1-790	Ac	H	CH_2CH_2-(5-CO_2H-1-Tez)	2-F	H	H
1-791	H	H	CH_2CH_2-(5-CO_2Me-1-Tez)	2-F	H	H
1-792	Ac	H	CH_2CH_2-(5-CO_2Me-1-Tez)	2-F	H	H
1-793	H	H	CH_2CH_2-(5-CO_2Et-1-Tez)	2-F	H	H
1-794	Ac	H	CH_2CH_2-(5-CO_2Et-1-Tez)	2-F	H	H
1-795	H	H	CH_2CH_2-(5-CH_2CO_2H-1-Tez)	2-F	H	H
1-796	Ac	H	CH_2CH_2-(5-CH_2CO_2H-1-Tez)	2-F	H	H
1-797	H	H	CH_2CH_2-(5-CH_2CO_2Me-1-Tez)	2-F	H	H
1-798	Ac	H	CH_2CH_2-(5-CH_2CO_2Me-1-Tez)	2-F	H	H
1-799	H	H	CH_2CH_2-(5-CH_2CO_2Et-1-Tez)	2-F	H	H
1-800	Ac	H	CH_2CH_2-(5-CH_2CO_2Et-1-Tez)	2-F	H	H
1-801	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2H$-1-Tez)	2-F	H	H

1-802	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2H$-1-Tez)	2-F	H	H
1-803	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2Me$-1-Tez)	2-F	H	H
1-804	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2Me$-1-Tez)	2-F	H	H
1-805	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2Et$-1-Tez)	2-F	H	H
1-806	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2Et$-1-Tez)	2-F	H	H
1-807	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2H$-1-Tez)	2-F	H	H
1-808	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2H$-1-Tez)	2-F	H	H
1-809	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Me$-1-Tez)	2-F	H	H
1-810	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Me$-1-Tez)	2-F	H	H
1-811	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Et$-1-Tez)	2-F	H	H
1-812	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Et$-1-Tez)	2-F	H	H
1-813	H	H	CH_2-2-Tez	2-F	H	H
1-814	Ac	H	CH_2-2-Tez	2-F	H	H
1-815	H	H	CH_2-(5-CO_2H-2-Tez)	2-F	H	H
1-816	Ac	H	CH_2-(5-CO_2H-2-Tez)	2-F	H	H
1-817	H	H	CH_2-(5-CO_2Me-2-Tez)	2-F	H	H
1-818	Ac	H	CH_2-(5-CO_2Me-2-Tez)	2-F	H	H
1-819	H	H	CH_2-(5-CO_2Et-2-Tez)	2-F	H	H
1-820	Ac	H	CH_2-(5-CO_2Et-2-Tez)	2-F	H	H
1-821	H	H	CH_2-(5-CH_2CO_2H-2-Tez)	2-F	H	H
1-822	Ac	H	CH_2-(5-CH_2CO_2H-2-Tez)	2-F	H	H
1-823	H	H	CH_2-(5-CH_2CO_2Me-2-Tez)	2-F	H	H
1-824	Ac	H	CH_2-(5-CH_2CO_2Me-2-Tez)	2-F	H	H
1-825	H	H	CH_2-(5-CH_2CO_2Et-2-Tez)	2-F	H	H
1-826	Ac	H	CH_2-(5-CH_2CO_2Et-2-Tez)	2-F	H	H
1-827	H	H	CH_2-(5-$CH_2CH_2CO_2H$-2-Tez)	2-F	H	H
1-828	Ac	H	CH_2-(5-$CH_2CH_2CO_2H$-2-Tez)	2-F	H	H
1-829	H	H	CH_2-(5-$CH_2CH_2CO_2Me$-2-Tez)	2-F	H	H
1-830	Ac	H	CH_2-(5-$CH_2CH_2CO_2Me$-2-Tez)	2-F	H	H
1-831	H	H	CH_2-(5-$CH_2CH_2CO_2Et$-2-Tez)	2-F	H	H
1-832	Ac	H	CH_2-(5-$CH_2CH_2CO_2Et$-2-Tez)	2-F	H	H
1-833	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2H$-2-Tez)	2-F	H	H
1-834	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2H$-2-Tez)	2-F	H	H
1-835	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2Me$-2-Tez)	2-F	H	H
1-836	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2Me$-2-Tez)	2-F	H	H
1-837	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2Et$-2-Tez)	2-F	H	H
1-838	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2Et$-2-Tez)	2-F	H	H
1-839	H	H	CH_2CH_2-2-Tez	2-F	H	H
1-840	Ac	H	CH_2CH_2-2-Tez	2-F	H	H
1-841	H	H	CH_2CH_2-(5-CO_2H-2-Tez)	2-F	H	H
1-842	Ac	H	CH_2CH_2-(5-CO_2H-2-Tez)	2-F	H	H
1-843	H	H	CH_2CH_2-(5-CO_2Me-2-Tez)	2-F	H	H
1-844	Ac	H	CH_2CH_2-(5-CO_2Me-2-Tez)	2-F	H	H
1-845	H	H	CH_2CH_2-(5-CO_2Et-2-Tez)	2-F	H	H
1-846	Ac	H	CH_2CH_2-(5-CO_2Et-2-Tez)	2-F	H	H
1-847	H	H	CH_2CH_2-(5-CH_2CO_2H-2-Tez)	2-F	H	H
1-848	Ac	H	CH_2CH_2-(5-CH_2CO_2H-2-Tez)	2-F	H	H
1-849	H	H	CH_2CH_2-(5-CH_2CO_2Me-2-Tez)	2-F	H	H
1-850	Ac	H	CH_2CH_2-(5-CH_2CO_2Me-2-Tez)	2-F	H	H
1-851	H	H	CH_2CH_2-(5-CH_2CO_2Et-2-Tez)	2-F	H	H
1-852	Ac	H	CH_2CH_2-(5-CH_2CO_2Et-2-Tez)	2-F	H	H
1-853	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2H$-2-Tez)	2-F	H	H
1-854	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2H$-2-Tez)	2-F	H	H
1-855	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2Me$-2-Tez)	2-F	H	H
1-856	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2Me$-2-Tez)	2-F	H	H
1-857	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2Et$-2-Tez)	2-F	H	H
1-858	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2Et$-2-Tez)	2-F	H	H

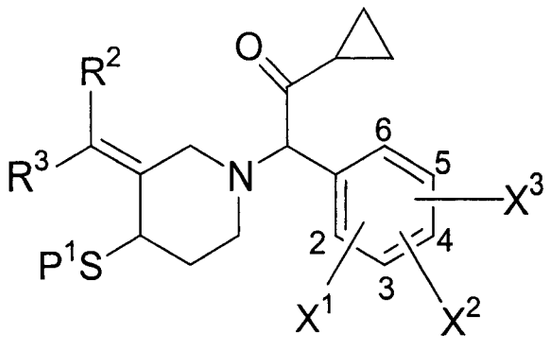
1-859	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2H$-2-Tez)	2-F	H	H
1-860	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2H$-2-Tez)	2-F	H	H
1-861	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Me$-2-Tez)	2-F	H	H
1-862	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Me$-2-Tez)	2-F	H	H
1-863	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Et$-2-Tez)	2-F	H	H
1-864	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Et$-2-Tez)	2-F	H	H
1-865	H	H	CH_2-5-Tez	2-F	H	H
1-866	Ac	H	CH_2-5-Tez	2-F	H	H
1-867	H	H	CH_2-5-Tez	2-F	4-F	H
1-868	Ac	H	CH_2-5-Tez	2-F	4-F	H
1-869	H	H	CH_2-(1-CO_2Me-5-Tez)	2-F	H	H
1-870	Ac	H	CH_2-(1-CO_2Me-5-Tez)	2-F	H	H
1-871	H	H	CH_2-(1-CO_2Et-5-Tez)	2-F	H	H
1-872	Ac	H	CH_2-(1-CO_2Et-5-Tez)	2-F	H	H
1-873	H	H	CH_2-(2-CO_2Me-5-Tez)	2-F	4-F	H
1-874	Ac	H	CH_2-(2-CO_2Me-5-Tez)	2-F	4-F	H
1-875	H	H	CH_2-(2-CO_2Me-5-Tez)	2-F	H	H
1-876	Ac	H	CH_2-(2-CO_2Me-5-Tez)	2-F	H	H
1-877	H	H	CH_2-(2-CO_2Et-5-Tez)	2-F	H	H
1-878	Ac	H	CH_2-(2-CO_2Et-5-Tez)	2-F	H	H
1-879	H	H	CH_2-(1-CH_2CO_2H-5-Tez)	2-F	H	H
1-880	Ac	H	CH_2-(1-CH_2CO_2H-5-Tez)	2-F	H	H
1-881	H	H	CH_2-(1-CH_2CO_2Me-5-Tez)	2-F	H	H
1-882	Ac	H	CH_2-(1-CH_2CO_2Me-5-Tez)	2-F	H	H
1-883	H	H	CH_2-(1-CH_2CO_2Et-5-Tez)	2-F	H	H
1-884	Ac	H	CH_2-(1-CH_2CO_2Et-5-Tez)	2-F	H	H
1-885	H	H	CH_2-(2-CH_2CO_2H-5-Tez)	2-F	H	H
1-886	Ac	H	CH_2-(2-CH_2CO_2H-5-Tez)	2-F	H	H
1-887	H	H	CH_2-(2-CH_2CO_2Me-5-Tez)	2-F	H	H
1-888	Ac	H	CH_2-(2-CH_2CO_2Me-5-Tez)	2-F	H	H
1-889	H	H	CH_2-(2-CH_2CO_2Et-5-Tez)	2-F	H	H
1-890	Ac	H	CH_2-(2-CH_2CO_2Et-5-Tez)	2-F	H	H
1-891	H	H	CH_2-(1-$CH_2CH_2CO_2H$-5-Tez)	2-F	H	H
1-892	Ac	H	CH_2-(1-$CH_2CH_2CO_2H$-5-Tez)	2-F	H	H
1-893	H	H	CH_2-(1-$CH_2CH_2CO_2Me$-5-Tez)	2-F	H	H
1-894	Ac	H	CH_2-(1-$CH_2CH_2CO_2Me$-5-Tez)	2-F	H	H
1-895	H	H	CH_2-(1-$CH_2CH_2CO_2Et$-5-Tez)	2-F	H	H
1-896	Ac	H	CH_2-(1-$CH_2CH_2CO_2Et$-5-Tez)	2-F	H	H
1-897	H	H	CH_2-(2-$CH_2CH_2CO_2H$-5-Tez)	2-F	H	H
1-898	Ac	H	CH_2-(2-$CH_2CH_2CO_2H$-5-Tez)	2-F	H	H
1-899	H	H	CH_2-(2-$CH_2CH_2CO_2Me$-5-Tez)	2-F	H	H
1-900	Ac	H	CH_2-(2-$CH_2CH_2CO_2Me$-5-Tez)	2-F	H	H
1-901	H	H	CH_2-(2-$CH_2CH_2CO_2Et$-5-Tez)	2-F	H	H
1-902	Ac	H	CH_2-(2-$CH_2CH_2CO_2Et$-5-Tez)	2-F	H	H
1-903	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2H$-5-Tez)	2-F	H	H
1-904	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2H$-5-Tez)	2-F	H	H
1-905	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2Me$-5-Tez)	2-F	H	H
1-906	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2Me$-5-Tez)	2-F	H	H
1-907	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2Et$-5-Tez)	2-F	H	H
1-908	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2Et$-5-Tez)	2-F	H	H
1-909	H	H	CH_2-(2-$CH_2CH_2CH_2CO_2H$-5-Tez)	2-F	H	H
1-910	Ac	H	CH_2-(2-$CH_2CH_2CH_2CO_2H$-5-Tez)	2-F	H	H
1-911	H	H	CH_2-(2-$CH_2CH_2CH_2CO_2Me$-5-Tez)	2-F	H	H
1-912	Ac	H	CH_2-(2-$CH_2CH_2CH_2CO_2Me$-5-Tez)	2-F	H	H
1-913	H	H	CH_2-(2-$CH_2CH_2CH_2CO_2Et$-5-Tez)	2-F	H	H
1-914	Ac	H	CH_2-(2-$CH_2CH_2CH_2CO_2Et$-5-Tez)	2-F	H	H
1-915	H	H	CH_2CH_2-5-Tez	2-F	H	H

1-916	Ac	H	CH_2CH_2-5-Tez	2-F	H	H
1-917	H	H	CH_2CH_2-5-Tez	2-F	4-F	H
1-918	Ac	H	CH_2CH_2-5-Tez	2-F	4-F	H
1-919	H	H	CH_2CH_2-(1-CO_2Me-5-Tez)	2-F	H	H
1-920	Ac	H	CH_2CH_2-(1-CO_2Me-5-Tez)	2-F	H	H
1-921	H	H	CH_2CH_2-(1-CO_2Et-5-Tez)	2-F	H	H
1-922	Ac	H	CH_2CH_2-(1-CO_2Et-5-Tez)	2-F	H	H
1-923	H	H	CH_2CH_2-(2-CO_2Me-5-Tez)	2-F	4-F	H
1-924	Ac	H	CH_2CH_2-(2-CO_2Me-5-Tez)	2-F	4-F	H
1-925	H	H	CH_2CH_2-(2-CO_2Me-5-Tez)	2-F	H	H
1-926	Ac	H	CH_2CH_2-(2-CO_2Me-5-Tez)	2-F	H	H
1-927	H	H	CH_2CH_2-(2-CO_2Et-5-Tez)	2-F	H	H
1-928	Ac	H	CH_2CH_2-(2-CO_2Et-5-Tez)	2-F	H	H
1-929	H	H	CH_2CH_2-(1-CH_2CO_2H-5-Tez)	2-F	H	H
1-930	Ac	H	CH_2CH_2-(1-CH_2CO_2H-5-Tez)	2-F	H	H
1-931	H	H	CH_2CH_2-(1-CH_2CO_2Me-5-Tez)	2-F	H	H
1-932	Ac	H	CH_2CH_2-(1-CH_2CO_2Me-5-Tez)	2-F	H	H
1-933	H	H	CH_2CH_2-(1-CH_2CO_2Et-5-Tez)	2-F	H	H
1-934	Ac	H	CH_2CH_2-(1-CH_2CO_2Et-5-Tez)	2-F	H	H
1-935	H	H	CH_2CH_2-(2-CH_2CO_2H-5-Tez)	2-F	H	H
1-936	Ac	H	CH_2CH_2-(2-CH_2CO_2H-5-Tez)	2-F	H	H
1-937	H	H	CH_2CH_2-(2-CH_2CO_2Me-5-Tez)	2-F	H	H
1-938	Ac	H	CH_2CH_2-(2-CH_2CO_2Me-5-Tez)	2-F	H	H
1-939	H	H	CH_2CH_2-(2-CH_2CO_2Et-5-Tez)	2-F	H	H
1-940	Ac	H	CH_2CH_2-(2-CH_2CO_2Et-5-Tez)	2-F	H	H
1-941	H	H	CH_2CH_2-(1-$CH_2CH_2CO_2$H-5-Tez)	2-F	H	H
1-942	Ac	H	CH_2CH_2-(1-$CH_2CH_2CO_2$H-5-Tez)	2-F	H	H
1-943	H	H	CH_2CH_2-(1-$CH_2CH_2CO_2$Me-5-Tez)	2-F	H	H
1-944	Ac	H	CH_2CH_2-(1-$CH_2CH_2CO_2$Me-5-Tez)	2-F	H	H
1-945	H	H	CH_2CH_2-(1-$CH_2CH_2CO_2$Et-5-Tez)	2-F	H	H
1-946	Ac	H	CH_2CH_2-(1-$CH_2CH_2CO_2$Et-5-Tez)	2-F	H	H
1-947	H	H	CH_2CH_2-(2-$CH_2CH_2CO_2$H-5-Tez)	2-F	H	H
1-948	Ac	H	CH_2CH_2-(2-$CH_2CH_2CO_2$H-5-Tez)	2-F	H	H
1-949	H	H	CH_2CH_2-(2-$CH_2CH_2CO_2$Me-5-Tez)	2-F	H	H
1-950	Ac	H	CH_2CH_2-(2-$CH_2CH_2CO_2$Me-5-Tez)	2-F	H	H
1-951	H	H	CH_2CH_2-(2-$CH_2CH_2CO_2$Et-5-Tez)	2-F	H	H
1-952	Ac	H	CH_2CH_2-(2-$CH_2CH_2CO_2$Et-5-Tez)	2-F	H	H
1-953	H	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2$H-5-Tez)	2-F	H	H
1-954	Ac	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2$H-5-Tez)	2-F	H	H
1-955	H	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2$Me-5-Tez)	2-F	H	H
1-956	Ac	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2$Me-5-Tez)	2-F	H	H
1-957	H	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2$Et-5-Tez)	2-F	H	H
1-958	Ac	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2$Et-5-Tez)	2-F	H	H
1-959	H	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2$H-5-Tez)	2-F	H	H
1-960	Ac	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2$H-5-Tez)	2-F	H	H
1-961	H	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2$Me-5-Tez)	2-F	H	H
1-962	Ac	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2$Me-5-Tez)	2-F	H	H
1-963	H	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2$Et-5-Tez)	2-F	H	H
1-964	Ac	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2$Et-5-Tez)	2-F	H	H
1-965	H	Me	CH_2-1-Pyza	2-F	H	H
1-966	Ac	Me	CH_2-1-Pyza	2-F	H	H
1-967	H	Me	CH_2-(3-CO_2H-1-Pyza)	2-F	H	H
1-968	Ac	Me	CH_2-(3-CO_2H-1-Pyza)	2-F	H	H
1-969	H	Me	CH_2-(3-CO_2Me-1-Pyza)	2-F	H	H
1-970	Ac	Me	CH_2-(3-CO_2Me-1-Pyza)	2-F	H	H
1-971	H	Me	CH_2-(3-CO_2Et-1-Pyza)	2-F	H	H
1-972	Ac	Me	CH_2-(3-CO_2Et-1-Pyza)	2-F	H	H

1-973	H	Me	CH_2-(4-CO_2H-1-Pyza)	2-F	H	H
1-974	Ac	Me	CH_2-(4-CO_2H-1-Pyza)	2-F	H	H
1-975	H	Me	CH_2-(4-CO_2Me-1-Pyza)	2-F	H	H
1-976	Ac	Me	CH_2-(4-CO_2Me-1-Pyza)	2-F	H	H
1-977	H	Me	CH_2-(4-CO_2Et-1-Pyza)	2-F	H	H
1-978	Ac	Me	CH_2-(4-CO_2Et-1-Pyza)	2-F	H	H
1-979	H	Me	CH_2-(3-CH_2CO_2H-1-Pyza)	2-F	H	H
1-980	Ac	Me	CH_2-(3-CH_2CO_2H-1-Pyza)	2-F	H	H
1-981	H	Me	CH_2-(3-CH_2CO_2Me-1-Pyza)	2-F	H	H
1-982	Ac	Me	CH_2-(3-CH_2CO_2Me-1-Pyza)	2-F	H	H
1-983	H	Me	CH_2-(3-CH_2CO_2Et-1-Pyza)	2-F	H	H
1-984	Ac	Me	CH_2-(3-CH_2CO_2Et-1-Pyza)	2-F	H	H
1-985	H	Me	CH_2-(4-CH_2CO_2H-1-Pyza)	2-F	H	H
1-986	Ac	Me	CH_2-(4-CH_2CO_2H-1-Pyza)	2-F	H	H
1-987	H	Me	CH_2-(4-CH_2CO_2Me-1-Pyza)	2-F	H	H
1-988	Ac	Me	CH_2-(4-CH_2CO_2Me-1-Pyza)	2-F	H	H
1-989	H	Me	CH_2-(4-CH_2CO_2Et-1-Pyza)	2-F	H	H
1-990	Ac	Me	CH_2-(4-CH_2CO_2Et-1-Pyza)	2-F	H	H
1-991	H	Me	CH_2-(3-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
1-992	Ac	Me	CH_2-(3-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
1-993	H	Me	CH_2-(3-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
1-994	Ac	Me	CH_2-(3-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
1-995	H	Me	CH_2-(3-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
1-996	Ac	Me	CH_2-(3-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
1-997	H	Me	CH_2-(4-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
1-998	Ac	Me	CH_2-(4-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
1-999	H	Me	CH_2-(4-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
1-1000	Ac	Me	CH_2-(4-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
1-1001	H	Me	CH_2-(4-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
1-1002	Ac	Me	CH_2-(4-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
1-1003	H	Me	CH_2CH_2-1-Pyza	2-F	H	H
1-1004	Ac	Me	CH_2CH_2-1-Pyza	2-F	H	H
1-1005	H	Me	CH_2CH_2-(3-CO_2H-1-Pyza)	2-F	H	H
1-1006	Ac	Me	CH_2CH_2-(3-CO_2H-1-Pyza)	2-F	H	H
1-1007	H	Me	CH_2CH_2-(3-CO_2Me-1-Pyza)	2-F	H	H
1-1008	Ac	Me	CH_2CH_2-(3-CO_2Me-1-Pyza)	2-F	H	H
1-1009	H	Me	CH_2CH_2-(3-CO_2Et-1-Pyza)	2-F	H	H
1-1010	Ac	Me	CH_2CH_2-(3-CO_2Et-1-Pyza)	2-F	H	H
1-1011	H	Me	CH_2CH_2-(4-CO_2H-1-Pyza)	2-F	H	H
1-1012	Ac	Me	CH_2CH_2-(4-CO_2H-1-Pyza)	2-F	H	H
1-1013	H	Me	CH_2CH_2-(4-CO_2Me-1-Pyza)	2-F	H	H
1-1014	Ac	Me	CH_2CH_2-(4-CO_2Me-1-Pyza)	2-F	H	H
1-1015	H	Me	CH_2CH_2-(4-CO_2Et-1-Pyza)	2-F	H	H
1-1016	Ac	Me	CH_2CH_2-(4-CO_2Et-1-Pyza)	2-F	H	H
1-1017	H	Me	CH_2CH_2-(3-CH_2CO_2H-1-Pyza)	2-F	H	H
1-1018	Ac	Me	CH_2CH_2-(3-CH_2CO_2H-1-Pyza)	2-F	H	H
1-1019	H	Me	CH_2CH_2-(3-CH_2CO_2Me-1-Pyza)	2-F	H	H
1-1020	Ac	Me	CH_2CH_2-(3-CH_2CO_2Me-1-Pyza)	2-F	H	H
1-1021	H	Me	CH_2CH_2-(3-CH_2CO_2Et-1-Pyza)	2-F	H	H
1-1022	Ac	Me	CH_2CH_2-(3-CH_2CO_2Et-1-Pyza)	2-F	H	H
1-1023	H	Me	CH_2CH_2-(4-CH_2CO_2H-1-Pyza)	2-F	H	H
1-1024	Ac	Me	CH_2CH_2-(4-CH_2CO_2H-1-Pyza)	2-F	H	H
1-1025	H	Me	CH_2CH_2-(4-CH_2CO_2Me-1-Pyza)	2-F	H	H
1-1026	Ac	Me	CH_2CH_2-(4-CH_2CO_2Me-1-Pyza)	2-F	H	H
1-1027	H	Me	CH_2CH_2-(4-CH_2CO_2Et-1-Pyza)	2-F	H	H
1-1028	Ac	Me	CH_2CH_2-(4-CH_2CO_2Et-1-Pyza)	2-F	H	H
1-1029	H	Me	CH_2CH_2-(3-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H

1-1030	Ac	Me	CH_2CH_2-(3-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
1-1031	H	Me	CH_2CH_2-(3-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
1-1032	Ac	Me	CH_2CH_2-(3-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
1-1033	H	Me	CH_2CH_2-(3-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
1-1034	Ac	Me	CH_2CH_2-(3-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
1-1035	H	Me	CH_2CH_2-(4-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
1-1036	Ac	Me	CH_2CH_2-(4-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
1-1037	H	Me	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
1-1038	Ac	Me	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
1-1039	H	Me	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
1-1040	Ac	Me	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
1-1041	H	H	CH_2-(2-CO_2Me-4-Triz)	2-F	H	H
1-1042	Ac	H	CH_2-(2-CO_2Me-4-Triz)	2-F	H	H
1-1043	H	H	CH_2-(2-CO_2Et-4-Triz)	2-F	H	H
1-1044	Ac	H	CH_2-(2-CO_2Et-4-Triz)	2-F	H	H
1-1045	H	H	CH_2-(2-CH_2CO_2H-4-Triz)	2-F	H	H
1-1046	Ac	H	CH_2-(2-CH_2CO_2H-4-Triz)	2-F	H	H
1-1047	H	H	CH_2-(2-CH_2CO_2Me-4-Triz)	2-F	H	H
1-1048	Ac	H	CH_2-(2-CH_2CO_2Me-4-Triz)	2-F	H	H
1-1049	H	H	CH_2-(2-CH_2CO_2Et-4-Triz)	2-F	H	H
1-1050	Ac	H	CH_2-(2-CH_2CO_2Et-4-Triz)	2-F	H	H
1-1051	H	H	CH_2-(2-$CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
1-1052	Ac	H	CH_2-(2-$CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
1-1053	H	H	CH_2-(2-$CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
1-1054	Ac	H	CH_2-(2-$CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
1-1055	H	H	CH_2-(2-$CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
1-1056	Ac	H	CH_2-(2-$CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
1-1057	H	H	CH_2-(2-$CH_2CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
1-1058	Ac	H	CH_2-(2-$CH_2CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
1-1059	H	H	CH_2-(2-$CH_2CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
1-1060	Ac	H	CH_2-(2-$CH_2CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
1-1061	H	H	CH_2-(2-$CH_2CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
1-1062	Ac	H	CH_2-(2-$CH_2CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
1-1063	H	H	CH_2CH_2-(2-CO_2Me-4-Triz)	2-F	H	H
1-1064	Ac	H	CH_2CH_2-(2-CO_2Me-4-Triz)	2-F	H	H
1-1065	H	H	CH_2CH_2-(2-CO_2Et-4-Triz)	2-F	H	H
1-1066	Ac	H	CH_2CH_2-(2-CO_2Et-4-Triz)	2-F	H	H
1-1067	H	H	CH_2CH_2-(2-CH_2CO_2H-4-Triz)	2-F	H	H
1-1068	Ac	H	CH_2CH_2-(2-CH_2CO_2H-4-Triz)	2-F	H	H
1-1069	H	H	CH_2CH_2-(2-CH_2CO_2Me-4-Triz)	2-F	H	H
1-1070	Ac	H	CH_2CH_2-(2-CH_2CO_2Me-4-Triz)	2-F	H	H
1-1071	H	H	CH_2CH_2-(2-CH_2CO_2Et-4-Triz)	2-F	H	H
1-1072	Ac	H	CH_2CH_2-(2-CH_2CO_2Et-4-Triz)	2-F	H	H
1-1073	H	H	CH_2CH_2-(2-$CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
1-1074	Ac	H	CH_2CH_2-(2-$CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
1-1075	H	H	CH_2CH_2-(2-$CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
1-1076	Ac	H	CH_2CH_2-(2-$CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
1-1077	H	H	CH_2CH_2-(2-$CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
1-1078	Ac	H	CH_2CH_2-(2-$CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
1-1079	H	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
1-1080	Ac	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
1-1081	H	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
1-1082	Ac	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
1-1083	H	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
1-1084	Ac	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H

(Table 2)



Compound No.	P^1	R^2	R^3	X^1	X^2	X^3
2-1	H	H	CH_2-1-Pyza	2-F	H	H
2-2	Ac	H	CH_2-1-Pyza	2-F	H	H
2-3	H	H	CH_2-1-Pyza	2-F	4-F	H
2-4	Ac	H	CH_2-1-Pyza	2-F	4-F	H
2-5	H	H	CH_2-(3-CO_2H-1-Pyza)	2-F	H	H
2-6	Ac	H	CH_2-(3-CO_2H-1-Pyza)	2-F	H	H
2-7	H	H	CH_2-(3-CO_2H-1-Pyza)	2-F	4-F	H
2-8	Ac	H	CH_2-(3-CO_2H-1-Pyza)	2-F	4-F	H
2-9	H	H	CH_2-(3-CO_2Me-1-Pyza)	2-F	H	H
2-10	Ac	H	CH_2-(3-CO_2Me-1-Pyza)	2-F	H	H
2-11	H	H	CH_2-(3-CO_2Me-1-Pyza)	2-F	4-F	H
2-12	Ac	H	CH_2-(3-CO_2Me-1-Pyza)	2-F	4-F	H
2-13	H	H	CH_2-(3-CO_2Et-1-Pyza)	2-F	H	H
2-14	Ac	H	CH_2-(3-CO_2Et-1-Pyza)	2-F	H	H
2-15	H	H	CH_2-(3-CO_2Et-1-Pyza)	2-F	4-F	H
2-16	Ac	H	CH_2-(3-CO_2Et-1-Pyza)	2-F	4-F	H
2-17	H	H	CH_2-(4-CO_2H-1-Pyza)	2-F	H	H
2-18	Ac	H	CH_2-(4-CO_2H-1-Pyza)	2-F	H	H
2-19	H	H	CH_2-(4-CO_2H-1-Pyza)	2-F	4-F	H
2-20	Ac	H	CH_2-(4-CO_2H-1-Pyza)	2-F	4-F	H
2-21	H	H	CH_2-(4-CO_2Me-1-Pyza)	2-F	H	H
2-22	Ac	H	CH_2-(4-CO_2Me-1-Pyza)	2-F	H	H
2-23	H	H	CH_2-(4-CO_2Me-1-Pyza)	2-F	4-F	H
2-24	Ac	H	CH_2-(4-CO_2Me-1-Pyza)	2-F	4-F	H
2-25	H	H	CH_2-(4-CO_2Et-1-Pyza)	2-F	H	H
2-26	Ac	H	CH_2-(4-CO_2Et-1-Pyza)	2-F	H	H
2-27	H	H	CH_2-(4-CO_2Et-1-Pyza)	2-F	4-F	H
2-28	Ac	H	CH_2-(4-CO_2Et-1-Pyza)	2-F	4-F	H
2-29	H	H	CH_2-(5-CO_2H-1-Pyza)	2-F	H	H
2-30	Ac	H	CH_2-(5-CO_2H-1-Pyza)	2-F	H	H
2-31	H	H	CH_2-(5-CO_2H-1-Pyza)	2-F	4-F	H
2-32	Ac	H	CH_2-(5-CO_2H-1-Pyza)	2-F	4-F	H
2-33	H	H	CH_2-(5-CO_2Me-1-Pyza)	2-F	H	H
2-34	Ac	H	CH_2-(5-CO_2Me-1-Pyza)	2-F	H	H
2-35	H	H	CH_2-(5-CO_2Me-1-Pyza)	2-F	4-F	H
2-36	Ac	H	CH_2-(5-CO_2Me-1-Pyza)	2-F	4-F	H
2-37	H	H	CH_2-(5-CO_2Et-1-Pyza)	2-F	H	H
2-38	Ac	H	CH_2-(5-CO_2Et-1-Pyza)	2-F	H	H
2-39	H	H	CH_2-(5-CO_2Et-1-Pyza)	2-F	4-F	H
2-40	Ac	H	CH_2-(5-CO_2Et-1-Pyza)	2-F	4-F	H
2-41	H	H	CH_2-(3-CH_2CO_2H-1-Pyza)	2-F	H	H

2-42	Ac	H	CH_2-(3-CH_2CO_2H-1-Pyza)	2-F	H	H
2-43	H	H	CH_2-(3-CH_2CO_2H-1-Pyza)	2-F	4-F	H
2-44	Ac	H	CH_2-(3-CH_2CO_2H-1-Pyza)	2-F	4-F	H
2-45	H	H	CH_2-(3-CH_2CO_2Me-1-Pyza)	2-F	H	H
2-46	Ac	H	CH_2-(3-CH_2CO_2Me-1-Pyza)	2-F	H	H
2-47	H	H	CH_2-(3-CH_2CO_2Me-1-Pyza)	2-F	4-F	H
2-48	Ac	H	CH_2-(3-CH_2CO_2Me-1-Pyza)	2-F	4-F	H
2-49	H	H	CH_2-(3-CH_2CO_2Et-1-Pyza)	2-F	H	H
2-50	Ac	H	CH_2-(3-CH_2CO_2Et-1-Pyza)	2-F	H	H
2-51	H	H	CH_2-(3-CH_2CO_2Et-1-Pyza)	2-F	4-F	H
2-52	Ac	H	CH_2-(3-CH_2CO_2Et-1-Pyza)	2-F	4-F	H
2-53	H	H	CH_2-(4-CH_2CO_2H-1-Pyza)	2-F	H	H
2-54	Ac	H	CH_2-(4-CH_2CO_2H-1-Pyza)	2-F	H	H
2-55	H	H	CH_2-(4-CH_2CO_2H-1-Pyza)	2-F	4-F	H
2-56	Ac	H	CH_2-(4-CH_2CO_2H-1-Pyza)	2-F	4-F	H
2-57	H	H	CH_2-(4-CH_2CO_2Me-1-Pyza)	2-F	H	H
2-58	Ac	H	CH_2-(4-CH_2CO_2Me-1-Pyza)	2-F	H	H
2-59	H	H	CH_2-(4-CH_2CO_2Me-1-Pyza)	2-F	4-F	H
2-60	Ac	H	CH_2-(4-CH_2CO_2Me-1-Pyza)	2-F	4-F	H
2-61	H	H	CH_2-(4-CH_2CO_2Et-1-Pyza)	2-F	H	H
2-62	Ac	H	CH_2-(4-CH_2CO_2Et-1-Pyza)	2-F	H	H
2-63	H	H	CH_2-(4-CH_2CO_2Et-1-Pyza)	2-F	4-F	H
2-64	Ac	H	CH_2-(4-CH_2CO_2Et-1-Pyza)	2-F	4-F	H
2-65	H	H	CH_2-(5-CH_2CO_2H-1-Pyza)	2-F	H	H
2-66	Ac	H	CH_2-(5-CH_2CO_2H-1-Pyza)	2-F	H	H
2-67	H	H	CH_2-(5-CH_2CO_2H-1-Pyza)	2-F	4-F	H
2-68	Ac	H	CH_2-(5-CH_2CO_2H-1-Pyza)	2-F	4-F	H
2-69	H	H	CH_2-(5-CH_2CO_2Me-1-Pyza)	2-F	H	H
2-70	Ac	H	CH_2-(5-CH_2CO_2Me-1-Pyza)	2-F	H	H
2-71	H	H	CH_2-(5-CH_2CO_2Me-1-Pyza)	2-F	4-F	H
2-72	Ac	H	CH_2-(5-CH_2CO_2Me-1-Pyza)	2-F	4-F	H
2-73	H	H	CH_2-(5-CH_2CO_2Et-1-Pyza)	2-F	H	H
2-74	Ac	H	CH_2-(5-CH_2CO_2Et-1-Pyza)	2-F	H	H
2-75	H	H	CH_2-(5-CH_2CO_2Et-1-Pyza)	2-F	4-F	H
2-76	Ac	H	CH_2-(5-CH_2CO_2Et-1-Pyza)	2-F	4-F	H
2-77	H	H	CH_2-(3-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
2-78	Ac	H	CH_2-(3-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
2-79	H	H	CH_2-(3-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
2-80	Ac	H	CH_2-(3-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
2-81	H	H	CH_2-(3-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
2-82	Ac	H	CH_2-(3-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
2-83	H	H	CH_2-(4-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
2-84	Ac	H	CH_2-(4-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
2-85	H	H	CH_2-(4-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
2-86	Ac	H	CH_2-(4-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
2-87	H	H	CH_2-(4-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
2-88	Ac	H	CH_2-(4-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
2-89	H	H	CH_2-(5-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
2-90	Ac	H	CH_2-(5-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
2-91	H	H	CH_2-(5-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
2-92	Ac	H	CH_2-(5-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
2-93	H	H	CH_2-(5-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
2-94	Ac	H	CH_2-(5-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
2-95	H	H	CH_2-(3-$CH_2CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
2-96	Ac	H	CH_2-(3-$CH_2CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
2-97	H	H	CH_2-(3-$CH_2CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
2-98	Ac	H	CH_2-(3-$CH_2CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H

2-99	H	H	CH_2-(3-$CH_2CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
2-100	Ac	H	CH_2-(3-$CH_2CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
2-101	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
2-102	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
2-103	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
2-104	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
2-105	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
2-106	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
2-107	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
2-108	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
2-109	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
2-110	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
2-111	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
2-112	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
2-113	H	H	CH_2CH_2-1-Pyza	2-F	H	H
2-114	Ac	H	CH_2CH_2-1-Pyza	2-F	H	H
2-115	H	H	CH_2CH_2-(3-CO_2H-1-Pyza)	2-F	H	H
2-116	Ac	H	CH_2CH_2-(3-CO_2H-1-Pyza)	2-F	H	H
2-117	H	H	CH_2CH_2-(3-CO_2Me-1-Pyza)	2-F	H	H
2-118	Ac	H	CH_2CH_2-(3-CO_2Me-1-Pyza)	2-F	H	H
2-119	H	H	CH_2CH_2-(3-CO_2Et-1-Pyza)	2-F	H	H
2-120	Ac	H	CH_2CH_2-(3-CO_2Et-1-Pyza)	2-F	H	H
2-121	H	H	CH_2CH_2-(4-CO_2H-1-Pyza)	2-F	H	H
2-122	Ac	H	CH_2CH_2-(4-CO_2H-1-Pyza)	2-F	H	H
2-123	H	H	CH_2CH_2-(4-CO_2Me-1-Pyza)	2-F	H	H
2-124	Ac	H	CH_2CH_2-(4-CO_2Me-1-Pyza)	2-F	H	H
2-125	H	H	CH_2CH_2-(4-CO_2Et-1-Pyza)	2-F	H	H
2-126	Ac	H	CH_2CH_2-(4-CO_2Et-1-Pyza)	2-F	H	H
2-127	H	H	CH_2CH_2-(5-CO_2H-1-Pyza)	2-F	H	H
2-128	Ac	H	CH_2CH_2-(5-CO_2H-1-Pyza)	2-F	H	H
2-129	H	H	CH_2CH_2-(5-CO_2Me-1-Pyza)	2-F	H	H
2-130	Ac	H	CH_2CH_2-(5-CO_2Me-1-Pyza)	2-F	H	H
2-131	H	H	CH_2CH_2-(5-CO_2Et-1-Pyza)	2-F	H	H
2-132	Ac	H	CH_2CH_2-(5-CO_2Et-1-Pyza)	2-F	H	H
2-133	H	H	CH_2CH_2-(3-CH_2CO_2H-1-Pyza)	2-F	H	H
2-134	Ac	H	CH_2CH_2-(3-CH_2CO_2H-1-Pyza)	2-F	H	H
2-135	H	H	CH_2CH_2-(3-CH_2CO_2Me-1-Pyza)	2-F	H	H
2-136	Ac	H	CH_2CH_2-(3-CH_2CO_2Me-1-Pyza)	2-F	H	H
2-137	H	H	CH_2CH_2-(3-CH_2CO_2Et-1-Pyza)	2-F	H	H
2-138	Ac	H	CH_2CH_2-(3-CH_2CO_2Et-1-Pyza)	2-F	H	H
2-139	H	H	CH_2CH_2-(4-CH_2CO_2H-1-Pyza)	2-F	H	H
2-140	Ac	H	CH_2CH_2-(4-CH_2CO_2H-1-Pyza)	2-F	H	H
2-141	H	H	CH_2CH_2-(4-CH_2CO_2Me-1-Pyza)	2-F	H	H
2-142	Ac	H	CH_2CH_2-(4-CH_2CO_2Me-1-Pyza)	2-F	H	H
2-143	H	H	CH_2CH_2-(4-CH_2CO_2Et-1-Pyza)	2-F	H	H
2-144	Ac	H	CH_2CH_2-(4-CH_2CO_2Et-1-Pyza)	2-F	H	H
2-145	H	H	CH_2CH_2-(5-CH_2CO_2H-1-Pyza)	2-F	H	H
2-146	Ac	H	CH_2CH_2-(5-CH_2CO_2H-1-Pyza)	2-F	H	H
2-147	H	H	CH_2CH_2-(5-CH_2CO_2Me-1-Pyza)	2-F	H	H
2-148	Ac	H	CH_2CH_2-(5-CH_2CO_2Me-1-Pyza)	2-F	H	H
2-149	H	H	CH_2CH_2-(5-CH_2CO_2Et-1-Pyza)	2-F	H	H
2-150	Ac	H	CH_2CH_2-(5-CH_2CO_2Et-1-Pyza)	2-F	H	H
2-151	H	H	CH_2CH_2-(3-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
2-152	Ac	H	CH_2CH_2-(3-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
2-153	H	H	CH_2CH_2-(3-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
2-154	Ac	H	CH_2CH_2-(3-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
2-155	H	H	CH_2CH_2-(3-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H

2-156	Ac	H	CH_2CH_2-(3-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
2-157	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
2-158	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
2-159	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
2-160	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
2-161	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
2-162	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
2-163	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
2-164	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
2-165	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
2-166	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
2-167	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
2-168	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
2-169	H	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
2-170	Ac	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
2-171	H	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
2-172	Ac	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
2-173	H	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
2-174	Ac	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
2-175	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
2-176	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
2-177	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
2-178	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
2-179	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
2-180	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
2-181	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
2-182	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
2-183	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
2-184	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
2-185	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
2-186	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
2-187	H	H	CH_2-3-Pyza	2-F	H	H
2-188	Ac	H	CH_2-3-Pyza	2-F	H	H
2-189	H	H	CH_2-3-Pyza	2-F	4-F	H
2-190	Ac	H	CH_2-3-Pyza	2-F	4-F	H
2-191	H	H	CH_2-(1-CO_2Me-3-Pyza)	2-F	H	H
2-192	Ac	H	CH_2-(1-CO_2Me-3-Pyza)	2-F	H	H
2-193	H	H	CH_2-(1-CO_2Et-3-Pyza)	2-F	H	H
2-194	Ac	H	CH_2-(1-CO_2Et-3-Pyza)	2-F	H	H
2-195	H	H	CH_2-(4-CO_2H-3-Pyza)	2-F	H	H
2-196	Ac	H	CH_2-(4-CO_2H-3-Pyza)	2-F	H	H
2-197	H	H	CH_2-(4-CO_2Me-3-Pyza)	2-F	H	H
2-198	Ac	H	CH_2-(4-CO_2Me-3-Pyza)	2-F	H	H
2-199	H	H	CH_2-(4-CO_2Et-3-Pyza)	2-F	H	H
2-200	Ac	H	CH_2-(4-CO_2Et-3-Pyza)	2-F	H	H
2-201	H	H	CH_2-(5-CO_2H-3-Pyza)	2-F	H	H
2-202	Ac	H	CH_2-(5-CO_2H-3-Pyza)	2-F	H	H
2-203	H	H	CH_2-(5-CO_2Me-3-Pyza)	2-F	H	H
2-204	Ac	H	CH_2-(5-CO_2Me-3-Pyza)	2-F	H	H
2-205	H	H	CH_2-(5-CO_2Et-3-Pyza)	2-F	H	H
2-206	Ac	H	CH_2-(5-CO_2Et-3-Pyza)	2-F	H	H
2-207	H	H	CH_2-(1-CH_2CO_2H-3-Pyza)	2-F	H	H
2-208	Ac	H	CH_2-(1-CH_2CO_2H-3-Pyza)	2-F	H	H
2-209	H	H	CH_2-(1-CH_2CO_2Me-3-Pyza)	2-F	H	H
2-210	Ac	H	CH_2-(1-CH_2CO_2Me-3-Pyza)	2-F	H	H
2-211	H	H	CH_2-(1-CH_2CO_2Et-3-Pyza)	2-F	H	H
2-212	Ac	H	CH_2-(1-CH_2CO_2Et-3-Pyza)	2-F	H	H

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2-213	H	H	CH_2-(4-CH_2CO_2H-3-Pyza)	2-F	H	H
2-214	Ac	H	CH_2-(4-CH_2CO_2H-3-Pyza)	2-F	H	H
2-215	H	H	CH_2-(4-CH_2CO_2Me-3-Pyza)	2-F	H	H
2-216	Ac	H	CH_2-(4-CH_2CO_2Me-3-Pyza)	2-F	H	H
2-217	H	H	CH_2-(4-CH_2CO_2Et-3-Pyza)	2-F	H	H
2-218	Ac	H	CH_2-(4-CH_2CO_2Et-3-Pyza)	2-F	H	H
2-219	H	H	CH_2-(5-CH_2CO_2H-3-Pyza)	2-F	H	H
2-220	Ac	H	CH_2-(5-CH_2CO_2H-3-Pyza)	2-F	H	H
2-221	H	H	CH_2-(5-CH_2CO_2Me-3-Pyza)	2-F	H	H
2-222	Ac	H	CH_2-(5-CH_2CO_2Me-3-Pyza)	2-F	H	H
2-223	H	H	CH_2-(5-CH_2CO_2Et-3-Pyza)	2-F	H	H
2-224	Ac	H	CH_2-(5-CH_2CO_2Et-3-Pyza)	2-F	H	H
2-225	H	H	CH_2-(1-$CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
2-226	Ac	H	CH_2-(1-$CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
2-227	H	H	CH_2-(1-$CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
2-228	Ac	H	CH_2-(1-$CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
2-229	H	H	CH_2-(1-$CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
2-230	Ac	H	CH_2-(1-$CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
2-231	H	H	CH_2-(4-$CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
2-232	Ac	H	CH_2-(4-$CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
2-233	H	H	CH_2-(4-$CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
2-234	Ac	H	CH_2-(4-$CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
2-235	H	H	CH_2-(4-$CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
2-236	Ac	H	CH_2-(4-$CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
2-237	H	H	CH_2-(5-$CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
2-238	Ac	H	CH_2-(5-$CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
2-239	H	H	CH_2-(5-$CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
2-240	Ac	H	CH_2-(5-$CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
2-241	H	H	CH_2-(5-$CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
2-242	Ac	H	CH_2-(5-$CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
2-245	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
2-246	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
2-247	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
2-248	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
2-249	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
2-250	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
2-251	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
2-252	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
2-253	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
2-254	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
2-255	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
2-256	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
2-257	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
2-258	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
2-259	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
2-260	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
2-261	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
2-262	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
2-263	H	H	CH_2CH_2-3-Pyza	2-F	H	H
2-264	Ac	H	CH_2CH_2-3-Pyza	2-F	H	H
2-265	H	H	CH_2CH_2-3-Pyza	2-F	4-F	H
2-266	Ac	H	CH_2CH_2-3-Pyza	2-F	4-F	H
2-267	H	H	CH_2CH_2-(1-CO_2Me-3-Pyza)	2-F	H	H
2-268	Ac	H	CH_2CH_2-(1-CO_2Me-3-Pyza)	2-F	H	H
2-269	H	H	CH_2CH_2-(1-CO_2Et-3-Pyza)	2-F	H	H
2-270	Ac	H	CH_2CH_2-(1-CO_2Et-3-Pyza)	2-F	H	H
2-271	H	H	CH_2CH_2-(4-CO_2H-3-Pyza)	2-F	H	H

2-272	Ac	H	CH_2CH_2-(4-CO_2H-3-Pyza)	2-F	H	H
2-273	H	H	CH_2CH_2-(4-CO_2Me-3-Pyza)	2-F	H	H
2-274	Ac	H	CH_2CH_2-(4-CO_2Me-3-Pyza)	2-F	H	H
2-275	H	H	CH_2CH_2-(4-CO_2Et-3-Pyza)	2-F	H	H
2-276	Ac	H	CH_2CH_2-(4-CO_2Et-3-Pyza)	2-F	H	H
2-277	H	H	CH_2CH_2-(5-CO_2H-3-Pyza)	2-F	H	H
2-278	Ac	H	CH_2CH_2-(5-CO_2H-3-Pyza)	2-F	H	H
2-279	H	H	CH_2CH_2-(5-CO_2Me-3-Pyza)	2-F	H	H
2-280	Ac	H	CH_2CH_2-(5-CO_2Me-3-Pyza)	2-F	H	H
2-281	H	H	CH_2CH_2-(5-CO_2Et-3-Pyza)	2-F	H	H
2-282	Ac	H	CH_2CH_2-(5-CO_2Et-3-Pyza)	2-F	H	H
2-283	H	H	CH_2CH_2-(1-CH_2CO_2H-3-Pyza)	2-F	H	H
2-284	Ac	H	CH_2CH_2-(1-CH_2CO_2H-3-Pyza)	2-F	H	H
2-285	H	H	CH_2CH_2-(1-CH_2CO_2Me-3-Pyza)	2-F	H	H
2-286	Ac	H	CH_2CH_2-(1-CH_2CO_2Me-3-Pyza)	2-F	H	H
2-287	H	H	CH_2CH_2-(1-CH_2CO_2Et-3-Pyza)	2-F	H	H
2-288	Ac	H	CH_2CH_2-(1-CH_2CO_2Et-3-Pyza)	2-F	H	H
2-289	H	H	CH_2CH_2-(4-CH_2CO_2H-3-Pyza)	2-F	H	H
2-290	Ac	H	CH_2CH_2-(4-CH_2CO_2H-3-Pyza)	2-F	H	H
2-291	H	H	CH_2CH_2-(4-CH_2CO_2Me-3-Pyza)	2-F	H	H
2-292	Ac	H	CH_2CH_2-(4-CH_2CO_2Me-3-Pyza)	2-F	H	H
2-293	H	H	CH_2CH_2-(4-CH_2CO_2Et-3-Pyza)	2-F	H	H
2-294	Ac	H	CH_2CH_2-(4-CH_2CO_2Et-3-Pyza)	2-F	H	H
2-295	H	H	CH_2CH_2-(5-CH_2CO_2H-3-Pyza)	2-F	H	H
2-296	Ac	H	CH_2CH_2-(5-CH_2CO_2H-3-Pyza)	2-F	H	H
2-297	H	H	CH_2CH_2-(5-CH_2CO_2Me-3-Pyza)	2-F	H	H
2-298	Ac	H	CH_2CH_2-(5-CH_2CO_2Me-3-Pyza)	2-F	H	H
2-299	H	H	CH_2CH_2-(5-CH_2CO_2Et-3-Pyza)	2-F	H	H
2-300	Ac	H	CH_2CH_2-(5-CH_2CO_2Et-3-Pyza)	2-F	H	H
2-301	H	H	CH_2CH_2-(1-$CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
2-302	Ac	H	CH_2CH_2-(1-$CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
2-303	H	H	CH_2CH_2-(1-$CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
2-304	Ac	H	CH_2CH_2-(1-$CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
2-305	H	H	CH_2CH_2-(1-$CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
2-306	Ac	H	CH_2CH_2-(1-$CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
2-307	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
2-308	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
2-309	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
2-310	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
2-311	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
2-312	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
2-313	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
2-314	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
2-315	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
2-316	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
2-317	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
2-318	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
2-319	H	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
2-320	Ac	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
2-321	H	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
2-322	Ac	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
2-323	H	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
2-324	Ac	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
2-325	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
2-326	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
2-327	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
2-328	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H

2-329	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
2-330	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
2-331	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
2-332	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
2-333	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
2-334	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
2-335	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
2-336	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
2-337	H	H	CH_2-4-Pyza	2-F	H	H
2-338	Ac	H	CH_2-4-Pyza	2-F	H	H
2-339	H	H	CH_2-4-Pyza	2-F	4-F	H
2-340	Ac	H	CH_2-4-Pyza	2-F	4-F	H
2-341	H	H	CH_2-(1-CO_2Me-4-Pyza)	2-F	H	H
2-342	Ac	H	CH_2-(1-CO_2Me-4-Pyza)	2-F	H	H
2-343	H	H	CH_2-(1-CO_2Et-4-Pyza)	2-F	H	H
2-344	Ac	H	CH_2-(1-CO_2Et-4-Pyza)	2-F	H	H
2-345	H	H	CH_2-(3-CO_2H-4-Pyza)	2-F	H	H
2-346	Ac	H	CH_2-(3-CO_2H-4-Pyza)	2-F	H	H
2-347	H	H	CH_2-(3-CO_2Me-4-Pyza)	2-F	H	H
2-348	Ac	H	CH_2-(3-CO_2Me-4-Pyza)	2-F	H	H
2-349	H	H	CH_2-(3-CO_2Et-4-Pyza)	2-F	H	H
2-350	Ac	H	CH_2-(3-CO_2Et-4-Pyza)	2-F	H	H
2-351	H	H	CH_2-(1-CH_2CO_2H-4-Pyza)	2-F	H	H
2-352	Ac	H	CH_2-(1-CH_2CO_2H-4-Pyza)	2-F	H	H
2-353	H	H	CH_2-(1-CH_2CO_2Me-4-Pyza)	2-F	H	H
2-354	Ac	H	CH_2-(1-CH_2CO_2Me-4-Pyza)	2-F	H	H
2-355	H	H	CH_2-(1-CH_2CO_2Et-4-Pyza)	2-F	H	H
2-356	Ac	H	CH_2-(1-CH_2CO_2Et-4-Pyza)	2-F	H	H
2-357	H	H	CH_2-(3-CH_2CO_2H-4-Pyza)	2-F	H	H
2-358	Ac	H	CH_2-(3-CH_2CO_2H-4-Pyza)	2-F	H	H
2-359	H	H	CH_2-(3-CH_2CO_2Me-4-Pyza)	2-F	H	H
2-360	Ac	H	CH_2-(3-CH_2CO_2Me-4-Pyza)	2-F	H	H
2-361	H	H	CH_2-(3-CH_2CO_2Et-4-Pyza)	2-F	H	H
2-362	Ac	H	CH_2-(3-CH_2CO_2Et-4-Pyza)	2-F	H	H
2-363	H	H	CH_2-(1-$CH_2CH_2CO_2H$-4-Pyza)	2-F	H	H
2-364	Ac	H	CH_2-(1-$CH_2CH_2CO_2H$-4-Pyza)	2-F	H	H
2-365	H	H	CH_2-(1-$CH_2CH_2CO_2Me$-4-Pyza)	2-F	H	H
2-366	Ac	H	CH_2-(1-$CH_2CH_2CO_2Me$-4-Pyza)	2-F	H	H
2-367	H	H	CH_2-(1-$CH_2CH_2CO_2Et$-4-Pyza)	2-F	H	H
2-368	Ac	H	CH_2-(1-$CH_2CH_2CO_2Et$-4-Pyza)	2-F	H	H
2-369	H	H	CH_2-(3-$CH_2CH_2CO_2H$-4-Pyza)	2-F	H	H
2-370	Ac	H	CH_2-(3-$CH_2CH_2CO_2H$-4-Pyza)	2-F	H	H
2-371	H	H	CH_2-(3-$CH_2CH_2CO_2Me$-4-Pyza)	2-F	H	H
2-372	Ac	H	CH_2-(3-$CH_2CH_2CO_2Me$-4-Pyza)	2-F	H	H
2-373	H	H	CH_2-(3-$CH_2CH_2CO_2Et$-4-Pyza)	2-F	H	H
2-374	Ac	H	CH_2-(3-$CH_2CH_2CO_2Et$-4-Pyza)	2-F	H	H
2-375	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2H$-4-Pyza)	2-F	H	H
2-376	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2H$-4-Pyza)	2-F	H	H
2-377	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2Me$-4-Pyza)	2-F	H	H
2-378	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2Me$-4-Pyza)	2-F	H	H
2-379	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2Et$-4-Pyza)	2-F	H	H
2-380	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2Et$-4-Pyza)	2-F	H	H
2-381	H	H	CH_2-(3-$CH_2CH_2CH_2CO_2H$-4-Pyza)	2-F	H	H
2-382	Ac	H	CH_2-(3-$CH_2CH_2CH_2CO_2H$-4-Pyza)	2-F	H	H
2-383	H	H	CH_2-(3-$CH_2CH_2CH_2CO_2Me$-4-Pyza)	2-F	H	H
2-384	Ac	H	CH_2-(3-$CH_2CH_2CH_2CO_2Me$-4-Pyza)	2-F	H	H
2-385	H	H	CH_2-(3-$CH_2CH_2CH_2CO_2Et$-4-Pyza)	2-F	H	H

2-386	Ac	H	CH_2-(3-$CH_2CH_2CH_2CO_2Et$-4-Pyza)	2-F	H	H
2-387	H	H	CH_2CH_2-4-Pyza	2-F	H	H
2-388	Ac	H	CH_2CH_2-4-Pyza	2-F	H	H
2-389	H	H	CH_2CH_2-4-Pyza	2-F	4-F	H
2-390	Ac	H	CH_2CH_2-4-Pyza	2-F	4-F	H
2-391	H	H	CH_2CH_2-(1-CO_2Me-4-Pyza)	2-F	H	H
2-392	Ac	H	CH_2CH_2-(1-CO_2Me-4-Pyza)	2-F	H	H
2-393	H	H	CH_2CH_2-(1-CO_2Et-4-Pyza)	2-F	H	H
2-394	Ac	H	CH_2CH_2-(1-CO_2Et-4-Pyza)	2-F	H	H
2-395	H	H	CH_2CH_2-(3-CO_2H-4-Pyza)	2-F	H	H
2-396	Ac	H	CH_2CH_2-(3-CO_2H-4-Pyza)	2-F	H	H
2-397	H	H	CH_2CH_2-(3-CO_2Me-4-Pyza)	2-F	H	H
2-398	Ac	H	CH_2CH_2-(3-CO_2Me-4-Pyza)	2-F	H	H
2-399	H	H	CH_2CH_2-(3-CO_2Et-4-Pyza)	2-F	H	H
2-400	Ac	H	CH_2CH_2-(3-CO_2Et-4-Pyza)	2-F	H	H
2-401	H	H	CH_2CH_2-(1-CH_2CO_2H-4-Pyza)	2-F	H	H
2-402	Ac	H	CH_2CH_2-(1-CH_2CO_2H-4-Pyza)	2-F	H	H
2-403	H	H	CH_2CH_2-(1-CH_2CO_2Me-4-Pyza)	2-F	H	H
2-404	Ac	H	CH_2CH_2-(1-CH_2CO_2Me-4-Pyza)	2-F	H	H
2-405	H	H	CH_2CH_2-(1-CH_2CO_2Et-4-Pyza)	2-F	H	H
2-406	Ac	H	CH_2CH_2-(1-CH_2CO_2Et-4-Pyza)	2-F	H	H
2-407	H	H	CH_2CH_2-(3-CH_2CO_2H-4-Pyza)	2-F	H	H
2-408	Ac	H	CH_2CH_2-(3-CH_2CO_2H-4-Pyza)	2-F	H	H
2-409	H	H	CH_2CH_2-(3-CH_2CO_2Me-4-Pyza)	2-F	H	H
2-410	Ac	H	CH_2CH_2-(3-CH_2CO_2Me-4-Pyza)	2-F	H	H
2-411	H	H	CH_2CH_2-(3-CH_2CO_2Et-4-Pyza)	2-F	H	H
2-412	Ac	H	CH_2CH_2-(3-CH_2CO_2Et-4-Pyza)	2-F	H	H
2-413	H	H	CH_2CH_2-(1-$CH_2CH_2CO_2H$-4-Pyza)	2-F	H	H
2-414	Ac	H	CH_2CH_2-(1-$CH_2CH_2CO_2H$-4-Pyza)	2-F	H	H
2-415	H	H	CH_2CH_2-(1-$CH_2CH_2CO_2Me$-4-Pyza)	2-F	H	H
2-416	Ac	H	CH_2CH_2-(1-$CH_2CH_2CO_2Me$-4-Pyza)	2-F	H	H
2-417	H	H	CH_2CH_2-(1-$CH_2CH_2CO_2Et$-4-Pyza)	2-F	H	H
2-418	Ac	H	CH_2CH_2-(1-$CH_2CH_2CO_2Et$-4-Pyza)	2-F	H	H
2-419	H	H	CH_2CH_2-(3-$CH_2CH_2CO_2H$-4-Pyza)	2-F	H	H
2-420	Ac	H	CH_2CH_2-(3-$CH_2CH_2CO_2H$-4-Pyza)	2-F	H	H
2-421	H	H	CH_2CH_2-(3-$CH_2CH_2CO_2Me$-4-Pyza)	2-F	H	H
2-422	Ac	H	CH_2CH_2-(3-$CH_2CH_2CO_2Me$-4-Pyza)	2-F	H	H
2-423	H	H	CH_2CH_2-(3-$CH_2CH_2CO_2Et$-4-Pyza)	2-F	H	H
2-424	Ac	H	CH_2CH_2-(3-$CH_2CH_2CO_2Et$-4-Pyza)	2-F	H	H
2-425	H	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2H$-4-Pyza)	2-F	H	H
2-426	Ac	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2H$-4-Pyza)	2-F	H	H
2-427	H	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Me$-4-Pyza)	2-F	H	H
2-428	Ac	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Me$-4-Pyza)	2-F	H	H
2-429	H	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Et$-4-Pyza)	2-F	H	H
2-430	Ac	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Et$-4-Pyza)	2-F	H	H
2-431	H	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2H$-4-Pyza)	2-F	H	H
2-432	Ac	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2H$-4-Pyza)	2-F	H	H
2-433	H	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2Me$-4-Pyza)	2-F	H	H
2-434	Ac	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2Me$-4-Pyza)	2-F	H	H
2-435	H	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2Et$-4-Pyza)	2-F	H	H
2-436	Ac	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2Et$-4-Pyza)	2-F	H	H
2-437	H	H	CH_2-(1-CO_2Me-5-Pyza)	2-F	4-F	H
2-438	Ac	H	CH_2-(1-CO_2Me-5-Pyza)	2-F	4-F	H
2-439	H	H	CH_2-(1-CO_2Me-5-Pyza)	2-F	H	H
2-440	Ac	H	CH_2-(1-CO_2Me-5-Pyza)	2-F	H	H
2-441	H	H	CH_2-(1-CO_2Et-5-Pyza)	2-F	H	H
2-442	Ac	H	CH_2-(1-CO_2Et-5-Pyza)	2-F	H	H

2-443	H	H	CH_2-(1-CH_2CO_2H-5-Pyza)	2-F	H	H
2-444	Ac	H	CH_2-(1-CH_2CO_2H-5-Pyza)	2-F	H	H
2-445	H	H	CH_2-(1-CH_2CO_2Me-5-Pyza)	2-F	H	H
2-446	Ac	H	CH_2-(1-CH_2CO_2Me-5-Pyza)	2-F	H	H
2-447	H	H	CH_2-(1-CH_2CO_2Et-5-Pyza)	2-F	H	H
2-448	Ac	H	CH_2-(1-CH_2CO_2Et-5-Pyza)	2-F	H	H
2-449	H	H	CH_2-(1-$CH_2CH_2CO_2H$-5-Pyza)	2-F	H	H
2-450	Ac	H	CH_2-(1-$CH_2CH_2CO_2H$-5-Pyza)	2-F	H	H
2-451	H	H	CH_2-(1-$CH_2CH_2CO_2Me$-5-Pyza)	2-F	H	H
2-452	Ac	H	CH_2-(1-$CH_2CH_2CO_2Me$-5-Pyza)	2-F	H	H
2-453	H	H	CH_2-(1-$CH_2CH_2CO_2Et$-5-Pyza)	2-F	H	H
2-454	Ac	H	CH_2-(1-$CH_2CH_2CO_2Et$-5-Pyza)	2-F	H	H
2-455	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2H$-5-Pyza)	2-F	H	H
2-456	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2H$-5-Pyza)	2-F	H	H
2-457	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2Me$-5-Pyza)	2-F	H	H
2-458	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2Me$-5-Pyza)	2-F	H	H
2-459	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2Et$-5-Pyza)	2-F	H	H
2-460	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2Et$-5-Pyza)	2-F	H	H
2-461	H	H	CH_2CH_2-(1-CO_2Me-5-Pyza)	2-F	4-F	H
2-462	Ac	H	CH_2CH_2-(1-CO_2Me-5-Pyza)	2-F	4-F	H
2-463	H	H	CH_2CH_2-(1-CO_2Me-5-Pyza)	2-F	H	H
2-464	Ac	H	CH_2CH_2-(1-CO_2Me-5-Pyza)	2-F	H	H
2-465	H	H	CH_2CH_2-(1-CO_2Et-5-Pyza)	2-F	H	H
2-466	Ac	H	CH_2CH_2-(1-CO_2Et-5-Pyza)	2-F	H	H
2-467	H	H	CH_2CH_2-(1-CH_2CO_2H-5-Pyza)	2-F	H	H
2-468	Ac	H	CH_2CH_2-(1-CH_2CO_2H-5-Pyza)	2-F	H	H
2-469	H	H	CH_2CH_2-(1-CH_2CO_2Me-5-Pyza)	2-F	H	H
2-470	Ac	H	CH_2CH_2-(1-CH_2CO_2Me-5-Pyza)	2-F	H	H
2-471	H	H	CH_2CH_2-(1-CH_2CO_2Et-5-Pyza)	2-F	H	H
2-472	Ac	H	CH_2CH_2-(1-CH_2CO_2Et-5-Pyza)	2-F	H	H
2-473	H	H	CH_2CH_2-(1-$CH_2CH_2CO_2H$-5-Pyza)	2-F	H	H
2-474	Ac	H	CH_2CH_2-(1-$CH_2CH_2CO_2H$-5-Pyza)	2-F	H	H
2-475	H	H	CH_2CH_2-(1-$CH_2CH_2CO_2Me$-5-Pyza)	2-F	H	H
2-476	Ac	H	CH_2CH_2-(1-$CH_2CH_2CO_2Me$-5-Pyza)	2-F	H	H
2-477	H	H	CH_2CH_2-(1-$CH_2CH_2CO_2Et$-5-Pyza)	2-F	H	H
2-478	Ac	H	CH_2CH_2-(1-$CH_2CH_2CO_2Et$-5-Pyza)	2-F	H	H
2-479	H	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2H$-5-Pyza)	2-F	H	H
2-480	Ac	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2H$-5-Pyza)	2-F	H	H
2-481	H	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Me$-5-Pyza)	2-F	H	H
2-482	Ac	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Me$-5-Pyza)	2-F	H	H
2-483	H	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Et$-5-Pyza)	2-F	H	H
2-484	Ac	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Et$-5-Pyza)	2-F	H	H
2-485	H	H	CH_2-1-Triz	2-F	H	H
2-486	Ac	H	CH_2-1-Triz	2-F	H	H
2-487	H	H	CH_2-(4-CO_2H-1-Triz)	2-F	H	H
2-488	Ac	H	CH_2-(4-CO_2H-1-Triz)	2-F	H	H
2-489	H	H	CH_2-(4-CO_2Me-1-Triz)	2-F	H	H
2-490	Ac	H	CH_2-(4-CO_2Me-1-Triz)	2-F	H	H
2-491	H	H	CH_2-(4-CO_2Et-1-Triz)	2-F	H	H
2-492	Ac	H	CH_2-(4-CO_2Et-1-Triz)	2-F	H	H
2-493	H	H	CH_2-(5-CO_2H-1-Triz)	2-F	H	H
2-494	Ac	H	CH_2-(5-CO_2H-1-Triz)	2-F	H	H
2-495	H	H	CH_2-(5-CO_2Me-1-Triz)	2-F	H	H
2-496	Ac	H	CH_2-(5-CO_2Me-1-Triz)	2-F	H	H
2-497	H	H	CH_2-(5-CO_2Et-1-Triz)	2-F	H	H
2-498	Ac	H	CH_2-(5-CO_2Et-1-Triz)	2-F	H	H
2-499	H	H	CH_2-(4-CH_2CO_2H-1-Triz)	2-F	H	H

2-500	Ac	H	CH_2-(4-CH_2CO_2H-1-Triz)	2-F	H	H
2-501	H	H	CH_2-(4-CH_2CO_2Me-1-Triz)	2-F	H	H
2-502	Ac	H	CH_2-(4-CH_2CO_2Me-1-Triz)	2-F	H	H
2-503	H	H	CH_2-(4-CH_2CO_2Et-1-Triz)	2-F	H	H
2-504	Ac	H	CH_2-(4-CH_2CO_2Et-1-Triz)	2-F	H	H
2-505	H	H	CH_2-(5-CH_2CO_2H-1-Triz)	2-F	H	H
2-506	Ac	H	CH_2-(5-CH_2CO_2H-1-Triz)	2-F	H	H
2-507	H	H	CH_2-(5-CH_2CO_2Me-1-Triz)	2-F	H	H
2-508	Ac	H	CH_2-(5-CH_2CO_2Me-1-Triz)	2-F	H	H
2-509	H	H	CH_2-(5-CH_2CO_2Et-1-Triz)	2-F	H	H
2-510	Ac	H	CH_2-(5-CH_2CO_2Et-1-Triz)	2-F	H	H
2-511	H	H	CH_2-(4-$CH_2CH_2CO_2H$-1-Triz)	2-F	H	H
2-512	Ac	H	CH_2-(4-$CH_2CH_2CO_2H$-1-Triz)	2-F	H	H
2-513	H	H	CH_2-(4-$CH_2CH_2CO_2Me$-1-Triz)	2-F	H	H
2-514	Ac	H	CH_2-(4-$CH_2CH_2CO_2Me$-1-Triz)	2-F	H	H
2-515	H	H	CH_2-(4-$CH_2CH_2CO_2Et$-1-Triz)	2-F	H	H
2-516	Ac	H	CH_2-(4-$CH_2CH_2CO_2Et$-1-Triz)	2-F	H	H
2-517	H	H	CH_2-(5-$CH_2CH_2CO_2H$-1-Triz)	2-F	H	H
2-518	Ac	H	CH_2-(5-$CH_2CH_2CO_2H$-1-Triz)	2-F	H	H
2-519	H	H	CH_2-(5-$CH_2CH_2CO_2Me$-1-Triz)	2-F	H	H
2-520	Ac	H	CH_2-(5-$CH_2CH_2CO_2Me$-1-Triz)	2-F	H	H
2-521	H	H	CH_2-(5-$CH_2CH_2CO_2Et$-1-Triz)	2-F	H	H
2-522	Ac	H	CH_2-(5-$CH_2CH_2CO_2Et$-1-Triz)	2-F	H	H
2-523	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2H$-1-Triz)	2-F	H	H
2-524	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2H$-1-Triz)	2-F	H	H
2-525	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2Me$-1-Triz)	2-F	H	H
2-526	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2Me$-1-Triz)	2-F	H	H
2-527	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2Et$-1-Triz)	2-F	H	H
2-528	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2Et$-1-Triz)	2-F	H	H
2-529	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2H$-1-Triz)	2-F	H	H
2-530	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2H$-1-Triz)	2-F	H	H
2-531	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2Me$-1-Triz)	2-F	H	H
2-532	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2Me$-1-Triz)	2-F	H	H
2-533	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2Et$-1-Triz)	2-F	H	H
2-534	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2Et$-1-Triz)	2-F	H	H
2-535	H	H	CH_2CH_2-1-Triz	2-F	H	H
2-356[TY2]	Ac	H	CH_2CH_2-1-Triz	2-F	H	H
2-537	H	H	CH_2CH_2-(4-CO_2H-1-Triz)	2-F	H	H
2-538	Ac	H	CH_2CH_2-(4-CO_2H-1-Triz)	2-F	H	H
2-539	H	H	CH_2CH_2-(4-CO_2Me-1-Triz)	2-F	H	H
2-540	Ac	H	CH_2CH_2-(4-CO_2Me-1-Triz)	2-F	H	H
2-541	H	H	CH_2CH_2-(4-CO_2Et-1-Triz)	2-F	H	H
2-542	Ac	H	CH_2CH_2-(4-CO_2Et-1-Triz)	2-F	H	H
2-543	H	H	CH_2CH_2-(5-CO_2H-1-Triz)	2-F	H	H
2-544	Ac	H	CH_2CH_2-(5-CO_2H-1-Triz)	2-F	H	H
2-545	H	H	CH_2CH_2-(5-CO_2Me-1-Triz)	2-F	H	H
2-546	Ac	H	CH_2CH_2-(5-CO_2Me-1-Triz)	2-F	H	H
2-547	H	H	CH_2CH_2-(5-CO_2Et-1-Triz)	2-F	H	H
2-548	Ac	H	CH_2CH_2-(5-CO_2Et-1-Triz)	2-F	H	H
2-549	H	H	CH_2CH_2-(4-CH_2CO_2H-1-Triz)	2-F	H	H
2-550	Ac	H	CH_2CH_2-(4-CH_2CO_2H-1-Triz)	2-F	H	H
2-551	H	H	CH_2CH_2-(4-CH_2CO_2Me-1-Triz)	2-F	H	H
2-552	Ac	H	CH_2CH_2-(4-CH_2CO_2Me-1-Triz)	2-F	H	H
2-553	H	H	CH_2CH_2-(4-CH_2CO_2Et-1-Triz)	2-F	H	H
2-554	Ac	H	CH_2CH_2-(4-CH_2CO_2Et-1-Triz)	2-F	H	H
2-555	H	H	CH_2CH_2-(5-CH_2CO_2H-1-Triz)	2-F	H	H
2-556	Ac	H	CH_2CH_2-(5-CH_2CO_2H-1-Triz)	2-F	H	H

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2-557	H	H	CH_2CH_2-(5-CH_2CO_2Me-1-Triz)	2-F	H	H
2-558	Ac	H	CH_2CH_2-(5-CH_2CO_2Me-1-Triz)	2-F	H	H
2-559	H	H	CH_2CH_2-(5-CH_2CO_2Et-1-Triz)	2-F	H	H
2-560	Ac	H	CH_2CH_2-(5-CH_2CO_2Et-1-Triz)	2-F	H	H
2-561	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2H$-1-Triz)	2-F	H	H
2-562	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2H$-1-Triz)	2-F	H	H
2-563	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-1-Triz)	2-F	H	H
2-564	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-1-Triz)	2-F	H	H
2-565	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-1-Triz)	2-F	H	H
2-566	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-1-Triz)	2-F	H	H
2-567	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2H$-1-Triz)	2-F	H	H
2-568	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2H$-1-Triz)	2-F	H	H
2-569	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2Me$-1-Triz)	2-F	H	H
2-570	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2Me$-1-Triz)	2-F	H	H
2-571	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2Et$-1-Triz)	2-F	H	H
2-572	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2Et$-1-Triz)	2-F	H	H
2-573	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2H$-1-Triz)	2-F	H	H
2-574	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2H$-1-Triz)	2-F	H	H
2-575	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Me$-1-Triz)	2-F	H	H
2-576	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Me$-1-Triz)	2-F	H	H
2-577	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Et$-1-Triz)	2-F	H	H
2-578	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Et$-1-Triz)	2-F	H	H
2-579	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2H$-1-Triz)	2-F	H	H
2-580	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2H$-1-Triz)	2-F	H	H
2-581	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Me$-1-Triz)	2-F	H	H
2-582	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Me$-1-Triz)	2-F	H	H
2-583	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Et$-1-Triz)	2-F	H	H
2-584	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Et$-1-Triz)	2-F	H	H
2-585	H	H	CH_2-2-Triz	2-F	H	H
2-586	Ac	H	CH_2-2-Triz	2-F	H	H
2-587	H	H	CH_2-(4-CO_2H-2-Triz)	2-F	H	H
2-588	Ac	H	CH_2-(4-CO_2H-2-Triz)	2-F	H	H
2-589	H	H	CH_2-(4-CO_2Me-2-Triz)	2-F	H	H
2-590	Ac	H	CH_2-(4-CO_2Me-2-Triz)	2-F	H	H
2-591	H	H	CH_2-(4-CO_2Et-2-Triz)	2-F	H	H
2-592	Ac	H	CH_2-(4-CO_2Et-2-Triz)	2-F	H	H
2-593	H	H	CH_2-(4-CH_2CO_2H-2-Triz)	2-F	H	H
2-594	Ac	H	CH_2-(4-CH_2CO_2H-2-Triz)	2-F	H	H
2-595	H	H	CH_2-(4-CH_2CO_2Me-2-Triz)	2-F	H	H
2-596	Ac	H	CH_2-(4-CH_2CO_2Me-2-Triz)	2-F	H	H
2-597	H	H	CH_2-(4-CH_2CO_2Et-2-Triz)	2-F	H	H
2-598	Ac	H	CH_2-(4-CH_2CO_2Et-2-Triz)	2-F	H	H
2-599	H	H	CH_2-(4-$CH_2CH_2CO_2H$-2-Triz)	2-F	H	H
2-600	Ac	H	CH_2-(4-$CH_2CH_2CO_2H$-2-Triz)	2-F	H	H
2-601	H	H	CH_2-(4-$CH_2CH_2CO_2Me$-2-Triz)	2-F	H	H
2-602	Ac	H	CH_2-(4-$CH_2CH_2CO_2Me$-2-Triz)	2-F	H	H
2-603	H	H	CH_2-(4-$CH_2CH_2CO_2Et$-2-Triz)	2-F	H	H
2-604	Ac	H	CH_2-(4-$CH_2CH_2CO_2Et$-2-Triz)	2-F	H	H
2-605	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2H$-2-Triz)	2-F	H	H
2-606	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2H$-2-Triz)	2-F	H	H
2-607	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2Me$-2-Triz)	2-F	H	H
2-608	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2Me$-2-Triz)	2-F	H	H
2-609	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2Et$-2-Triz)	2-F	H	H
2-610	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2Et$-2-Triz)	2-F	H	H
2-611	H	H	CH_2CH_2-2-Triz	2-F	H	H
2-612	Ac	H	CH_2CH_2-2-Triz	2-F	H	H
2-613	H	H	CH_2CH_2-(4-CO_2H-2-Triz)	2-F	H	H

2-614	Ac	H	CH_2CH_2-(4-CO_2H-2-Triz)	2-F	H	H
2-615	H	H	CH_2CH_2-(4-CO_2Me-2-Triz)	2-F	H	H
2-616	Ac	H	CH_2CH_2-(4-CO_2Me-2-Triz)	2-F	H	H
2-617	H	H	CH_2CH_2-(4-CO_2Et-2-Triz)	2-F	H	H
2-618	Ac	H	CH_2CH_2-(4-CO_2Et-2-Triz)	2-F	H	H
2-619	H	H	CH_2CH_2-(4-CH_2CO_2H-2-Triz)	2-F	H	H
2-620	Ac	H	CH_2CH_2-(4-CH_2CO_2H-2-Triz)	2-F	H	H
2-621	H	H	CH_2CH_2-(4-CH_2CO_2Me-2-Triz)	2-F	H	H
2-622	Ac	H	CH_2CH_2-(4-CH_2CO_2Me-2-Triz)	2-F	H	H
2-623	H	H	CH_2CH_2-(4-CH_2CO_2Et-2-Triz)	2-F	H	H
2-624	Ac	H	CH_2CH_2-(4-CH_2CO_2Et-2-Triz)	2-F	H	H
2-625	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2H$-2-Triz)	2-F	H	H
2-626	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2H$-2-Triz)	2-F	H	H
2-627	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-2-Triz)	2-F	H	H
2-628	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-2-Triz)	2-F	H	H
2-629	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-2-Triz)	2-F	H	H
2-630	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-2-Triz)	2-F	H	H
2-631	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2H$-2-Triz)	2-F	H	H
2-632	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2H$-2-Triz)	2-F	H	H
2-633	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Me$-2-Triz)	2-F	H	H
2-634	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Me$-2-Triz)	2-F	H	H
2-635	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Et$-2-Triz)	2-F	H	H
2-636	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Et$-2-Triz)	2-F	H	H
2-637	H	H	CH_2-4-Triz	2-F	H	H
2-638	Ac	H	CH_2-4-Triz	2-F	H	H
2-639	H	H	CH_2-4-Triz	2-F	4-F	H
2-640	Ac	H	CH_2-4-Triz	2-F	4-F	H
2-641	H	H	CH_2-(1-CO_2Me-4-Triz)	2-F	H	H
2-642	Ac	H	CH_2-(1-CO_2Me-4-Triz)	2-F	H	H
2-643	H	H	CH_2-(1-CO_2Et-4-Triz)	2-F	H	H
2-644	Ac	H	CH_2-(1-CO_2Et-4-Triz)	2-F	H	H
2-645	H	H	CH_2-(5-CO_2H-4-Triz)	2-F	H	H
2-646	Ac	H	CH_2-(5-CO_2H-4-Triz)	2-F	H	H
2-647	H	H	CH_2-(5-CO_2Me-4-Triz)	2-F	H	H
2-648	Ac	H	CH_2-(5-CO_2Me-4-Triz)	2-F	H	H
2-649	H	H	CH_2-(5-CO_2Et-4-Triz)	2-F	H	H
2-650	Ac	H	CH_2-(5-CO_2Et-4-Triz)	2-F	H	H
2-651	H	H	CH_2-(1-CH_2CO_2H-4-Triz)	2-F	H	H
2-652	Ac	H	CH_2-(1-CH_2CO_2H-4-Triz)	2-F	H	H
2-653	H	H	CH_2-(1-CH_2CO_2Me-4-Triz)	2-F	H	H
2-654	Ac	H	CH_2-(1-CH_2CO_2Me-4-Triz)	2-F	H	H
2-655	H	H	CH_2-(1-CH_2CO_2Et-4-Triz)	2-F	H	H
2-656	Ac	H	CH_2-(1-CH_2CO_2Et-4-Triz)	2-F	H	H
2-657	H	H	CH_2-(5-CH_2CO_2H-4-Triz)	2-F	H	H
2-658	Ac	H	CH_2-(5-CH_2CO_2H-4-Triz)	2-F	H	H
2-659	H	H	CH_2-(5-CH_2CO_2Me-4-Triz)	2-F	H	H
2-660	Ac	H	CH_2-(5-CH_2CO_2Me-4-Triz)	2-F	H	H
2-661	H	H	CH_2-(5-CH_2CO_2Et-4-Triz)	2-F	H	H
2-662	Ac	H	CH_2-(5-CH_2CO_2Et-4-Triz)	2-F	H	H
2-663	H	H	CH_2-(1-$CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
2-664	Ac	H	CH_2-(1-$CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
2-665	H	H	CH_2-(1-$CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
2-666	Ac	H	CH_2-(1-$CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
2-667	H	H	CH_2-(1-$CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
2-668	Ac	H	CH_2-(1-$CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
2-669	H	H	CH_2-(5-$CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
2-670	Ac	H	CH_2-(5-$CH_2CH_2CO_2H$-4-Triz)	2-F	H	H

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2-671	H	H	CH_2-(5-$CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
2-672	Ac	H	CH_2-(5-$CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
2-673	H	H	CH_2-(5-$CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
2-674	Ac	H	CH_2-(5-$CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
2-675	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
2-676	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
2-677	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
2-678	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
2-679	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
2-680	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
2-681	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
2-682	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
2-683	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
2-684	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
2-685	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
2-686	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
2-687	H	H	CH_2CH_2-4-Triz	2-F	H	H
2-688	Ac	H	CH_2CH_2-4-Triz	2-F	H	H
2-689	H	H	CH_2CH_2-4-Triz	2-F	4-F	H
2-690	Ac	H	CH_2CH_2-4-Triz	2-F	4-F	H
2-691	H	H	CH_2CH_2-(1-CO_2Me-4-Triz)	2-F	H	H
2-692	Ac	H	CH_2CH_2-(1-CO_2Me-4-Triz)	2-F	H	H
2-693	H	H	CH_2CH_2-(1-CO_2Et-4-Triz)	2-F	H	H
2-694	Ac	H	CH_2CH_2-(1-CO_2Et-4-Triz)	2-F	H	H
2-695	H	H	CH_2CH_2-(5-CO_2H-4-Triz)	2-F	H	H
2-696	Ac	H	CH_2CH_2-(5-CO_2H-4-Triz)	2-F	H	H
2-697	H	H	CH_2CH_2-(5-CO_2Me-4-Triz)	2-F	H	H
2-698	Ac	H	CH_2CH_2-(5-CO_2Me-4-Triz)	2-F	H	H
2-699	H	H	CH_2CH_2-(5-CO_2Et-4-Triz)	2-F	H	H
2-700	Ac	H	CH_2CH_2-(5-CO_2Et-4-Triz)	2-F	H	H
2-701	H	H	CH_2CH_2-(1-CH_2CO_2H-4-Triz)	2-F	H	H
2-702	Ac	H	CH_2CH_2-(1-CH_2CO_2H-4-Triz)	2-F	H	H
2-703	H	H	CH_2CH_2-(1-CH_2CO_2Me-4-Triz)	2-F	H	H
2-704	Ac	H	CH_2CH_2-(1-CH_2CO_2Me-4-Triz)	2-F	H	H
2-705	H	H	CH_2CH_2-(1-CH_2CO_2Et-4-Triz)	2-F	H	H
2-706	Ac	H	CH_2CH_2-(1-CH_2CO_2Et-4-Triz)	2-F	H	H
2-707	H	H	CH_2CH_2-(5-CH_2CO_2H-4-Triz)	2-F	H	H
2-708	Ac	H	CH_2CH_2-(5-CH_2CO_2H-4-Triz)	2-F	H	H
2-709	H	H	CH_2CH_2-(5-CH_2CO_2Me-4-Triz)	2-F	H	H
2-710	Ac	H	CH_2CH_2-(5-CH_2CO_2Me-4-Triz)	2-F	H	H
2-711	H	H	CH_2CH_2-(5-CH_2CO_2Et-4-Triz)	2-F	H	H
2-712	Ac	H	CH_2CH_2-(5-CH_2CO_2Et-4-Triz)	2-F	H	H
2-713	H	H	CH_2CH_2-(1-$CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
2-714	Ac	H	CH_2CH_2-(1-$CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
2-715	H	H	CH_2CH_2-(1-$CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
2-716	Ac	H	CH_2CH_2-(1-$CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
2-717	H	H	CH_2CH_2-(1-$CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
2-718	Ac	H	CH_2CH_2-(1-$CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
2-719	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
2-720	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
2-721	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
2-722	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
2-723	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
2-724	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
2-725	H	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
2-726	Ac	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
2-727	H	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H

2-728	Ac	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
2-729	H	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
2-730	Ac	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
2-731	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
2-732	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
2-733	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
2-734	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
2-735	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
2-736	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
2-737	H	H	CH_2-(1-CO_2Me-5-Triz)	2-F	4-F	H
2-738	Ac	H	CH_2-(1-CO_2Me-5-Triz)	2-F	4-F	H
2-739	H	H	CH_2-(1-CO_2Me-5-Triz)	2-F	H	H
2-740	Ac	H	CH_2-(1-CO_2Me-5-Triz)	2-F	H	H
2-741	H	H	CH_2-(1-CO_2Et-5-Triz)	2-F	H	H
2-742	Ac	H	CH_2-(1-CO_2Et-5-Triz)	2-F	H	H
2-743	H	H	CH_2-(1-CH_2CO_2H-5-Triz)	2-F	H	H
2-744	Ac	H	CH_2-(1-CH_2CO_2H-5-Triz)	2-F	H	H
2-745	H	H	CH_2-(1-CH_2CO_2Me-5-Triz)	2-F	H	H
2-746	Ac	H	CH_2-(1-CH_2CO_2Me-5-Triz)	2-F	H	H
2-747	H	H	CH_2-(1-CH_2CO_2Et-5-Triz)	2-F	H	H
2-748	Ac	H	CH_2-(1-CH_2CO_2Et-5-Triz)	2-F	H	H
2-749	H	H	CH_2-(1-$CH_2CH_2CO_2H$-5-Triz)	2-F	H	H
2-750	Ac	H	CH_2-(1-$CH_2CH_2CO_2H$-5-Triz)	2-F	H	H
2-751	H	H	CH_2-(1-$CH_2CH_2CO_2Me$-5-Triz)	2-F	H	H
2-752	Ac	H	CH_2-(1-$CH_2CH_2CO_2Me$-5-Triz)	2-F	H	H
2-753	H	H	CH_2-(1-$CH_2CH_2CO_2Et$-5-Triz)	2-F	H	H
2-754	Ac	H	CH_2-(1-$CH_2CH_2CO_2Et$-5-Triz)	2-F	H	H
2-755	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2H$-5-Triz)	2-F	H	H
2-756	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2H$-5-Triz)	2-F	H	H
2-757	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2Me$-5-Triz)	2-F	H	H
2-758	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2Me$-5-Triz)	2-F	H	H
2-759	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2Et$-5-Triz)	2-F	H	H
2-760	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2Et$-5-Triz)	2-F	H	H
2-761	H	H	CH_2-1-Tez	2-F	H	H
2-762	Ac	H	CH_2-1-Tez	2-F	H	H
2-763	H	H	CH_2-(5-CO_2H-1-Tez)	2-F	H	H
2-764	Ac	H	CH_2-(5-CO_2H-1-Tez)	2-F	H	H
2-765	H	H	CH_2-(5-CO_2Me-1-Tez)	2-F	H	H
2-766	Ac	H	CH_2-(5-CO_2Me-1-Tez)	2-F	H	H
2-767	H	H	CH_2-(5-CO_2Et-1-Tez)	2-F	H	H
2-768	Ac	H	CH_2-(5-CO_2Et-1-Tez)	2-F	H	H
2-769	H	H	CH_2-(5-CH_2CO_2H-1-Tez)	2-F	H	H
2-770	Ac	H	CH_2-(5-CH_2CO_2H-1-Tez)	2-F	H	H
2-771	H	H	CH_2-(5-CH_2CO_2Me-1-Tez)	2-F	H	H
2-772	Ac	H	CH_2-(5-CH_2CO_2Me-1-Tez)	2-F	H	H
2-773	H	H	CH_2-(5-CH_2CO_2Et-1-Tez)	2-F	H	H
2-774	Ac	H	CH_2-(5-CH_2CO_2Et-1-Tez)	2-F	H	H
2-775	H	H	CH_2-(5-$CH_2CH_2CO_2H$-1-Tez)	2-F	H	H
2-776	Ac	H	CH_2-(5-$CH_2CH_2CO_2H$-1-Tez)	2-F	H	H
2-777	H	H	CH_2-(5-$CH_2CH_2CO_2Me$-1-Tez)	2-F	H	H
2-778	Ac	H	CH_2-(5-$CH_2CH_2CO_2Me$-1-Tez)	2-F	H	H
2-779	H	H	CH_2-(5-$CH_2CH_2CO_2Et$-1-Tez)	2-F	H	H
2-780	Ac	H	CH_2-(5-$CH_2CH_2CO_2Et$-1-Tez)	2-F	H	H
2-781	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2H$-1-Tez)	2-F	H	H
2-782	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2H$-1-Tez)	2-F	H	H
2-783	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2Me$-1-Tez)	2-F	H	H
2-784	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2Me$-1-Tez)	2-F	H	H

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2-785	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2Et$-1-Tez)	2-F	H	H
2-786	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2Et$-1-Tez)	2-F	H	H
2-787	H	H	CH_2CH_2-1-Tez	2-F	H	H
2-788	Ac	H	CH_2CH_2-1-Tez	2-F	H	H
2-789	H	H	CH_2CH_2-(5-CO_2H-1-Tez)	2-F	H	H
2-790	Ac	H	CH_2CH_2-(5-CO_2H-1-Tez)	2-F	H	H
2-791	H	H	CH_2CH_2-(5-CO_2Me-1-Tez)	2-F	H	H
2-792	Ac	H	CH_2CH_2-(5-CO_2Me-1-Tez)	2-F	H	H
2-793	H	H	CH_2CH_2-(5-CO_2Et-1-Tez)	2-F	H	H
2-794	Ac	H	CH_2CH_2-(5-CO_2Et-1-Tez)	2-F	H	H
2-795	H	H	CH_2CH_2-(5-CH_2CO_2H-1-Tez)	2-F	H	H
2-796	Ac	H	CH_2CH_2-(5-CH_2CO_2H-1-Tez)	2-F	H	H
2-797	H	H	CH_2CH_2-(5-CH_2CO_2Me-1-Tez)	2-F	H	H
2-798	Ac	H	CH_2CH_2-(5-CH_2CO_2Me-1-Tez)	2-F	H	H
2-799	H	H	CH_2CH_2-(5-CH_2CO_2Et-1-Tez)	2-F	H	H
2-800	Ac	H	CH_2CH_2-(5-CH_2CO_2Et-1-Tez)	2-F	H	H
2-801	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2H$-1-Tez)	2-F	H	H
2-802	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2H$-1-Tez)	2-F	H	H
2-803	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2Me$-1-Tez)	2-F	H	H
2-804	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2Me$-1-Tez)	2-F	H	H
2-805	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2Et$-1-Tez)	2-F	H	H
2-806	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2Et$-1-Tez)	2-F	H	H
2-807	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2H$-1-Tez)	2-F	H	H
2-808	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2H$-1-Tez)	2-F	H	H
2-809	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Me$-1-Tez)	2-F	H	H
2-810	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Me$-1-Tez)	2-F	H	H
2-811	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Et$-1-Tez)	2-F	H	H
2-812	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Et$-1-Tez)	2-F	H	H
2-813	H	H	CH_2-2-Tez	2-F	H	H
2-814	Ac	H	CH_2-2-Tez	2-F	H	H
2-815	H	H	CH_2-(5-CO_2H-2-Tez)	2-F	H	H
2-816	Ac	H	CH_2-(5-CO_2H-2-Tez)	2-F	H	H
2-817	H	H	CH_2-(5-CO_2Me-2-Tez)	2-F	H	H
2-818	Ac	H	CH_2-(5-CO_2Me-2-Tez)	2-F	H	H
2-819	H	H	CH_2-(5-CO_2Et-2-Tez)	2-F	H	H
2-820	Ac	H	CH_2-(5-CO_2Et-2-Tez)	2-F	H	H
2-821	H	H	CH_2-(5-CH_2CO_2H-2-Tez)	2-F	H	H
2-822	Ac	H	CH_2-(5-CH_2CO_2H-2-Tez)	2-F	H	H
2-823	H	H	CH_2-(5-CH_2CO_2Me-2-Tez)	2-F	H	H
2-824	Ac	H	CH_2-(5-CH_2CO_2Me-2-Tez)	2-F	H	H
2-825	H	H	CH_2-(5-CH_2CO_2Et-2-Tez)	2-F	H	H
2-826	Ac	H	CH_2-(5-CH_2CO_2Et-2-Tez)	2-F	H	H
2-827	H	H	CH_2-(5-$CH_2CH_2CO_2H$-2-Tez)	2-F	H	H
2-828	Ac	H	CH_2-(5-$CH_2CH_2CO_2H$-2-Tez)	2-F	H	H
2-829	H	H	CH_2-(5-$CH_2CH_2CO_2Me$-2-Tez)	2-F	H	H
2-830	Ac	H	CH_2-(5-$CH_2CH_2CO_2Me$-2-Tez)	2-F	H	H
2-831	H	H	CH_2-(5-$CH_2CH_2CO_2Et$-2-Tez)	2-F	H	H
2-832	Ac	H	CH_2-(5-$CH_2CH_2CO_2Et$-2-Tez)	2-F	H	H
2-833	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2H$-2-Tez)	2-F	H	H
2-834	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2H$-2-Tez)	2-F	H	H
2-835	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2Me$-2-Tez)	2-F	H	H
2-836	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2Me$-2-Tez)	2-F	H	H
2-837	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2Et$-2-Tez)	2-F	H	H
2-838	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2Et$-2-Tez)	2-F	H	H
2-839	H	H	CH_2CH_2-2-Tez	2-F	H	H
2-840	Ac	H	CH_2CH_2-2-Tez	2-F	H	H
2-841	H	H	CH_2CH_2-(5-CO_2H-2-Tez)	2-F	H	H

2-842	Ac	H	CH_2CH_2-(5-CO_2H-2-Tez)	2-F	H	H
2-843	H	H	CH_2CH_2-(5-CO_2Me-2-Tez)	2-F	H	H
2-844	Ac	H	CH_2CH_2-(5-CO_2Me-2-Tez)	2-F	H	H
2-845	H	H	CH_2CH_2-(5-CO_2Et-2-Tez)	2-F	H	H
2-846	Ac	H	CH_2CH_2-(5-CO_2Et-2-Tez)	2-F	H	H
2-847	H	H	CH_2CH_2-(5-CH_2CO_2H-2-Tez)	2-F	H	H
2-848	Ac	H	CH_2CH_2-(5-CH_2CO_2H-2-Tez)	2-F	H	H
2-849	H	H	CH_2CH_2-(5-CH_2CO_2Me-2-Tez)	2-F	H	H
2-850	Ac	H	CH_2CH_2-(5-CH_2CO_2Me-2-Tez)	2-F	H	H
2-851	H	H	CH_2CH_2-(5-CH_2CO_2Et-2-Tez)	2-F	H	H
2-852	Ac	H	CH_2CH_2-(5-CH_2CO_2Et-2-Tez)	2-F	H	H
2-853	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2H$-2-Tez)	2-F	H	H
2-854	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2H$-2-Tez)	2-F	H	H
2-855	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2Me$-2-Tez)	2-F	H	H
2-856	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2Me$-2-Tez)	2-F	H	H
2-857	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2Et$-2-Tez)	2-F	H	H
2-858	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2Et$-2-Tez)	2-F	H	H
2-859	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2H$-2-Tez)	2-F	H	H
2-860	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2H$-2-Tez)	2-F	H	H
2-861	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Me$-2-Tez)	2-F	H	H
2-862	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Me$-2-Tez)	2-F	H	H
2-863	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Et$-2-Tez)	2-F	H	H
2-864	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Et$-2-Tez)	2-F	H	H
2-865	H	H	CH_2-5-Tez	2-F	H	H
2-866	Ac	H	CH_2-5-Tez	2-F	H	H
2-867	H	H	CH_2-5-Tez	2-F	4-F	H
2-868	Ac	H	CH_2-5-Tez	2-F	4-F	H
2-869	H	H	CH_2-(1-CO_2Me-5-Tez)	2-F	H	H
2-870	Ac	H	CH_2-(1-CO_2Me-5-Tez)	2-F	H	H
2-871	H	H	CH_2-(1-CO_2Et-5-Tez)	2-F	H	H
2-872	Ac	H	CH_2-(1-CO_2Et-5-Tez)	2-F	H	H
2-873	H	H	CH_2-(2-CO_2Me-5-Tez)	2-F	4-F	H
2-874	Ac	H	CH_2-(2-CO_2Me-5-Tez)	2-F	4-F	H
2-875	H	H	CH_2-(2-CO_2Me-5-Tez)	2-F	H	H
2-876	Ac	H	CH_2-(2-CO_2Me-5-Tez)	2-F	H	H
2-877	H	H	CH_2-(2-CO_2Et-5-Tez)	2-F	H	H
2-878	Ac	H	CH_2-(2-CO_2Et-5-Tez)	2-F	H	H
2-879	H	H	CH_2-(1-CH_2CO_2H-5-Tez)	2-F	H	H
2-880	Ac	H	CH_2-(1-CH_2CO_2H-5-Tez)	2-F	H	H
2-881	H	H	CH_2-(1-CH_2CO_2Me-5-Tez)	2-F	H	H
2-882	Ac	H	CH_2-(1-CH_2CO_2Me-5-Tez)	2-F	H	H
2-883	H	H	CH_2-(1-CH_2CO_2Et-5-Tez)	2-F	H	H
2-884	Ac	H	CH_2-(1-CH_2CO_2Et-5-Tez)	2-F	H	H
2-885	H	H	CH_2-(2-CH_2CO_2H-5-Tez)	2-F	H	H
2-886	Ac	H	CH_2-(2-CH_2CO_2H-5-Tez)	2-F	H	H
2-887	H	H	CH_2-(2-CH_2CO_2Me-5-Tez)	2-F	H	H
2-888	Ac	H	CH_2-(2-CH_2CO_2Me-5-Tez)	2-F	H	H
2-889	H	H	CH_2-(2-CH_2CO_2Et-5-Tez)	2-F	H	H
2-890	Ac	H	CH_2-(2-CH_2CO_2Et-5-Tez)	2-F	H	H
2-891	H	H	CH_2-(1-$CH_2CH_2CO_2H$-5-Tez)	2-F	H	H
2-892	Ac	H	CH_2-(1-$CH_2CH_2CO_2H$-5-Tez)	2-F	H	H
2-893	H	H	CH_2-(1-$CH_2CH_2CO_2Me$-5-Tez)	2-F	H	H
2-894	Ac	H	CH_2-(1-$CH_2CH_2CO_2Me$-5-Tez)	2-F	H	H
2-895	H	H	CH_2-(1-$CH_2CH_2CO_2Et$-5-Tez)	2-F	H	H
2-896	Ac	H	CH_2-(1-$CH_2CH_2CO_2Et$-5-Tez)	2-F	H	H
2-897	H	H	CH_2-(2-$CH_2CH_2CO_2H$-5-Tez)	2-F	H	H
2-898	Ac	H	CH_2-(2-$CH_2CH_2CO_2H$-5-Tez)	2-F	H	H

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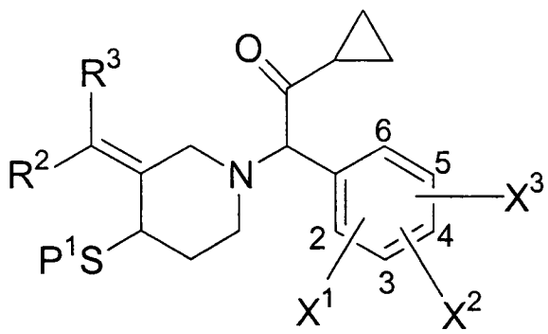
2-899	H	H	CH_2-(2-$CH_2CH_2CO_2Me$-5-Tez)	2-F	H	H
2-900	Ac	H	CH_2-(2-$CH_2CH_2CO_2Me$-5-Tez)	2-F	H	H
2-901	H	H	CH_2-(2-$CH_2CH_2CO_2Et$-5-Tez)	2-F	H	H
2-902	Ac	H	CH_2-(2-$CH_2CH_2CO_2Et$-5-Tez)	2-F	H	H
2-903	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2H$-5-Tez)	2-F	H	H
2-904	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2H$-5-Tez)	2-F	H	H
2-905	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2Me$-5-Tez)	2-F	H	H
2-906	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2Me$-5-Tez)	2-F	H	H
2-907	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2Et$-5-Tez)	2-F	H	H
2-908	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2Et$-5-Tez)	2-F	H	H
2-909	H	H	CH_2-(2-$CH_2CH_2CH_2CO_2H$-5-Tez)	2-F	H	H
2-910	Ac	H	CH_2-(2-$CH_2CH_2CH_2CO_2H$-5-Tez)	2-F	H	H
2-911	H	H	CH_2-(2-$CH_2CH_2CH_2CO_2Me$-5-Tez)	2-F	H	H
2-912	Ac	H	CH_2-(2-$CH_2CH_2CH_2CO_2Me$-5-Tez)	2-F	H	H
2-913	H	H	CH_2-(2-$CH_2CH_2CH_2CO_2Et$-5-Tez)	2-F	H	H
2-914	Ac	H	CH_2-(2-$CH_2CH_2CH_2CO_2Et$-5-Tez)	2-F	H	H
2-915	H	H	CH_2CH_2-5-Tez	2-F	H	H
2-916	Ac	H	CH_2CH_2-5-Tez	2-F	H	H
2-917	H	H	CH_2CH_2-5-Tez	2-F	4-F	H
2-918	Ac	H	CH_2CH_2-5-Tez	2-F	4-F	H
2-919	H	H	CH_2CH_2-(1-CO_2Me-5-Tez)	2-F	H	H
2-920	Ac	H	CH_2CH_2-(1-CO_2Me-5-Tez)	2-F	H	H
2-921	H	H	CH_2CH_2-(1-CO_2Et-5-Tez)	2-F	H	H
2-922	Ac	H	CH_2CH_2-(1-CO_2Et-5-Tez)	2-F	H	H
2-923	H	H	CH_2CH_2-(2-CO_2Me-5-Tez)	2-F	H	H
2-924	Ac	H	CH_2CH_2-(2-CO_2Me-5-Tez)	2-F	H	H
2-925	H	H	CH_2CH_2-(2-CO_2Me-5-Tez)	2-F	H	H
2-926	Ac	H	CH_2CH_2-(2-CO_2Me-5-Tez)	2-F	H	H
2-927	H	H	CH_2CH_2-(2-CO_2Et-5-Tez)	2-F	H	H
2-928	Ac	H	CH_2CH_2-(2-CO_2Et-5-Tez)	2-F	H	H
2-929	H	H	CH_2CH_2-(1-CH_2CO_2H-5-Tez)	2-F	H	H
2-930	Ac	H	CH_2CH_2-(1-CH_2CO_2H-5-Tez)	2-F	H	H
2-931	H	H	CH_2CH_2-(1-CH_2CO_2Me-5-Tez)	2-F	H	H
2-932	Ac	H	CH_2CH_2-(1-CH_2CO_2Me-5-Tez)	2-F	H	H
2-933	H	H	CH_2CH_2-(1-CH_2CO_2Et-5-Tez)	2-F	H	H
2-934	Ac	H	CH_2CH_2-(1-CH_2CO_2Et-5-Tez)	2-F	H	H
2-935	H	H	CH_2CH_2-(2-CH_2CO_2H-5-Tez)	2-F	H	H
2-936	Ac	H	CH_2CH_2-(2-CH_2CO_2H-5-Tez)	2-F	H	H
2-937	H	H	CH_2CH_2-(2-CH_2CO_2Me-5-Tez)	2-F	H	H
2-938	Ac	H	CH_2CH_2-(2-CH_2CO_2Me-5-Tez)	2-F	H	H
2-939	H	H	CH_2CH_2-(2-CH_2CO_2Et-5-Tez)	2-F	H	H
2-940	Ac	H	CH_2CH_2-(2-CH_2CO_2Et-5-Tez)	2-F	H	H
2-941	H	H	CH_2CH_2-(1-$CH_2CH_2CO_2H$-5-Tez)	2-F	H	H
2-942	Ac	H	CH_2CH_2-(1-$CH_2CH_2CO_2H$-5-Tez)	2-F	H	H
2-943	H	H	CH_2CH_2-(1-$CH_2CH_2CO_2Me$-5-Tez)	2-F	H	H
2-944	Ac	H	CH_2CH_2-(1-$CH_2CH_2CO_2Me$-5-Tez)	2-F	H	H
2-945	H	H	CH_2CH_2-(1-$CH_2CH_2CO_2Et$-5-Tez)	2-F	H	H
2-946	Ac	H	CH_2CH_2-(1-$CH_2CH_2CO_2Et$-5-Tez)	2-F	H	H
2-947	H	H	CH_2CH_2-(2-$CH_2CH_2CO_2H$-5-Tez)	2-F	H	H
2-948	Ac	H	CH_2CH_2-(2-$CH_2CH_2CO_2H$-5-Tez)	2-F	H	H
2-949	H	H	CH_2CH_2-(2-$CH_2CH_2CO_2Me$-5-Tez)	2-F	H	H
2-950	Ac	H	CH_2CH_2-(2-$CH_2CH_2CO_2Me$-5-Tez)	2-F	H	H
2-951	H	H	CH_2CH_2-(2-$CH_2CH_2CO_2Et$-5-Tez)	2-F	H	H
2-952	Ac	H	CH_2CH_2-(2-$CH_2CH_2CO_2Et$-5-Tez)	2-F	H	H
2-953	H	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2H$-5-Tez)	2-F	H	H
2-954	Ac	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2H$-5-Tez)	2-F	H	H
2-955	H	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Me$-5-Tez)	2-F	H	H

2-956	Ac	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Me$-5-Tez)	2-F	H	H
2-957	H	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Et$-5-Tez)	2-F	H	H
2-958	Ac	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Et$-5-Tez)	2-F	H	H
2-959	H	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2H$-5-Tez)	2-F	H	H
2-960	Ac	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2H$-5-Tez)	2-F	H	H
2-961	H	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2Me$-5-Tez)	2-F	H	H
2-962	Ac	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2Me$-5-Tez)	2-F	H	H
2-963	H	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2Et$-5-Tez)	2-F	H	H
2-964	Ac	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2Et$-5-Tez)	2-F	H	H
2-965	H	Me	CH_2-1-Pyza	2-F	H	H
2-966	Ac	Me	CH_2-1-Pyza	2-F	H	H
2-967	H	Me	CH_2-(3-CO_2H-1-Pyza)	2-F	H	H
2-968	Ac	Me	CH_2-(3-CO_2H-1-Pyza)	2-F	H	H
2-969	H	Me	CH_2-(3-CO_2Me-1-Pyza)	2-F	H	H
2-970	Ac	Me	CH_2-(3-CO_2Me-1-Pyza)	2-F	H	H
2-971	H	Me	CH_2-(3-CO_2Et-1-Pyza)	2-F	H	H
2-972	Ac	Me	CH_2-(3-CO_2Et-1-Pyza)	2-F	H	H
2-973	H	Me	CH_2-(4-CO_2H-1-Pyza)	2-F	H	H
2-974	Ac	Me	CH_2-(4-CO_2H-1-Pyza)	2-F	H	H
2-975	H	Me	CH_2-(4-CO_2Me-1-Pyza)	2-F	H	H
2-976	Ac	Me	CH_2-(4-CO_2Me-1-Pyza)	2-F	H	H
2-977	H	Me	CH_2-(4-CO_2Et-1-Pyza)	2-F	H	H
2-978	Ac	Me	CH_2-(4-CO_2Et-1-Pyza)	2-F	H	H
2-979	H	Me	CH_2-(3-CH_2CO_2H-1-Pyza)	2-F	H	H
2-980	Ac	Me	CH_2-(3-CH_2CO_2H-1-Pyza)	2-F	H	H
2-981	H	Me	CH_2-(3-CH_2CO_2Me-1-Pyza)	2-F	H	H
2-982	Ac	Me	CH_2-(3-CH_2CO_2Me-1-Pyza)	2-F	H	H
2-983	H	Me	CH_2-(3-CH_2CO_2Et-1-Pyza)	2-F	H	H
2-984	Ac	Me	CH_2-(3-CH_2CO_2Et-1-Pyza)	2-F	H	H
2-985	H	Me	CH_2-(4-CH_2CO_2H-1-Pyza)	2-F	H	H
2-986	Ac	Me	CH_2-(4-CH_2CO_2H-1-Pyza)	2-F	H	H
2-987	H	Me	CH_2-(4-CH_2CO_2Me-1-Pyza)	2-F	H	H
2-988	Ac	Me	CH_2-(4-CH_2CO_2Me-1-Pyza)	2-F	H	H
2-989	H	Me	CH_2-(4-CH_2CO_2Et-1-Pyza)	2-F	H	H
2-990	Ac	Me	CH_2-(4-CH_2CO_2Et-1-Pyza)	2-F	H	H
2-991	H	Me	CH_2-(3-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
2-992	Ac	Me	CH_2-(3-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
2-993	H	Me	CH_2-(3-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
2-994	Ac	Me	CH_2-(3-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
2-995	H	Me	CH_2-(3-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
2-996	Ac	Me	CH_2-(3-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
2-997	H	Me	CH_2-(4-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
2-998	Ac	Me	CH_2-(4-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
2-999	H	Me	CH_2-(4-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
2-1000	Ac	Me	CH_2-(4-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
2-1001	H	Me	CH_2-(4-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
2-1002	Ac	Me	CH_2-(4-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
2-1003	H	Me	CH_2CH_2-1-Pyza	2-F	H	H
2-1004	Ac	Me	CH_2CH_2-1-Pyza	2-F	H	H
2-1005	H	Me	CH_2CH_2-(3-CO_2H-1-Pyza)	2-F	H	H
2-1006	Ac	Me	CH_2CH_2-(3-CO_2H-1-Pyza)	2-F	H	H
2-1007	H	Me	CH_2CH_2-(3-CO_2Me-1-Pyza)	2-F	H	H
2-1008	Ac	Me	CH_2CH_2-(3-CO_2Me-1-Pyza)	2-F	H	H
2-1009	H	Me	CH_2CH_2-(3-CO_2Et-1-Pyza)	2-F	H	H
2-1010	Ac	Me	CH_2CH_2-(3-CO_2Et-1-Pyza)	2-F	H	H
2-1011	H	Me	CH_2CH_2-(4-CO_2H-1-Pyza)	2-F	H	H
2-1012	Ac	Me	CH_2CH_2-(4-CO_2H-1-Pyza)	2-F	H	H

2-1013	H	Me	CH_2CH_2-(4-CO_2Me-1-Pyza)	2-F	H	H
2-1014	Ac	Me	CH_2CH_2-(4-CO_2Me-1-Pyza)	2-F	H	H
2-1015	H	Me	CH_2CH_2-(4-CO_2Et-1-Pyza)	2-F	H	H
2-1016	Ac	Me	CH_2CH_2-(4-CO_2Et-1-Pyza)	2-F	H	H
2-1017	H	Me	CH_2CH_2-(3-CH_2CO_2H-1-Pyza)	2-F	H	H
2-1018	Ac	Me	CH_2CH_2-(3-CH_2CO_2H-1-Pyza)	2-F	H	H
2-1019	H	Me	CH_2CH_2-(3-CH_2CO_2Me-1-Pyza)	2-F	H	H
2-1020	Ac	Me	CH_2CH_2-(3-CH_2CO_2Me-1-Pyza)	2-F	H	H
2-1021	H	Me	CH_2CH_2-(3-CH_2CO_2Et-1-Pyza)	2-F	H	H
2-1022	Ac	Me	CH_2CH_2-(3-CH_2CO_2Et-1-Pyza)	2-F	H	H
2-1023	H	Me	CH_2CH_2-(4-CH_2CO_2H-1-Pyza)	2-F	H	H
2-1024	Ac	Me	CH_2CH_2-(4-CH_2CO_2H-1-Pyza)	2-F	H	H
2-1025	H	Me	CH_2CH_2-(4-CH_2CO_2Me-1-Pyza)	2-F	H	H
2-1026	Ac	Me	CH_2CH_2-(4-CH_2CO_2Me-1-Pyza)	2-F	H	H
2-1027	H	Me	CH_2CH_2-(4-CH_2CO_2Et-1-Pyza)	2-F	H	H
2-1028	Ac	Me	CH_2CH_2-(4-CH_2CO_2Et-1-Pyza)	2-F	H	H
2-1029	H	Me	CH_2CH_2-(3-$CH_2CH_2CO_2$H-1-Pyza)	2-F	H	H
2-1030	Ac	Me	CH_2CH_2-(3-$CH_2CH_2CO_2$H-1-Pyza)	2-F	H	H
2-1031	H	Me	CH_2CH_2-(3-$CH_2CH_2CO_2$Me-1-Pyza)	2-F	H	H
2-1032	Ac	Me	CH_2CH_2-(3-$CH_2CH_2CO_2$Me-1-Pyza)	2-F	H	H
2-1033	H	Me	CH_2CH_2-(3-$CH_2CH_2CO_2$Et-1-Pyza)	2-F	H	H
2-1034	Ac	Me	CH_2CH_2-(3-$CH_2CH_2CO_2$Et-1-Pyza)	2-F	H	H
2-1035	H	Me	CH_2CH_2-(4-$CH_2CH_2CO_2$H-1-Pyza)	2-F	H	H
2-1036	Ac	Me	CH_2CH_2-(4-$CH_2CH_2CO_2$H-1-Pyza)	2-F	H	H
2-1037	H	Me	CH_2CH_2-(4-$CH_2CH_2CO_2$Me-1-Pyza)	2-F	H	H
2-1038	Ac	Me	CH_2CH_2-(4-$CH_2CH_2CO_2$Me-1-Pyza)	2-F	H	H
2-1039	H	Me	CH_2CH_2-(4-$CH_2CH_2CO_2$Et-1-Pyza)	2-F	H	H
2-1040	Ac	Me	CH_2CH_2-(4-$CH_2CH_2CO_2$Et-1-Pyza)	2-F	H	H
2-1041	H	H	CH_2-(2-CO_2Me-4-Triz)	2-F	H	H
2-1042	Ac	H	CH_2-(2-CO_2Me-4-Triz)	2-F	H	H
2-1043	H	H	CH_2-(2-CO_2Et-4-Triz)	2-F	H	H
2-1044	Ac	H	CH_2-(2-CO_2Et-4-Triz)	2-F	H	H
2-1045	H	H	CH_2-(2-CH_2CO_2H-4-Triz)	2-F	H	H
2-1046	Ac	H	CH_2-(2-CH_2CO_2H-4-Triz)	2-F	H	H
2-1047	H	H	CH_2-(2-CH_2CO_2Me-4-Triz)	2-F	H	H
2-1048	Ac	H	CH_2-(2-CH_2CO_2Me-4-Triz)	2-F	H	H
2-1049	H	H	CH_2-(2-CH_2CO_2Et-4-Triz)	2-F	H	H
2-1050	Ac	H	CH_2-(2-CH_2CO_2Et-4-Triz)	2-F	H	H
2-1051	H	H	CH_2-(2-$CH_2CH_2CO_2$H-4-Triz)	2-F	H	H
2-1052	Ac	H	CH_2-(2-$CH_2CH_2CO_2$H-4-Triz)	2-F	H	H
2-1053	H	H	CH_2-(2-$CH_2CH_2CO_2$Me-4-Triz)	2-F	H	H
2-1054	Ac	H	CH_2-(2-$CH_2CH_2CO_2$Me-4-Triz)	2-F	H	H
2-1055	H	H	CH_2-(2-$CH_2CH_2CO_2$Et-4-Triz)	2-F	H	H
2-1056	Ac	H	CH_2-(2-$CH_2CH_2CO_2$Et-4-Triz)	2-F	H	H
2-1057	H	H	CH_2-(2-$CH_2CH_2CH_2CO_2$H-4-Triz)	2-F	H	H
2-1058	Ac	H	CH_2-(2-$CH_2CH_2CH_2CO_2$H-4-Triz)	2-F	H	H
2-1059	H	H	CH_2-(2-$CH_2CH_2CH_2CO_2$Me-4-Triz)	2-F	H	H
2-1060	Ac	H	CH_2-(2-$CH_2CH_2CH_2CO_2$Me-4-Triz)	2-F	H	H
2-1061	H	H	CH_2-(2-$CH_2CH_2CH_2CO_2$Et-4-Triz)	2-F	H	H
2-1062	Ac	H	CH_2-(2-$CH_2CH_2CH_2CO_2$Et-4-Triz)	2-F	H	H
2-1063	H	H	CH_2CH_2-(2-CO_2Me-4-Triz)	2-F	H	H
2-1064	Ac	H	CH_2CH_2-(2-CO_2Me-4-Triz)	2-F	H	H
2-1065	H	H	CH_2CH_2-(2-CO_2Et-4-Triz)	2-F	H	H
2-1066	Ac	H	CH_2CH_2-(2-CO_2Et-4-Triz)	2-F	H	H
2-1067	H	H	CH_2CH_2-(2-CH_2CO_2H-4-Triz)	2-F	H	H
2-1068	Ac	H	CH_2CH_2-(2-CH_2CO_2H-4-Triz)	2-F	H	H
2-1069	H	H	CH_2CH_2-(2-CH_2CO_2Me-4-Triz)	2-F	H	H

2-1070	Ac	H	CH_2CH_2-(2-CH_2CO_2Me-4-Triz)	2-F	H	H
2-1071	H	H	CH_2CH_2-(2-CH_2CO_2Et-4-Triz)	2-F	H	H
2-1072	Ac	H	CH_2CH_2-(2-CH_2CO_2Et-4-Triz)	2-F	H	H
2-1073	H	H	CH_2CH_2-(2-$CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
2-1074	Ac	H	CH_2CH_2-(2-$CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
2-1075	H	H	CH_2CH_2-(2-$CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
2-1076	Ac	H	CH_2CH_2-(2-$CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
2-1077	H	H	CH_2CH_2-(2-$CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
2-1078	Ac	H	CH_2CH_2-(2-$CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
2-1079	H	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
2-1080	Ac	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
2-1081	H	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
2-1082	Ac	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
2-1083	H	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
2-1084	Ac	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H

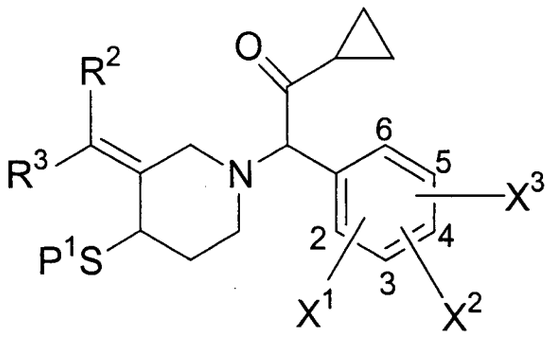
(Table 3)



Compound No.	P^1	R^2	R^3	X^1	X^2	X^3
3-1	H	H	CH_2OH	2-F	H	H
3-2	Ac	H	CH_2OH	2-F	H	H
3-3	H	H	CH_2CH_2OH	2-F	H	H
3-4	Ac	H	CH_2CH_2OH	2-F	H	H
3-5	H	H	CH_2OMe	2-F	H	H
3-6	Ac	H	CH_2OMe	2-F	H	H
3-7	H	H	CH_2CH_2OMe	2-F	H	H
3-8	Ac	H	CH_2CH_2OMe	2-F	H	H
3-9	H	H	CH_2OEt	2-F	H	H
3-10	Ac	H	CH_2OEt	2-F	H	H
3-11	H	H	CH_2CH_2OEt	2-F	H	H
3-12	Ac	H	CH_2CH_2OEt	2-F	H	H
3-13	H	H	CH_2CO_2H	2-F	H	H
3-14	Ac	H	CH_2CO_2H	2-F	H	H
3-15	H	H	CH_2CO_2Me	2-F	H	H
3-16	Ac	H	CH_2CO_2Me	2-F	H	H
3-17	H	H	CH_2CO_2Et	2-F	H	H
3-18	Ac	H	CH_2CO_2Et	2-F	H	H
3-19	H	H	4-Pip	2-F	H	H
3-20	Ac	H	4-Pip	2-F	H	H
3-21	H	H	4-Pip	2-F	4-F	H
3-22	Ac	H	4-Pip	2-F	4-F	H
3-23	H	H	1-CO_2Me-4-Pip	2-F	H	H

3-24	Ac	H	1-CO_2Me-4-Pip	2-F	H	H
3-25	H	H	1-CO_2Et-4-Pip	2-F	H	H
3-26	Ac	H	1-CO_2Et-4-Pip	2-F	H	H
3-27	H	H	1-CH_2CO_2H-4-Pip	2-F	H	H
3-28	Ac	H	1-CH_2CO_2H-4-Pip	2-F	H	H
3-29	H	H	1-CH_2CO_2Me-4-Pip	2-F	H	H
3-30	Ac	H	1-CH_2CO_2Me-4-Pip	2-F	H	H
3-31	H	H	1-CH_2CO_2Et-4-Pip	2-F	H	H
3-32	Ac	H	1-CH_2CO_2Et-4-Pip	2-F	H	H
3-33	H	H	1-$CH_2CH_2CO_2H$-4-Pip	2-F	H	H
3-34	Ac	H	1-$CH_2CH_2CO_2H$-4-Pip	2-F	H	H
3-35	H	H	1-$CH_2CH_2CO_2Me$-4-Pip	2-F	H	H
3-36	Ac	H	1-$CH_2CH_2CO_2Me$-4-Pip	2-F	H	H
3-37	H	H	1-$CH_2CH_2CO_2Et$-4-Pip	2-F	H	H
3-38	Ac	H	1-$CH_2CH_2CO_2Et$-4-Pip	2-F	H	H
3-39	Ac	H	1-$CH_2CH_2CO_2Et$-4-Pip	2-F	4-F	H
3-40	H	H	1-$CH_2CH_2CH_2CO_2H$-4-Pip	2-F	H	H
3-41	Ac	H	1-$CH_2CH_2CH_2CO_2H$-4-Pip	2-F	H	H
3-42	H	H	1-$CH_2CH_2CH_2CO_2Me$-4-Pip	2-F	H	H
3-43	Ac	H	1-$CH_2CH_2CH_2CO_2Me$-4-Pip	2-F	H	H
3-44	H	H	1-$CH_2CH_2CH_2CO_2Et$-4-Pip	2-F	H	H
3-45	Ac	H	1-$CH_2CH_2CH_2CO_2Et$-4-Pip	2-F	H	H
3-46	H	H	CH_2CN	2-F	H	H
3-47	Ac	H	CH_2CN	2-F	H	H
3-48	H	H	CH_2CH_2CN	2-F	H	H
3-49	Ac	H	CH_2CH_2CN	2-F	H	H
3-50	H	H	$CH_2N(Me)CH_2CO_2H$	2-F	H	H
3-51	Ac	H	$CH_2N(Me)CH_2CO_2H$	2-F	H	H
3-52	H	H	$CH_2N(Me)CH_2CO_2Me$	2-F	H	H
3-53	Ac	H	$CH_2N(Me)CH_2CO_2Me$	2-F	H	H
3-54	H	H	$CH_2N(Me)CH_2CO_2Et$	2-F	H	H
3-55	Ac	H	$CH_2N(Me)CH_2CO_2Et$	2-F	H	H
3-56	H	H	$CH_2N(Me)CH_2CH_2CO_2H$	2-F	H	H
3-57	Ac	H	$CH_2N(Me)CH_2CH_2CO_2H$	2-F	H	H
3-58	H	H	$CH_2N(Me)CH_2CH_2CO_2Me$	2-F	H	H
3-59	Ac	H	$CH_2N(Me)CH_2CH_2CO_2Me$	2-F	H	H
3-60	H	H	$CH_2N(Me)CH_2CH_2CO_2Et$	2-F	H	H
3-61	Ac	H	$CH_2N(Me)CH_2CH_2CO_2Et$	2-F	H	H
3-62	H	H	$CH_2N(Me)CH_2CH_2CH_2CO_2H$	2-F	H	H
3-63	Ac	H	$CH_2N(Me)CH_2CH_2CH_2CO_2H$	2-F	H	H
3-64	H	H	$CH_2N(Me)CH_2CH_2CH_2CO_2Me$	2-F	H	H
3-65	Ac	H	$CH_2N(Me)CH_2CH_2CH_2CO_2Me$	2-F	H	H
3-66	H	H	$CH_2N(Me)CH_2CH_2CH_2CO_2Et$	2-F	H	H
3-67	Ac	H	$CH_2N(Me)CH_2CH_2CH_2CO_2Et$	2-F	H	H
3-68	H	H	$CH_2N(Et)CH_2CO_2H$	2-F	H	H
3-69	Ac	H	$CH_2N(Et)CH_2CO_2H$	2-F	H	H
3-70	H	H	$CH_2N(Et)CH_2CO_2Me$	2-F	H	H
3-71	Ac	H	$CH_2N(Et)CH_2CO_2Me$	2-F	H	H
3-72	H	H	$CH_2N(Et)CH_2CO_2Et$	2-F	H	H
3-73	Ac	H	$CH_2N(Et)CH_2CO_2Et$	2-F	H	H
3-74	H	H	$CH_2N(iPr)CH_2CO_2H$	2-F	H	H
3-75	Ac	H	$CH_2N(iPr)CH_2CO_2H$	2-F	H	H
3-76	H	H	$CH_2N(iPr)CH_2CO_2Me$	2-F	H	H
3-77	Ac	H	$CH_2N(iPr)CH_2CO_2Me$	2-F	H	H
3-78	H	H	$CH_2N(iPr)CH_2CO_2Et$	2-F	H	H
3-79	Ac	H	$CH_2N(iPr)CH_2CO_2Et$	2-F	H	H

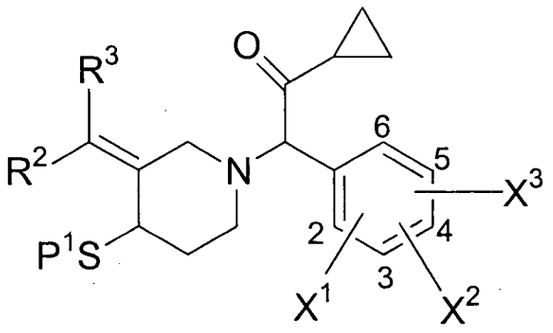
(Table 4)



Compound No.	P^1	R^2	R^3	X^1	X^2	X^3
4-1	H	H	CH_2OH	2-F	H	H
4-2	Ac	H	CH_2OH	2-F	H	H
4-3	H	H	CH_2CH_2OH	2-F	H	H
4-4	Ac	H	CH_2CH_2OH	2-F	H	H
4-5	H	H	CH_2OMe	2-F	H	H
4-6	Ac	H	CH_2OMe	2-F	H	H
4-7	H	H	CH_2CH_2OMe	2-F	H	H
4-8	Ac	H	CH_2CH_2OMe	2-F	H	H
4-9	H	H	CH_2OEt	2-F	H	H
4-10	Ac	H	CH_2OEt	2-F	H	H
4-11	H	H	CH_2CH_2OEt	2-F	H	H
4-12	Ac	H	CH_2CH_2OEt	2-F	H	H
4-13	H	H	CH_2CO_2H	2-F	H	H
4-14	Ac	H	CH_2CO_2H	2-F	H	H
4-15	H	H	CH_2CO_2Me	2-F	H	H
4-16	Ac	H	CH_2CO_2Me	2-F	H	H
4-17	H	H	CH_2CO_2Et	2-F	H	H
4-18	Ac	H	CH_2CO_2Et	2-F	H	H
4-19	H	H	4-Pip	2-F	H	H
4-20	Ac	H	4-Pip	2-F	H	H
4-21	H	H	4-Pip	2-F	4-F	H
4-22	Ac	H	4-Pip	2-F	4-F	H
4-23	H	H	1-CO_2Me-4-Pip	2-F	H	H
4-24	Ac	H	1-CO_2Me-4-Pip	2-F	H	H
4-25	H	H	1-CO_2Et-4-Pip	2-F	H	H
4-26	Ac	H	1-CO_2Et-4-Pip	2-F	H	H
4-27	H	H	1-CH_2CO_2H-4-Pip	2-F	H	H
4-28	Ac	H	1-CH_2CO_2H-4-Pip	2-F	H	H
4-29	H	H	1-CH_2CO_2Me-4-Pip	2-F	H	H
4-30	Ac	H	1-CH_2CO_2Me-4-Pip	2-F	H	H
4-31	H	H	1-CH_2CO_2Et-4-Pip	2-F	H	H
4-32	Ac	H	1-CH_2CO_2Et-4-Pip	2-F	H	H
4-33	H	H	1-$CH_2CH_2CO_2H$-4-Pip	2-F	H	H
4-34	Ac	H	1-$CH_2CH_2CO_2H$-4-Pip	2-F	H	H
4-35	H	H	1-$CH_2CH_2CO_2Me$-4-Pip	2-F	H	H
4-36	Ac	H	1-$CH_2CH_2CO_2Me$-4-Pip	2-F	H	H
4-37	H	H	1-$CH_2CH_2CO_2Et$-4-Pip	2-F	H	H
4-38	Ac	H	1-$CH_2CH_2CO_2Et$-4-Pip	2-F	H	H
4-39	Ac	H	1-$CH_2CH_2CO_2Et$-4-Pip	2-F	4-F	H

4-40	H	H	1-$CH_2CH_2CH_2CO_2H$-4-Pip	2-F	H	H
4-41	Ac	H	1-$CH_2CH_2CH_2CO_2H$-4-Pip	2-F	H	H
4-42	H	H	1-$CH_2CH_2CH_2CO_2Me$-4-Pip	2-F	H	H
4-43	Ac	H	1-$CH_2CH_2CH_2CO_2Me$-4-Pip	2-F	H	H
4-44	H	H	1-$CH_2CH_2CH_2CO_2Et$-4-Pip	2-F	H	H
4-45	Ac	H	1-$CH_2CH_2CH_2CO_2Et$-4-Pip	2-F	H	H
4-46	H	H	CH_2CN	2-F	H	H
4-47	Ac	H	CH_2CN	2-F	H	H
4-48	H	H	CH_2CH_2CN	2-F	H	H
4-49	Ac	H	CH_2CH_2CN	2-F	H	H
4-50	H	H	$CH_2N(Me)CH_2CO_2H$	2-F	H	H
4-51	Ac	H	$CH_2N(Me)CH_2CO_2H$	2-F	H	H
4-52	H	H	$CH_2N(Me)CH_2CO_2Me$	2-F	H	H
4-53	Ac	H	$CH_2N(Me)CH_2CO_2Me$	2-F	H	H
4-54	H	H	$CH_2N(Me)CH_2CO_2Et$	2-F	H	H
4-55	Ac	H	$CH_2N(Me)CH_2CO_2Et$	2-F	H	H
4-56	H	H	$CH_2N(Me)CH_2CH_2CO_2H$	2-F	H	H
4-57	Ac	H	$CH_2N(Me)CH_2CH_2CO_2H$	2-F	H	H
4-58	H	H	$CH_2N(Me)CH_2CH_2CO_2Me$	2-F	H	H
4-59	Ac	H	$CH_2N(Me)CH_2CH_2CO_2Me$	2-F	H	H
4-60	H	H	$CH_2N(Me)CH_2CH_2CO_2Et$	2-F	H	H
4-61	Ac	H	$CH_2N(Me)CH_2CH_2CO_2Et$	2-F	H	H
4-62	H	H	$CH_2N(Me)CH_2CH_2CH_2CO_2H$	2-F	H	H
4-63	Ac	H	$CH_2N(Me)CH_2CH_2CH_2CO_2H$	2-F	H	H
4-64	H	H	$CH_2N(Me)CH_2CH_2CH_2CO_2Me$	2-F	H	H
4-65	Ac	H	$CH_2N(Me)CH_2CH_2CH_2CO_2Me$	2-F	H	H
4-66	H	H	$CH_2N(Me)CH_2CH_2CH_2CO_2Et$	2-F	H	H
4-67	Ac	H	$CH_2N(Me)CH_2CH_2CH_2CO_2Et$	2-F	H	H
4-68	H	H	$CH_2N(Et)CH_2CO_2H$	2-F	H	H
4-69	Ac	H	$CH_2N(Et)CH_2CO_2H$	2-F	H	H
4-70	H	H	$CH_2N(Et)CH_2CO_2Me$	2-F	H	H
4-71	Ac	H	$CH_2N(Et)CH_2CO_2Me$	2-F	H	H
4-72	H	H	$CH_2N(Et)CH_2CO_2Et$	2-F	H	H
4-73	Ac	H	$CH_2N(Et)CH_2CO_2Et$	2-F	H	H
4-74	H	H	$CH_2N(iPr)CH_2CO_2H$	2-F	H	H
4-75	Ac	H	$CH_2N(iPr)CH_2CO_2H$	2-F	H	H
4-76	H	H	$CH_2N(iPr)CH_2CO_2Me$	2-F	H	H
4-77	Ac	H	$CH_2N(iPr)CH_2CO_2Me$	2-F	H	H
4-78	H	H	$CH_2N(iPr)CH_2CO_2Et$	2-F	H	H
4-79	Ac	H	$CH_2N(iPr)CH_2CO_2Et$	2-F	H	H

(Table 5)



Compound	P^1	R^2	R^3	X^1	X^2	X^3

No.						
5-1	H	H	CH_2-1-Pip	2-F	H	H
5-2	Ac	H	CH_2-1-Pip	2-F	H	H
5-3	H	H	CH_2-(4-CO_2H-1-Pip)	2-F	H	H
5-4	Ac	H	CH_2-(4-CO_2H-1-Pip)	2-F	H	H
5-5	H	H	CH_2-(4-CO_2Me-1-Pip)	2-F	H	H
5-6	Ac	H	CH_2-(4-CO_2Me-1-Pip)	2-F	H	H
5-7	H	H	CH_2-(4-CO_2Et-1-Pip)	2-F	H	H
5-8	Ac	H	CH_2-(4-CO_2Et-1-Pip)	2-F	H	H
5-9	H	H	CH_2-(4-CH_2CO_2H-1-Pip)	2-F	H	H
5-10	Ac	H	CH_2-(4-CH_2CO_2H-1-Pip)	2-F	H	H
5-11	H	H	CH_2-(4-CH_2CO_2Me-1-Pip)	2-F	H	H
5-12	Ac	H	CH_2-(4-CH_2CO_2Me-1-Pip)	2-F	H	H
5-13	H	H	CH_2-(4-CH_2CO_2Et-1-Pip)	2-F	H	H
5-14	Ac	H	CH_2-(4-CH_2CO_2Et-1-Pip)	2-F	H	H
5-15	H	H	CH_2-(4-$CH_2CH_2CO_2H$-1-Pip)	2-F	H	H
5-16	Ac	H	CH_2-(4-$CH_2CH_2CO_2H$-1-Pip)	2-F	H	H
5-17	H	H	CH_2-(4-$CH_2CH_2CO_2Me$-1-Pip)	2-F	H	H
5-18	Ac	H	CH_2-(4-$CH_2CH_2CO_2Me$-1-Pip)	2-F	H	H
5-19	H	H	CH_2-(4-$CH_2CH_2CO_2Et$-1-Pip)	2-F	H	H
5-20	Ac	H	CH_2-(4-$CH_2CH_2CO_2Et$-1-Pip)	2-F	H	H
5-21	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2H$-1-Pip)	2-F	H	H
5-22	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2H$-1-Pip)	2-F	H	H
5-23	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2Me$-1-Pip)	2-F	H	H
5-24	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2Me$-1-Pip)	2-F	H	H
5-25	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2Et$-1-Pip)	2-F	H	H
5-26	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2Et$-1-Pip)	2-F	H	H
5-27	H	H	CH_2-Mor	2-F	H	H
5-28	Ac	H	CH_2-Mor	2-F	H	H
5-29	H	H	CH_2-Thim	2-F	H	H
5-30	Ac	H	CH_2-Thim	2-F	H	H
5-31	H	H	CH_2-1-Piz	2-F	H	H
5-32	Ac	H	CH_2-1-Piz	2-F	H	H
5-33	H	H	CH_2-(4-Ac-1-Piz)	2-F	H	H
5-34	Ac	H	CH_2-(4-Ac-1-Piz)	2-F	H	H
5-35	H	H	CH_2-(4-Ac-1-Piz)	2-F	4-F	H
5-36	Ac	H	CH_2-(4-Ac-1-Piz)	2-F	4-F	H
5-37	H	H	CH_2-(4-CO_2Me-1-Piz)	2-F	H	H
5-38	Ac	H	CH_2-(4-CO_2Me-1-Piz)	2-F	H	H
5-39	H	H	CH_2-(4-CO_2Et-1-Piz)	2-F	H	H
5-40	Ac	H	CH_2-(4-CO_2Et-1-Piz)	2-F	H	H
5-41	H	H	CH_2-(4-CH_2CO_2H-1-Piz)	2-F	H	H
5-42	Ac	H	CH_2-(4-CH_2CO_2H-1-Piz)	2-F	H	H
5-43	H	H	CH_2-(4-CH_2CO_2Me-1-Piz)	2-F	H	H
5-44	Ac	H	CH_2-(4-CH_2CO_2Me-1-Piz)	2-F	H	H
5-45	H	H	CH_2-(4-CH_2CO_2Et-1-Piz)	2-F	H	H
5-46	Ac	H	CH_2-(4-CH_2CO_2Et-1-Piz)	2-F	H	H
5-47	H	H	CH_2-(4-$CH_2CH_2CO_2H$-1-Piz)	2-F	H	H
5-48	Ac	H	CH_2-(4-$CH_2CH_2CO_2H$-1-Piz)	2-F	H	H
5-49	H	H	CH_2-(4-$CH_2CH_2CO_2Me$-1-Piz)	2-F	H	H
5-50	Ac	H	CH_2-(4-$CH_2CH_2CO_2Me$-1-Piz)	2-F	H	H
5-51	H	H	CH_2-(4-$CH_2CH_2CO_2Et$-1-Piz)	2-F	H	H
5-52	Ac	H	CH_2-(4-$CH_2CH_2CO_2Et$-1-Piz)	2-F	H	H
5-53	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2H$-1-Piz)	2-F	H	H
5-54	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2H$-1-Piz)	2-F	H	H
5-55	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2Me$-1-Piz)	2-F	H	H

5-56	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2Me$-1-Piz)	2-F	H	H
5-57	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2Et$-1-Piz)	2-F	H	H
5-58	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2Et$-1-Piz)	2-F	H	H
5-59	H	H	CH_2-(2-oxo-1-Piz)	2-F	H	H
5-60	Ac	H	CH_2-(2-oxo-1-Piz)	2-F	H	H
5-61	H	H	CH_2-(4-Ac-2-oxo-1-Piz)	2-F	H	H
5-62	Ac	H	CH_2-(4-Ac-2-oxo-1-Piz)	2-F	H	H
5-63	H	H	CH_2-(4-Ac-2-oxo-1-Piz)	2-F	4-F	H
5-64	Ac	H	CH_2-(4-Ac-2-oxo-1-Piz)	2-F	4-F	H
5-65	H	H	CH_2-(4-CO_2Me-2-oxo-1-Piz)	2-F	H	H
5-66	Ac	H	CH_2-(4-CO_2Me-2-oxo-1-Piz)	2-F	H	H
5-67	H	H	CH_2-(4-CO_2Et-2-oxo-1-Piz)	2-F	H	H
5-68	Ac	H	CH_2-(4-CO_2Et-2-oxo-1-Piz)	2-F	H	H
5-69	H	H	CH_2-(4-CH_2CO_2H-2-oxo-1-Piz)	2-F	H	H
5-70	Ac	H	CH_2-(4-CH_2CO_2H-2-oxo-1-Piz)	2-F	H	H
5-71	H	H	CH_2-(4-CH_2CO_2Me-2-oxo-1-Piz)	2-F	H	H
5-72	Ac	H	CH_2-(4-CH_2CO_2Me-2-oxo-1-Piz)	2-F	H	H
5-73	H	H	CH_2-(4-CH_2CO_2Et-2-oxo-1-Piz)	2-F	H	H
5-74	Ac	H	CH_2-(4-CH_2CO_2Et-2-oxo-1-Piz)	2-F	H	H
5-75	H	H	CH_2-(4-$CH_2CH_2CO_2H$-2-oxo-1-Piz)	2-F	H	H
5-76	Ac	H	CH_2-(4-$CH_2CH_2CO_2H$-2-oxo-1-Piz)	2-F	H	H
5-77	H	H	CH_2-(4-$CH_2CH_2CO_2Me$-2-oxo-1-Piz)	2-F	H	H
5-78	Ac	H	CH_2-(4-$CH_2CH_2CO_2Me$-2-oxo-1-Piz)	2-F	H	H
5-79	H	H	CH_2-(4-$CH_2CH_2CO_2Et$-2-oxo-1-Piz)	2-F	H	H
5-80	Ac	H	CH_2-(4-$CH_2CH_2CO_2Et$-2-oxo-1-Piz)	2-F	H	H
5-81	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2H$-2-oxo-1-Piz)	2-F	H	H
5-82	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2H$-2-oxo-1-Piz)	2-F	H	H
5-83	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2Me$-2-oxo-1-Piz)	2-F	H	H
5-84	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2Me$-2-oxo-1-Piz)	2-F	H	H
5-85	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2Et$-2-oxo-1-Piz)	2-F	H	H
5-86	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2Et$-2-oxo-1-Piz)	2-F	H	H
5-87	H	H	CH_2-(3-oxo-1-Piz)	2-F	H	H
5-88	Ac	H	CH_2-(3-oxo-1-Piz)	2-F	H	H
5-89	H	H	CH_2-(4-Ac-3-oxo-1-Piz)	2-F	H	H
5-90	Ac	H	CH_2-(4-Ac-3-oxo-1-Piz)	2-F	H	H
5-91	H	H	CH_2-(4-Ac-3-oxo-1-Piz)	2-F	4-F	H
5-92	Ac	H	CH_2-(4-Ac-3-oxo-1-Piz)	2-F	4-F	H
5-93	H	H	CH_2-(4-CO_2Me-3-oxo-1-Piz)	2-F	H	H
5-94	Ac	H	CH_2-(4-CO_2Me-3-oxo-1-Piz)	2-F	H	H
5-95	H	H	CH_2-(4-CO_2Et-3-oxo-1-Piz)	2-F	H	H
5-96	Ac	H	CH_2-(4-CO_2Et-3-oxo-1-Piz)	2-F	H	H
5-97	H	H	CH_2-(4-CH_2CO_2H-3-oxo-1-Piz)	2-F	H	H
5-98	Ac	H	CH_2-(4-CH_2CO_2H-3-oxo-1-Piz)	2-F	H	H
5-99	H	H	CH_2-(4-CH_2CO_2Me-3-oxo-1-Piz)	2-F	H	H
5-100	Ac	H	CH_2-(4-CH_2CO_2Me-3-oxo-1-Piz)	2-F	H	H
5-101	H	H	CH_2-(4-CH_2CO_2Et-3-oxo-1-Piz)	2-F	H	H
5-102	Ac	H	CH_2-(4-CH_2CO_2Et-3-oxo-1-Piz)	2-F	H	H
5-103	H	H	CH_2-(4-$CH_2CH_2CO_2H$-3-oxo-1-Piz)	2-F	H	H
5-104	Ac	H	CH_2-(4-$CH_2CH_2CO_2H$-3-oxo-1-Piz)	2-F	H	H
5-105	H	H	CH_2-(4-$CH_2CH_2CO_2Me$-3-oxo-1-Piz)	2-F	H	H
5-106	Ac	H	CH_2-(4-$CH_2CH_2CO_2Me$-3-oxo-1-Piz)	2-F	H	H
5-107	H	H	CH_2-(4-$CH_2CH_2CO_2Et$-3-oxo-1-Piz)	2-F	H	H
5-108	Ac	H	CH_2-(4-$CH_2CH_2CO_2Et$-3-oxo-1-Piz)	2-F	H	H
5-109	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2H$-3-oxo-1-Piz)	2-F	H	H
5-110	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2H$-3-oxo-1-Piz)	2-F	H	H
5-111	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2Me$-3-oxo-1-Piz)	2-F	H	H
5-112	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2Me$-3-oxo-1-Piz)	2-F	H	H

5-113	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2Et$-3-oxo-1-Piz)	2-F	H	H
5-114	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2Et$-3-oxo-1-Piz)	2-F	H	H
5-115	H	H	CH_2-(2,5-dioxo-1-Piz)	2-F	H	H
5-116	Ac	H	CH_2-(2,5-dioxo-1-Piz)	2-F	H	H
5-117	H	H	CH_2-(4-Ac-2,5-dioxo-1-Piz)	2-F	H	H
5-118	Ac	H	CH_2-(4-Ac-2,5-dioxo-1-Piz)	2-F	H	H
5-119	H	H	CH_2-(4-Ac-2,5-dioxo-1-Piz)	2-F	4-F	H
5-120	Ac	H	CH_2-(4-Ac-2,5-dioxo-1-Piz)	2-F	4-F	H
5-121	H	H	CH_2-(4-CO_2Me-2,5-dioxo-1-Piz)	2-F	H	H
5-122	Ac	H	CH_2-(4-CO_2Me-2,5-dioxo-1-Piz)	2-F	H	H
5-123	H	H	CH_2-(4-CO_2Et-2,5-dioxo-1-Piz)	2-F	H	H
5-124	Ac	H	CH_2-(4-CO_2Et-2,5-dioxo-1-Piz)	2-F	H	H
5-125	H	H	CH_2-(4-CH_2CO_2H-2,5-dioxo-1-Piz)	2-F	H	H
5-126	Ac	H	CH_2-(4-CH_2CO_2H-2,5-dioxo-1-Piz)	2-F	H	H
5-127	H	H	CH_2-(4-CH_2CO_2Me-2,5-dioxo-1-Piz)	2-F	H	H
5-128	Ac	H	CH_2-(4-CH_2CO_2Me-2,5-dioxo-1-Piz)	2-F	H	H
5-129	H	H	CH_2-(4-CH_2CO_2Et-2,5-dioxo-1-Piz)	2-F	H	H
5-130	Ac	H	CH_2-(4-CH_2CO_2Et-2,5-dioxo-1-Piz)	2-F	H	H
5-131	H	H	CH_2-(4-$CH_2CH_2CO_2H$-2,5-dioxo-1-Piz)	2-F	H	H
5-132	Ac	H	CH_2-(4-$CH_2CH_2CO_2H$-2,5-dioxo-1-Piz)	2-F	H	H
5-133	H	H	CH_2-(4-$CH_2CH_2CO_2Me$-2,5-dioxo-1-Piz)	2-F	H	H
5-134	Ac	H	CH_2-(4-$CH_2CH_2CO_2Me$-2,5-dioxo-1-Piz)	2-F	H	H
5-135	H	H	CH_2-(4-$CH_2CH_2CO_2Et$-2,5-dioxo-1-Piz)	2-F	H	H
5-136	Ac	H	CH_2-(4-$CH_2CH_2CO_2Et$-2,5-dioxo-1-Piz)	2-F	H	H
5-137	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2H$-2,5-dioxo-1-Piz)	2-F	H	H
5-138	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2H$-2,5-dioxo-1-Piz)	2-F	H	H
5-139	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2Me$-2,5-dioxo-1-Piz)	2-F	H	H
5-140	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2Me$-2,5-dioxo-1-Piz)	2-F	H	H
5-141	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2Et$-2,5-dioxo-1-Piz)	2-F	H	H
5-142	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2Et$-2,5-dioxo-1-Piz)	2-F	H	H
5-143	H	H	CH_2-1-Pyrd	2-F	H	H
5-144	Ac	H	CH_2-1-Pyrd	2-F	H	H
5-145	H	H	CH_2-(2-CO_2H-1-Pyrd)	2-F	H	H
5-146	Ac	H	CH_2-(2-CO_2H-1-Pyrd)	2-F	H	H
5-147	H	H	CH_2-(2-CO_2Me-1-Pyrd)	2-F	H	H
5-148	Ac	H	CH_2-(2-CO_2Me-1-Pyrd)	2-F	H	H
5-149	H	H	CH_2-(2-CO_2Et-1-Pyrd)	2-F	H	H
5-150	Ac	H	CH_2-(2-CO_2Et-1-Pyrd)	2-F	H	H
5-151	H	H	CH_2-(2-CH_2CO_2H-1-Pyrd)	2-F	H	H
5-152	Ac	H	CH_2-(2-CH_2CO_2H-1-Pyrd)	2-F	H	H
5-153	H	H	CH_2-(2-CH_2CO_2Me-1-Pyrd)	2-F	H	H
5-154	Ac	H	CH_2-(2-CH_2CO_2Me-1-Pyrd)	2-F	H	H
5-155	H	H	CH_2-(2-CH_2CO_2Et-1-Pyrd)	2-F	H	H
5-156	Ac	H	CH_2-(2-CH_2CO_2Et-1-Pyrd)	2-F	H	H
5-157	H	H	CH_2-(2-$CH_2CH_2CO_2H$-1-Pyrd)	2-F	H	H
5-158	Ac	H	CH_2-(2-$CH_2CH_2CO_2H$-1-Pyrd)	2-F	H	H
5-159	H	H	CH_2-(2-$CH_2CH_2CO_2Me$-1-Pyrd)	2-F	H	H
5-160	Ac	H	CH_2-(2-$CH_2CH_2CO_2Me$-1-Pyrd)	2-F	H	H
5-161	H	H	CH_2-(2-$CH_2CH_2CO_2Et$-1-Pyrd)	2-F	H	H
5-162	Ac	H	CH_2-(2-$CH_2CH_2CO_2Et$-1-Pyrd)	2-F	H	H
5-163	H	H	CH_2-(2-$CH_2CH_2CH_2CO_2H$-1-Pyrd)	2-F	H	H
5-164	Ac	H	CH_2-(2-$CH_2CH_2CH_2CO_2H$-1-Pyrd)	2-F	H	H
5-165	H	H	CH_2-(2-$CH_2CH_2CH_2CO_2Me$-1-Pyrd)	2-F	H	H
5-166	Ac	H	CH_2-(2-$CH_2CH_2CH_2CO_2Me$-1-Pyrd)	2-F	H	H
5-167	H	H	CH_2-(2-$CH_2CH_2CH_2CO_2Et$-1-Pyrd)	2-F	H	H

5-168	Ac	H	CH_2-(2-$CH_2CH_2CH_2CO_2Et$-1-Pyrd)	2-F	H	H
5-169	H	H	CH_2CH_2-1-Pip	2-F	H	H
5-170	Ac	H	CH_2CH_2-1-Pip	2-F	H	H
5-171	H	H	CH_2CH_2-(4-CO_2H-1-Pip)	2-F	H	H
5-172	Ac	H	CH_2CH_2-(4-CO_2H-1-Pip)	2-F	H	H
5-173	H	H	CH_2CH_2-(4-CO_2Me-1-Pip)	2-F	H	H
5-174	Ac	H	CH_2CH_2-(4-CO_2Me-1-Pip)	2-F	H	H
5-175	H	H	CH_2CH_2-(4-CO_2Et-1-Pip)	2-F	H	H
5-176	Ac	H	CH_2CH_2-(4-CO_2Et-1-Pip)	2-F	H	H
5-177	H	H	CH_2CH_2-(4-CH_2CO_2H-1-Pip)	2-F	H	H
5-178	Ac	H	CH_2CH_2-(4-CH_2CO_2H-1-Pip)	2-F	H	H
5-179	H	H	CH_2CH_2-(4-CH_2CO_2Me-1-Pip)	2-F	H	H
5-180	Ac	H	CH_2CH_2-(4-CH_2CO_2Me-1-Pip)	2-F	H	H
5-181	H	H	CH_2CH_2-(4-CH_2CO_2Et-1-Pip)	2-F	H	H
5-182	Ac	H	CH_2CH_2-(4-CH_2CO_2Et-1-Pip)	2-F	H	H
5-183	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2H$-1-Pip)	2-F	H	H
5-184	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2H$-1-Pip)	2-F	H	H
5-185	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-1-Pip)	2-F	H	H
5-186	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-1-Pip)	2-F	H	H
5-187	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-1-Pip)	2-F	H	H
5-188	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-1-Pip)	2-F	H	H
5-189	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2H$-1-Pip)	2-F	H	H
5-190	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2H$-1-Pip)	2-F	H	H
5-191	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Me$-1-Pip)	2-F	H	H
5-192	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Me$-1-Pip)	2-F	H	H
5-193	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Et$-1-Pip)	2-F	H	H
5-194	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Et$-1-Pip)	2-F	H	H
5-195	H	H	CH_2CH_2-Mor	2-F	H	H
5-196	Ac	H	CH_2CH_2-Mor	2-F	H	H
5-197	H	H	CH_2CH_2-Thim	2-F	H	H
5-198	Ac	H	CH_2CH_2-Thim	2-F	H	H
5-199	H	H	CH_2CH_2-1-Piz	2-F	H	H
5-200	Ac	H	CH_2CH_2-1-Piz	2-F	H	H
5-201	H	H	CH_2CH_2-(4-Ac-1-Piz)	2-F	H	H
5-202	Ac	H	CH_2CH_2-(4-Ac-1-Piz)	2-F	H	H
5-203	H	H	CH_2CH_2-(4-Ac-1-Piz)	2-F	4-F	H
5-204	Ac	H	CH_2CH_2-(4-Ac-1-Piz)	2-F	4-F	H
5-205	H	H	CH_2CH_2-(4-CO_2Me-1-Piz)	2-F	H	H
5-206	Ac	H	CH_2CH_2-(4-CO_2Me-1-Piz)	2-F	H	H
5-207	H	H	CH_2CH_2-(4-CO_2Et-1-Piz)	2-F	H	H
5-208	Ac	H	CH_2CH_2-(4-CO_2Et-1-Piz)	2-F	H	H
5-209	H	H	CH_2CH_2-(4-CH_2CO_2H-1-Piz)	2-F	H	H
5-210	Ac	H	CH_2CH_2-(4-CH_2CO_2H-1-Piz)	2-F	H	H
5-211	H	H	CH_2CH_2-(4-CH_2CO_2Me-1-Piz)	2-F	H	H
5-212	Ac	H	CH_2CH_2-(4-CH_2CO_2Me-1-Piz)	2-F	H	H
5-213	H	H	CH_2CH_2-(4-CH_2CO_2Et-1-Piz)	2-F	H	H
5-214	Ac	H	CH_2CH_2-(4-CH_2CO_2Et-1-Piz)	2-F	H	H
5-215	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2H$-1-Piz)	2-F	H	H
5-216	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2H$-1-Piz)	2-F	H	H
5-217	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-1-Piz)	2-F	H	H
5-218	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-1-Piz)	2-F	H	H
5-219	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-1-Piz)	2-F	H	H
5-220	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-1-Piz)	2-F	H	H
5-221	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2H$-1-Piz)	2-F	H	H
5-222	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2H$-1-Piz)	2-F	H	H
5-223	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Me$-1-Piz)	2-F	H	H
5-224	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Me$-1-Piz)	2-F	H	H

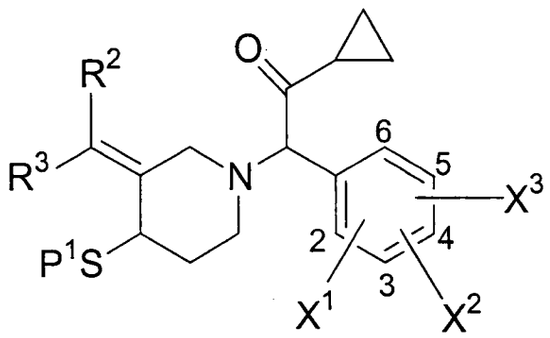
5-225	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Et$-1-Piz)	2-F	H	H
5-226	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Et$-1-Piz)	2-F	H	H
5-227	H	H	CH_2CH_2-(2-oxo-1-Piz)	2-F	H	H
5-228	Ac	H	CH_2CH_2-(2-oxo-1-Piz)	2-F	H	H
5-229	H	H	CH_2CH_2-(4-Ac-2-oxo-1-Piz)	2-F	H	H
5-230	Ac	H	CH_2CH_2-(4-Ac-2-oxo-1-Piz)	2-F	H	H
5-231	H	H	CH_2CH_2-(4-Ac-2-oxo-1-Piz)	2-F	4-F	H
5-232	Ac	H	CH_2CH_2-(4-Ac-2-oxo-1-Piz)	2-F	4-F	H
5-233	H	H	CH_2CH_2-(4-CO_2Me-2-oxo-1-Piz)	2-F	H	H
5-234	Ac	H	CH_2CH_2-(4-CO_2Me-2-oxo-1-Piz)	2-F	H	H
5-235	H	H	CH_2CH_2-(4-CO_2Et-2-oxo-1-Piz)	2-F	H	H
5-236	Ac	H	CH_2CH_2-(4-CO_2Et-2-oxo-1-Piz)	2-F	H	H
5-237	H	H	CH_2CH_2-(4-CH_2CO_2H-2-oxo-1-Piz)	2-F	H	H
5-238	Ac	H	CH_2CH_2-(4-CH_2CO_2H-2-oxo-1-Piz)	2-F	H	H
5-239	H	H	CH_2CH_2-(4-CH_2CO_2Me-2-oxo-1-Piz)	2-F	H	H
5-240	Ac	H	CH_2CH_2-(4-CH_2CO_2Me-2-oxo-1-Piz)	2-F	H	H
5-241	H	H	CH_2CH_2-(4-CH_2CO_2Et-2-oxo-1-Piz)	2-F	H	H
5-242	Ac	H	CH_2CH_2-(4-CH_2CO_2Et-2-oxo-1-Piz)	2-F	H	H
5-243	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2H$-2-oxo-1-Piz)	2-F	H	H
5-244	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2H$-2-oxo-1-Piz)	2-F	H	H
5-245	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-2-oxo-1-Piz)	2-F	H	H
5-246	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-2-oxo-1-Piz)	2-F	H	H
5-247	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-2-oxo-1-Piz)	2-F	H	H
5-248	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-2-oxo-1-Piz)	2-F	H	H
5-249	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2H$-2-oxo-1-Piz)	2-F	H	H
5-250	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2H$-2-oxo-1-Piz)	2-F	H	H
5-251	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Me$-2-oxo-1-Piz)	2-F	H	H
5-252	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Me$-2-oxo-1-Piz)	2-F	H	H
5-253	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Et$-2-oxo-1-Piz)	2-F	H	H
5-254	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Et$-2-oxo-1-Piz)	2-F	H	H
5-255	H	H	CH_2CH_2-(3-oxo-1-Piz)	2-F	H	H
5-256	Ac	H	CH_2CH_2-(3-oxo-1-Piz)	2-F	H	H
5-257	H	H	CH_2CH_2-(4-Ac-3-oxo-1-Piz)	2-F	H	H
5-258	Ac	H	CH_2CH_2-(4-Ac-3-oxo-1-Piz)	2-F	H	H
5-259	H	H	CH_2CH_2-(4-Ac-3-oxo-1-Piz)	2-F	4-F	H
5-260	Ac	H	CH_2CH_2-(4-Ac-3-oxo-1-Piz)	2-F	4-F	H
5-261	H	H	CH_2CH_2-(4-CO_2Me-3-oxo-1-Piz)	2-F	H	H
5-262	Ac	H	CH_2CH_2-(4-CO_2Me-3-oxo-1-Piz)	2-F	H	H
5-263	H	H	CH_2CH_2-(4-CO_2Et-3-oxo-1-Piz)	2-F	H	H
5-264	Ac	H	CH_2CH_2-(4-CO_2Et-3-oxo-1-Piz)	2-F	H	H
5-265	H	H	CH_2CH_2-(4-CH_2CO_2H-3-oxo-1-Piz)	2-F	H	H
5-266	Ac	H	CH_2CH_2-(4-CH_2CO_2H-3-oxo-1-Piz)	2-F	H	H
5-267	H	H	CH_2CH_2-(4-CH_2CO_2Me-3-oxo-1-Piz)	2-F	H	H
5-268	Ac	H	CH_2CH_2-(4-CH_2CO_2Me-3-oxo-1-Piz)	2-F	H	H
5-269	H	H	CH_2CH_2-(4-CH_2CO_2Et-3-oxo-1-Piz)	2-F	H	H
5-270	Ac	H	CH_2CH_2-(4-CH_2CO_2Et-3-oxo-1-Piz)	2-F	H	H
5-271	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2H$-3-oxo-1-Piz)	2-F	H	H
5-272	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2H$-3-oxo-1-Piz)	2-F	H	H
5-273	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-3-oxo-1-Piz)	2-F	H	H
5-274	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-3-oxo-1-Piz)	2-F	H	H
5-275	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-3-oxo-1-Piz)	2-F	H	H
5-276	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-3-oxo-1-Piz)	2-F	H	H
5-277	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2H$-3-oxo-1-Piz)	2-F	H	H
5-278	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2H$-3-oxo-1-Piz)	2-F	H	H
5-279	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Me$-3-oxo-1-	2-F	H	H

			Piz)			
5-280	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Me$-3-oxo-1-Piz)	2-F	H	H
5-281	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Et$-3-oxo-1-Piz)	2-F	H	H
5-282	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Et$-3-oxo-1-Piz)	2-F	H	H
5-283	H	H	CH_2CH_2-(2,5-dioxo-1-Piz)	2-F	H	H
5-284	Ac	H	CH_2CH_2-(2,5-dioxo-1-Piz)	2-F	H	H
5-285	H	H	CH_2CH_2-(4-Ac-2,5-dioxo-1-Piz)	2-F	H	H
5-286	Ac	H	CH_2CH_2-(4-Ac-2,5-dioxo-1-Piz)	2-F	H	H
5-287	H	H	CH_2CH_2-(4-Ac-2,5-dioxo-1-Piz)	2-F	4-F	H
5-288	Ac	H	CH_2CH_2-(4-Ac-2,5-dioxo-1-Piz)	2-F	4-F	H
5-289	H	H	CH_2CH_2-(4-CO_2Me-2,5-dioxo-1-Piz)	2-F	H	H
5-290	Ac	H	CH_2CH_2-(4-CO_2Me-2,5-dioxo-1-Piz)	2-F	H	H
5-291	H	H	CH_2CH_2-(4-CO_2Et-2,5-dioxo-1-Piz)	2-F	H	H
5-292	Ac	H	CH_2CH_2-(4-CO_2Et-2,5-dioxo-1-Piz)	2-F	H	H
5-293	H	H	CH_2CH_2-(4-CH_2CO_2H-2,5-dioxo-1-Piz)	2-F	H	H
5-294	Ac	H	CH_2CH_2-(4-CH_2CO_2H-2,5-dioxo-1-Piz)	2-F	H	H
5-295	H	H	CH_2CH_2-(4-CH_2CO_2Me-2,5-dioxo-1-Piz)	2-F	H	H
5-296	Ac	H	CH_2CH_2-(4-CH_2CO_2Me-2,5-dioxo-1-Piz)	2-F	H	H
5-297	H	H	CH_2CH_2-(4-CH_2CO_2Et-2,5-dioxo-1-Piz)	2-F	H	H
5-298	Ac	H	CH_2CH_2-(4-CH_2CO_2Et-2,5-dioxo-1-Piz)	2-F	H	H
5-299	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2H$-2,5-dioxo-1-Piz)	2-F	H	H
5-300	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2H$-2,5-dioxo-1-Piz)	2-F	H	H
5-301	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-2,5-dioxo-1-Piz)	2-F	H	H
5-302	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-2,5-dioxo-1-Piz)	2-F	H	H
5-303	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-2,5-dioxo-1-Piz)	2-F	H	H
5-304	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-2,5-dioxo-1-Piz)	2-F	H	H
5-305	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2H$-2,5-dioxo-1-Piz)	2-F	H	H
5-306	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2H$-2,5-dioxo-1-Piz)	2-F	H	H
5-307	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Me$-2,5-dioxo-1-Piz)	2-F	H	H
5-308	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Me$-2,5-dioxo-1-Piz)	2-F	H	H
5-309	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Et$-2,5-dioxo-1-Piz)	2-F	H	H
5-310	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Et$-2,5-dioxo-1-Piz)	2-F	H	H
5-311	H	H	CH_2CH_2-1-Pyrd	2-F	H	H
5-312	Ac	H	CH_2CH_2-1-Pyrd	2-F	H	H
5-313	H	H	CH_2CH_2-(2-CO_2H-1-Pyrd)	2-F	H	H
5-314	Ac	H	CH_2CH_2-(2-CO_2H-1-Pyrd)	2-F	H	H
5-315	H	H	CH_2CH_2-(2-CO_2Me-1-Pyrd)	2-F	H	H
5-316	Ac	H	CH_2CH_2-(2-CO_2Me-1-Pyrd)	2-F	H	H
5-317	H	H	CH_2CH_2-(2-CO_2Et-1-Pyrd)	2-F	H	H
5-318	Ac	H	CH_2CH_2-(2-CO_2Et-1-Pyrd)	2-F	H	H
5-319	H	H	CH_2CH_2-(2-CH_2CO_2H-1-Pyrd)	2-F	H	H
5-320	Ac	H	CH_2CH_2-(2-CH_2CO_2H-1-Pyrd)	2-F	H	H
5-321	H	H	CH_2CH_2-(2-CH_2CO_2Me-1-Pyrd)	2-F	H	H
5-322	Ac	H	CH_2CH_2-(2-CH_2CO_2Me-1-Pyrd)	2-F	H	H
5-323	H	H	CH_2CH_2-(2-CH_2CO_2Et-1-Pyrd)	2-F	H	H
5-324	Ac	H	CH_2CH_2-(2-CH_2CO_2Et-1-Pyrd)	2-F	H	H
5-325	H	H	CH_2CH_2-(2-$CH_2CH_2CO_2H$-1-Pyrd)	2-F	H	H
5-326	Ac	H	CH_2CH_2-(2-$CH_2CH_2CO_2H$-1-Pyrd)	2-F	H	H

5-327	H	H	CH_2CH_2-(2-$CH_2CH_2CO_2Me$-1-Pyrd)	2-F	H	H
5-328	Ac	H	CH_2CH_2-(2-$CH_2CH_2CO_2Me$-1-Pyrd)	2-F	H	H
5-329	H	H	CH_2CH_2-(2-$CH_2CH_2CO_2Et$-1-Pyrd)	2-F	H	H
5-330	Ac	H	CH_2CH_2-(2-$CH_2CH_2CO_2Et$-1-Pyrd)	2-F	H	H
5-331	H	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2H$-1-Pyrd)	2-F	H	H
5-332	Ac	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2H$-1-Pyrd)	2-F	H	H
5-333	H	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2Me$-1-Pyrd)	2-F	H	H
5-334	Ac	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2Me$-1-Pyrd)	2-F	H	H
5-335	H	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2Et$-1-Pyrd)	2-F	H	H
5-336	Ac	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2Et$-1-Pyrd)	2-F	H	H
5-337	H	H	CH_2-(3-CO_2H-1-Pip)	2-F	H	H
5-338	Ac	H	CH_2-(3-CO_2H-1-Pip)	2-F	H	H
5-339	H	H	CH_2-(3-CO_2Me-1-Pip)	2-F	H	H
5-340	Ac	H	CH_2-(3-CO_2Me-1-Pip)	2-F	H	H
5-341	H	H	CH_2-(3-CO_2Et-1-Pip)	2-F	H	H
5-342	Ac	H	CH_2-(3-CO_2Et-1-Pip)	2-F	H	H
5-343	H	H	CH_2-(3-CH_2CO_2H-1-Pip)	2-F	H	H
5-344	Ac	H	CH_2-(3-CH_2CO_2H-1-Pip)	2-F	H	H
5-345	H	H	CH_2-(3-CH_2CO_2Me-1-Pip)	2-F	H	H
5-346	Ac	H	CH_2-(3-CH_2CO_2Me-1-Pip)	2-F	H	H
5-347	H	H	CH_2-(3-CH_2CO_2Et-1-Pip)	2-F	H	H
5-348	Ac	H	CH_2-(3-CH_2CO_2Et-1-Pip)	2-F	H	H
5-349	H	H	CH_2-(3-$CH_2CH_2CO_2H$-1-Pip)	2-F	H	H
5-350	Ac	H	CH_2-(3-$CH_2CH_2CO_2H$-1-Pip)	2-F	H	H
5-351	H	H	CH_2-(3-$CH_2CH_2CO_2Me$-1-Pip)	2-F	H	H
5-352	Ac	H	CH_2-(3-$CH_2CH_2CO_2Me$-1-Pip)	2-F	H	H
5-353	H	H	CH_2-(3-$CH_2CH_2CO_2Et$-1-Pip)	2-F	H	H
5-354	Ac	H	CH_2-(3-$CH_2CH_2CO_2Et$-1-Pip)	2-F	H	H
5-355	H	H	CH_2-(3-$CH_2CH_2CH_2CO_2H$-1-Pip)	2-F	H	H
5-356	Ac	H	CH_2-(3-$CH_2CH_2CH_2CO_2H$-1-Pip)	2-F	H	H
5-357	H	H	CH_2-(3-$CH_2CH_2CH_2CO_2Me$-1-Pip)	2-F	H	H
5-358	Ac	H	CH_2-(3-$CH_2CH_2CH_2CO_2Me$-1-Pip)	2-F	H	H
5-359	H	H	CH_2-(3-$CH_2CH_2CH_2CO_2Et$-1-Pip)	2-F	H	H
5-360	Ac	H	CH_2-(3-$CH_2CH_2CH_2CO_2Et$-1-Pip)	2-F	H	H
5-361	H	H	CH_2CH_2-(3-CO_2H-1-Pip)	2-F	H	H
5-362	Ac	H	CH_2CH_2-(3-CO_2H-1-Pip)	2-F	H	H
5-363	H	H	CH_2CH_2-(3-CO_2Me-1-Pip)	2-F	H	H
5-364	Ac	H	CH_2CH_2-(3-CO_2Me-1-Pip)	2-F	H	H
5-365	H	H	CH_2CH_2-(3-CO_2Et-1-Pip)	2-F	H	H
5-366	Ac	H	CH_2CH_2-(3-CO_2Et-1-Pip)	2-F	H	H
5-367	H	H	CH_2CH_2-(3-CH_2CO_2H-1-Pip)	2-F	H	H
5-368	Ac	H	CH_2CH_2-(3-CH_2CO_2H-1-Pip)	2-F	H	H
5-369	H	H	CH_2CH_2-(3-CH_2CO_2Me-1-Pip)	2-F	H	H
5-370	Ac	H	CH_2CH_2-(3-CH_2CO_2Me-1-Pip)	2-F	H	H
5-371	H	H	CH_2CH_2-(3-CH_2CO_2Et-1-Pip)	2-F	H	H
5-372	Ac	H	CH_2CH_2-(3-CH_2CO_2Et-1-Pip)	2-F	H	H
5-373	H	H	CH_2CH_2-(3-$CH_2CH_2CO_2H$-1-Pip)	2-F	H	H
5-374	Ac	H	CH_2CH_2-(3-$CH_2CH_2CO_2H$-1-Pip)	2-F	H	H
5-375	H	H	CH_2CH_2-(3-$CH_2CH_2CO_2Me$-1-Pip)	2-F	H	H
5-376	Ac	H	CH_2CH_2-(3-$CH_2CH_2CO_2Me$-1-Pip)	2-F	H	H
5-377	H	H	CH_2CH_2-(3-$CH_2CH_2CO_2Et$-1-Pip)	2-F	H	H
5-378	Ac	H	CH_2CH_2-(3-$CH_2CH_2CO_2Et$-1-Pip)	2-F	H	H
5-379	H	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2H$-1-Pip)	2-F	H	H
5-380	Ac	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2H$-1-Pip)	2-F	H	H
5-381	H	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2Me$-1-Pip)	2-F	H	H
5-382	Ac	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2Me$-1-Pip)	2-F	H	H
5-383	H	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2Et$-1-Pip)	2-F	H	H

5-384	Ac	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2Et$-1-Pip)	2-F	H	H
5-385	H	H	CH_2-(4-OH-2-CO_2H-1-Pyrd)	2-F	H	H
5-386	Ac	H	CH_2-(4-OH-2-CO_2H-1-Pyrd)	2-F	H	H
5-387	H	H	CH_2-(4-OH-2-CO_2Me-1-Pyrd)	2-F	H	H
5-388	Ac	H	CH_2-(4-OH-2-CO_2Me-1-Pyrd)	2-F	H	H
5-389	H	H	CH_2-(4-OH-2-CO_2Et-1-Pyrd)	2-F	H	H
5-390	Ac	H	CH_2-(4-OH-2-CO_2Et-1-Pyrd)	2-F	H	H

(Table 6)



Compound No.	P^1	R^2	R^3	X^1	X^2	X^3
6-1	H	H	CH_2-1-Pip	2-F	H	H
6-2	Ac	H	CH_2-1-Pip	2-F	H	H
6-3	H	H	CH_2-(4-CO_2H-1-Pip)	2-F	H	H
6-4	Ac	H	CH_2-(4-CO_2H-1-Pip)	2-F	H	H
6-5	H	H	CH_2-(4-CO_2Me-1-Pip)	2-F	H	H
6-6	Ac	H	CH_2-(4-CO_2Me-1-Pip)	2-F	H	H
6-7	H	H	CH_2-(4-CO_2Et-1-Pip)	2-F	H	H
6-8	Ac	H	CH_2-(4-CO_2Et-1-Pip)	2-F	H	H
6-9	H	H	CH_2-(4-CH_2CO_2H-1-Pip)	2-F	H	H
6-10	Ac	H	CH_2-(4-CH_2CO_2H-1-Pip)	2-F	H	H
6-11	H	H	CH_2-(4-CH_2CO_2Me-1-Pip)	2-F	H	H
6-12	Ac	H	CH_2-(4-CH_2CO_2Me-1-Pip)	2-F	H	H
6-13	H	H	CH_2-(4-CH_2CO_2Et-1-Pip)	2-F	H	H
6-14	Ac	H	CH_2-(4-CH_2CO_2Et-1-Pip)	2-F	H	H
6-15	H	H	CH_2-(4-$CH_2CH_2CO_2H$-1-Pip)	2-F	H	H
6-16	Ac	H	CH_2-(4-$CH_2CH_2CO_2H$-1-Pip)	2-F	H	H
6-17	H	H	CH_2-(4-$CH_2CH_2CO_2Me$-1-Pip)	2-F	H	H
6-18	Ac	H	CH_2-(4-$CH_2CH_2CO_2Me$-1-Pip)	2-F	H	H
6-19	H	H	CH_2-(4-$CH_2CH_2CO_2Et$-1-Pip)	2-F	H	H
6-20	Ac	H	CH_2-(4-$CH_2CH_2CO_2Et$-1-Pip)	2-F	H	H
6-21	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2H$-1-Pip)	2-F	H	H
6-22	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2H$-1-Pip)	2-F	H	H
6-23	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2Me$-1-Pip)	2-F	H	H
6-24	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2Me$-1-Pip)	2-F	H	H
6-25	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2Et$-1-Pip)	2-F	H	H
6-26	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2Et$-1-Pip)	2-F	H	H
6-27	H	H	CH_2-Mor	2-F	H	H
6-28	Ac	H	CH_2-Mor	2-F	H	H
6-29	H	H	CH_2-Thim	2-F	H	H
6-30	Ac	H	CH_2-Thim	2-F	H	H
6-31	H	H	CH_2-1-Piz	2-F	H	H

6-32	Ac	H	CH_2-1-Piz	2-F	H	H
6-33	H	H	CH_2-(4-Ac-1-Piz)	2-F	H	H
6-34	Ac	H	CH_2-(4-Ac-1-Piz)	2-F	H	H
6-35	H	H	CH_2-(4-Ac-1-Piz)	2-F	4-F	H
6-36	Ac	H	CH_2-(4-Ac-1-Piz)	2-F	4-F	H
6-37	H	H	CH_2-(4-CO_2Me-1-Piz)	2-F	H	H
6-38	Ac	H	CH_2-(4-CO_2Me-1-Piz)	2-F	H	H
6-39	H	H	CH_2-(4-CO_2Et-1-Piz)	2-F	H	H
6-40	Ac	H	CH_2-(4-CO_2Et-1-Piz)	2-F	H	H
6-41	H	H	CH_2-(4-CH_2CO_2H-1-Piz)	2-F	H	H
6-42	Ac	H	CH_2-(4-CH_2CO_2H-1-Piz)	2-F	H	H
6-43	H	H	CH_2-(4-CH_2CO_2Me-1-Piz)	2-F	H	H
6-44	Ac	H	CH_2-(4-CH_2CO_2Me-1-Piz)	2-F	H	H
6-45	H	H	CH_2-(4-CH_2CO_2Et-1-Piz)	2-F	H	H
6-46	Ac	H	CH_2-(4-CH_2CO_2Et-1-Piz)	2-F	H	H
6-47	H	H	CH_2-(4-$CH_2CH_2CO_2H$-1-Piz)	2-F	H	H
6-48	Ac	H	CH_2-(4-$CH_2CH_2CO_2H$-1-Piz)	2-F	H	H
6-49	H	H	CH_2-(4-$CH_2CH_2CO_2Me$-1-Piz)	2-F	H	H
6-50	Ac	H	CH_2-(4-$CH_2CH_2CO_2Me$-1-Piz)	2-F	H	H
6-51	H	H	CH_2-(4-$CH_2CH_2CO_2Et$-1-Piz)	2-F	H	H
6-52	Ac	H	CH_2-(4-$CH_2CH_2CO_2Et$-1-Piz)	2-F	H	H
6-53	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2H$-1-Piz)	2-F	H	H
6-54	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2H$-1-Piz)	2-F	H	H
6-55	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2Me$-1-Piz)	2-F	H	H
6-56	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2Me$-1-Piz)	2-F	H	H
6-57	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2Et$-1-Piz)	2-F	H	H
6-58	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2Et$-1-Piz)	2-F	H	H
6-59	H	H	CH_2-(2-oxo-1-Piz)	2-F	H	H
6-60	Ac	H	CH_2-(2-oxo-1-Piz)	2-F	H	H
6-61	H	H	CH_2-(4-Ac-2-oxo-1-Piz)	2-F	H	H
6-62	Ac	H	CH_2-(4-Ac-2-oxo-1-Piz)	2-F	H	H
6-63	H	H	CH_2-(4-Ac-2-oxo-1-Piz)	2-F	4-F	H
6-64	Ac	H	CH_2-(4-Ac-2-oxo-1-Piz)	2-F	4-F	H
6-65	H	H	CH_2-(4-CO_2Me-2-oxo-1-Piz)	2-F	H	H
6-66	Ac	H	CH_2-(4-CO_2Me-2-oxo-1-Piz)	2-F	H	H
6-67	H	H	CH_2-(4-CO_2Et-2-oxo-1-Piz)	2-F	H	H
6-68	Ac	H	CH_2-(4-CO_2Et-2-oxo-1-Piz)	2-F	H	H
6-69	H	H	CH_2-(4-CH_2CO_2H-2-oxo-1-Piz)	2-F	H	H
6-70	Ac	H	CH_2-(4-CH_2CO_2H-2-oxo-1-Piz)	2-F	H	H
6-71	H	H	CH_2-(4-CH_2CO_2Me-2-oxo-1-Piz)	2-F	H	H
6-72	Ac	H	CH_2-(4-CH_2CO_2Me-2-oxo-1-Piz)	2-F	H	H
6-73	H	H	CH_2-(4-CH_2CO_2Et-2-oxo-1-Piz)	2-F	H	H
6-74	Ac	H	CH_2-(4-CH_2CO_2Et-2-oxo-1-Piz)	2-F	H	H
6-75	H	H	CH_2-(4-$CH_2CH_2CO_2H$-2-oxo-1-Piz)	2-F	H	H
6-76	Ac	H	CH_2-(4-$CH_2CH_2CO_2H$-2-oxo-1-Piz)	2-F	H	H
6-77	H	H	CH_2-(4-$CH_2CH_2CO_2Me$-2-oxo-1-Piz)	2-F	H	H
6-78	Ac	H	CH_2-(4-$CH_2CH_2CO_2Me$-2-oxo-1-Piz)	2-F	H	H
6-79	H	H	CH_2-(4-$CH_2CH_2CO_2Et$-2-oxo-1-Piz)	2-F	H	H
6-80	Ac	H	CH_2-(4-$CH_2CH_2CO_2Et$-2-oxo-1-Piz)	2-F	H	H
6-81	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2H$-2-oxo-1-Piz)	2-F	H	H
6-82	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2H$-2-oxo-1-Piz)	2-F	H	H
6-83	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2Me$-2-oxo-1-Piz)	2-F	H	H
6-84	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2Me$-2-oxo-1-Piz)	2-F	H	H
6-85	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2Et$-2-oxo-1-Piz)	2-F	H	H
6-86	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2Et$-2-oxo-1-Piz)	2-F	H	H
6-87	H	H	CH_2-(3-oxo-1-Piz)	2-F	H	H
6-88	Ac	H	CH_2-(3-oxo-1-Piz)	2-F	H	H

6-89	H	H	CH_2-(4-Ac-3-oxo-1-Piz)	2-F	H	H
6-90	Ac	H	CH_2-(4-Ac-3-oxo-1-Piz)	2-F	H	H
6-91	H	H	CH_2-(4-Ac-3-oxo-1-Piz)	2-F	4-F	H
6-92	Ac	H	CH_2-(4-Ac-3-oxo-1-Piz)	2-F	4-F	H
6-93	H	H	CH_2-(4-CO_2Me-3-oxo-1-Piz)	2-F	H	H
6-94	Ac	H	CH_2-(4-CO_2Me-3-oxo-1-Piz)	2-F	H	H
6-95	H	H	CH_2-(4-CO_2Et-3-oxo-1-Piz)	2-F	H	H
6-96	Ac	H	CH_2-(4-CO_2Et-3-oxo-1-Piz)	2-F	H	H
6-97	H	H	CH_2-(4-CH_2CO_2H-3-oxo-1-Piz)	2-F	H	H
6-98	Ac	H	CH_2-(4-CH_2CO_2H-3-oxo-1-Piz)	2-F	H	H
6-99	H	H	CH_2-(4-CH_2CO_2Me-3-oxo-1-Piz)	2-F	H	H
6-100	Ac	H	CH_2-(4-CH_2CO_2Me-3-oxo-1-Piz)	2-F	H	H
6-101	H	H	CH_2-(4-CH_2CO_2Et-3-oxo-1-Piz)	2-F	H	H
6-102	Ac	H	CH_2-(4-CH_2CO_2Et-3-oxo-1-Piz)	2-F	H	H
6-103	H	H	CH_2-(4-$CH_2CH_2CO_2H$-3-oxo-1-Piz)	2-F	H	H
6-104	Ac	H	CH_2-(4-$CH_2CH_2CO_2H$-3-oxo-1-Piz)	2-F	H	H
6-105	H	H	CH_2-(4-$CH_2CH_2CO_2Me$-3-oxo-1-Piz)	2-F	H	H
6-106	Ac	H	CH_2-(4-$CH_2CH_2CO_2Me$-3-oxo-1-Piz)	2-F	H	H
6-107	H	H	CH_2-(4-$CH_2CH_2CO_2Et$-3-oxo-1-Piz)	2-F	H	H
6-108	Ac	H	CH_2-(4-$CH_2CH_2CO_2Et$-3-oxo-1-Piz)	2-F	H	H
6-109	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2H$-3-oxo-1-Piz)	2-F	H	H
6-110	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2H$-3-oxo-1-Piz)	2-F	H	H
6-111	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2Me$-3-oxo-1-Piz)	2-F	H	H
6-112	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2Me$-3-oxo-1-Piz)	2-F	H	H
6-113	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2Et$-3-oxo-1-Piz)	2-F	H	H
6-114	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2Et$-3-oxo-1-Piz)	2-F	H	H
6-115	H	H	CH_2-(2,5-dioxo-1-Piz)	2-F	H	H
6-116	Ac	H	CH_2-(2,5-dioxo-1-Piz)	2-F	H	H
6-117	H	H	CH_2-(4-Ac-2,5-dioxo-1-Piz)	2-F	H	H
6-118	Ac	H	CH_2-(4-Ac-2,5-dioxo-1-Piz)	2-F	H	H
6-119	H	H	CH_2-(4-Ac-2,5-dioxo-1-Piz)	2-F	4-F	H
6-120	Ac	H	CH_2-(4-Ac-2,5-dioxo-1-Piz)	2-F	4-F	H
6-121	H	H	CH_2-(4-CO_2Me-2,5-dioxo-1-Piz)	2-F	H	H
6-122	Ac	H	CH_2-(4-CO_2Me-2,5-dioxo-1-Piz)	2-F	H	H
6-123	H	H	CH_2-(4-CO_2Et-2,5-dioxo-1-Piz)	2-F	H	H
6-124	Ac	H	CH_2-(4-CO_2Et-2,5-dioxo-1-Piz)	2-F	H	H
6-125	H	H	CH_2-(4-CH_2CO_2H-2,5-dioxo-1-Piz)	2-F	H	H
6-126	Ac	H	CH_2-(4-CH_2CO_2H-2,5-dioxo-1-Piz)	2-F	H	H
6-127	H	H	CH_2-(4-CH_2CO_2Me-2,5-dioxo-1-Piz)	2-F	H	H
6-128	Ac	H	CH_2-(4-CH_2CO_2Me-2,5-dioxo-1-Piz	2-F	H	H
6-130	Ac	H	CH_2-(4-CH_2CO_2Et-2,5-dioxo-1-Piz)	2-F	H	H
6-131	H	H	CH_2-(4-$CH_2CH_2CO_2H$-2,5-dioxo-1-Piz)	2-F	H	H
6-132	Ac	H	CH_2-(4-$CH_2CH_2CO_2H$-2,5-dioxo-1-Piz)	2-F	H	H
6-133	H	H	CH_2-(4-$CH_2CH_2CO_2Me$-2,5-dioxo-1-Piz)	2-F	H	H
6-134	Ac	H	CH_2-(4-$CH_2CH_2CO_2Me$-2,5-dioxo-1-Piz)	2-F	H	H
6-135	H	H	CH_2-(4-$CH_2CH_2CO_2Et$-2,5-dioxo-1-Piz)	2-F	H	H
6-136	Ac	H	CH_2-(4-$CH_2CH_2CO_2Et$-2,5-dioxo-1-Piz)	2-F	H	H
6-137	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2H$-2,5-dioxo-1-Piz)	2-F	H	H
6-138	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2H$-2,5-dioxo-1-Piz)	2-F	H	H
6-139	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2Me$-2,5-dioxo-1-Piz)	2-F	H	H
5-140	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2Me$-2,5-dioxo-1-Piz)	2-F	H	H
6-141	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2Et$-2,5-dioxo-1-Piz)	2-F	H	H
6-142	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2Et$-2,5-dioxo-1-Piz)	2-F	H	H
6-143	H	H	CH_2-1-Pyrd	2-F	H	H
6-144	Ac	H	CH_2-1-Pyrd	2-F	H	H

6-145	H	H	CH_2-(2-CO_2H-1-Pyrd)	2-F	H	H
6-146	Ac	H	CH_2-(2-CO_2H-1-Pyrd)	2-F	H	H
6-147	H	H	CH_2-(2-CO_2Me-1-Pyrd)	2-F	H	H
6-148	Ac	H	CH_2-(2-CO_2Me-1-Pyrd)	2-F	H	H
6-149	H	H	CH_2-(2-CO_2Et-1-Pyrd)	2-F	H	H
6-150	Ac	H	CH_2-(2-CO_2Et-1-Pyrd)	2-F	H	H
6-151	H	H	CH_2-(2-CH_2CO_2H-1-Pyrd)	2-F	H	H
6-152	Ac	H	CH_2-(2-CH_2CO_2H-1-Pyrd)	2-F	H	H
6-153	H	H	CH_2-(2-CH_2CO_2Me-1-Pyrd)	2-F	H	H
6-154	Ac	H	CH_2-(2-CH_2CO_2Me-1-Pyrd)	2-F	H	H
6-155	H	H	CH_2-(2-CH_2CO_2Et-1-Pyrd)	2-F	H	H
6-156	Ac	H	CH_2-(2-CH_2CO_2Et-1-Pyrd)	2-F	H	H
6-157	H	H	CH_2-(2-$CH_2CH_2CO_2H$-1-Pyrd)	2-F	H	H
6-158	Ac	H	CH_2-(2-$CH_2CH_2CO_2H$-1-Pyrd)	2-F	H	H
6-159	H	H	CH_2-(2-$CH_2CH_2CO_2Me$-1-Pyrd)	2-F	H	H
6-160	Ac	H	CH_2-(2-$CH_2CH_2CO_2Me$-1-Pyrd)	2-F	H	H
6-161	H	H	CH_2-(2-$CH_2CH_2CO_2Et$-1-Pyrd)	2-F	H	H
6-162	Ac	H	CH_2-(2-$CH_2CH_2CO_2Et$-1-Pyrd)	2-F	H	H
6-163	H	H	CH_2-(2-$CH_2CH_2CH_2CO_2H$-1-Pyrd)	2-F	H	H
6-164	Ac	H	CH_2-(2-$CH_2CH_2CH_2CO_2H$-1-Pyrd)	2-F	H	H
6-165	H	H	CH_2-(2-$CH_2CH_2CH_2CO_2Me$-1-Pyrd)	2-F	H	H
6-166	Ac	H	CH_2-(2-$CH_2CH_2CH_2CO_2Me$-1-Pyrd)	2-F	H	H
6-167	H	H	CH_2-(2-$CH_2CH_2CH_2CO_2Et$-1-Pyrd)	2-F	H	H
6-168	Ac	H	CH_2-(2-$CH_2CH_2CH_2CO_2Et$-1-Pyrd)	2-F	H	H
6-169	H	H	CH_2CH_2-1-Pip	2-F	H	H
6-170	Ac	H	CH_2CH_2-1-Pip	2-F	H	H
6-171	H	H	CH_2CH_2-(4-CO_2H-1-Pip)	2-F	H	H
6-172	Ac	H	CH_2CH_2-(4-CO_2H-1-Pip)	2-F	H	H
6-173	H	H	CH_2CH_2-(4-CO_2Me-1-Pip)	2-F	H	H
6-174	Ac	H	CH_2CH_2-(4-CO_2Me-1-Pip)	2-F	H	H
6-175	H	H	CH_2CH_2-(4-CO_2Et-1-Pip)	2-F	H	H
6-176	Ac	H	CH_2CH_2-(4-CO_2Et-1-Pip)	2-F	H	H
6-177	H	H	CH_2CH_2-(4-CH_2CO_2H-1-Pip)	2-F	H	H
6-178	Ac	H	CH_2CH_2-(4-CH_2CO_2H-1-Pip)	2-F	H	H
6-179	H	H	CH_2CH_2-(4-CH_2CO_2Me-1-Pip)	2-F	H	H
6-180	Ac	H	CH_2CH_2-(4-CH_2CO_2Me-1-Pip)	2-F	H	H
6-181	H	H	CH_2CH_2-(4-CH_2CO_2Et-1-Pip)	2-F	H	H
6-182	Ac	H	CH_2CH_2-(4-CH_2CO_2Et-1-Pip)	2-F	H	H
6-183	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2H$-1-Pip)	2-F	H	H
6-184	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2H$-1-Pip)	2-F	H	H
6-185	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-1-Pip)	2-F	H	H
6-186	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-1-Pip)	2-F	H	H
6-187	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-1-Pip)	2-F	H	H
6-188	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-1-Pip)	2-F	H	H
6-189	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2H$-1-Pip)	2-F	H	H
6-190	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2H$-1-Pip)	2-F	H	H
6-191	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Me$-1-Pip)	2-F	H	H
6-192	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Me$-1-Pip)	2-F	H	H
6-193	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Et$-1-Pip)	2-F	H	H
6-194	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Et$-1-Pip)	2-F	H	H
6-195	H	H	CH_2CH_2-Mor	2-F	H	H
6-196	Ac	H	CH_2CH_2-Mor	2-F	H	H
6-197	H	H	CH_2CH_2-Thim	2-F	H	H
6-198	Ac	H	CH_2CH_2-Thim	2-F	H	H
6-199	H	H	CH_2CH_2-1-Piz	2-F	H	H
6-200	Ac	H	CH_2CH_2-1-Piz	2-F	H	H
6-201	H	H	CH_2CH_2-(4-Ac-1-Piz)	2-F	H	H

6-202	Ac	H	CH_2CH_2-(4-Ac-1-Piz)	2-F	H	H
6-203	H	H	CH_2CH_2-(4-Ac-1-Piz)	2-F	4-F	H
6-204	Ac	H	CH_2CH_2-(4-Ac-1-Piz)	2-F	4-F	H
6-205	H	H	CH_2CH_2-(4-CO_2Me-1-Piz)	2-F	H	H
6-206	Ac	H	CH_2CH_2-(4-CO_2Me-1-Piz)	2-F	H	H
6-207	H	H	CH_2CH_2-(4-CO_2Et-1-Piz)	2-F	H	H
6-208	Ac	H	CH_2CH_2-(4-CO_2Et-1-Piz)	2-F	H	H
6-209	H	H	CH_2CH_2-(4-CH_2CO_2H-1-Piz)	2-F	H	H
6-210	Ac	H	CH_2CH_2-(4-CH_2CO_2H-1-Piz)	2-F	H	H
6-211	H	H	CH_2CH_2-(4-CH_2CO_2Me-1-Piz)	2-F	H	H
6-212	Ac	H	CH_2CH_2-(4-CH_2CO_2Me-1-Piz)	2-F	H	H
6-213	H	H	CH_2CH_2-(4-CH_2CO_2Et-1-Piz)	2-F	H	H
6-214	Ac	H	CH_2CH_2-(4-CH_2CO_2Et-1-Piz)	2-F	H	H
6-215	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2H$-1-Piz)	2-F	H	H
6-216	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2H$-1-Piz)	2-F	H	H
6-217	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-1-Piz)	2-F	H	H
6-218	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-1-Piz)	2-F	H	H
6-219	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-1-Piz)	2-F	H	H
6-220	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-1-Piz)	2-F	H	H
6-221	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2H$-1-Piz)	2-F	H	H
6-222	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2H$-1-Piz)	2-F	H	H
6-223	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Me$-1-Piz)	2-F	H	H
6-224	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Me$-1-Piz)	2-F	H	H
6-225	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Et$-1-Piz)	2-F	H	H
6-226	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Et$-1-Piz)	2-F	H	H
6-227	H	H	CH_2CH_2-(2-oxo-1-Piz)	2-F	H	H
6-228	Ac	H	CH_2CH_2-(2-oxo-1-Piz)	2-F	H	H
6-229	H	H	CH_2CH_2-(4-Ac-2-oxo-1-Piz)	2-F	H	H
6-230	Ac	H	CH_2CH_2-(4-Ac-2-oxo-1-Piz)	2-F	H	H
6-231	H	H	CH_2CH_2-(4-Ac-2-oxo-1-Piz)	2-F	4-F	H
6-232	Ac	H	CH_2CH_2-(4-Ac-2-oxo-1-Piz)	2-F	4-F	H
6-233	H	H	CH_2CH_2-(4-CO_2Me-2-oxo-1-Piz)	2-F	H	H
6-234	Ac	H	CH_2CH_2-(4-CO_2Me-2-oxo-1-Piz)	2-F	H	H
6-235	H	H	CH_2CH_2-(4-CO_2Et-2-oxo-1-Piz)	2-F	H	H
6-236	Ac	H	CH_2CH_2-(4-CO_2Et-2-oxo-1-Piz)	2-F	H	H
6-237	H	H	CH_2CH_2-(4-CH_2CO_2H-2-oxo-1-Piz)	2-F	H	H
6-238	Ac	H	CH_2CH_2-(4-CH_2CO_2H-2-oxo-1-Piz)	2-F	H	H
6-239	H	H	CH_2CH_2-(4-CH_2CO_2Me-2-oxo-1-Piz)	2-F	H	H
6-240	Ac	H	CH_2CH_2-(4-CH_2CO_2Me-2-oxo-1-Piz)	2-F	H	H
6-241	H	H	CH_2CH_2-(4-CH_2CO_2Et-2-oxo-1-Piz)	2-F	H	H
6-242	Ac	H	CH_2CH_2-(4-CH_2CO_2Et-2-oxo-1-Piz)	2-F	H	H
6-243	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2H$-2-oxo-1-Piz)	2-F	H	H
6-244	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2H$-2-oxo-1-Piz)	2-F	H	H
6-245	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-2-oxo-1-Piz)	2-F	H	H
6-246	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-2-oxo-1-Piz)	2-F	H	H
6-247	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-2-oxo-1-Piz)	2-F	H	H
6-248	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-2-oxo-1-Piz)	2-F	H	H
6-249	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2H$-2-oxo-1-Piz)	2-F	H	H
6-250	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2H$-2-oxo-1-Piz)	2-F	H	H
6-251	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Me$-2-oxo-1-Piz)	2-F	H	H
6-252	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Me$-2-oxo-1-Piz)	2-F	H	H
6-253	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Et$-2-oxo-1-Piz)	2-F	H	H
6-254	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Et$-2-oxo-1-Piz)	2-F	H	H
6-255	H	H	CH_2CH_2-(3-oxo-1-Piz)	2-F	H	H
6-256	Ac	H	CH_2CH_2-(3-oxo-1-Piz)	2-F	H	H

6-257	H	H	CH_2CH_2-(4-Ac-3-oxo-1-Piz)	2-F	H	H
6-258	Ac	H	CH_2CH_2-(4-Ac-3-oxo-1-Piz)	2-F	H	H
6-259	H	H	CH_2CH_2-(4-Ac-3-oxo-1-Piz)	2-F	4-F	H
6-260	Ac	H	CH_2CH_2-(4-Ac-3-oxo-1-Piz)	2-F	4-F	H
6-261	H	H	CH_2CH_2-(4-CO_2Me-3-oxo-1-Piz)	2-F	H	H
6-262	Ac	H	CH_2CH_2-(4-CO_2Me-3-oxo-1-Piz)	2-F	H	H
6-263	H	H	CH_2CH_2-(4-CO_2Et-3-oxo-1-Piz)	2-F	H	H
6-264	Ac	H	CH_2CH_2-(4-CO_2Et-3-oxo-1-Piz)	2-F	H	H
6-265	H	H	CH_2CH_2-(4-CH_2CO_2H-3-oxo-1-Piz)	2-F	H	H
6-266	Ac	H	CH_2CH_2-(4-CH_2CO_2H-3-oxo-1-Piz)	2-F	H	H
6-267	H	H	CH_2CH_2-(4-CH_2CO_2Me-3-oxo-1-Piz)	2-F	H	H
6-268	Ac	H	CH_2CH_2-(4-CH_2CO_2Me-3-oxo-1-Piz)	2-F	H	H
6-269	H	H	CH_2CH_2-(4-CH_2CO_2Et-3-oxo-1-Piz)	2-F	H	H
6-270	Ac	H	CH_2CH_2-(4-CH_2CO_2Et-3-oxo-1-Piz)	2-F	H	H
6-271	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2H$-3-oxo-1-Piz)	2-F	H	H
6-272	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2H$-3-oxo-1-Piz)	2-F	H	H
6-273	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-3-oxo-1-Piz)	2-F	H	H
6-274	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-3-oxo-1-Piz)	2-F	H	H
6-275	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-3-oxo-1-Piz)	2-F	H	H
6-276	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-3-oxo-1-Piz)	2-F	H	H
6-277	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2H$-3-oxo-1-Piz)	2-F	H	H
6-278	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2H$-3-oxo-1-Piz)	2-F	H	H
6-279	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Me$-3-oxo-1-Piz)	2-F	H	H
6-280	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Me$-3-oxo-1-Piz)	2-F	H	H
6-281	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Et$-3-oxo-1-Piz)	2-F	H	H
6-282	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Et$-3-oxo-1-Piz)	2-F	H	H
6-283	H	H	CH_2CH_2-(2,5-dioxo-1-Piz)	2-F	H	H
6-284	Ac	H	CH_2CH_2-(2,5-dioxo-1-Piz)	2-F	H	H
6-285	H	H	CH_2CH_2-(4-Ac-2,5-dioxo-1-Piz)	2-F	H	H
6-286	Ac	H	CH_2CH_2-(4-Ac-2,5-dioxo-1-Piz)	2-F	H	H
6-287	H	H	CH_2CH_2-(4-Ac-2,5-dioxo-1-Piz)	2-F	4-F	H
6-288	Ac	H	CH_2CH_2-(4-Ac-2,5-dioxo-1-Piz)	2-F	4-F	H
6-289	H	H	CH_2CH_2-(4-CO_2Me-2,5-dioxo-1-Piz)	2-F	H	H
6-290	Ac	H	CH_2CH_2-(4-CO_2Me-2,5-dioxo-1-Piz)	2-F	H	H
6-291	H	H	CH_2CH_2-(4-CO_2Et-2,5-dioxo-1-Piz)	2-F	H	H
6-292	Ac	H	CH_2CH_2-(4-CO_2Et-2,5-dioxo-1-Piz)	2-F	H	H
6-293	H	H	CH_2CH_2-(4-CH_2CO_2H-2,5-dioxo-1-Piz)	2-F	H	H
6-294	Ac	H	CH_2CH_2-(4-CH_2CO_2H-2,5-dioxo-1-Piz)	2-F	H	H
6-295	H	H	CH_2CH_2-(4-CH_2CO_2Me-2,5-dioxo-1-Piz)	2-F	H	H
6-296	Ac	H	CH_2CH_2-(4-CH_2CO_2Me-2,5-dioxo-1-Piz)	2-F	H	H
6-297	H	H	CH_2CH_2-(4-CH_2CO_2Et-2,5-dioxo-1-Piz)	2-F	H	H
6-298	Ac	H	CH_2CH_2-(4-CH_2CO_2Et-2,5-dioxo-1-Piz)	2-F	H	H
6-299	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2H$-2,5-dioxo-1-Piz)	2-F	H	H
6-300	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2H$-2,5-dioxo-1-Piz)	2-F	H	H
6-301	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-2,5-dioxo-1-Piz)	2-F	H	H
6-302	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-2,5-dioxo-1-Piz)	2-F	H	H
6-303	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-2,5-dioxo-1-Piz)	2-F	H	H
6-304	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-2,5-dioxo-1-Piz)	2-F	H	H
6-305	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2H$-2,5-dioxo-1-Piz)	2-F	H	H
6-306	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2H$-2,5-dioxo-1-Piz)	2-F	H	H
6-307	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Me$-2,5-dioxo-	2-F	H	H

100

			1-Piz)			
6-308	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Me$-2,5-dioxo-1-Piz)	2-F	H	H
6-309	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Et$-2,5-dioxo-1-Piz)	2-F	H	H
6-310	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Et$-2,5-dioxo-1-Piz)	2-F	H	H
6-311	H	H	CH_2CH_2-1-Pyrd	2-F	H	H
6-312	Ac	H	CH_2CH_2-1-Pyrd	2-F	H	H
6-313	H	H	CH_2CH_2-(2-CO_2H-1-Pyrd)	2-F	H	H
6-314	Ac	H	CH_2CH_2-(2-CO_2H-1-Pyrd)	2-F	H	H
6-315	H	H	CH_2CH_2-(2-CO_2Me-1-Pyrd)	2-F	H	H
6-316	Ac	H	CH_2CH_2-(2-CO_2Me-1-Pyrd)	2-F	H	H
6-317	H	H	CH_2CH_2-(2-CO_2Et-1-Pyrd)	2-F	H	H
6-318	Ac	H	CH_2CH_2-(2-CO_2Et-1-Pyrd)	2-F	H	H
6-319	H	H	CH_2CH_2-(2-CH_2CO_2H-1-Pyrd)	2-F	H	H
6-320	Ac	H	CH_2CH_2-(2-CH_2CO_2H-1-Pyrd)	2-F	H	H
6-321	H	H	CH_2CH_2-(2-CH_2CO_2Me-1-Pyrd)	2-F	H	H
6-322	Ac	H	CH_2CH_2-(2-CH_2CO_2Me-1-Pyrd)	2-F	H	H
6-323	H	H	CH_2CH_2-(2-CH_2CO_2Et-1-Pyrd)	2-F	H	H
6-324	Ac	H	CH_2CH_2-(2-CH_2CO_2Et-1-Pyrd)	2-F	H	H
6-325	H	H	CH_2CH_2-(2-$CH_2CH_2CO_2H$-1-Pyrd)	2-F	H	H
6-326	Ac	H	CH_2CH_2-(2-$CH_2CH_2CO_2H$-1-Pyrd)	2-F	H	H
6-327	H	H	CH_2CH_2-(2-$CH_2CH_2CO_2Me$-1-Pyrd)	2-F	H	H
6-328	Ac	H	CH_2CH_2-(2-$CH_2CH_2CO_2Me$-1-Pyrd)	2-F	H	H
6-329	H	H	CH_2CH_2-(2-$CH_2CH_2CO_2Et$-1-Pyrd)	2-F	H	H
6-330	Ac	H	CH_2CH_2-(2-$CH_2CH_2CO_2Et$-1-Pyrd)	2-F	H	H
6-331	H	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2H$-1-Pyrd)	2-F	H	H
6-332	Ac	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2H$-1-Pyrd)	2-F	H	H
6-333	H	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2Me$-1-Pyrd)	2-F	H	H
6-334	Ac	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2Me$-1-Pyrd)	2-F	H	H
6-335	H	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2Et$-1-Pyrd)	2-F	H	H
6-336	Ac	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2Et$-1-Pyrd)	2-F	H	H
6-337	H	H	CH_2-(3-CO_2H-1-Pip)	2-F	H	H
6-338	Ac	H	CH_2-(3-CO_2H-1-Pip)	2-F	H	H
6-339	H	H	CH_2-(3-CO_2Me-1-Pip)	2-F	H	H
6-340	Ac	H	CH_2-(3-CO_2Me-1-Pip)	2-F	H	H
6-341	H	H	CH_2-(3-CO_2Et-1-Pip)	2-F	H	H
6-342	Ac	H	CH_2-(3-CO_2Et-1-Pip)	2-F	H	H
6-343	H	H	CH_2-(3-CH_2CO_2H-1-Pip)	2-F	H	H
6-344	Ac	H	CH_2-(3-CH_2CO_2H-1-Pip)	2-F	H	H
6-345	H	H	CH_2-(3-CH_2CO_2Me-1-Pip)	2-F	H	H
6-346	Ac	H	CH_2-(3-CH_2CO_2Me-1-Pip)	2-F	H	H
6-347	H	H	CH_2-(3-CH_2CO_2Et-1-Pip)	2-F	H	H
6-348	Ac	H	CH_2-(3-CH_2CO_2Et-1-Pip)	2-F	H	H
6-349	H	H	CH_2-(3-$CH_2CH_2CO_2H$-1-Pip)	2-F	H	H
6-350	Ac	H	CH_2-(3-$CH_2CH_2CO_2H$-1-Pip)	2-F	H	H
6-351	H	H	CH_2-(3-$CH_2CH_2CO_2Me$-1-Pip)	2-F	H	H
6-352	Ac	H	CH_2-(3-$CH_2CH_2CO_2Me$-1-Pip)	2-F	H	H
6-353	H	H	CH_2-(3-$CH_2CH_2CO_2Et$-1-Pip)	2-F	H	H
6-354	Ac	H	CH_2-(3-$CH_2CH_2CO_2Et$-1-Pip)	2-F	H	H
6-355	H	H	CH_2-(3-$CH_2CH_2CH_2CO_2H$-1-Pip)	2-F	H	H
6-356	Ac	H	CH_2-(3-$CH_2CH_2CH_2CO_2H$-1-Pip)	2-F	H	H
6-357	H	H	CH_2-(3-$CH_2CH_2CH_2CO_2Me$-1-Pip)	2-F	H	H
6-358	Ac	H	CH_2-(3-$CH_2CH_2CH_2CO_2Me$-1-Pip)	2-F	H	H
6-359	H	H	CH_2-(3-$CH_2CH_2CH_2CO_2Et$-1-Pip)	2-F	H	H
6-360	Ac	H	CH_2-(3-$CH_2CH_2CH_2CO_2Et$-1-Pip)	2-F	H	H

6-361	H	H	CH_2CH_2-(3-CO_2H-1-Pip)	2-F	H	H
6-362	Ac	H	CH_2CH_2-(3-CO_2H-1-Pip)	2-F	H	H
6-363	H	H	CH_2CH_2-(3-CO_2Me-1-Pip)	2-F	H	H
6-364	Ac	H	CH_2CH_2-(3-CO_2Me-1-Pip)	2-F	H	H
6-365	H	H	CH_2CH_2-(3-CO_2Et-1-Pip)	2-F	H	H
6-366	Ac	H	CH_2CH_2-(3-CO_2Et-1-Pip)	2-F	H	H
6-367	H	H	CH_2CH_2-(3-CH_2CO_2H-1-Pip)	2-F	H	H
6-368	Ac	H	CH_2CH_2-(3-CH_2CO_2H-1-Pip)	2-F	H	H
6-369	H	H	CH_2CH_2-(3-CH_2CO_2Me-1-Pip)	2-F	H	H
6-370	Ac	H	CH_2CH_2-(3-CH_2CO_2Me-1-Pip)	2-F	H	H
6-371	H	H	CH_2CH_2-(3-CH_2CO_2Et-1-Pip)	2-F	H	H
6-372	Ac	H	CH_2CH_2-(3-CH_2CO_2Et-1-Pip)	2-F	H	H
6-373	H	H	CH_2CH_2-(3-$CH_2CH_2CO_2H$-1-Pip)	2-F	H	H
6-374	Ac	H	CH_2CH_2-(3-$CH_2CH_2CO_2H$-1-Pip)	2-F	H	H
6-375	H	H	CH_2CH_2-(3-$CH_2CH_2CO_2Me$-1-Pip)	2-F	H	H
6-376	Ac	H	CH_2CH_2-(3-$CH_2CH_2CO_2Me$-1-Pip)	2-F	H	H
6-377	H	H	CH_2CH_2-(3-$CH_2CH_2CO_2Et$-1-Pip)	2-F	H	H
6-378	Ac	H	CH_2CH_2-(3-$CH_2CH_2CO_2Et$-1-Pip)	2-F	H	H
6-379	H	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2H$-1-Pip)	2-F	H	H
6-380	Ac	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2H$-1-Pip)	2-F	H	H
6-381	H	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2Me$-1-Pip)	2-F	H	H
6-382	Ac	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2Me$-1-Pip)	2-F	H	H
6-383	H	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2Et$-1-Pip)	2-F	H	H
6-384	Ac	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2Et$-1-Pip)	2-F	H	H
6-385	H	H	CH_2-(4-OH-2-CO_2H-1-Pyrd)	2-F	H	H
6-386	Ac	H	CH_2-(4-OH-2-CO_2H-1-Pyrd)	2-F	H	H
6-387	H	H	CH_2-(4-OH-2-CO_2Me-1-Pyrd)	2-F	H	H
6-388	Ac	H	CH_2-(4-OH-2-CO_2Me-1-Pyrd)	2-F	H	H
6-389	H	H	CH_2-(4-OH-2-CO_2Et-1-Pyrd)	2-F	H	H
6-390	Ac	H	CH_2-(4-OH-2-CO_2Et-1-Pyrd)	2-F	H	H

Exemplification Compound Nos. of Compounds obtained by substituting a cyclopropyl group of the compounds of Exemplification Compound Nos. 1-1 to 1-1084, 2-1 to 2-1084, 3-1 to 3-79, 4-1 to 4-79, 5-1 to 5-390 and 6-1 to 6-390 in Tables 1 to 6 with a methoxy group are respectively 7-1 to 7-1084, 8-1 to 8-1084, 9-1 to 9-79, 10-1 to 10-79, 11-1 to 11-390 and 12-1 to 12-390. For example, a compound obtained by substituting a cyclopropyl group of the compound of Exemplification Compound No. 5-103 in Table 7 with a methoxy group is a compound of Exemplification Compound No. 11-103.

Among the above compounds, preferred compounds are the compounds of Exemplification Compound Nos. 1-1, 1-2, 1-5, 1-6, 1-9, 1-10, 1-13, 1-14, 1-17, 1-18, 1-21, 1-22, 1-25, 1-26, 1-29, 1-30, 1-33, 1-34, 1-37, 1-38, 1-41, 1-42, 1-45, 1-46, 1-49, 1-50, 1-53, 1-54, 1-57, 1-58, 1-61, 1-62, 1-87, 1-88, 1-115, 1-116, 1-121, 1-122,

1-127, 1-128, 1-133, 1-134, 1-139, 1-140, 1-187, 1-188, 1-207, 1-208, 1-209, 1-210, 1-211, 1-212, 1-337, 1-338, 1-351, 1-352, 1-353, 1-354, 1-355, 1-356, 1-443, 1-444, 1-445, 1-446, 1-447, 1-448, 1-485, 1-486, 1-487, 1-488, 1-489, 1-490, 1-491, 1-492, 1-493, 1-494, 1-495, 1-496, 1-497, 1-498, 1-499, 1-500, 1-501, 1-502, 1-503, 1-504, 1-537, 1-538, 1-549, 1-550, 1-585, 1-586, 1-587, 1-588, 1-589, 1-590, 1-591, 1-592, 1-593, 1-594, 1-595, 1-596, 1-597, 1-598, 1-613, 1-614, 1-619, 1-620, 1-637, 1-638, 1-651, 1-652, 1-653, 1-654, 1-655, 1-656, 1-663, 1-664, 1-665, 1-666, 1-667, 1-668, 1-743, 1-744, 1-745, 1-746, 1-747, 1-748, 1-749, 1-750, 1-751, 1-752, 1-753, 1-754, 1-761, 1-762, 1-763, 1-764, 1-765, 1-766, 1-767, 1-768, 1-789, 1-790, 1-813, 1-814, 1-815, 1-816, 1-817, 1-818, 1-819, 1-820, 1-841, 1-842, 1-865, 1-866, 1-879, 1-880, 1-881, 1-882, 1-883, 1-884, 1-885, 1-886, 1-887, 1-888, 1-889, 1-890, 1-965, 1-966, 1-967, 1-968, 1-969, 1-970, 1-971, 1-972, 1-973, 1-974, 1-975, 1-976, 1-977, 1-978, 1-979, 1-980, 1-981, 1-982, 1-983, 1-984, 1-985, 1-986, 1-987, 1-988, 1-989, 1-990, 1-1005, 1-1006, 1-1011, 1-1012, 1-1017, 1-1018, 1-1023, 1-1024, 1-1045, 1-1046, 1-1047, 1-1048, 1-1049, 1-1050, 2-1, 2-2, 2-5, 2-6, 2-9, 2-10, 2-13, 2-14, 2-17, 2-18, 2-21, 2-22, 2-25, 2-26, 2-29, 2-30, 2-33, 2-34, 2-37, 2-38, 2-41, 2-42, 2-45, 2-46, 2-49, 2-50, 2-53, 2-54, 2-57, 2-58, 2-61, 2-62, 2-87, 2-88, 2-115, 2-116, 2-121, 2-122, 2-127, 2-128, 2-133, 2-134, 2-139, 2-140, 2-187, 2-188, 2-207, 2-208, 2-209, 2-210, 2-211, 2-212, 2-337, 2-338, 2-351, 2-352, 2-353, 2-354, 2-355, 2-356, 2-443, 2-444, 2-445, 2-446, 2-447, 2-448, 2-485, 2-486, 2-487, 2-488, 2-489, 2-490, 2-491, 2-492, 2-493, 2-494, 2-495, 2-496, 2-497, 2-498, 2-499, 2-500, 2-501, 2-502, 2-503, 2-504, 2-537, 2-538, 2-549, 2-550, 2-585, 2-586, 2-587, 2-588, 2-589, 2-590, 2-591, 2-592, 2-593, 2-594, 2-595, 2-596, 2-597, 2-598, 2-613, 2-614, 2-619, 2-620, 2-637, 2-638, 2-651, 2-652, 2-653, 2-654, 2-655, 2-656, 2-663, 2-664, 2-665, 2-666, 2-667, 2-668, 2-743, 2-744, 2-745, 2-746, 2-747, 2-748, 2-749, 2-750, 2-751, 2-752, 2-753, 2-754, 2-761, 2-762, 2-763, 2-764, 2-765, 2-766, 2-767, 2-768, 2-789, 2-790, 2-813, 2-814, 2-815, 2-816, 2-817, 2-818, 2-819, 2-820, 2-841, 2-842, 2-865, 2-866, 2-879, 2-880, 2-

881, 2-882, 2-883, 2-884, 2-885, 2-886, 2-887, 2-888, 2-889, 2-890, 2-965, 2-966, 2-967, 2-968, 2-969, 2-970, 2-971, 2-972, 2-973, 2-974, 2-975, 2-976, 2-977, 2-978, 2-979, 2-980, 2-981, 2-982, 2-983, 2-984, 2-985, 2-986, 2-987, 2-988, 2-989, 2-990, 2-1005, 2-1006, 2-1011, 2-1012, 2-1017, 2-1018, 2-1023, 2-1024, 2-1045, 2-1046, 2-1047, 2-1048, 2-1049, 2-1050, 3-1, 3-2, 3-5, 3-6, 3-13, 3-14, 3-15, 3-16, 3-17, 3-18, 3-27, 3-28, 3-29, 3-30, 3-31, 3-32, 3-33, 3-34, 3-35, 3-36, 3-37, 3-38, 3-39, 3-46, 3-47, 3-50, 3-51, 3-52, 3-53, 3-54, 3-55, 3-56, 3-57, 3-58, 3-59, 3-60, 3-61, 3-62, 3-63, 3-64, 3-65, 3-66, 3-67, 3-68, 3-69, 3-70, 3-71, 3-72, 3-73, 3-74, 3-75, 3-76, 3-77, 3-78, 3-79, 4-1, 4-2, 4-5, 4-6, 4-13, 4-14, 4-15, 4-16, 4-17, 4-18, 4-27, 4-28, 4-29, 4-30, 4-31, 4-32, 4-33, 4-34, 4-35, 4-36, 4-37, 4-38, 4-39, 4-46, 4-47, 4-50, 4-51, 4-52, 4-53, 4-54, 4-55, 4-56, 4-57, 4-58, 4-59, 4-60, 4-61, 4-62, 4-63, 4-64, 4-65, 4-66, 4-67, 4-68, 4-69, 4-70, 4-71, 4-72, 4-73, 4-74, 4-75, 4-76, 4-77, 4-78, 4-79, 5-1, 5-2, 5-3, 5-4, 5-5, 5-6, 5-7, 5-8, 5-9, 5-10, 5-11, 5-12, 5-13, 5-14, 5-27, 5-28, 5-29, 5-30, 5-31, 5-32, 5-33, 5-34, 5-41, 5-42, 5-43, 5-44, 5-45, 5-46, 5-59, 5-60, 5-61, 5-62, 5-69, 5-70, 5-71, 5-72, 5-73, 5-74, 5-75, 5-76, 5-77, 5-78, 5-79, 5-80, 5-81, 5-82, 5-85, 5-86, 5-87, 5-88, 5-89, 5-90, 5-93, 5-94, 5-95, 5-96, 5-97, 5-98, 5-99, 5-100, 5-101, 5-102, 5-103, 5-104, 5-105, 5-106, 5-107, 5-108, 5-115, 5-116, 5-117, 5-118, 5-125, 5-126, 5-127, 5-128, 5-129, 5-130, 5-131, 5-132, 5-133, 5-134, 5-135, 5-136, 5-143, 5-144, 5-145, 5-146, 5-147, 5-148, 5-149, 5-150, 5-151, 5-152, 5-153, 5-154, 5-155, 5-156, 5-171, 5-172, 5-177, 5-178, 5-209, 5-210, 5-237, 5-238, 5-265, 5-266, 5-293, 5-294, 5-313, 5-314, 5-319, 5-320, 5-337, 5-338, 5-339, 5-340, 5-341, 5-342, 5-343, 5-344, 5-345, 5-346, 5-347, 5-348, 5-361, 5-362, 5-367, 5-368, 5-385, 5-386, 5-387, 5-388, 6-1, 6-2, 6-3, 6-4, 6-5, 6-6, 6-7, 6-8, 6-9, 6-10, 6-11, 6-12, 6-13, 6-14, 6-27, 6-28, 6-29, 6-30, 6-31, 6-32, 6-33, 6-34, 6-41, 6-42, 6-43, 6-44, 6-45, 6-46, 6-59, 6-60, 6-61, 6-62, 6-69, 6-70, 6-71, 6-72, 6-73, 6-74, 6-75, 6-76, 6-77, 6-78, 6-79, 6-80, 6-81, 6-82, 6-85, 6-86, 6-87, 6-88, 6-89, 6-90, 6-93, 6-94, 6-95, 6-96, 6-97, 6-98, 6-99, 6-100, 6-101, 6-102, 6-103, 6-104, 6-105, 6-106, 6-107, 6-108, 6-115, 6-116, 6-117, 6-118,

6-125, 6-126, 6-127, 6-128, 6-129, 6-130, 6-131, 6-132, 6-133, 6-134, 6-135, 6-136, 6-143, 6-144, 6-145, 6-146, 6-147, 6-148, 6-149, 6-150, 6-151, 6-152, 6-153, 6-154, 6-155, 6-156, 6-171, 6-172, 6-177, 6-178, 6-209, 6-210, 6-237, 6-238, 6-265, 6-266, 6-293, 6-294, 6-313, 6-314, 6-319, 6-320, 6-337, 6-338, 6-339, 6-340, 6-341, 6-342, 6-343, 6-344, 6-345, 6-346, 6-347, 6-348, 6-361, 6-362, 6-367, 6-368, 6-385, 6-386, 6-387 and 6-388,

more preferred compounds are the compounds of Exemplification Compound Nos. 1-1, 1-2, 1-5, 1-6, 1-17, 1-18, 1-21, 1-22, 1-25, 1-26, 1-53, 1-54, 1-207, 1-208, 1-351, 1-352, 1-443, 1-444, 1-485, 1-486, 1-487, 1-488, 1-489, 1-490, 1-491, 1-492, 1-493, 1-494, 1-587, 1-588, 1-589, 1-590, 1-591, 1-592, 1-651, 1-652, 1-743, 1-744, 1-763, 1-764, 1-815, 1-816, 1-967, 1-968, 1-973, 1-974, 1-975, 1-976, 1-977, 1-978, 2-1, 2-2, 2-5, 2-6, 2-17, 2-18, 2-21, 2-22, 2-25, 2-26, 2-53, 2-54, 2-207, 2-208, 2-351, 2-352, 2-443, 2-444, 2-485, 2-486, 2-487, 2-488, 2-489, 2-490, 2-491, 2-492, 2-493, 2-494, 2-587, 2-588, 2-589, 2-590, 2-591, 2-592, 2-651, 2-652, 2-743, 2-744, 2-763, 2-764, 2-815, 2-816, 2-967, 2-968, 2-973, 2-974, 2-975, 2-976, 2-977, 2-978, 3-1, 3-2, 3-13, 3-14, 3-15, 3-16, 3-17, 3-18, 3-27, 3-28, 3-29, 3-30, 3-31, 3-32, 3-50, 3-51, 3-54, 3-55, 3-62, 3-63, 3-66, 3-67, 4-1, 4-2, 4-13, 4-14, 4-15, 4-16, 4-17, 4-18, 4-27, 4-28, 4-29, 4-30, 4-31, 4-32, 4-50, 4-51, 4-54, 4-55, 4-62, 4-63, 4-66, 4-67, 5-3, 5-4, 5-5, 5-6, 5-7, 5-8, 5-9, 5-10, 5-11, 5-12, 5-13, 5-14, 5-27, 5-28, 5-29, 5-30, 5-33, 5-34, 5-69, 5-70, 5-71, 5-72, 5-73, 5-74, 5-75, 5-76, 5-77, 5-78, 5-79, 5-80, 5-81, 5-82, 5-85, 5-86, 5-87, 5-88, 5-89, 5-90, 5-93, 5-94, 5-95, 5-96, 5-97, 5-98, 5-99, 5-100, 5-101, 5-102, 5-103, 5-104, 5-105, 5-106, 5-107, 5-108, 5-145, 5-146, 5-147, 5-148, 5-149, 5-150, 5-151, 5-152, 5-153, 5-154, 5-155, 5-156, 5-337, 5-338, 5-339, 5-340, 5-341, 5-342, 5-343, 5-344, 5-345, 5-346, 5-347, 5-348, 5-387, 5-388, 6-3, 6-4, 6-5, 6-6, 6-7, 6-8, 6-9, 6-10, 6-11, 6-12, 6-13, 6-14, 6-27, 6-28, 6-29, 6-30, 6-33, 6-34, 6-69, 6-70, 6-71, 6-72, 6-73, 6-74, 6-75, 6-76, 6-77, 6-78, 6-79, 6-80, 6-81, 6-82, 6-85, 6-86, 6-87, 6-88, 6-89, 6-90, 6-93, 6-94, 6-95, 6-96, 6-97, 6-98, 6-99, 6-100, 6-101, 6-

102, 6-103, 6-104, 6-105, 6-106, 6-107, 6-108, 6-145, 6-146, 6-147, 6-148, 6-149, 6-150, 6-151, 6-152, 6-153, 6-154, 6-155, 6-156, 6-337, 6-338, 6-339, 6-340, 6-341, 6-342, 6-343, 6-344, 6-345, 6-346, 6-347, 6-348, 6-387 and 6-388,

further more preferred compounds are the compounds of Exemplification Compound Nos. 1-17, 1-18, 1-53, 1-54, 1-487, 1-488, 1-489, 1-490, 1-491, 1-492, 1-587, 1-588, 1-589, 1-590, 1-591, 1-592, 1-973, 1-974, 2-17, 2-18, 2-53, 2-54, 2-487, 2-488, 2-489, 2-490, 2-491, 2-492, 2-587, 2-588, 2-589, 2-590, 2-591, 2-592, 2-973, 2-974, 3-1, 3-2, 3-13, 3-14, 3-31, 3-32, 3-50, 3-51, 3-54, 3-55, 3-62, 3-63, 3-66, 3-67, 4-1, 4-2, 4-13, 4-14, 4-31, 4-32, 4-50, 4-51, 4-54, 4-55, 4-62, 4-63, 4-66, 4-67, 5-3, 5-4, 5-5, 5-6, 5-7, 5-8, 5-75, 5-76, 5-77, 5-78, 5-79, 5-80, 5-81, 5-82, 5-89, 5-90, 5-93, 5-94, 5-95, 5-96, 5-97, 5-98, 5-99, 5-100, 5-101, 5-102, 5-103, 5-104, 5-105, 5-106, 5-107, 5-108, 5-145, 5-146, 5-147, 5-148, 5-149, 5-150, 5-151, 5-152, 5-153, 5-154, 5-155, 5-156, 5-337, 5-338, 5-339, 5-340, 5-341, 5-342, 5-387, 5-388, 6-3, 6-4, 6-5, 6-6, 6-7, 6-8, 6-75, 6-76, 6-77, 6-78, 6-79, 6-80, 6-81, 6-82, 6-89, 6-90, 6-93, 6-94, 6-95, 6-96, 6-97, 6-98, 6-99, 6-100, 6-101, 6-102, 6-103, 6-104, 6-105, 6-106, 6-107, 6-108, 6-145, 6-146, 6-147, 6-148, 6-149, 6-150, 6-151, 6-152, 6-153, 6-154, 6-155, 6-156, 6-337, 6-338, 6-339, 6-340, 6-341, 6-342, 6-387 and 6-388, and

particularly preferred compounds are

Exemplification Compound No. 1-17:

(E)-3-[2-(4-carboxy-1H-pyrazol-1-yl)ethylidene]-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-sulfanylpiperidine,

Exemplification Compound No. 1-53:

(E)-3-{2-[4-(carboxymethyl)-1H-pyrazol-1-yl]ethylidene}-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-sulfanylpiperidine,

Exemplification Compound No. 1-487:

(E)-3-[2-(4-carboxy-1H-1,2,3-triazol-1-yl)ethylidene]-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-sulfanylpiperidine,

Exemplification Compound No. 1-587:

(E)-3-[2-(4-carboxy-2H-1,2,3-triazol-2-yl)ethylidene]-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-sulfanylpiperidine

Exemplification Compound No. 1-973:

(E)-3-{[2-(4-carboxy-1H-pyrazol-1-yl)-1-methyl]ethylidene}-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-sulfanylpiperidine,

Exemplification Compound No. 3-1:

(E)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-hydroxyethylidene)-4-sulfanylpiperidine,

Exemplification Compound No. 3-13:

(E)-3-(2-carboxyethylidene)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-sulfanylpiperidine,

Exemplification Compound No. 3-31:

(E)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{[1-(ethoxycarbonylmethyl)piperidin-4-yl]methylidene}-4-sulfanylpiperidine,

Exemplification Compound No. 3-50:

(E)-3-{2-[N-(carboxymethyl)-N-methylamino]ethylidene}-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-sulfanylpiperidine,

Exemplification Compound No. 3-54:

(E)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{2-[N-(ethoxycarbonylmethyl)-N-methylamino]ethylidene}-4-sulfanylpiperidine,

Exemplification Compound No. 3-62:

(E)-3-(2-{N-[3-(carboxy)propyl]-N-methylamino}ethylidene)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-sulfanylpiperidine,

Exemplification Compound No. 3-66:

(E)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-{N-[3-(ethoxycarbonyl)propyl]-N-methylamino}ethylidene)-4-sulfanylpiperidine,

Exemplification Compound No. 5-3:

(E)-3-{2-[4-(carboxypiperidin)-1-yl]ethylidene}-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-sulfanylpiperidine,

Exemplification Compound No. 5-7:

(E)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{2-[4-(ethoxycarbonyl)piperidin-1-yl]ethylidene}-4-sulfanylpiperidine,

Exemplification Compound No. 5-75:

(E)-3-(2-{4-[2-(carboxyethyl)]-2-oxopiperazin-1-yl}ethylidene)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-sulfanylpiperidine,

Exemplification Compound No. 5-79:

(E)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-{4-[2-(ethoxycarbonyl)ethyl]-2-oxopiperazin-1-yl}ethylidene)-4-sulfanylpiperidine,

Exemplification Compound No. 5-81:

(E)-3-(2-{4-[3-(carboxypropyl)]-2-oxopiperazin-1-yl}ethylidene)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-sulfanylpiperidine,

Exemplification Compound No. 5-97:

(E)-3-{2-[4-(carboxymethyl)-3-oxopiperazin-1-yl]ethylidene}-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-sulfanylpiperidine,

Exemplification Compound No. 5-101:

(E)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{2-[4-(ethoxycarbonylmethyl)-3-oxopiperazin-1-yl]ethylidene}-4-sulfanylpiperidine,

Exemplification Compound No. 5-103:

(E)-3-(2-{4-[2-(carboxyethyl)]-3-oxopiperazin-1-yl}ethylidene)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-sulfanylpiperidine,

Exemplification Compound No. 5-105:

(E)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-{4-[2-(methoxycarbonyl)ethyl]-3-oxopiperazin-1-yl}ethylidene)-4-sulfanylpiperidine,

Exemplification Compound No. 5-107:

(E)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-{4-[2-(ethoxycarbonyl)ethyl]-3-oxopiperazin-1-yl}ethylidene)-4-sulfanylpiperidine,

Exemplification Compound No. 5-147:

(E)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{2-[(2S)-(methoxycarbonyl)pyrrolidin-1-yl]ethylidene}-4-sulfanylpiperidine,

Exemplification Compound No. 5-151:

(E)-3-{2-[(2S)-(carboxymethyl)pyrrolidin-1-yl]ethylidene}-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-sulfanylpiperidine,

Exemplification Compound No. 5-153:

(E)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{2-[(2S)-(methoxycarbonylmethyl)pyrrolidin-1-yl]ethylidene}-4-sulfanylpiperidine,

Exemplification Compound No. 5-337:

(E)-3-{2-[3-(carboxypiperidin)-1-yl]ethylidene}-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-sulfanylpiperidine,

Exemplification Compound No. 5-387:

(E)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{2-[(2S,4R)-4-hydroxy-2-(methoxycarbonyl)pyrrolidin-1-yl]ethylidene}-4-sulfanylpiperidine, and

S-acetyl derivatives thereof (Compound Nos.: 1-18, 1-54, 1-488, 1-588, 1-974, 3-2, 3-14, 3-32, 3-51, 3-55, 3-63, 3-67, 5-4, 5-8, 5-76, 5-80, 5-82, 5-98, 5-102, 5-104, 5-106, 5-108, 5-148, 5-152, 5-154, 5-338 and 5-388) or geometrical isomers thereof ((Z)-isomers, Compound Nos.: 2-17, 2-18, 2-53, 2-54, 2-487, 2-488, 2-587, 2-588, 2-973, 2-974, 4-1, 4-2, 4-13, 4-14, 4-31, 4-32, 4-50, 4-51, 4-54, 4-55, 4-62, 4-63, 4-66, 4-67, 6-3, 6-4, 6-7, 6-8, 6-75, 6-76, 6-79, 6-80, 6-81, 6-82, 6-97, 6-98, 6-101, 6-102, 6-103, 6-104, 6-105, 6-106, 6-107, 6-108, 6-147, 6-148, 6-151, 6-152, 6-153, 6-154, 6-337, 6-338, 6-387 and 6-388).

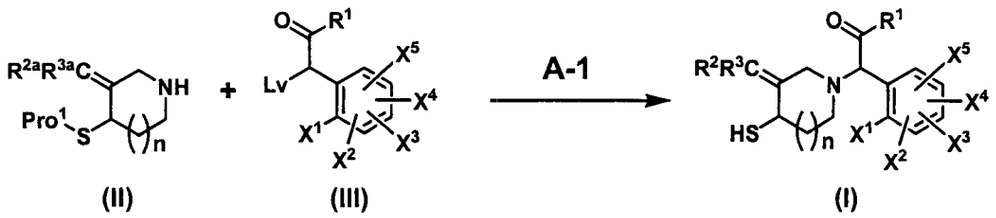
[Effect of the Invention]

The compounds of the present invention are chemically stable and exert excellent platelet anticoagulation activities and inhibiting action against thrombosis formation. Furthermore, the compounds of the present invention exert the said actions with short onset latencies and exhibit low toxicities. Thus, the compounds of the present invention may be useful in the prophylactic, prevention of recurrence, and therapeutic settings (particularly the latter) against diseases induced by platelet activation such as thrombosis formation and platelet coagulation and releasing responses of platelets, for example in percutaneous coronary intervention (PCI), angioplasty, endarterectomy, restenosis after stenting; acute coronary syndrome, stable or unstable angina, myocardial infarction, atrial fibrillation, cerebral ischemic attack, cerebral infarction, and atherosclerosis and diseases induced by thrombosis formation or embolus formation that are associated with diabetes mellitus, peripheral arterial disease, heparin-induced thrombocytopenia (HIT), thrombotic thrombocytopenic purpura (TTP), antiphospholipid antibody syndrome, venous thrombosis, and ichorrhemia.

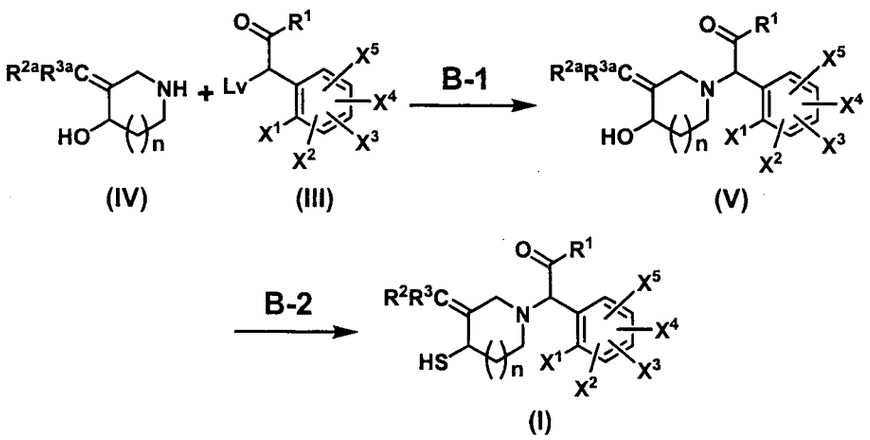
[Best Mode for Carrying out the Invention]

The compound (I) in the present invention can be obtained by Process A or Process B described below.

Process A



Process B



In the above, from R^1 to R^3 and X^1 to X^5 have the same meanings as defined above; R^{2a} and R^{3a} represent R^2 and R^3 described above or a group by which an amino group or a hydroxyl group on R^2 and R^3 may be protected, if necessary, by a protective group for an amino group or a hydroxyl group; Pro^1 represents a protective group for a sulfanyl group; and Lv represents a leaving group.

The protective group for a sulfanyl group as Pro^1 can be the same group as that described as the protective group for a sulfanyl group of the above "prodrug", and is preferably an acetyl group.

The protective group for an amino group of R^{2a} and R^{3a} is not particularly restricted provided that it can usually protect an amino group in chemical reactions, and specifically indicates a protective group that can be cleaved by a chemical process such as hydrogenolysis, hydrolysis, electrolysis and photolysis. Such protective group can be, for example, the above "aliphatic acyl group"; the above

"aromatic acyl group"; the above "alkoxycarbonyl group"; the above "aralkyloxycarbonyl group"; the above "silyl group"; the above "aralkyl group"; a "substituted methylene group" that can form a Schiff base such as N,N-dimethylaminomethylene, benzylidene, 4-methoxybenzylidene, 4-nitrobenzylidene, salicylidene, 5-chlorosalicylidene, diphenylmethylene or (5-chloro-2-hydroxyphenyl)phenylmethylene group; an "aromatic sulfonyl group" consisting of: an arylsulfonyl group such as a benzenesulfonyl group, and an arylsulfonyl group substituted with lower alkyl or lower alkoxy group(s) such as a p-toluenesulfonyl, pentamethylbenzenesulfonyl, p-methoxybenzenesulfonyl, 2,4,6-trimethoxybenzenesulfonyl or 3-methoxy-4-t-butylbenzenesulfonyl group; and an "aliphatic sulfonyl group", including an alkylsulfonyl group such as a methanesulfonyl or t-butylsulfonyl group, and an alkylsulfonyl group substituted with halogen atom(s), silyl group(s), or aryl group(s) such as a trifluoromethylsulfonyl, trisilylethanesulfonyl or benzylsulfonyl group.

The protective group for a hydroxyl group of R^{2a} and R^{3a} is not particulary restricted provided that it can usually protect a hydroxyl group in chemical reactions, and specifically indicates a protective group that can be cleaved by a chemical process such as hydrogenolysis, hydrolysis, electrolysis and photolysis. Such protective group can be, for example, the above "aliphatic acyl group"; the above "aromatic acyl group"; the above "carbonyloxyalkyl group"; the above "residual group of a salt of a succinic acid half-ester"; the above "residual group of a salt of a phosphoric acid ester"; the above "residual group forming an amino acid ester"; a carbamoyl group; a carbamoyl group substituted with 1 or 2 lower alkyl groups; the above "carbonyloxyalkyloxycarbonyl group"; or the above "silyl group", and is preferably a group which forms a pharmacologically acceptable ester such as an "aliphatic acyl group", an "aromatic acyl group" or a "silyl group", more preferably a "C1-C6 alkanoyl group" such as an acetyl, propionyl, butyryl, isobutyryl, pentanoyl,

or pivaloyl group, or a "silyl group" such as a t-butyldimethylsilyl or t-butyldiphenylsilyl group, and particularly preferably an acetyl group, a t-butyldimethylsilyl group or a t-butyldiphenylsilyl group.

The leaving group of Lv is not particularly restricted provided that this group is a functional group that can achieve displacement reaction by reacting with a nucleophilic substituent, and can be, for example, the above "halogen atom"; a "lower alkylsulfonyloxy group" such as a methanesulfonyloxy or ethanesulfonyloxy group; a "halogenated lower alkylsulfonyloxy group" such as a trifluoromethanesulfonyloxy group; or an "aromatic sulfonyloxy group" including an arylsulfonyloxy group such as a benzenesulfonyloxy group, a lower alkylated arylsulfonyloxy group such as a p-toluenesulfonyloxy group, a halogenated arylsulfonyloxy group such as a p-chlorobenzenesulfonyloxy group and a nitrated arylsulfonyloxy group such as a p-nitrobenzenesulfonyloxy group.

Each step of Process A and Process B is hereinafter described in detail.

(Process A)

Process A is a step for the preparation of compound (I) by conducting a nucleophilic displacement reaction in the presence of a base using compound (II) obtainable by Process C and a compound (III) that is well known or easily prepared from known compounds (A-1). Furthermore, if necessary, several reactions such as deprotection of a protective group of a sulfanyl group (A-2), introduction of a substituent onto a sulfanyl group (A-3), hydrolysis of an ester group (A-4), conversion of a carboxy group into an amide group (A-5), conversion of a carboxy group into an ester group (A-6), deprotection of a protective group for an amino group (A-7), conversion of a carboxy group into a hydroxyamino group (A-8) and conversion of a R^{3a} group including a hydroxyl group into a R^3 group (A-9) can also be carried out. The steps from A-2 to A-9 can be conducted either before or after

the step A-1, and the order of these steps can easily be selected according to circumstances by a person having ordinary skill in the art.

(A-1)

The solvent employed can be, for example, an aromatic hydrocarbon such as benzene, toluene or xylene; a halogenated hydrocarbon such as dichloromethane, chloroform, carbon tetrachloride, dichloroethane, chlorobenzene or dichlorobenzene; an ether such as diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane, dimethoxyethane or di(ethylene glycol) dimethyl ether; a ketone such as acetone, methyl ethyl ketone, methyl isobutyl ketone, isophorone or cyclohexanone; a nitrile such as acetonitrile or isobutyronitrile; an amide such as formamide, N,N-dimethylformamide, N,N-dimethylacetamide, N-methyl-2-pyrrolidinone or hexamethylphosphoric triamide; or a sulfoxide such as dimethyl sulfoxide or sulfolane, and is preferably a halogenated hydrocarbon, a nitrile or an amide, and more preferably N,N-dimethylformamide, N,N-dimethylacetamide, acetonitrile or dichloromethane.

The base employed can be, for example, an inorganic base, including an alkali metal carbonate such as sodium carbonate, potassium carbonate or lithium carbonate; an alkali metal hydrogencarbonate such as sodium hydrogencarbonate, potassium hydrogencarbonate or lithium hydrogencarbonate; an alkali metal hydride such as lithium hydride, sodium hydride or potassium hydride; an alkali metal hydroxide such as sodium hydroxide, potassium hydroxide or lithium hydroxide; and an alkali metal fluoride such as sodium fluoride or potassium fluoride; an alkali metal alkoxide such as sodium methoxide, sodium ethoxide, potassium methoxide, potassium ethoxide, potassium t-butoxide or lithium methoxide; an alkali metal mercaptan such as sodium methylmercaptan or sodium ethylmercaptan; or an organic base such as N-methylmorpholine, triethylamine, tripropylamine, tributylamine, diisopropylethylamine, dicyclohexylamine, N-methylpiperidine, pyridine, 4-

pyrrolidinopyridine, picoline, 4-(N,N-dimethylamino)pyridine, 2,6-di(t-butyl)-4-methylpyridine, quinoline, N,N-dimethylaniline, N,N-diethylaniline, 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), 1,4-diazabicyclo[2.2.2]octane (DABCO) or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and is preferably an alkali metal carbonate or an organic base, and more preferably potassium carbonate or triethylamine.

The reaction temperature varies depending on the starting material and the reagent, and is between -50°C and 100°C, and preferably between 0°C and 50°C.

The reaction time varies depending on the reaction temperature, the starting material, the reagent and the kind of solvent employed, and is generally from 30 minutes to 48 hours, and preferably from 1 hour to 24 hours.

After completion of the reaction, the desired compound of this reaction can be obtained, for example, by concentration of the reaction mixture, addition to the mixture of an organic solvent immiscible with water such as ethyl acetate, washing the mixture with water, separation of the organic layer containing the desired compound, drying the organic layer over anhydrous magnesium sulfate or the like, and then evaporation of the organic solvent to give the desired product.

The obtained product, if necessary, is further purified by conventional treatments, for example, by recrystallization, reprecipitation, silica gel column chromatography or the like.

(A-2)

This step is a step for the deprotection of a protective group for a sulfanyl group, and can easily be achieved according to procedures that are well known by a person having skill in the art (for example, the procedure described in Protective Groups in Organic Synthesis, Third Edition, T. W. Green, et al., John Wiley & Sons, Inc. (1999)), and is preferably carried out by a method for deprotection in the

presence of an acid (A-2a) or a method for deprotection in the presence of a base (A-2b).

(A-2a)

The solvent employed can be, for example, an aromatic hydrocarbon such as benzene, toluene or xylene; a halogenated hydrocarbon such as dichloromethane, chloroform, carbon tetrachloride, dichloroethane, chlorobenzene or dichlorobenzene; an ester such as ethyl formate, ethyl acetate, propyl acetate, butyl acetate or diethyl carbonate; an ether such as diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane, dimethoxyethane or di(ethylene glycol) dimethyl ether; an alcohol such as methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutanol, t-butanol, isoamyl alcohol, diethylene glycol, glycerol, octanol, cyclohexanol or 2-methoxyethanol; an amide such as formamide, N,N-dimethylformamide, N,N-dimethylacetamide, N-methyl-2-pyrrolidinone or hexamethylphosphoric triamide; a sulfoxide such as dimethyl sulfoxide or sulfolane; or a mixture of the above solvents, and is preferably an alcohol or a mixture solvent of a halogenated hydrocarbon and an alcohol, and more preferably methanol, ethanol or a mixture solvent of dichloromethane and methanol or ethanol.

The acid employed is not particularly restricted provided that it can be used in general reactions, and can be preferably an inorganic acid such as hydrochloric acid, hydrogen chloride, hydrobromic acid, sulfuric acid, perchloric acid or phosphoric acid; or an organic acid such as acetic acid, formic acid, oxalic acid, methanesulfonic acid, p-toluenesulfonic acid, camphorsulfonic acid, trifluoroacetic acid or trifluoromethanesulfonic acid, and is preferably an inorganic acid, and more preferably hydrogen chloride or hydrochloric acid.

The reaction temperature varies depending on the starting material and the reagent, and is between -50°C and 100°C, and preferably between 0°C and 50°C.

The reaction time varies depending on the reaction temperature, the starting material, the reagent and the kind of solvent employed, and is generally from 30 minutes to 48 hours, and preferably from 1 hour to 24 hours.

After completion of the reaction, the desired compound of this reaction can be obtained, for example, by concentration of the reaction mixture; addition to the mixture of an organic solvent immiscible with water such as ethyl acetate, washing the mixture with water, separation of the organic layer containing the desired compound, drying the organic layer over anhydrous magnesium sulfate or the like, and then evaporation of the organic solvent to give the desired product.

The obtained product, if necessary, is further purified by conventional treatments, for example, by recrystallization, reprecipitation, silica gel column chromatography or the like.

(A-2b)

The solvent employed can be, for example, an aromatic hydrocarbon such as benzene, toluene or xylene; a halogenated hydrocarbon such as dichloromethane, chloroform, carbon tetrachloride, dichloroethane, chlorobenzene or dichlorobenzene; an ether such as diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane, dimethoxyethane or di(ethylene glycol) dimethyl ether; an alcohol such as methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutanol, t-butanol, isoamyl alcohol, diethylene glycol, glycerol, octanol, cyclohexanol or 2-methoxyethanol; an amide such as formamide, N,N-dimethylformamide, N,N-dimethylacetamide, N-methyl-2-pyrrolidinone or hexamethylphosphoric triamide; a sulfoxide such as dimethyl sulfoxide or sulfolane; water; or a mixture of the above solvents, and is preferably an alcohol or a mixed solvent of an alcohol and water, and more preferably methanol, ethanol, methanol containing water or ethanol containing water.

The base employed can be, for example, an inorganic base, including an alkali metal carbonate such as sodium carbonate, potassium carbonate or lithium carbonate;

an alkali metal hydrogencarbonate such as sodium hydrogencarbonate, potassium hydrogencarbonate or lithium hydrogencarbonate; an alkali metal hydride such as lithium hydride, sodium hydride or potassium hydride; an alkali metal hydroxide such as sodium hydroxide, potassium hydroxide or lithium hydroxide; and an alkali metal fluoride such as sodium fluoride or potassium fluoride; an alkali metal alkoxide such as sodium methoxide, sodium ethoxide, potassium methoxide, potassium ethoxide, potassium t-butoxide or lithium methoxide; an alkali metal mercaptan such as sodium methylmercaptan or sodium ethylmercaptan; or an organic base such as N-methylmorpholine, triethylamine, tripropylamine, tributylamine, diisopropylethylamine, dicyclohexylamine, N-methylpiperidine, pyridine, 4-pyrrolidinopyridine, picoline, 4-(N,N-dimethylamino)pyridine, 2,6-di(t-butyl)-4-methylpyridine, quinoline, N,N-dimethylaniline, N,N-diethylaniline, 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), 1,4-diazabicyclo[2.2.2]octane (DABCO) or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and is preferably an alkali metal carbonate or an alkali metal hydroxide, and more preferably potassium carbonate or sodium hydroxide.

The reaction temperature varies depending on the starting material and the reagent, and is between -50°C and 100°C, and preferably between -20°C and 50°C.

The reaction time varies depending on the reaction temperature, the starting material, the reagent and the kind of solvent employed, and is generally from 1 minute to 24 hours, and preferably from 5 minutes to 5 hours.

After completion of the reaction, the desired compound of this reaction can be obtained, for example, by concentration of the reaction mixture, addition to the mixture of an organic solvent immiscible with water such as ethyl acetate, washing the mixture with water, separation of the organic layer containing the desired compound, drying the organic layer over anhydrous magnesium sulfate or the like, and then evaporation of the organic solvent to give the desired product.

The obtained product, if necessary, is further purified by conventional treatments, for example, by recrystallization, reprecipitation, silica gel column chromatography or the like.

(A-3)

This step is a step for introducing a substituent onto a sulfanyl group in the presence of a base or the like. When an acid chloride, an acid anhydride, a sulfanyl halide or an active ester is employed as a reagent, this step is carried out in the presence of a base (A-3a), when a carboxylic acid is employed, this step is carried out in the presence of a condensation agent (A-3b), and when a thiol is employed, this step is carried out in the presence of iodine or a base (A-3c).

(A-3a)

The solvent employed can be, for example, an aromatic hydrocarbon such as benzene, toluene or xylene; a halogenated hydrocarbon such as dichloromethane, chloroform, carbon tetrachloride, dichloroethane, chlorobenzene or dichlorobenzene; an ester such as ethyl formate, ethyl acetate, propyl acetate, butyl acetate or diethyl carbonate; an ether such as diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane, dimethoxyethane or di(ethylene glycol) dimethyl ether; a ketone such as acetone, methyl ethyl ketone, methyl isobutyl ketone, isophorone or cyclohexanone; an amide such as formamide, N,N-dimethylformamide, N,N-dimethylacetamide, N-methyl-2-pyrrolidinone or hexamethylphosphoric triamide; or a sulfoxide such as dimethyl sulfoxide or sulfolane, and is preferably a halogenated hydrocarbon, a ketone or an amide, and more preferably N,N-dimethylformamide, N,N-dimethylacetamide, dichloromethane or acetone.

The base employed can be, for example, an inorganic base, including an alkali metal carbonate such as sodium carbonate, potassium carbonate or lithium carbonate; an alkali metal hydrogencarbonate such as sodium hydrogencarbonate, potassium hydrogencarbonate or lithium hydrogencarbonate; an alkali metal hydride such as

lithium hydride, sodium hydride or potassium hydride; an alkali metal hydroxide such as sodium hydroxide, potassium hydroxide or lithium hydroxide; and an alkali metal fluoride such as sodium fluoride or potassium fluoride; an alkali metal alkoxide such as sodium methoxide, sodium ethoxide, potassium methoxide, potassium ethoxide, potassium t-butoxide or lithium methoxide; an alkali metal mercaptan such as sodium methylmercaptan or sodium ethylmercaptan; or an organic base such as N-methylmorpholine, triethylamine, tripropylamine, tributylamine, diisopropylethylamine, dicyclohexylamine, N-methylpiperidine, pyridine, 4-pyrrolidinopyridine, picoline, 4-(N,N-dimethylamino)pyridine, 2,6-di(t-butyl)-4-methylpyridine, quinoline, N,N-dimethylaniline, N,N-diethylaniline, 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), 1,4-diazabicyclo[2.2.2]octane (DABCO) or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and is preferably an alkali metal carbonate, an alkali metal hydride or an organic base, and more preferably sodium hydride, potassium carbonate or triethylamine.

The reaction temperature varies depending on the starting material and the reagent, and is between -30°C and 100°C, and preferably between -10°C and 50°C.

The reaction time varies depending on the reaction temperature, the starting material, the reagent and the kind of solvent employed, and is generally from 5 minutes to 24 hours, and preferably from 15 minutes to 10 hours.

After completion of the reaction, the desired compound of this reaction can be obtained, for example, by concentration of the reaction mixture, addition to the mixture of an organic solvent immiscible with water such as ethyl acetate, washing the mixture with water, separation of the organic layer containing the desired compound, drying the organic layer over anhydrous magnesium sulfate or the like, and then evaporation of the organic solvent to give the desired product.

The obtained product, if necessary, is further purified by conventional treatments, for example, by recrystallization, reprecipitation, silica gel column chromatography or the like.

(A-3b)

The solvent employed can be, for example, an aromatic hydrocarbon such as benzene, toluene or xylene; a halogenated hydrocarbon such as dichloromethane, chloroform, carbon tetrachloride, dichloroethane, chlorobenzene or dichlorobenzene; an ester such as ethyl formate, ethyl acetate, propyl acetate, butyl acetate or diethyl carbonate; an ether such as diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane, dimethoxyethane or di(ethylene glycol) dimethyl ether; a ketone such as acetone, methyl ethyl ketone, methyl isobutyl ketone, isophorone or cyclohexanone; an amide such as formamide, N,N-dimethylformamide, N,N-dimethylacetamide, N-methyl-2-pyrrolidinone or hexamethylphosphoric triamide; or a sulfoxide such as dimethyl sulfoxide or sulfolane, and is preferably a halogenated hydrocarbon or an amide, and more preferably N,N-dimethylformamide, N,N-dimethylacetamide or dichloromethane.

The "condensation agent" employed can be,

(i) a combination of a phosphate ester such as diethylphosphoryl cyanide, diphenylphosphoryl azide or diethyl cyanophosphonate and a base shown below;

(ii) a carbodiimide such as 1,3-dicyclohexylcarbodiimide (DCC), 1,3-diisopropylcarbodiimide or 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide (WSC); a combination of said carbodiimide and a base shown below; a combination of said carbodiimide and an N-hydroxyimide such as N-hydroxysuccinimide, 1-hydroxybenzotriazole or N-hydroxy-5-norbornene-2,3-dicarboxyimide; and a combination of said carbodiimide, said N-hydroxyimide and a base shown below;

(iii) a combination of a disulfide such as 2,2'-dipyridyl disulfide or 2,2'-dibenzothiazolyl disulfide and a phosphine such as triphenylphosphine or tributylphosphine;

(iv) a carbonate such as N,N'-disuccinimidyl carbonate, diethyl pyrocarbonate (DEPC), di-2-pyridyl carbonate or S,S'-bis(1-phenyl-1H-tetrazol-5-yl)dithiocarbonate;

(v) a phosphinic chloride such as N,N'-bis(2-oxo-3-oxazolidinyl)phosphinic chloride;

(vi) an oxalate such as N,N'-disuccinimidyl oxalate, N,N'-diphthalimide oxalate, N,N'-bis(5-norbornene-2,3-dicarboxyimidyl) oxalate, 1,1'-bis(benzotriazolyl) oxalate, 1,1'-bis(6-chlorobenzotriazolyl) oxalate or 1,1'-bis(6-trifluoromethylbenzotriazolyl) oxalate;

(vii) a combination of said phosphine and azodicarboxylate or an azodicarboxyamide such as diethyl azodicarboxylate or 1,1'-(azodicarbonyl)dipiperidine;

(viii) an N-lower alkyl-5-arylisoxazolium-3'-sulfonate such as N-ethyl-5-phenylisoxazolium-3'-sulfonate;

(ix) a di-heteroaryl diselenide such as di-2-pyridyl diselenide;

(x) an arylsulfonyl triazolide such as p-nitrobenzenesulfonyl triazolide;

(xi) a 2-halo-1-lower alkylpyridinium halide such as 2-chloro-1-methylpyridinium iodide;

(xii) an imidazole such as 1,1'-oxalyldiimidazole or N,N'-carbonyldiimidazole (CDI);

(xiii) a 3-lower alkyl-2-halogen-benzothiazolium fluoroborate such as 3-ethyl-2-chloro-benzothiazolium fluoroborate;

(xiv) a 3-lower alkyl-benzothiazole-2-selone such as 3-methyl-benzothiazole-2-selone;

(xv) a phosphate such as phenyl dichlorophosphate or polyphosphate ester;

(xvi) a halogenosulfonyl isocyanate such as chlorosulfonyl isocyanate;

(xvii) a halogenosilane such as trimethylsilyl chloride or triethylsilyl chloride;

(xviii) a combination of a lower alkanesulfonyl halide such as methanesulfonyl chloride and a base shown below;

(xix) an N,N,N',N'-tetra-lower alkylhalogenoformamidium chloride such as N,N,N',N'-tetramethylchloroformamidium chloride; or

(xx) a combination of a pyridinium salt (Mukaiyama reagent) such as 1-methyl-2-chloropyridinium chloride or 1-ethyl-2-bromopyridinium chloride and a base shown below,

and is preferably a carbodiimide, and more preferably 1-(3-dimethylaminopropyl)-3-ethylcarbodiimide or 1,3-dicyclohexylcarbodiimide.

The base employed can be, for example, an organic base such as pyrrolidine, piperidine, morpholene, N-methylmorpholine, triethylamine, tributylamine, diisopropylethylamine, dicyclohexylamine, N-methylpiperidine, pyridine, 4-pyrrolidinopyridine, picoline, 4-(N,N-dimethylamino)pyridine, 2,6-di(t-butyl)-4-methylpyridine, quinoline, N,N-dimethylaniline or N,N-diethylaniline.

The reaction temperature varies depending on the starting material and the reagent, and is between -30°C and 100°C, and preferably between -10°C and 50°C.

The reaction time varies depending on the reaction temperature, the starting material, the reagent and the kind of solvent employed, and is generally from 5 minutes to 24 hours, and preferably from 30 minutes to 10 hours.

After completion of the reaction, the desired compound of this reaction can be obtained, for example, by concentration of the reaction mixture; addition to the mixture of an organic solvent immiscible with water such as ethyl acetate, washing the mixture with water, separation of the organic layer containing the desired compound, drying the organic layer over anhydrous magnesium sulfate or the like, and then evaporation of the organic solvent to give the desired product.

The obtained compound, if necessary, is further purified by conventional treatments, for example, by recrystallization, reprecipitation, silica gel column chromatography or the like.

(A-3c)

The solvent employed can be, for example, an aromatic hydrocarbon such as benzene, toluene or xylene; a halogenated hydrocarbon such as dichloromethane, chloroform, carbon tetrachloride, dichloroethane, chlorobenzene or dichlorobenzene; an ester such as ethyl formate, ethyl acetate, propyl acetate, butyl acetate or diethyl carbonate; an ether such as diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane, dimethoxyethane or di(ethylene glycol) dimethyl ether; a ketone such as acetone, methyl ethyl ketone, methyl isobutyl ketone, isophorone or cyclohexanone; an amide such as formamide, N,N-dimethylformamide, N,N-dimethylacetamide, N-methyl-2-pyrrolidinone or hexamethylphosphoric triamide; or a sulfoxide such as dimethyl sulfoxide or sulfolane, and is preferably an ether, and more preferably tetrahydrofuran.

The reaction temperature varies depending on the starting material and the reagent, and is between -30°C and 100°C, and preferably between -10°C and 50°C.

The reaction time varies depending on the reaction temperature, the starting material, the reagent and the kind of solvent employed, and is generally from 1 minute to 5 hours, and preferably from 5 minutes to 1 hour.

After completion of the reaction, the desired compound of this reaction can be obtained, for example, by concentration of the reaction mixture; addition to the mixture of an organic solvent immiscible with water such as ethyl acetate, washing the mixture with water, separation of the organic layer containing the desired compound, drying the organic layer over anhydrous magnesium sulfate or the like, and then evaporation of the organic solvent to give the desired product.

The obtained product, if necessary, is further purified by conventional treatments, for example, by recrystallization, reprecipitation, silica gel column chromatography or the like.

(A-4)

This step is achieved by hydrolysis of an ester group (A-4).

This step is carried out in a similar manner to that indicated hereinbefore (A-2).

(A-5)

This step is achieved by converting a carboxy group obtained in Step A-4 into an active ester, followed by reacting said active ester with a desired amino compound.

The solvent employed can be, for example, an aromatic hydrocarbon such as benzene, toluene or xylene; a halogenated hydrocarbon such as dichloromethane, chloroform, carbon tetrachloride, dichloroethane, chlorobenzene or dichlorobenzene; an ester such as ethyl formate, ethyl acetate, propyl acetate, butyl acetate or diethyl carbonate; an ether such as diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane, dimethoxyethane or di(ethylene glycol) dimethyl ether; a ketone such as acetone, methyl ethyl ketone, methyl isobutyl ketone, isophorone or cyclohexanone; an amide such as formamide, N,N-dimethylformamide, N,N-dimethylacetamide, N-methyl-2-pyrrolidinone or hexamethylphosphoric triamide; or a sulfoxide such as dimethyl sulfoxide or sulfolane, and is preferably a halogenated hydrocarbon or an amide, and more preferably N,N-dimethylformamide, N,N-dimethylacetamide or dichloromethane.

The reagent employed is not particularly restricted provided that it is used for an active ester formation, and, for example, can be isobutyl chloroformate.

The base employed can be, for example, an inorganic base, including an alkali metal carbonate such as sodium carbonate, potassium carbonate or lithium carbonate; an alkali metal hydrogencarbonate such as sodium hydrogencarbonate, potassium

hydrogencarbonate or lithium hydrogencarbonate; an alkali metal hydride such as lithium hydride, sodium hydride or potassium hydride; an alkali metal hydroxide such as sodium hydroxide, potassium hydroxide or lithium hydroxide; and an alkali metal fluoride such as sodium fluoride or potassium fluoride; an alkali metal alkoxide such as sodium methoxide, sodium ethoxide, potassium methoxide, potassium ethoxide, potassium t-butoxide or lithium methoxide; an alkali metal mercaptan such as sodium methylmercaptan or sodium ethylmercaptan; or an organic base such as N-methylmorpholine, triethylamine, tripropylamine, tributylamine, diisopropylethylamine, dicyclohexylamine, N-methylpiperidine, pyridine, 4-pyrrolidinopyridine, picoline, 4-(N,N-dimethylamino)pyridine, 2,6-di(t-butyl)-4-methylpyridine, quinoline, N,N-dimethylaniline, N,N-diethylaniline, 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), 1,4-diazabicyclo[2.2.2]octane (DABCO) or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and is preferably an alkali metal carbonate or an organic base, and more preferably potassium carbonate or triethylamine.

The reaction temperature varies depending on the starting material and the reagent, and is between -30°C and 100°C, and preferably between -10°C and 50°C.

The reaction time varies depending on the reaction temperature, the starting material, the reagent and the kind of solvent employed, and is generally from 10 minutes to 24 hours, and preferably from 30 minutes to 10 hours.

After completion of the reaction, the desired compound of this reaction can be obtained, for example, by concentration of the reaction mixture, addition to the mixture of an organic solvent immiscible with water such as ethyl acetate, washing the mixture with water, separation of the organic layer containing the desired compound; drying the organic layer over anhydrous magnesium sulfate or the like; and then evaporation of the organic solvent to give the desired product.

The obtained product, if necessary, is further purified by conventional treatments, for example, by recrystallization, reprecipitation, silica gel column chromatography or the like.

(A-6)

This step is carried out by conducting a dehydrating condensation reaction between a carboxylic acid obtained in Step A-4 and an alcohol (A-6a) or by conducting an ester interchange reaction using an ester in the presence of an acid or a base directly without performing the process of Step A-4 (A-6b).

(A-6a)

The solvent employed can be, for example, an aromatic hydrocarbon such as benzene, toluene or xylene; a halogenated hydrocarbon such as dichloromethane, chloroform, carbon tetrachloride, dichloroethane, chlorobenzene or dichlorobenzene; an ether such as diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane, dimethoxyethane or di(ethylene glycol) dimethyl ether; an alcohol such as methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutanol, t-butanol, isoamyl alcohol, diethylene glycol, glycerol, octanol, cyclohexanol or 2-methoxyethanol; an amide such as formamide, N,N-dimethylformamide, N,N-dimethylacetamide, N-methyl-2-pyrrolidinone or hexamethylphosphorotriamide; a sulfoxide such as dimethyl sulfoxide or sulfolane; or a mixed solvent of an alcohol and the above solvent. However, when an alcohol is employed as a solvent in the above reaction, an addition of the alcohol as a reagent is not necessary.

The acid employed can be, for example, an inorganic acid such as hydrochloric acid, hydrogen chloride, hydrobromic acid, sulfuric acid, perchloric acid or phosphoric acid; or a sulfonic acid such as methanesulfonic acid, p-toluenesulfonic acid or camphorsulfonic acid, and is preferably an inorganic acid, and more preferably hydrogen chloride.

The reaction temperature varies depending on the starting material and the reagent, is between -30°C and 100°C, and preferably between -10°C and 50°C.

The reaction time varies depending on the reaction temperature, the starting material, the reagent and the kind of solvent employed, and is generally from 10 minutes to 24 hours, and preferably from 30 minutes to 10 hours.

After completion of the reaction, the desired compound of this reaction can be obtained, for example, by concentration of the reaction mixture, addition to the mixture of an organic solvent immiscible with water such as ethyl acetate, washing the mixture with water, separation of the organic layer containing the desired compound; drying the organic layer over anhydrous magnesium sulfate or the like; and then evaporation of the organic solvent to give the desired product.

The obtained product, if necessary, is further purified by conventional treatments, for example, by recrystallization, reprecipitation, silica gel column chromatography or the like.

This step is carried out in a similar manner to that indicated hereinbefore in (A-3b).

(A-6b)

In this step, an alcohol corresponding to the desired alkoxy group is employed as a solvent. When an acid is employed, such acid employed can be, for example, an inorganic acid such as hydrochloric acid, hydrogen chloride, hydrobromic acid, sulfuric acid, perchloric acid or phosphoric acid; or a sulfonic acid such as methanesulfonic acid, p-toluenesulfonic acid or camphorsulfonic acid, and is preferably an inorganic acid, and more preferably hydrogen chloride.

When a base is employed, such base employed can be, for example, an inorganic base, including an alkali metal carbonate such as sodium carbonate, potassium carbonate or lithium carbonate; an alkali metal hydrogencarbonate such as sodium hydrogencarbonate, potassium hydrogencarbonate or lithium

hydrogencarbonate; an alkali metal hydride such as lithium hydride, sodium hydride or potassium hydride; an alkali metal hydroxide such as sodium hydroxide, potassium hydroxide or lithium hydroxide; or an alkali metal fluoride such as sodium fluoride or potassium fluoride, and is preferably an alkali metal carbonate, and more preferably potassium carbonate.

The reaction temperature varies depending on the starting material and the reagent, and is between -30°C and 100°C, and preferably between -10°C and 50°C.

The reaction time varies depending on the reaction temperature, the starting material, the reagent and the kind of solvent employed, and is generally from 10 minutes to 24 hours, and preferably from 30 minutes to 10 hours.

After completion of the reaction, the desired compound of this reaction can be obtained, for example, by concentration of the reaction mixture, addition to the mixture of an organic solvent immiscible with water such as ethyl acetate, washing the mixture with water, separation of the organic layer containing the desired compound, drying the organic layer over anhydrous magnesium sulfate or the like, and then evaporation of the organic solvent to give the desired product.

The obtained compound, if necessary, is further purified by conventional treatments, for example, by recrystallization, reprecipitation, silica gel column chromatography or the like.

(A-7)

This step is carried out in a similar manner to that indicated hereinbefore in Step A-2. When an acid is employed, trifluoroacetic acid or hydrogen chloride is employed as a particularly preferred reagent.

When the desired compound is obtained as its geometrical isomer, the desired compound can be obtained by conducting the photoisomerization reaction shown below.

The solvent employed can be, for example, an ester such as ethyl formate, ethyl acetate, propyl acetate, butyl acetate or diethyl carbonate; an ether such as diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane, dimethoxyethane or di(ethylene glycol) dimethyl ether; an alcohol such as methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutanol, t-butanol, isoamyl alcohol, diethylene glycol, glycerol, octanol, cyclohexanol or methyl cellosolve; a nitrile such as acetonitrile or isobutyronitrile; an amide such as formamide, N,N-dimethylformamide, N,N-dimethylacetamide, N-methyl-2-pyrroridone, N-methylpyrrolidinone or hexamethylphosphorotriamide; a sulfoxide such as dimethyl sulfoxide or sulfolane; water; or a mixture of these solvents, and is preferably water, an alcohol, a nitrile or a mixture of these solvents.

The light source employed is a low-pressure mercury lamp (having 20 W to 100 W, preferably 32 W).

The sensitizer employed can be, for example, benzophenone, fluorenone or anthraquinone.

This reaction can also be carried out by addition of an organic sulfur compound such as dimethyl disulfide, diethyl disulfide or diphenyl disulfide in order to accelerate the reaction.

The reaction temperature varies depending on the starting material and the reagent, and is between -20°C and 100°C, and preferably between 0°C and 50°C.

The reaction time varies depending on the reaction temperature, the starting material, the reagent and the kind of solvent employed, and is generally from 5 minutes to 8 hours, and preferably from 10 minutes to 3 hours.

After completion of the reaction, the desired compound of this reaction can be obtained, for example, by concentration of the reaction mixture, addition to the mixture of an organic solvent immiscible with water such as ethyl acetate, washing the mixture with water, separation of the organic layer containing the desired

compound, drying the organic layer over anhydrous magnesium sulfate or the like, and then evaporation of the organic solvent to give the desired product.

The obtained product, if necessary, is further purified by conventional treatments, for example, by recrystallization, reprecipitation, silica gel column chromatography or the like.

(A-8)

This step is a step for the conversion of a carboxy group into a hydroxylamino group, and can easily be carried out according to procedures that are well known by a person having ordinary skill in the art (for example, methods disclosed in A. Sekar Reddy, M. Suresh Kumar and G. Rabindra Reddy: Tetrahedron Letters, (2000), 41, 6285-6288).

(A-9)

This step can be carried out according to a Mitsunobu reaction using an amine in an inert solvent or by conversion of a hydroxyl group into a leaving group followed by conducting a displacement reaction using an amine, and carried out in a similar manner to that indicated hereinunder (C-2e).

(Process B)

Process B is steps comprising the preparation of compound (V) by conducting a nucleophilic displacement reaction in the presence of a base using a compound (III) that are well known or easily prepared from known compounds and the compounds (IV) obtained by the Process C described hereinafter (B-1) and the preparation of compound (I) by conversion of a hydroxyl group of the compound (V) (B-2). Furthermore, if necessary, in Process B, deprotection of the protective group for a sulfanyl group (B-3), introduction of a substituent onto a sulfanyl group (B-4), hydrolysis of an ester group (B-5), conversion of a carboxy group into an amide group (B-6), conversion of a carboxy group into an ester group (B-7), deprotection of a protective group for an amino group (B-8) and conversion of a carboxy group into

a hydroxyamino group (B-9) can be also carried out. The steps from B-3 to B-9 can be conducted either before or after the steps B-1 and B-2, and the order of these steps can be selected according to circumstances by a person having ordinary skill in the art.

(B-1)

The solvent employed can be, for example, an aromatic hydrocarbon such as benzene, toluene or xylene; a halogenated hydrocarbon such as dichloromethane, chloroform, carbon tetrachloride, dichloroethane, chlorobenzene or dichlorobenzene; an ester such as ethyl formate, ethyl acetate, propyl acetate, butyl acetate or diethyl carbonate; an ether such as diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane, dimethoxyethane or di(ethylene glycol) dimethyl ether; a ketone such as acetone, methyl ethyl ketone, methyl isobutyl ketone, isophorone or cyclohexanone; an amide such as formamide, N,N-dimethylformamide, N,N-dimethylacetamide, N-methyl-2-pyrrolidinone or hexamethylphosphoric triamide; or a sulfoxide such as dimethyl sulfoxide or sulfolane, and is preferably a halogenated hydrocarbon or an amide, and more preferably N,N-dimethylformamide, N,N-dimethylacetamide or dichloromethane.

The base employed can be, for example, an inorganic base, including an alkali metal carbonate such as sodium carbonate, potassium carbonate or lithium carbonate; an alkali metal hydrogencarbonate such as sodium hydrogencarbonate, potassium hydrogencarbonate or lithium hydrogencarbonate; an alkali metal hydride such as lithium hydride, sodium hydride or potassium hydride; an alkali metal hydroxide such as sodium hydroxide, potassium hydroxide or lithium hydroxide; and an alkali metal fluoride such as sodium fluoride or potassium fluoride; an alkali metal alkoxide such as sodium methoxide, sodium ethoxide, potassium methoxide, potassium ethoxide, potassium t-butoxide or lithium methoxide; an alkali metal mercaptan such as sodium methylmercaptan or sodium ethylmercaptan; or an organic

base such as N-methylmorpholine, triethylamine, tripropylamine, tributylamine, diisopropylethylamine, dicyclohexylamine, N-methylpiperidine, pyridine, 4-pyrrolidinopyridine, picoline, 4-(N,N-dimethylamino)pyridine, 2,6-di-(t-butyl)-4-methylpyridine, quinoline, N,N-dimethylaniline, N,N-diethylaniline, 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), 1,4-diazabicyclo[2.2.2]octane (DABCO) or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and is preferably an alkali metal carbonate or an organic base, and more preferably potassium carbonate or triethylamine.

The reaction temperature varies depending on the starting material and the reagent, and is between -30°C and 100°C, and preferably between -10°C and 50°C.

The reaction time varies depending on the reaction temperature, the starting material, the reagent and the kind of solvent employed, and is generally from 10 minutes to 48 hours, and preferably from 30 minutes to 24 hours.

After completion of the reaction, the desired compound of this reaction can be obtained, for example, by concentration of the reaction mixture, addition to the mixture of an organic solvent immiscible with water such as ethyl acetate, washing the mixture with water, separation of the organic layer containing the desired compound, drying of the organic layer over anhydrous magnesium sulfate or the like, and then evaporation of the organic solvent to give the desired product.

The obtained product, if necessary, is further purified by conventional treatments, for example, by recrystallization, reprecipitation, silica gel column chromatography or the like.

(B-2)

This step is carried out by the Mitsunobu reaction in an inert solvent (B-2a), by a reaction in the presence of an amide-acetal reagent (B-2b), by converting a hydroxyl group into a leaving group and conducting a substitution reaction using Pro^1-SM (M represents an alkali metal, preferably potassium) (B-2c) or by

converting a hydroxyl group into a leaving group and conducting a substitution reaction using Pro^1-SM in the presence of a palladium catalyst and a phosphine (B-2d).

(B-2a)

The solvent employed can be, for example, an aromatic hydrocarbon such as benzene, toluene or xylene; a halogenated hydrocarbon such as dichloromethane, chloroform, carbon tetrachloride, dichloroethane, chlorobenzene or dichlorobenzene; or an ether such as diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane, dimethoxyethane or di(ethylene glycol) dimethyl ether, and is preferably a halogenated hydrocarbon or an ether, and more preferably dichloromethane or tetrahydrofuran.

The reagent employed in the Mitsunobu reaction is not particularly restricted provided that it can generally be used for the Mitsunobu reaction, and, for example, is preferably a combination of an azo compound, including a di-lower-alkyl azodicarboxylate such as diethyl azodicarboxylate or diisopropyl azodicarboxylate or a heterocyclyl azodicarbonyl such as 1,1'-(azodicarbonyl)dipiperidine, and a phosphine, including a triarylphosphine such as triphenylphosphine or a tri-lower-alkylphosphine such as tri-n-butylphosphine, and more preferably a combination of a di-lower-alkyl azodicarboxylate and a triarylphosphine, and most preferably a combination of diethyl azodicarboxylate or diisopropyl azodicarboxylate and triphenylphosphine.

The reaction temperature varies depending on the starting material and the reagent, and is between -50°C and 100°C, and preferably between -10°C and 60°C.

The reaction time varies depending on the reaction temperature, the starting material, the reagent and the kind of solvent employed, and is generally from 10 minutes to 48 hours, and preferably from 30 minutes to 24 hours.

After completion of the reaction, the desired compound of this reaction can be obtained, for example, by concentration of the reaction mixture, addition to the mixture of an organic solvent immiscible with water such as ethyl acetate, washing the mixture with water, separation of the organic layer containing the desired compound, drying of the organic layer over anhydrous magnesium sulfate or the like, and then evaporation of the organic solvent to give the desired product.

The obtained product, if necessary, is further purified by conventional treatments, for example, by recrystallization, reprecipitation, silica gel column chromatography or the like.

(B-2b)

The solvent employed can be, for example, an aromatic hydrocarbon such as benzene, toluene or xylene; a halogenated hydrocarbon such as dichloromethane, chloroform, carbon tetrachloride, dichloroethane, chlorobenzene or dichlorobenzene; an ether such as diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane, dimethoxyethane or di(ethylene glycol) dimethyl ether; or an amide such as formamide, N,N-dimethylformamide, N,N-dimethylacetamide, N-methyl-2-pyrrolidinone or hexamethylphosphoric triamide, and is preferably an aromatic hydrocarbon, and more preferably toluene.

The amide acetal reagent employed can be, for example, a group of general formula $(CH_3)_2NCH(OR')_2$ (wherein R' represents a C_1-C_6 alkyl group or a C_7-C_{15} aralkyl group), and is preferably N,N-dimethylformamide dineopentyl acetal.

The reaction temperature varies depending on the starting material and the reagent, and is between -50°C and 150°C, and preferably between -10°C and 120°C.

The reaction time varies depending on the reaction temperature, the starting material, the reagent and the kind of solvent employed, and is generally from 1 minute to 24 hours, and preferably from 5 minutes to 5 hours.

After completion of the reaction, the desired compound of this reaction can be obtained, for example, by concentration of the reaction mixture, addition to the mixture of an organic solvent immiscible with water such as ethyl acetate, washing the mixture with water, separation of the organic layer containing the desired compound, drying of the organic layer over anhydrous magnesium sulfate or the like, and then evaporation of the organic solvent to give the desired product.

The obtained product, if necessary, is further purified by conventional treatments, for example, by recrystallization, reprecipitation, silica gel column chromatography or the like.

(B-2c)

The solvent employed for the conversion reaction of a hydroxyl group into a leaving group can be, for example, a halogenated hydrocarbon such as dichloromethane, chloroform, carbon tetrachloride, dichloroethane, chlorobenzene or dichlorobenzene; or an ether such as diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane, dimethoxyethane or di(ethylene glycol) dimethyl ether, and is preferably a halogenated hydrocarbon, and more preferably dichloromethane.

The base employed can be, for example, an organic base such as pyrrolidine, piperidine, morpholine, N-methylmorpholine, triethylamine, tripropylamine, tributylamine, diisopropylethylamine, dicyclohexylamine, N-methylpiperidine, pyridine, 4-pyrrolidinopyridine, picoline, 4-(N,N-dimethylamino)pyridine, 2,6-di(t-butyl)-4-methylpyridine, quinoline, N,N-dimethylaniline, N,N-diethylaniline, 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), 1,4-diazabicyclo[2.2.2]octane (DABCO) or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and is preferably 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

The reagent employed is not particularly restricted provided that it forms a leaving group by reacting with a hydroxyl group, and the conversion into the leaving group is achieved by addition of a halogenation agent, sulfonylation agent or

acylation agent. The halogenation agent employed can be a carbon tetrahalide such as carbon tetrabromide or carbon tetrachloride, and in these cases, a phosphine is used as a reagent. Such phosphine can be, for example, a tri-C_1-C_6 alkylphosphine such as trimethylphosphine, triethylphosphine, tripropylphosphine, tributylphosphine, tripentylphosphine or trihexylphosphine; a tri-C_6-C_{10} arylphosphine such as triphenylphosphine, triindenylphosphine or trinaphthylphosphine; or a tri-C_6-C_{10} arylphosphine which may have C_1-C_4 alkyl group(s) as substituent(s), such as tolyldiphenylphosphine, tritolylphosphine, trimesitylphosphine, tributylphenylphosphine or tri-6-ethyl-2-naphthylphosphine, and is preferably a tri-C_1-C_6 alkylphosphine (particularly trimethylphosphine, triethylphosphine, tripropylphosphine or tributylphosphine) or a tri-C_6-C_{10} arylphosphine (particularly triphenylphosphine, triindenylphosphine or trinaphthylphosphine), and more preferably a tri-C_6-C_{10} arylphosphine (particularly triphenylphosphine). The sulfonylation agent employed can be, for example, a sulfonyl halide such as methanesulfonyl chloride, ethanesulfonyl chloride or tosyl chloride, and is preferably methanesulfonyl chloride. The acylation agent employed can be, for example, acetyl chloride, acetic anhydride, trifluoroacetic anhydride or the like.

The reaction temperature varies depending on the starting material and the reagent, and is between -50°C and 100°C, and preferably between -20°C and 80°C.

The reaction time varies depending on the reaction temperature, the starting material, the reagent and the kind of solvent employed, and is generally from 30 minutes to 24 hours, and preferably from 1 hour to 10 hours.

The solvent employed in the substitution reaction of Pro^1-SM can be, for example, an aromatic hydrocarbon such as benzene, toluene or xylene; a halogenated hydrocarbon such as dichloromethane, chloroform, carbon tetrachloride, dichloroethane, chlorobenzene or dichlorobenzene; an ester such as ethyl formate, ethyl acetate, propyl acetate, butyl acetate or diethyl carbonate; an ether such as

diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane, dimethoxyethane or di(ethylene glycol) dimethyl ether; a ketone such as acetone, methyl ethyl ketone, methyl isobutyl ketone, isophorone or cyclohexanone; a nitro compound such as nitroethane or nitrobenzene; a nitrile such as acetonitrile or isobutyronitrile; an amide such as formamide, N,N-dimethylformamide, N,N-dimethylacetamide, N-methyl-2-pyrrolidinone or hexamethylphosphoric triamide; or a sulfoxide such as dimethyl sulfoxide or sulfolane, and is preferably a halogenated hydrocarbon, an amide or a sulfoxide, and more preferably N,N-dimethylformamide, N,N-dimethylacetamide, dichloromethane or dimethyl sulfoxide.

The base employed can be, for example, an inorganic base containing an alkali metal carbonate such as sodium carbonate, potassium carbonate or lithium carbonate; an alkali metal hydrogencarbonate such as sodium hydrogencarbonate, potassium hydrogencarbonate or lithium hydrogencarbonate; an alkali metal hydride such as lithium hydride, sodium hydride or potassium hydride; an alkali metal hydroxide such as sodium hydroxide, potassium hydroxide or lithium hydroxide; and an alkali metal fluoride such as sodium fluoride or potassium fluoride; an alkali metal alkoxide such as sodium methoxide, sodium ethoxide, potassium methoxide, potassium ethoxide, potassium t-butoxide or lithium methoxide; an alkali metal mercaptan such as sodium methylmercaptan or sodium ethylmercaptan; or an organic base such as N-methylmorpholine, triethylamine, tripropylamine, tributylamine, diisopropylethylamine, dicyclohexylamine, N-methylpiperidine, pyridine, 4-pyrrolidinopyridine, picoline, 4-(N,N-dimethylamino)pyridine, 2,6-di-(t-butyl)-4-methylpyridine, quinoline, N,N-dimethylaniline, N,N-diethylaniline, 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), 1,4-diazabicyclo[2.2.2]octane (DABCO) or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and is preferably an alkali metal carbonate or an organic base, and more preferably potassium carbonate or triethylamine.

The reaction temperature varies depending on the starting material and the reagent, and is between -50°C and 100°C, and preferably between -20°C and 80°C.

The reaction time varies depending on the reaction temperature, the starting material, the reagent and the kind of solvent employed, and is generally from 30 minutes to 24 hours, and preferably from 1 hour to 10 hours.

After completion of the reaction, the desired compound of this reaction can be obtained, for example, by concentration of the reaction mixture, addition to the mixture of an organic solvent immiscible with water such as ethyl acetate, washing the mixture with water, separation of the organic layer containing the desired compound, drying of the organic layer over anhydrous magnesium sulfate or the like, and then evaporation of the organic solvent to give the desired product.

The obtained product, if necessary, is further purified by conventional treatments, for example, by recrystallization, reprecipitation, silica gel column chromatography or the like.

(B-2d)

The reaction for converting a hydroxyl group into a leaving group can be carried out in a similar manner to (B-2c).

The solvent of the subsequent substitution reaction employed can be, for example, an aliphatic hydrocarbon such as hexane, cyclohexane, heptane, ligroin, or petroleum ether; an aromatic hydrocarbon such as benzene, toluene, or xylene; a halogenated hydrocarbon such as dichloromethane, chloroform, carbon tetrachloride, dichloroethane, chlorobenzene, or dichlorobenzene; an ether such as diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane, dimethoxyethane, or di(ethylene glycol) dimethyl ether; a nitrile such as acetonitrile or isobutyronitrile; or a mixture of water and the above-mentioned solvents, and is preferably a mixture of water and dioxane.

The palladium catalyst employed can be, for example, palladium chloride, palladium acetate, tris(dibenzylideneacetone)dipalladium-chloroform adduct,

tris(dibenzylideneacetone)dipalladium, bis(dibenzylideneacetone)palladium, π-allylpalladium chloride dimer, tetrakis(triphenylphosphine)palladium, 1,1'-bis(diphenylphosphino)ferrocene palladium dichloride, bis(triphenylphosphine)palladium chloride, bis(triphenylphosphine)palladium acetate, dichloro(1,5-cyclooctadiene)palladium, dichlorobis(acetonitrile)palladium, bis(tricyclohexylphosphine)palladium dichloride, bis(tricyclohexylphosphine)palladium, or bis(tri-O-tolylphosphine)palladium dichloride, and is preferably palladium chloride, palladium acetate, tris(dibenzylideneacetone)dipalladium-chloroform adduct or tris(dibenzylideneacetone)dipalladium.

The phosphine employed can be, for example, a tri-C_1-C_6 alkylphosphine such as trimethylphosphine, triethylphosphine, tripropylphosphine, tributylphosphine, tripentylphosphine or trihexylphosphine; a tri-C_6-C_{10} arylphosphine such as triphenylphosphine, triindenylphosphine or trinaphthylphosphine; a tri-C_6-C_{10} arylphosphine which may be substituted with a C_1-C_4 alkyl group such as tolyldiphenylphosphine, tritolylphosphine, trimesitylphosphine, tributylphenylphosphine or tri-6-ethyl-2-naphthylphosphine; a bis(diphenylphosphino)C_1-C_6 alkane such as bis(diphenylphosphino)methane, 1,2-bis(diphenylphosphino)ethane, 1,3-bis(diphenylphosphino)propane, 1,4-bis(diphenylphosphino)butane, 1,5-bis(diphenylphosphino)pentane or 1,6-bis(diphenylphosphino)hexane; or bis(diphenylphosphino)acetylene, 1,2-bis(diphenylphosphino)benzene, (R)-(+)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, (S)-(-)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, 1,1'-bis(diphenylphosphino)ferrocene, 1,1-bis(diphenylphosphino)ethylene or 4,5-bis(diphenylphosphino)-9,9-dimethylxanthene, and is preferably 1,1'-bis(diphenylphosphino)ferrocene, (R)-(+)-

2,2'-bis(diphenylphosphino)-1,1'-binaphthyl, 2,2'-bis(diphenylphosphino)-1,1'-binaphthyl or (S)-(-)-2,2'-bis(diphenylphosphino)-1,1'-binaphthyl.

The reaction temperature varies depending on the starting material and the reagent, and is between 0°C and 150°C, and preferably between 50°C and 120°C.

The reaction time varies depending on the reaction temperature, the starting material, the reagent and the kind of solvent employed, and is generally from 1 hour to 24 hours, and preferably from 6 hours to 20 hours.

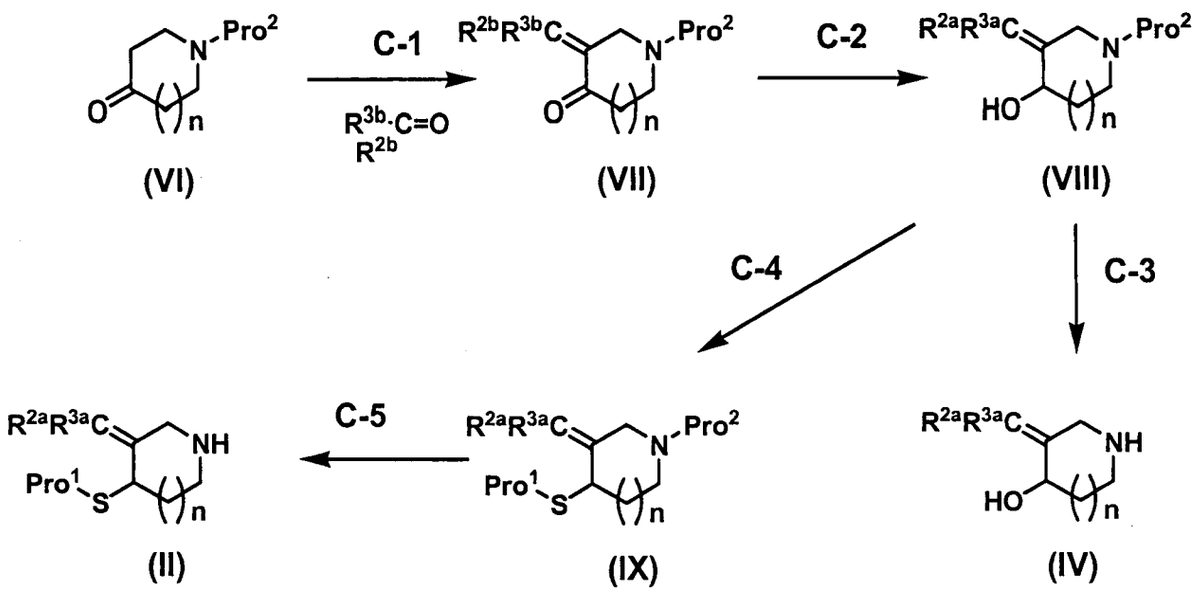
After completion of the reaction, the desired compound of this reaction can be obtained, for example, by concentration of the reaction mixture, addition to the mixture of an organic solvent immiscible with water such as ethyl acetate, washing the mixture with water, separation of the organic layer containing the desired compound, drying of the organic layer over anhydrous magnesium sulfate or the like, and then evaporation of the organic solvent to give the desired product.

The obtained product, if necessary, is further purified by conventional treatments, for example, by recrystallization, reprecipitation, silica gel column chromatography or the like.

From (B-3) to (B-9)

Each of these steps is carried out in a similar manner to that indicated in (A-2) to (A-8) hereinbefore, respectively.

Process C



(Process C)

In the above, Pro^1, R^{2a}, R^{3a} and, n have the same meanings as those indicated hereinbefore; R^{2b} and R^{3b} represent the same groups as those indicated for R^{2a} and R^{3a} described hereinbefore; and Pro^2 represents a protective group for an amino group.

The protective group for an amino group shown as Pro^2 is the same as that indicated for R^{2a} and R^{3a}.

Process C is hereinafter described in detail.

(C-1)

This step is a step for the preparation of compound (VII) by reacting compound (VI) that is well known or easily prepared from known compounds with a compound having of formula R^{2b}-C(=O)-R^{3b} that is well known or can be easily prepared from known compounds, and is carried out by a route via the enamination (C-1a) or by the cross aldol reaction (C-1b).

(C-1a)

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The base employed can be, for example, an organic base such as pyrrolidine, piperidine, morpholine, N-methylmorpholine, triethylamine, tripropylamine, tributylamine, diisopropylethylamine, dicyclohexylamine, N-methylpiperidine, pyridine, 4-pyrrolidinopyridine, picoline, 4-(N,N-dimethylamino)pyridine, 2,6-di-(t-butyl)-4-methylpyridine, quinoline, N,N-dimethylaniline, N,N-diethylaniline, 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), 1,4-diazabicyclo[2.2.2]octane (DABCO) or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and is preferably pyrrolidine, piperidine or morpholine.

The solvent employed can be, for example, an aromatic hydrocarbon such as benzene, toluene or xylene; a halogenated hydrocarbon such as dichloromethane, chloroform, carbon tetrachloride, dichloroethane, chlorobenzene or dichlorobenzene; an alcohol such as methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutanol, t-butanol, isoamyl alcohol, diethylene glycol, glycerol, octanol, cyclohexanol or 2-methoxyethanol; or an ether such as diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane, dimethoxyethane or di(ethylene glycol) dimethyl ether; and is preferably benzene, toluene or ethanol.

The reaction temperature varies depending on the starting material and the reagent, and is between 0°C and 200°C, and preferably between 50°C and 150°C.

The reaction time varies depending on the reaction temperature, the starting material, the reagent and the kind of solvent employed, and is generally from 30 minutes to 24 hours, and preferably from 1 hour to 10 hours.

After completion of the reaction, the desired compound of this reaction can be obtained, for example, by concentration of the reaction mixture, addition to the mixture of an organic solvent immiscible with water such as ethyl acetate, washing the mixture with water, separation of the organic layer containing the desired compound, drying of the organic layer over anhydrous magnesium sulfate or the like, and then evaporation of the organic solvent to give the desired product.

The obtained product, if necessary, is further purified by conventional treatments, for example, by recrystallization, reprecipitation, silica gel column chromatography or the like.

When the compound having a hydroxyl group that is a reaction intermediate remains and the reaction is not completed, the desired product can be obtained by conducting furthermore a dehydration reaction in the presence of a base.

The solvent employed can be, for example, a halogenated hydrocarbon such as dichloromethane, chloroform, carbon tetrachloride, dichloroethane, chlorobenzene or dichlorobenzene; or an ether such as diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane, dimethoxyethane or di(ethylene glycol) dimethyl ether, and is preferably a halogenated hydrocarbon, and more preferably dichloromethane.

The base employed can be an organic base such as pyrrolidine, piperidine, morpholine, N-methylmorpholine, triethylamine, tripropylamine, tributylamine, diisopropylethylamine, dicyclohexylamine, N-methylpiperidine, pyridine, 4-pyrrolidinopyridine, picoline, 4-(N,N-dimethylamino)pyridine, 2,6-di-(t-butyl)-4-methylpyridine, quinoline, N,N-dimethylaniline, N,N-diethylaniline, 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), 1,4-diazabicyclo[2.2.2]octane (DABCO) or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and is preferably 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU).

The reagent employed is not particularly restricted provided that it forms a leaving group by reacting with a hydroxyl group, and the conversion into the leaving group is achieved by addition of a halogenation agent, sulfonylation agent or acylation agent. The halogenation agent employed can be, for example, a carbon tetrahalide such as carbon tetrabromide or carbon tetrachloride, and in these cases, a phosphine is used as a reagent. Such phosphine can be, for example, a tri-C_1-C_6 alkylphosphine such as trimethylphosphine, triethylphosphine, tripropylphosphine, tributylphosphine, tripentylphosphine or trihexylphosphine; a tri-C_6-C_{10}

arylphosphine such as triphenylphosphine, triindenylphosphine or trinaphthylphosphine; or tri-C_6-C_{10} arylphosphine which may have C_1-C_4 alkyl group(s) as substituent(s), such as tolyldiphenylphosphine, tritolylphosphine, trimesitylphosphine, tributylphenylphosphine or tri-6-ethyl-2-naphthylphosphine, and is preferably a tri-C_1-C_6 alkylphosphine (particularly trimethylphosphine, triethylphosphine, tripropylphosphine or tributylphosphine) or a tri-C_6-C_{10} arylphosphine (particularly triphenylphosphine, triindenylphosphine or trinaphthylphosphine), and more preferably a tri-C_6-C_{10} arylphosphine (particularly triphenylphosphine). The sulfonylation agent employed can be, for example, a sulfonyl halide such as methanesulfonyl chloride, ethanesulfonyl chloride or tosyl chloride, and is preferably methanesulfonyl chloride. The acylation agent employed can be, for example, acetyl chloride, acetic anhydride, trifluoroacetic anhydride or the like.

The reaction temperature varies depending on the starting material and the reagent, and is between -50°C and 100°C, and preferably between -20°C and 80°C.

The reaction time varies depending on the reaction temperature, the starting material, the reagent and the kind of solvent employed, and is generally from 30 minutes to 24 hours, and preferably from 1 hour to 10 hours.

After completion of the reaction, the desired compound of this reaction can be obtained, for example, by concentration of the reaction mixture, addition to the mixture of an organic solvent immiscible with water such as ethyl acetate, washing the mixture with water, separation of the organic layer containing the desired compound, drying of the organic layer over anhydrous magnesium sulfate or the like, and then evaporation of the organic solvent to give the desired product.

The obtained product, if necessary, is further purified by conventional treatments, for example, by recrystallization, reprecipitation, silica gel column chromatography or the like.

(C-1b)

The base employed can be, for example, an organic base such as pyrrolidine, piperidine, morpholine, N-methylmorpholine, triethylamine, tripropylamine, tributylamine, diisopropylethylamine, dicyclohexylamine, N-methylpiperidine, pyridine, 4-pyrrolidinopyridine, picoline, 4-(N,N-dimethylamino)pyridine, 2,6-di-(t-butyl)-4-methylpyridine, quinoline, N,N-dimethylaniline, N,N-diethylaniline, 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), 1,4-diazabicyclo[2.2.2]octane (DABCO) or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU); or an organometallic base such as butyllithium, lithium diisopropylamide, lithium bis(trimethylsilyl)amide, sodium bis(trimethylsilyl)amide or potassium bis(trimethylsilyl)amide, and is preferably lithium diisopropylamide, lithium bis(trimethylsilyl)amide, sodium bis(trimethylsilyl)amide or potassium bis(trimethylsilyl)amide.

The solvent employed can be, for example, an aromatic hydrocarbon such as benzene, toluene or xylene; a halogenated hydrocarbon such as dichloromethane, chloroform, carbon tetrachloride, dichloroethane, chlorobenzene or dichlorobenzene; an alcohol such as methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutanol, t-butanol, isoamyl alcohol, diethylene glycol, glycerol, octanol, cyclohexanol or 2-methoxyethanol; or an ether such as diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane, dimethoxyethane or di(ethylene glycol) dimethyl ether, and is preferably tetrahydrofuran.

The reaction temperature varies depending on the starting material and the reagent, and is between -100°C and 20°C, and preferably between -78°C and 0°C.

The reaction time varies depending on the reaction temperature, the starting material, the reagent and the kind of solvent employed, and is generally from 30 minutes to 24 hours, and preferably from 1 hour to 5 hours.

After completion of the reaction, the desired compound of this reaction can be obtained, for example, by concentration of the reaction mixture, addition to the

mixture of an organic solvent immiscible with water such as ethyl acetate, washing the mixture with water, separation of the organic layer containing the desired compound, drying of the organic layer over anhydrous magnesium sulfate or the like, and then evaporation of the organic solvent to give the desired product.

The obtained product, if necessary, is further purified by conventional treatments, for example, by recrystallization, reprecipitation, silica gel column chromatography or the like.

When the compound having a hydroxyl group that is a reaction intermediate is remained, a dehydration reaction can be carried out in a similar manner to that indicated in (C-1a).

(C-2)

This step is a step for the reduction reaction by conversion of a carbonyl group of compound (VII) obtained in C-1 into a hydroxyl group (C-2a). In addition, when R^{2b} is a hydrogen atom, R^{2a} is not a hydrogen atom and R^{3b} is an alkoxycarbonyl group, a reaction for introducing an R^{2a} group can be carried out (C-2b). Furthermore, when the R^{3b} group contains an ester group, if necessary, a reaction for introducing a suitable protective group to the hydroxyl group (C-2c), a reduction reaction for converting the ester group into a hydroxymethyl group (C-2d), a reaction for converting the R^{3b} group containing the hydroxyl group into an R^{3a} group (C-2e) and a reaction for removing the protective group for the hydroxyl group (C-2f) can be carried out. The steps from C-2c to C-2f can be conducted either before or after the steps C-2a and C-2b, and it is easy for a person having skill in the art to determine an appropriate order of these steps.

(C-2a)

The solvent employed can be, for example, an aromatic hydrocarbon such as benzene, toluene or xylene; a halogenated hydrocarbon such as dichloromethane, chloroform, carbon tetrachloride, dichloroethane, chlorobenzene or dichlorobenzene;

an ether such as diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane, dimethoxyethane or di(ethylene glycol) dimethyl ether; an alcohol such as methanol, ethanol, n-propanol, isopropanol, n-butanol, isobutanol, t-butanol, isoamyl alcohol, diethylene glycol, glycerol, octanol, cyclohexanol or 2-methoxyethanol; or a mixture of an alcohol and a halogenated hydrocarbon, and is preferably an alcohol, a mixture of an alcohol and a halogenated hydrocarbon, or an ether, and more preferably methanol, ethanol, tetrahydrofuran or a mixture of said alcohol and dichloromethane.

The reagent employed is not particularly restricted provided that it can be used for a reduction reaction of a carbonyl group to a hydroxyl group, and can be, for example, an aluminium hydride reagent or boron compound such as sodium borohydride or diborane, and is preferably sodium borohydride.

The reaction temperature varies depending on the starting material and the reagent, and is between -78°C and 100°C, and preferably between 0°C and 50°C.

The reaction time varies depending on the reaction temperature, the starting material, the reagent and the kind of solvent employed, and is generally from 10 minutes to 12 hours, and preferably from 30 minutes to 5 hours.

After completion of the reaction, the desired compound of this reaction can be obtained, for example, by concentration of the reaction mixture, addition to the mixture of an organic solvent immiscible with water such as ethyl acetate, washing the mixture with water, separation of the organic layer containing the desired compound, drying of the organic layer over anhydrous magnesium sulfate or the like, and then evaporation of the organic solvent to give the desired product.

The obtained product, if necessary, is further purified by conventional treatments, for example, by recrystallization, reprecipitation, silica gel column chromatography or the like.

When R^{3b} is different from R^{3a}, it can be possible to introduce a substituent onto an amino group, if necessary. In this case, after removing a protective group

for the amino group in a similar manner to that described in (A-7), the introduction of the substituent can be carried out as described below.

The solvent employed can be, for example, an aromatic hydrocarbon such as benzene, toluene or xylene; a halogenated hydrocarbon such as dichloromethane, chloroform, carbon tetrachloride, dichloroethane, chlorobenzene or dichlorobenzene; an ester such as ethyl formate, ethyl acetate, propyl acetate, butyl acetate or diethyl carbonate; an ether such as diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane, dimethoxyethane or di(ethylene glycol) dimethyl ether; a ketone such as acetone, methyl ethyl ketone, methyl isobutyl ketone, isophorone or cyclohexanone; an amide such as formamide, N,N-dimethylformamide, N,N-dimethylacetamide, N-methyl-2-pyrrolidinone or hexamethylphosphoric triamide; or a sulfoxide such as dimethyl sulfoxide or sulfolane, and is preferably a halogenated hydrocarbon or an amide, and more preferably N,N-dimethylformamide, N,N-dimethylacetamide or dichloromethane.

The reagent employed is not particularly restricted provided that it can be used in the displacement reaction by an amino group, and can be, for example, a reagent in which a leaving group such as a halogen atom or a sulfonyl group is bonded to a desired functional group.

The base employed can be, for example, an inorganic base, including an alkali metal carbonate such as sodium carbonate, potassium carbonate or lithium carbonate; an alkali metal hydrogencarbonate such as sodium hydrogencarbonate, potassium hydrogencarbonate or lithium hydrogencarbonate; an alkali metal hydride such as lithium hydride, sodium hydride or potassium hydride; an alkali metal hydroxide such as sodium hydroxide, potassium hydroxide or lithium hydroxide; and an alkali metal fluoride such as sodium fluoride or potassium fluoride; an alkali metal alkoxide such as sodium methoxide, sodium ethoxide, potassium methoxide, potassium ethoxide, potassium t-butoxide or lithium methoxide; an alkali metal

mercaptan such as sodium methylmercaptan or sodium ethylmercaptan; or an organic base such as N-methylmorpholine, triethylamine, tripropylamine, tributylamine, diisopropylethylamine, dicyclohexylamine, N-methylpiperidine, pyridine, 4-pyrrolidinopyridine, picoline, 4-(N,N-dimethylamino)pyridine, 2,6-di-(t-butyl)-4-methylpyridine, quinoline, N,N-dimethylaniline, N,N-diethylaniline, 1,5-diazabicyclo[4.3.0]non-5-ene (DBN), 1,4-diazabicyclo[2.2.2]octane (DABCO) or 1,8-diazabicyclo[5.4.0]undec-7-ene (DBU), and is preferably potassium carbonate, sodium hydride or DBU.

The reaction temperature varies depending on the starting material and the reagent, and is between -30°C and 150°C, and preferably between 0°C and 100°C.

The reaction time varies depending on the reaction temperature, the starting material, the reagent and the kind of solvent employed, and is generally from 5 minutes to 48 hours, and preferably from 10 minutes to 15 hours.

After completion of the reaction, the desired compound of this reaction can be obtained, for example, by concentration of the reaction mixture, addition to the mixture of an organic solvent immiscible with water such as ethyl acetate, washing the mixture with water, separation of the organic layer containing the desired compound, drying of the organic layer over anhydrous magnesium sulfate or the like, and then evaporation of the organic solvent to give the desired product.

The obtained product, if necessary, is further purified by conventional treatments, for example, by recrystallization, reprecipitation, silica gel column chromatography or the like.

(C-2b)

This step can be achieved by using an R^{2a}-Lv or an aldehyde or ketone which forms a R^{2a} group in an inert solvent in the presence of a base to give a compound of general formula (VII).

The solvent employed can be, for example, an aliphatic hydrocarbon such as hexane, cyclohexane, heptane, ligroin or petroleum ether; an aromatic hydrocarbon such as benzene, toluene or xylene; a halogenated hydrocarbon such as dichloromethane, chloroform, carbon tetrachloride, dichloroethane, chlorobenzene or dichlorobenzene; an ether such as diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane, dimethoxyethane or di(ethylene glycol) dimethyl ether; or a nitrile such as acetonitrile or isobutyronitrile, and is preferably tetrahydrofuran.

The base employed can be, for example, lithium diisopropylamide, lithium benzyl(trimethylsilyl)amide, lithium dimethylamide, lithium diethylamide, lithium bis(trimethylsilyl)amide or lithium dicyclohexylamide, and is preferably lithium diisopropylamide.

The reagent employed can be, for example, a C_1-C_6 alkyl halide such as methyl iodide, ethyl iodide or propyl iodide; a C_1-C_6 alkyl mesylate; a C_1-C_6 alkyl tosylate; a C_7-C_{15} aralkyl halide such as benzyl bromide, 1-naphthylmethyl bromide, 2-naphthylmethyl bromide or phenethyl bromide; a C_7-C_{15} aralkyl mesylate; a C_7-C_{15} aralkyl tosylate; a C_1-C_6 alkyl aldehyde such as formaldehyde or acetoaldehyde; or a C_1-C_6 alkyl ketone such as acetone.

The reaction temperature varies depending on the starting material and the reagent, and is between -100°C and 150°C, and preferably between -80°C and 50°C.

The reaction time varies depending on the reaction temperature, the starting material, the reagent and the kind of solvent employed, and is generally from 1 hour to 48 hours, and preferably from 1 hour to 10 hours.

After completion of the reaction, the desired compound of this reaction can be obtained, for example, by concentration of the reaction mixture, addition to the mixture of an organic solvent immiscible with water such as ethyl acetate, washing the mixture with water, separation of the organic layer containing the desired

compound, drying the organic layer over anhydrous magnesium sulfate or the like, and then evaporation of the organic solvent to give the desired product.

The obtained product, if necessary, is further purified by conventional treatments, for example, by recrystallization, reprecipitation, silica gel column chromatography or the like.

(C-2c)

This step is a step for the protection of a hydroxyl group, and can easily be achieved according to procedures that are well known by a person having skill in the art (for example, the procedure described in Protective Groups in Organic Synthesis, Third Edition, T. W. Green, et al., John Wiley & Sons, Inc. (1999)), and is preferably silyl protection (particularly t-butyldimethylsilyl group).

(C-2d)

This step is achieved by reducing compound (VII) in an inert solvent in the presence of a reducing agent.

The solvent employed can be, for example, an aliphatic hydrocarbon such as hexane, cyclohexane, heptane, ligroin or petroleum ether; an aromatic hydrocarbon such as benzene, toluene or xylene; a halogenated hydrocarbon such as dichloromethane, chloroform, carbon tetrachloride, dichloroethane, chlorobenzene or dichlorobenzene; an ether such as diethyl ether, diisopropyl ether, tetrahydrofuran, dioxane, dimethoxyethane or di(ethylene glycol) dimethyl ether; or an alcohol such as methanol, ethanol, propanol or isobutanol. When the reducing agent is lithium aluminum hydride, diisobutyl aluminum hydride or diborane, the solvent employed can be an aliphatic hydrocarbon (particularly hexane or cyclohexane), an aromatic hydrocarbon (particularly benzene or toluene), a halogenated hydrocarbon (particularly dichloromethane) or an ether (particularly diethyl ether or tetrahydrofuran). When the reducing agent is sodium borohydride, the solvent employed can be an alcohol (particularly methanol or ethanol).

The reducing agent employed can be, for example, an aluminum hydride compound such as lithium aluminum hydride or diisobutyl aluminum hydride; sodium borohydride; or diborane, and is preferably diisobutyl aluminum hydride.

The reaction temperature varies depending on the starting material and the reagent, and is between -100°C and 100°C, and preferably between -80°C and 50°C.

The reaction time varies depending on the reaction temperature, the starting material, the reaction reagent and the kind of solvent employed, and is generally from 10 minutes to 24 hours, and preferably from 30 minutes to 5 hours.

After completion of the reaction, the desired compound of this reaction can be obtained, for example, by concentration of the reaction mixture, addition to the mixture of an organic solvent immiscible with water such as ethyl acetate, washing the mixture with water, separation of the organic layer containing the desired compound, drying the organic layer over anhydrous magnesium sulfate or the like, and then evaporation of the organic solvent to give the desired product.

The obtained product, if necessary, is further purified by conventional treatments, for example, by recrystallization, reprecipitation, silica gel column chromatography or the like.

(C-2e)

This step is carried out by the Mitsunobu reaction in an inert solvent using an amine or the like (C-2e1) or by a substitution reaction using an amine or the like after converting a hydroxyl group into a leaving group (C-2e2). The step (C-2e1) can be carried out in a similar manner to that indicated in (B-2a) except that an amine or the like is employed instead of Pro^1-SM. The step (C-2e2) can be carried out in a similar manner to that indicated in (B-2c) except that an amine or the like is employed instead of Pro^1-SM.

(C-2f)

This step is a step for the deprotection of a protective group for a hydroxyl group, and can easily be achieved according to procedures that are well known by a person having skill in the art (for example, the procedure discribed in Protective Groups in Organic Synthesis, Third Edition, T. W. Green, et al., John Wiley & Sons, Inc. (1999)).

(C-3)

This step is carried out as in a similar manner to that indicated in A-7, and is carried out most preferably by using trifluoroacetic acid or acetic acid.

(C-4)

This step is carried out in a similar manner to that indicated in B-2.

(C-5)

This step is carried out in a similar manner to that indicated in C-3.

Compound (I) of the present invention, pharmacologically acceptable salts thereof or prodrugs thereof exert inhibiting activity in the inhibition of platelet aggregation. In addition, compound (I) of the present invention, pharmacologically acceptable salts thereof or prodrugs thereof exhibit excellent pharmacokinetics such as absorption, distribution, plasma half-life, and the like, and low toxicities in organs such as the kidney, liver and the like. Thus compound (I) of the present invention, pharmacologically acceptable salts thereof or prodrugs thereof are useful, for example as medicinal drugs, and particularly useful as therapeutic or prophylactic agents for various thrombotic diseases.

When a compound of the present invention is used as a prophylactic or therapeutic agent for diseases as described above, said compound having the general formula (I), or pharmacologically acceptable salts thereof or prodrugs thereof, can be administered alone or as a mixture with pharmaceutically acceptable excipients, diluents and the like, in various dosage forms such as tablets, capsules, granules,

powders, syrups or the like for oral administration; and injections, suppositories, patches, external application or the like for parenteral administration.

Each of the above formulations can be prepared by well-known methods using additives for the formulation such as excipients (for example, organic excipients, including sugar derivatives such as lactose, sucrose, glucose, mannitol or sorbitol; starch derivatives such as corn starch, potato starch, α-starch or dextrin; cellulose derivatives such as crystalline cellulose; acacia; dextran; pullulan; and inorganic excipients including silicate derivatives such as light silicic acid anhydride, synthetic aluminium silicate, calcium silicate, or magnesium aluminate metasilicate; phosphate derivatives such as calcium hydrogenphosphate; carbonate derivatives such as calcium carbonate; or sulfate derivatives such as calcium sulfate), lubricants (for example, stearic acid; metal stearate derivatives such as calcium stearate or magnesium stearate; talc; colloidal silica; waxes such as beeswax or spermaceti; boric acid; adipic acid; sulfate derivatives such as sodium sulfate; glycol; fumaric acid; sodium benzoate; DL-leucine; lauryl sulfate derivatives such as sodium lauryl sulfate or magnesium lauryl sulfate; silicic acid derivatives such as silicic anhydride or silicic acid hydrate; or starch derivatives described above), binders (for example, hydroxypropylcellulose, hydroxypropylmethylcellulose, polyvinylpyrrolidone, macrogol or excipients as described above), disintegrants (for example, cellulose derivatives such as lower-substituted hydroxypropylcellulose, carboxymethylcellulose, calcium carboxymethylcellulose or internally cross-linked sodium carboxymethylcellulose; or chemically modified starch or cellulose derivatives such as carboxymethylstarch, sodium carboxymethylstarch, or cross-linked polyvinylpyrrolidone), emulsifiers (for example, colloidal clay such as bentonite or veegum; metal hydroxides such as magnesium hydroxide or aluminium hydroxide; anionic surfactants such as sodium lauryl sulfate or calcium stearate; cationic surfactants such as benzalkonium chloride; and non-ionic surfactants such as

polyoxyethylene alkyl ethers, polyoxyethylene sorbitan fatty acid esters or sucrose esters of fatty acids), stabilizers (for example, para-hydroxybenzoic acid ester derivatives such as methylparaben or propylparaben; alcohol derivatives such as chlorobutanol, benzyl alcohol or phenylethyl alcohol; benzalkonium chloride; phenol derivatives such as phenol or cresol; thimerosal; dehydroacetic acid; or sorbic acid), corrigents (for example, sweeteners, souring agents, flavourings or the like which are conventionally used) and diluents.

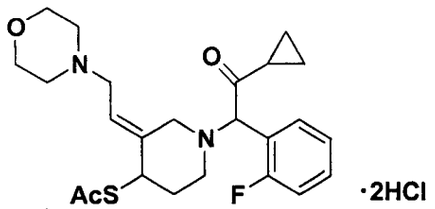
The specific dose of a compound of the present invention will be varied according to the severity of the patient's symptoms, age and the like. For oral administration to a human adult the quantity of active ingredient in a unit dosage may be in the range of 0.016 mg/kg (preferably 0.5 mg/kg) to 33.3 mg/kg (preferably 25 mg/kg). A unit dose for intravenous administration may be in the range of 0.008 mg/kg (preferably 0.08 mg/kg) to 8.3 mg/kg (preferably 4.2 mg/kg) of a compound of the present invention. The unit dose may be administered to a human adult from 1 to 6 times per a day depending on the severity of the patient's symptoms.

Examples

Hereinbelow, the present invention is described in more detail by way of Examples, Test Examples and Formulation Examples.

When $CDCl_3$ is used as a solvent for measurement of hydrochloride compounds in the Examples, NMR data for corresponding free bases are shown. The free bases can be obtained by treating a small amount of a hydrochloride compound with an aqueous sodium hydrogen carbonate solution and performing extraction with ethyl acetate or dichloromethane.

(Example 1) (E)-4-(Acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-[2-(morpholin-4-yl)ethylidene]piperidine dihydrochloride (Hydrochloride of the compound of Compound No. 5-28)



(a) (E)-4-(t-Butyldimethylsilyloxy)-3-[(ethoxycarbonyl)methylidene]-1-(triphenylmethyl)piperidine

To a solution of (E)-3-[(ethoxycarbonyl)methylidene]-1-(triphenylmethyl)piperidin-4-ol (14.97 g) in N,N-dimethylformamide (130 ml) were added t-butyldimethylsilyl chloride (6.86 g), imidazole (3.34 g) and 4-dimethylaminopyridine (0.43 g) under ice cooling, and the resulting mixture was stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate and washed with a saturated aqueous sodium chloride solution, and the organic layer was dried over anhydrous sodium sulfate. The solvent was removed in vacuo, and the residue was purified by chromatography on a silica gel column (ethyl acetate / hexane = 1 / 19) to afford the title compound (16.38 g, yield 86%) as a colorless amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 0.01 (3H, s), 0.02 (3H, s), 0.90 (9H, s), 1.12 (3H, t, J=7.0), 1.59-1.74 (1H, m), 1.83-2.01 (3H, m), 3.00-3.12 (1H, m), 3.90 (1H, t, J=9.0), 3.96-4.15 (2H, m), 4.73 (1H, m), 6.06 (1H, s), 7.11-7.18 (3H, m), 7.20-7.28 (6H, m), 7.36-7.54 (6H, m).

(b) (E)-4-(t-Butyldimethylsilyloxy)-3-(2-hydroxyethylidene)-1-(triphenylmethyl)piperidine

To a solution of (E)-4-(t-butyldimethylsilyloxy)-3-[(ethoxycarbonyl)methylidene]-1-(triphenylmethyl)piperidine (15.14 g) obtained in (a) above in dichloromethane (110 ml) was added a 1.01N solution of diisobutylaluminum hydride in toluene (66.40 ml) at -70°C, and the resulting mixture was stirred at the same temperature for 3 hours. The reaction mixture was charged

with an aqueous ammonium chloride solution and then extracted with ethyl acetate. The extract was washed with a saturated aqueous sodium chloride solution, and the organic layer was dried over anhydrous sodium sulfate. The solvent was removed in vacuo, and the residue was purified by chromatography on a silica gel column (ethyl acetate / hexane = 1 / 3) to afford the title compound (13.22 g, yield 95%) as a colorless amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 0.01 (6H, s), 0.88 (9H, s), 1.62-2.00 (4H, m), 2.88-3.05 (1H, m), 3.51-3.71 (1H, m), 3.86 (1H, m), 4.07-4.24 (2H, m), 5.79 (1H, t, J=7.0), 7.11-7.33 (9H, m), 7.36-7.58 (6H, m).

(c) (E)-4-(t-Butyldimethylsilyloxy)-3-[2-(tosyloxy)ethylidene]-1-(triphenylmethyl)piperidine

To a solution of (E)-4-(t-butyldimethylsilyloxy)-3-(2-hydroxyethylidene)-1-(triphenylmethyl)piperidine (1.11 g) obtained in (b) above and p-toluenesulfonic anhydride (0.90 g) in dichloromethane (25 ml) was added triethylamine (0.37 ml) under ice cooling, and the resulting mixture was stirred at room temperature for 2.5 hours. The reaction mixture was charged with a saturated aqueous sodium chloride solution and then extracted with ethyl acetate. The extract was washed with a saturated aqueous sodium chloride solution, and the organic layer was dried over anhydrous sodium sulfate. The solvent was removed in vacuo to afford the title compound (1.64 g, quantitative yield) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : -0.04 (3H, s), -0.01 (3H, s), 0.86 (9H, s), 1.60-1.92 (4H, m), 2.47 (3H, s), 2.96 (1H, bs), 3.47 (1H, m), 3.79 (1H, m), 4.61 (2H, m), 5.65 (1H, t, J=7.5), 7.13-7.48 (17H, m), 7.73 (2H, d, J=9.0).

(d) (E)-4-(t-Butyldimethylsilyloxy)-3-[2-(morpholin-4-yl)ethylidene]-1-(triphenylmethyl)piperidine

To a solution of (E)-4-(t-butyldimethylsilyloxy)-3-[2-(tosyloxy)ethylidene]-1-(triphenylmethyl)piperidine (1.64 g) obtained in (c) above and morpholine (0.29 ml)

in a mixed solvent of N,N-dimethylformamide (25 ml) and dichloromethane (5 ml) was added potassium carbonate (0.34 g) under ice cooling, and the resulting mixture was stirred at room temperature overnight. The reaction mixture was charged with a saturated aqueous sodium chloride solution and then extracted with ethyl acetate. The extract was washed with a saturated aqueous sodium chloride solution, and the organic layer was dried over anhydrous sodium sulfate. The solvent was removed in vacuo, and the residue was purified by chromatography on a silica gel column (ethyl acetate / hexane = 2 / 3) to afford the title compound (1.01 g, yield: 80%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : -0.03 (3H, s), -0.02 (3H, s), 0.84 (9H, s), 1.74-2.06 (4H, m), 2.42 (4H, bs), 2.77-2.93 (1H, m), 2.99 (1H, dd, J=13.5, 6.5), 3.07 (1H, dd, J=13.5, 6.5), 3.38-3.56 (1H, m), 3.71 (4H, t, J=4.5), 3.87 (1H, m), 5.62 (1H, t, J=6.5), 7.11-7.30 (9H, m), 7.38-7.55 (6H, m).

(e) (E)-4-Hydroxy-3-[2-(morpholin-4-yl)ethylidene]-1-(triphenylmethyl)piperidine

To a solution of (E)-4-(t-butyldimethylsilyloxy)-3-[2-(morpholin-4-yl)ethylidene]-1-(triphenylmethyl)piperidine (1.00 g) obtained in (d) above in tetrahydrofuran (20 ml) was added tetrabutylammonium fluoride (0.99 g) under ice cooling, and the resulting mixture was stirred at room temperature for 14 hours. The reaction mixture was charged with water and then extracted with ethyl acetate. The extract was washed with a saturated aqueous sodium chloride solution, and the organic layer was dried over anhydrous sodium sulfate. The solvent was removed in vacuo, and the residue was purified by chromatography on a silica gel column (methanol / dichloromethane = 9 / 91) to afford the title compound (0.80 g, quantitative yield) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 1.74-1.86 (1H, m), 1.96-2.14 (2H, m), 2.45 (5H, bs), 2.59-2.69 (1H, m), 3.01 (2H, m), 3.10-3.34 (1H, m), 3.72 (4H, t, J=4.5), 3.98 (1H, m), 5.61 (1H, t, J=6.5), 7.11-7.32 (9H, m), 7.39-7.57 (6H, m).

(f) (E)-4-Hydroxy-3-[2-(morpholin-4-yl)ethylidene]piperidine dihydrochloride

To a solution of (E)-4-hydroxy-3-[2-(morpholin-4-yl)ethylidene]-1-(triphenylmethyl)piperidine (1.08 g) obtained in (e) above in dioxane (9 ml) was added a 4N solution of hydrogen chloride in dioxane (3 ml) under ice cooling, and the resulting mixture was stirred at room temperature for 15 minutes. The reaction mixture was evaporated in vacuo, and the residue was partitioned with water and ethyl acetate. The aqueous layer was removed in vacuo to afford the title compound (0.69 g, quantitative yield) as a pale yellow amorphous solid.

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm : 1.66-1.77 (1H, m), 1.95-2.07 (1H, m), 3.10 (4H, m), 3.21-3.65 (3H, m), 3.73-4.02 (6H, m), 4.06 (1H, d, J=13.5), 4.19 (1H, m), 5.90 (1H, t, J=8.0).

(g) (E)-1-[2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-hydroxy-3-[2-(morpholin-4-yl)ethylidene]piperidine

To a solution of (E)-4-hydroxy-3-[2-(morpholin-4-yl)ethylidene]piperidine dihydrochloride (0.65 g) obtained in (f) above and 2-bromo-2-(2-fluorophenyl)-1-cyclopropylethanone (0.73 g) in N,N-dimethylformamide (12 ml) was added triethylamine (1.16 ml) under ice cooling, and the resulting mixture was stirred at room temperature overnight. The reaction mixture was diluted with ethyl acetate and washed with water and a saturated aqueous sodium chloride solution, and the organic layer was dried over anhydrous sodium sulfate. The solvent was removed in vacuo, and the residue was purified by chromatography on a silica gel column (methanol / dichloromethane = 3 / 17) to afford the title compound (0.65 g, yield 74%) as a pale yellow amorphous solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm : 0.78-0.90 (2H, m), 0.96-1.09 (2H, m), 1.66-1.78 (1H, m), 1.95-2.04 (1H, m), 2.15-2.25 (1H, m), 2.42 (4H, bs), 2.45-2.55 (1H, m), 2.78 and 3.00 (total 1H, each d, J=12.5), 2.79-2.88 (1H, m), 2.95 (2H, d, J=6.5), 3.31 and 3.45 (total 1H, each d, J=12.5), 3.70 (4H, t, J=4.5), 4.09 and 4.13

(total 1H, each m), 4.69 and 4.71 (total 1H, each s), 5.59 and 5.61 (total 1H, each t, J=6.5), 7.11 (1H, m), 7.17 (1H, m), 7.29-7.36 (1H, m), 7.38-7.45 (1H, m).

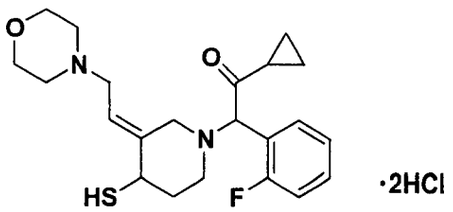
(h) (E)-4-(Acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-[2-(morpholin-4-yl)ethylidene]piperidine dihydrochloride

To a solution of (E)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-hydroxy-3-[2-(morpholin-4-yl)ethylidene]piperidine (890 mg) obtained in (g) above in toluene (15 ml) were added thioacetic acid (0.33 ml) and N,N-dimethylformamide dineopentyl acetal (1.92 ml) under ice cooling, and the resulting mixture was stirred at room temperature for 3 hours. The reaction mixture was diluted with ethyl acetate and washed with a saturated aqueous sodium chloride solution, and the organic layer was dried over anhydrous sodium sulfate. The solvent was removed in vacuo, and the residue was purified by chromatography on a silica gel column (methanol / dichloromethane = 1 / 19) to afford the free form (393 mg, yield 38%) of the title compound as a colorless amorphous solid. To a solution of a part of this compound (88 mg) in dioxane (4 ml) was added a 4N solution of hydrogen chloride in dioxane (0.25 ml) at room temperature, and the solvent was removed in vacuo to afford the title compound (111 mg, quantitative yield) as a colorless amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 0.76-0.90 (2H, m), 0.95-1.10 (2H, m), 1.74-1.85 (1H, m), 2.06-2.24 (2H, m), 2.28 and 2.29 (total 3H, each s), 2.38 (4H, bs), 2.47-2.79 (2H, m), 2.80 and 3.06 (total 1H, each d, J=12.5), 2.88 and 2.94 (total 2H, each d, J=6.5), 3.29 and 3.37 (total 1H, each d, J=12.5), 3.69 (4H, m), 4.30 and 4.33 (total 1H, each t, J=4.5), 4.68 and 4.70 (total 1H, each s), 5.64 (1H, t, J=6.5), 7.07-7.20 (2H, m), 7.29-7.43 (2H, m);

IR (KBr, cm^{-1}) : 1700, 1494.

(Example 2) (E)-1-[2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-[2-(morpholin-4-yl)ethylidene]-4-sulfanylpiperidine dihydrochloride (Hydrochloride of the compound of Compound No. 5-27)



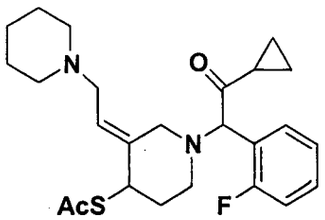
To a solution of (E)-4-(acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-[2-(morpholin-4-yl)ethylidene]piperidine (180 mg) obtained in Example 1 (h) in methanol (4 ml) was added potassium carbonate (48 mg) under ice cooling, and the resulting mixture was stirred at room temperature for 15 minutes. The reaction mixture was diluted with ethyl acetate and washed with a saturated aqueous sodium chloride solution, and the organic layer was dried over anhydrous sodium sulfate. The solvent was removed in vacuo, and the residue was purified using a preparative HPLC (YMC-Pack ODS-A; YMC, eluent: acetonitrile / 0.024N hydrochloric acid = 15 / 85) to afford the title compound (83 mg, yield 50%) as a colorless amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 0.77-0.91 (2H, m), 0.95-1.10 (2H, m), 1.67-1.77 (1H, m), 2.12-2.26 (2H, m), 2.39 (4H, bs), 2.46-2.95 (3H, m), 2.88 and 3.20 (total 2H, each d, J=7.0), 3.13 and 3.37 (total 1H, each d, J=12.5), 3.69 (4H, m), 3.80 (1H, m), 4.71 and 4.73 (total 1H, each s), 5.59 and 5.62 (total 1H, each t, J=7.0), 7.07-7.21 (2H, m), 7.28-7.37 (1H, m), 7.39-7.45 (1H, m);

IR (KBr, cm^{-1}) : 2556, 1712, 1494.

(Example 3)

(E)-4-(Acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-[2-(piperidin-1-yl)ethylidene]piperidine (Compound of Compound No. 5-2)



(a) (E)-4-(t-Butyldimethylsilyloxy)-3-[2-(piperidin-1-yl)ethylidene]-1-(triphenylmethyl)piperidine

The title compound was synthesized in a yield of 67% as a colorless oil using piperidine instead of morpholine by conducting a reaction similar to that mentioned in Example 1 (d).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : -0.01 (6H, s), 0.81 (9H, s), 1.37-1.61 (8H, m), 1.74-1.93 (2H, m), 2.31-2.39 (4H, m), 2.75-3.07 (4H, m), 3.86 (1H, m), 5.63 (1H, t, J=6.5), 7.11-7.18 (3H, m), 7.21-7.28 (6H, m), 7.41-7.51 (6H, m).

(b) (E)-4-Hydroxy-3-[2-(piperidin-1-yl)ethylidene]-1-(triphenylmethyl)piperidine

The title compound was synthesized in a quantitative yield as a colorless oil using (E)-4-(t-butyldimethylsilyloxy)-3-[2-(piperidin-1-yl)ethylidene]-1-(triphenylmethyl)piperidine obtained in (a) above by conducting a reaction similar to that mentioned in Example 1 (e).

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm : 1.48-2.11 (14H, m), 2.69-3.46 (4H, m), 4.01 (1H, m), 5.89 (1H, t, J=5.0), 7.15-7.21 (3H, m), 7.24-7.31 (6H, m), 7.40-7.51 (6H, m).

(c) (E)-4-Hydroxy-3-[2-(piperidin-1-yl)ethylidene]piperidine bis(hydrogen trifluoroacetate)

To a solution of (E)-4-hydroxy-3-[2-(piperidin-1-yl)ethylidene]-1-(triphenylmethyl)piperidine (412 mg) obtained in (b) above in dichloromethane (10 ml) was added trifluoroacetic acid (0.21 ml) under ice cooling, and the resulting mixture was stirred at room temperature for 3 hours. To the rection mixture was added trifluoroacetic acid (0.21 ml), and the resulting mixture was stirred at room

temperature for further 1 hour. To the reaction mixture was added methanol (5 ml), and the resulting mixture was evaporated in vacuo. The residue was partitioned with water and ethyl acetate, and the aqueous layer was removed in vacuo to afford the title compound (403 mg, quantitative yield) as a pale yellow amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 1.35-1.49 (2H, m), 1.82-2.21 (6H, m), 2.73-2.82 (2H, m), 3.45-3.88 (7H, m), 4.12 (1H, d, J=13.0), 4.31-4.36 (1H, m), 6.01 (1H, t, J=8.0).

(d) (E)-1-[2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-hydroxy-3-[2-(piperidin-1-yl)ethylidene]piperidine

The title compound was synthesized in a yield of 60% as a pale yellow oil using (E)-4-hydroxy-3-[2-(piperidin-1-yl)ethylidene]piperidine bis(hydrogen trifluoroacetate) obtained in (c) above by conducting a reaction similar to that mentioned in Example 1 (g).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 0.79-1.10 (4H, m), 1.38-1.84 (8H, m), 1.93-2.03 (1H, m), 2.21-2.55 (6H, m), 2.78-3.01 (3H, m), 3.32 and 3.41 (total 1H, each d, J=12.5), 4.08-4.14 (1H, m), 4.67 and 4.69 (total 1H, each s), 5.63 and 5.64 (total 1H, each t, J=7.0), 7.07-7.19 (2H, m), 7.28-7.46 (2H, m).

(e) (E)-4-(Acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-[2-(piperidin-1-yl)ethylidene]piperidine

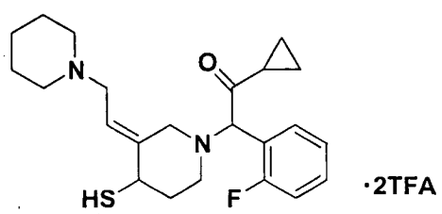
To a solution of triphenylphosphine (290 mg) in tetrahydrofuran (4.5 ml) under a nitrogen gas stream was added a 40% solution of diisopropyl azodicarboxylate in toluene (0.59 ml) at -10°C, and the resulting mixture was stirred at the same temperature for 1 hour. Subsequently, to a reaction mixture were added dropwise a solution of (E)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-hydroxy-3-[2-(piperidin-1-yl)ethylidene]piperidine (211 mg) in tetrahydrofuran (1.5 ml) obtained in (d) above and thioacetic acid (0.14 ml), and further the resulting mixture was stirred at room temperature for 22 hours. The reaction mixture was

evaporated in vacuo, and the residue was purified by chromatography on a silica gel column (methanol / dichloromethane = 1 / 49) to afford the title compound (138 mg, yield 57%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 0.78-0.90 (2H, m), 0.96-1.08 (2H, m), 1.41-1.50 (2H, m), 1.59-1.71 (4H, m), 1.75-1.84 (1H, m), 2.07-2.23 (2H, m), 2.28 and 2.29 (total 3H, each s), 2.40-3.10 (9H, m), 3.16-3.39 (1H, m), 4.29 and 4.33 (total 1H, each t, J=4.5), 4.68 and 4.72 (total 1H, each s), 5.69 (1H, t, J=6.5), 7.08-7.21 (2H, m), 7.29-7.41 (2H, m);

IR (liquid film, cm^{-1}) : 1696, 1488.

(Example 4) (E)-1-[2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-[2-(piperidin-1-yl)ethylidene]-4-sulfanylpiperidine bis(hydrogen trifluoroacetate) (Trifluoroacetate of the compound of Compound No. 5-1)

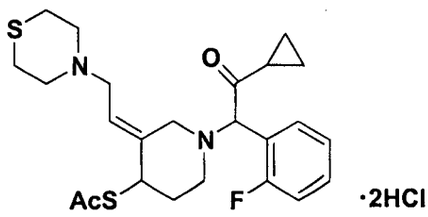


The title compound was synthesized in a yield of 11% as a colorless oil using (E)-4-(acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-[2-(piperidin-1-yl)ethylidene]piperidine obtained in Example 3 (e) by conducting a reaction similar to that mentioned in Example 2.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 0.76-0.93 (2H, m), 0.99-1.10 (2H, m), 1.31-1.47 (2H, m), 1.63-2.07 (7H, m), 2.22-2.32 (1H, m), 2.56-3.87 (10H, m), 4.93 and 4.98 (total 1H, each s), 5.74 (1H, t, J=6.5), 7.15-7.31 (3H, m), 7.36-7.46 (1H, m);

MS (FAB) m/z : 403 $(M+H)^+$.

(Example 5) (E)-4-(Acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-[2-(thiomorpholin-4-yl)ethylidene]piperidine dihydrochloride (Hydrochloride of the compound of Compound No. 5-30)



(a) (E)-4-(t-Butyldimethylsilyloxy)-3-[2-(thiomorpholin-4-yl)ethylidene]-1-(triphenylmethyl)piperidine

The title compound was synthesized in a yield of 62% as a colorless oil using thiomorpholine instead of morpholine by conducting a reaction similar to that mentioned in Example 1 (d).

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm : -0.03 (3H, s), -0.02 (3H, s), 0.84 (9H, s), 1.76-1.95 (4H, m), 2.61-2.72 (7H, m), 2.77-2.91 (1H, m), 2.98-3.10 (2H, m), 3.31-3.66 (2H, m), 3.87 (1H, m), 5.56-5.63 (1H, m), 7.10-7.19 (3H, m), 7.21-7.35 (6H ,m), 7.38-7.53 (6H, m).

(b) (E)-4-Hydroxy-3-[2-(thiomorpholin-4-yl)ethylidene]-1-(triphenylmethyl)piperidine .

The title compound was synthesized in a yield of 99% as a pale yellow amorphous solid using (E)-4-(t-butyldimethylsilyloxy)-3-[2-(thiomorpholin-4-yl)ethylidene]-1-(triphenylmethyl)piperidine obtained in (a) above by conducting a reaction similar to that mentioned in Example 1 (e).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 1.61-1.87 (2H, m), 1.98-2.14 (2H, m), 2.60-2.80 (8H, m), 2.98-3.06 (2H, m), 3.35-3.46 (2H, m), 3.93-4.02 (1H, m), 5.58 (1H, t, J=6.0), 7.12-7.20 (3H, m), 7.22-7.32 (6H, m), 7.38-7.56 (6H, m).

(c) (E)-4-Hydroxy-3-[2-(thiomorpholin-4-yl)ethylidene]piperidine bis(hydrogen acetate)

To a solution of (E)-4-hydroxy-3-[2-(thiomorpholin-4-yl)ethylidene]-1-(triphenylmethyl)piperidine (4.91 g) obtained in (b) above in dichloromethane (100 ml) was added acetic acid (44 ml) at room temperature, and the resulting mixture was

refluxed for 1 hour. The reaction mixture was evaporated in vacuo, and the residue was purified by chromatography on a silica gel column on a silica gel column (methanol / dichloromethane = 1 / 4) to afford the title compound (3.56 g, yield 98%) as a pale brown crystal.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 1.61-1.70 (1H, m), 1.97-2.02 (1H, m), 2.62-2.77 (8H, m), 2.82-2.90 (1H, m), 3.02-3.08 (2H, m), 3.17-3.23 (2H, m), 3.74-3.78 (1H, m), 4.15-4.20 (1H, m), 5.58 (1H, t, J=6.0).

(d) (E)-1-[2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-hydroxy-3-[2-(thiomorpholin-4-yl)ethylidene]piperidine

The title compound was synthesized in a yield of 65% as a pale brown amorphous solid using (E)-4-hydroxy-3-[2-(thiomorpholin-4-yl)ethylidene]piperidine bis(hydrogen acetate) obtained in (c) above by conducting a reaction similar to that mentioned in Example 1 (g).

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm : 0.76-1.12 (4H, m), 1.61-1.82 (1H, m), 1.94-2.04 (1H, m), 2.14-2.24 (1H, m), 2.44-2.54 (1H, m), 2.59-2.73 (8H, m), 2.76 and 2.98 (total 1H, each d, J=12.5), 2.77-2.89 (1H, m), 2.96 (2H, d, J=7.0), 3.30 and 3.45 (total 1H, each d, J=12.5), 4.05-4.16 (1H, m), 4.69 and 4.70 (total 1H, each s), 5.54-5.62 (1H, m), 7.06-7.22 (2H, m), 7.28-7.46 (2H, m).

(e) (E)-4-(Acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-[2-(thiomorpholin-4-yl)ethylidene]piperidine dihydrochloride

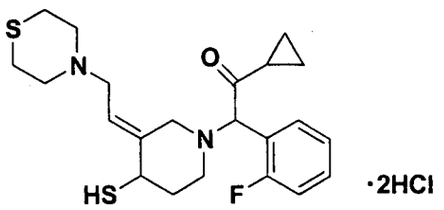
The title compound was synthesized in a yield of 26% as a pale yellow powder crystal using (E)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-hydroxy-3-[2-(thiomorpholin-4-yl)ethylidene]piperidine obtained in (d) above by conducting a reaction similar to that mentioned in Example 1 (h).

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm : 0.74-1.12 (4H, m), 1.50-1.62 (1H, m), 1.74-1.85 (1H, m), 2.06-2.27 (2H, m), 2.29 and 2.30 (total 3H, each s), 2.44-2.72 (9H, m), 2.77 and 3.04 (total 1H, each d, J=12.5), 2.84-2.98 (2H, m), 3.27 and 3.35 (total

1H, each d, J=12.5), 4.26-4.36 (1H, m), 4.67 and 4.70 (total 1H, each s), 5.57-5.64 (1H, m), 7.07-7.22 (2H, m), 7.28-2.45 (2H, m);

MS (FAB) m/z : 463 $(M+H)^+$.

(Example 6) (E)-1-[2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-sulfanyl-3-[2-(thiomorpholin-4-yl)ethylidene]piperidine dihydrochloride (Hydrochloride of the compound of Compound No. 5-29)

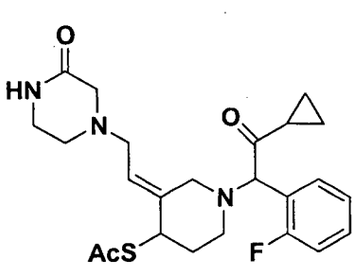


The title compound was synthesized in a yield of 94% as a pale yellow powder crystal using (E)-4-(acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-[2-(thiomorpholin-4-yl)ethylidene]piperidine obtained in Example 5 (e) by conducting a reaction similar to that mentioned in Example 2.

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm : 0.77-1.12 (4H, m), 1.68-1.77 (1H, m), 2.11-2.27 (2H, m), 2.55-2.71 (9H, m), 2.72-2.85 (1H, m), 2.86-2.97 (2H, m), 3.13-3.24 (1H, m), 3.11 and 3.36 (total 1H, each d, J=12.5), 3.70-3.82 (1H, m), 4.72 and 4.70 (total 1H, each s), 5.51-5.63 (1H, m), 7.07-7.21 (2H, m), 7.29-7.45 (2H, m);

MS (FAB) m/z : 418 $(M+H)^+$.

(Example 7) (E)-4-(Acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-[2-(3-oxopiperazin-1-yl)ethylidene]piperidine (Compound of Compound No. 5-88)



(a) (E)-4-(t-Butyldimethylsilyloxy)-3-[2-(3-oxopiperazin-1-yl)ethylidene]-1-(triphenylmethyl)piperidine

The title compound was synthesized in a yield of 66% as a pale brown oil using 2-oxopiperazine instead of morpholine by conducting a reaction similar to that mentioned in Example 1 (d).

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm : 0.02 (6H, s), 0.85 (9H, s), 1.72-1.95 (4H, m), 2.60-2.66 (2H, m), 2.80-3.19 (5H, m), 3.25-3.47 (3H, m), 3.82-3.90 (1H, m), 5.57-5.64 (1H, m), 7.13-7.21 (3H, m), 7.22-7.32 (6H, m), 7.39-7.57 (6H, m).

(b) (E)-4-Hydroxy-3-[2-(3-oxopiperazin-1-yl)ethylidene]-1-(triphenylmethyl)piperidine

The title compound was synthesized in a yield of 96% as a pale yellow oil using (E)-4-(t-butyldimethylsilyloxy)-3-[2-(3-oxopiperazin-1-yl)ethylidene]-1-(triphenylmethyl)piperidine obtained in (a) above by conducting a reaction similar to that mentioned in Example 1 (e)

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 1.75-2.12 (4H, m), 2.62-2.69 (2H, m), 3.02-3.16 (2H, m), 3.32-3.42 (6H, m), 3.92-4.01 (1H, m), 5.57-5.62 (1H, m), 7.12-7.20 (3H, m), 7.22-7.31 (6H, m), 7.38-7.56 (6H, m).

(c) (E)-4-Hydroxy-3-[2-(3-oxopiperazin-1-yl)ethylidene]piperidine bis(hydrogen acetate)

The title compound was synthesized in a yield of 85% as a pale brown crystal using (E)-4-hydroxy-3-[2-(3-oxopiperazin-1-yl)ethylidene]-1-(triphenylmethyl)piperidine obtained in (b) above by conducting a reaction similar to that mentioned in Example 5 (c).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 1.59-1.73 (2H, m), 2.57-2.61 (1H, m), 2.64-2.70 (2H, m), 3.08-3.25 (5H, m), 3.29-3.39 (3H, m), 3.73-3.78 (1H, m), 4.16-4.22 (1H, m), 5.56-5.63 (1H, m).

(d) (E)-1-[2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-hydroxy-3-[2-(3-oxopiperazin-1-yl)ethylidene]piperidine

The title compound was synthesized in a yield of 63% as a pale brown amorphous solid using (E)-4-hydroxy-3-[2-(3-oxopiperazin-1-yl)ethylidene]piperidine bis(hydrogen acetate) obtained in (c) above, by conducting a reaction similar to that mentioned in Example 1 (g).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 0.76-1.10 (4H, m), 1.62-1.80 (2H, m), 1.94-2.05 (1H, m), 2.12-2.23 (1H, m), 2.43-2.53 (1H, m), 2.57-2.68 (2H, m), 2.73 and 2.98 (total 1H, each d, J=12.5), 2.78-2.92 (1H, m), 2.94-3.08 (2H, m), 3.28-3.42 (3H, m), 3.45-3.52 (1H, m), 4.05-4.19 (1H, m), 4.67-4.74 (1H, m), 5.53-5.65 (1H, m), 7.06-7.23 (2H, m), 7.28-7.48 (2H, m).

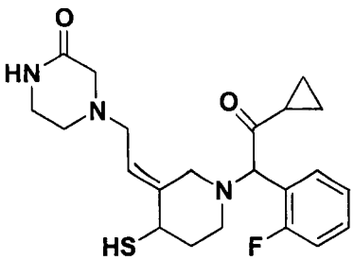
(e) (E)-4-(Acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-[2-(3-oxopiperazin-1-yl)ethylidene]piperidine

The title compound was synthesized in a yield of 22% as a pale yellow amorphous solid using (E)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-hydroxy-3-[2-(3-oxopiperazin-1-yl)ethylidene]piperidine obtained in (d) above by conducting a reaction similar to that mentioned in Example 1 (h).

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm : 0.69-1.10 (4H, m), 1.73-1.86 (1H, m), 2.06-2.26 (2H, m), 2.29 and 2.30 (total 3H, each s), 2.44-2.72 (4H, m), 2.74-2.85 (1H, m), 2.95 and 3.01 (total 2H, each d, J=7.0), 3.03-3.10 (2H, m), 3.28 and 3.38 (total 1H, each d, J=12.5), 3.29-3.38 (2H, m), 4.26-4.36 (1H, m), 4.69 and 4.71 (total 1H, each s), 5.62 (1H, t, J=7.0), 5.78 (1H, bs), 7.07-7.24 (2H, m), 7.28-7.48 (2H, m);

MS (FAB) m/z : 460 $(M+H)^+$.

(Example 8) (E)-1-[2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-[2-(3-oxopiperazin-1-yl)ethylidene]-4-sulfanylpiperidine dihydrochloride (Hydrochloride of the compound of Compound No. 5-87)



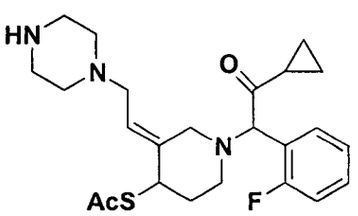
·2HCl

The title compound was synthesized in a yield of 91% as a pale yellow powder crystal using (E)-4-(acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-[2-(3-oxopiperazin-1-yl)ethylidene]piperidine obtained in Example 7 (e) by conducting a reaction similar to that mentioned in Example 2.

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm : 0.75-1.10 (4H, m), 1.69-1.78 (1H, m), 2.11-2.28 (2H, m), 2.53-2.70 (3H, m), 2.73-2.86 (1H, m), 2.92-3.22 (4H, m), 3.30-3.45 (3H, m), 3.66-3.82 (1H, m), 4.72 and 4.73 (total 1H, each s), 5.52-5.64 (1H, m), 7.07-7.22 (2H, m), 7.29-7.44 (2H, m);

MS (FAB) m/z : 418 $(M+H)^+$.

(Example 9) (E)-4-(Acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-[2-(piperazin-1-yl)ethylidene]piperidine trihydrochloride (Hydrochloride of the compound of Compound No. 5-32)



·3HCl

(a) (E)-3-{2-[4-(t-Butoxycarbonyl)piperazin-1-yl]ethylidene}-4-(t-butyldimethylsilyloxy)-1-(triphenylmethyl)piperidine

The title compound was synthesized in a yield of 61% as a colorless amorphous solid using 1-(t-butoxycarbonyl)piperazine instead of morpholine by conducting a reaction similar to that mentioned in Example 1 (d).

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm : -0.03 (3H, s), -0.02 (3H, s), 0.84 (9H, s), 1.46 (9H, s), 1.73-1.96 (3H, m), 2.30-2.41 (4H, m), 2.74-3.12 (4H, m), 3.36-3.46 (4H, m), 3.47-3.52 (1H, m), 3.81-3.92 (1H, m), 5.66 (1H, t, J=6.0), 7.10-7.19 (3H, m), 7.20-7.32 (6H, m), 7.34-7.57 (6H, m).

(b) (E)-3-{2-[4-(t-Butoxycarbonyl)piperazin-1-yl]ethylidene}-4-hydroxy-1-(triphenylmethyl)piperidine

The title compound was synthesized in a yield of 99% as a colorless amorphous solid using (E)-3-{2-[4-(t-butoxycarbonyl)piperazin-1-yl]ethylidene}-4-(t-butyldimethylsilyloxy)-1-(triphenylmethyl)piperidine obtained in (a) above by conducting a reaction similar to that mentioned in Example 1 (e).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 1.47 (9H, s), 1.57-1.84 (4H, m), 2.32-2.45 (4H, m), 2.92-3.08 (2H, m), 3.36-3.52 (6H, m), 3.93-4.03 (1H, m), 5.61 (1H, t, J=6.0), 7.11-7.20 (3H, m), 7.21-7.33 (6H, m), 7.40-7.55 (6H, m).

(c) (E)-3-{2-[4-(t-Butoxycarbonyl)piperazin-1-yl]ethylidene}-4-hydroxypiperidine bis(hydrogen acetate)

The title compound was synthesized in a yield of 99% as a pale brown crystal using (E)-3-{2-[4-(t-butoxycarbonyl)piperazin-1-yl]ethylidene}-4-hydroxy-1-(triphenylmethyl)piperidine obtained in (b) above by conducting a reaction similar to that mentioned in Example 5 (c).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 1.45 (9H, s), 1.56-1.73 (1H, m), 1.86-2.04 (1H, m), 2.32-2.46 (4H, m), 2.80-2.91 (1H, m), 2.94-3.07 (2H, m), 3.17-3.29 (2H, m), 3.35-3.46 (4H, m), 3.51 and 3.74 (total 1H, each d, J=13.5), 4.03-4.11 (1H, m), 5.57-5.66 (1H, m).

(d) (E)-3-{2-[4-(t-Butoxycarbonyl)piperazin-1-yl]ethylidene}-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-hydroxypiperidine

The title compound was synthesized in a yield of 64% as a pale brown amorphous solid using (E)-3-{2-[4-(t-butoxycarbonyl)piperazin-1-yl]ethylidene}-4-

hydroxypiperidine bis(hydrogen acetate) obtained in (c) above by conducting a reaction similar to that mentioned in Example 1 (g).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 0.76-1.11 (4H, m), 1.46 (9H, s), 1.64-1.81 (2H, m), 1.93-2.04 (1H, m), 2.13-2.25 (1H, m), 2.28-2.40 (4H, m), 2.44-2.55 (1H, m), 2.76 and 2.99 (total 1H, each d, J=13.0), 2.78-2.90 (1H, m), 2.90-2.98 (1H, m), 3.31 and 3.45 (total 1H, each d, J=13.0), 3.37-3.45 (4H, m), 4.04-4.18 (1H, m), 4.69 and 4.70 (total 1H, each s), 5.55-5.64 (1H, m), 7.06-7.21 (2H, m), 7.27-7.36 (1H, m), 7.37-7.45 (1H, m).

(e) (E)-4-(Acetylsulfanyl)-3-{2-[4-(t-butoxycarbonyl)piperazin-1-yl]ethylidene}-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]piperidine

The title compound was synthesized in a yield of 36% as a brown oil using (E)-3-{2-[4-(t-butoxycarbonyl)piperazin-1-yl]ethylidene}-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-hydroxypiperidine obtained in (d) above by conducting a reaction similar to that mentioned in Example 1 (h).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 0.76-1.10 (4H, m), 1.46 (9H, s), 1.75-1.84 (1H, m), 2.07-2.28 (2H, m), 2.22-2.37 (4H, m), 2.28 and 2.29 (total 3H, each s), 2.47-2.62 (1H, m), 2.65-2.80 (1H, m), 2.79 and 3.05 (total 1H, each d, J=13.0), 2.84-2.90 (1H, m), 2.91-2.96 (1H, m), 3.29 and 3.36 (total 1H, each d, J=13.0), 3.36-3.45 (4H, m), 4.27-4.36 (1H, m), 4.67 and 4.69 (total 1H, each s), 5.63 (1H, t, J=6.5), 7.08-7.20 (2H, m), 7.28-7.36 (1H, m), 7.40 (1H, m).

(f) (E)-4-(Acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-[2-(piperazin-1-yl)ethylidene]piperidine trihydrochloride

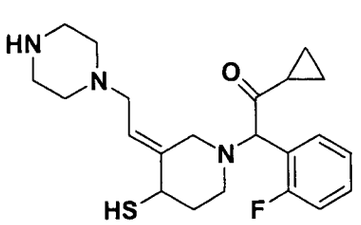
To a solution of (E)-4-(acetylsulfanyl)-3-{2-[4-(t-butoxycarbonyl)piperazin-1-yl]ethylidene}-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]piperidine (1.06 g) obtained in (e) above in dioxane (21 ml) was added a 4N solution of hydrogen chloride in dioxane (24 ml) under ice cooling, and the resulting mixture was stirred at

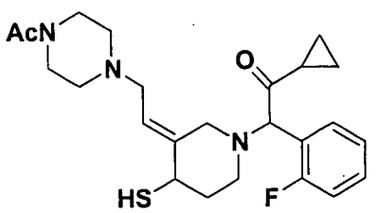
room temperature for 3 hours. The reaction mixture was evaporated in vacuo to afford the title compound (1.25 g, quantitative yield) as a pale yellow crystal.

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm : 0.76-1.10 (4H, m), 1.62-1.85 (2H, m), 2.09-2.25 (2H, m), 2.28 (3H, s), 2.31-2.45 (4H, m), 2.47-2.62 (1H, m), 2.64-2.81 (1H, m), 2.80 and 3.05 (total 1H, each d, J=12.5), 2.84-2.97 (4H, m), 3.29 and 3.35 (total 1H, each d, J=12.5), 3.40-3.67 (1H, m), 4.26-4.36 (1H, m), 4.67 and 4.69 (total 1H, each s), 5.64 (1H, t, J=7.0), 7.07-7.21 (2H, m), 7.28-7.45 (2H, m);

MS (FAB) m/z : 446 $(M+H)^+$.

(Example 10) (E)-1-[2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-[2-(piperazin-1-yl)ethylidene]-4-sulfanylpiperidine (Compound of Compound No. 5-31) and (E)-3-[2-(4-acetylpiperazin-1-yl)ethylidene]-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-sulfanylpiperidine (Compound of Compound No. 5-33)





Both title compounds were synthesized using (E)-4-(acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-[2-(piperazin-1-yl)ethylidene]piperidine obtained in Example 9 (f) by conducting a reaction similar to that mentioned in Example 2.

(E)-1-[2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-[2-(piperazin-1-yl)ethylidene]-4-sulfanylpiperidine having a high polarity: a pale yellow oil, yield 12%.

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm : 0.77-1.09 (4H, m), 1.67-1.76 (2H, m), 2.12-2.26 (2H, m), 2.29-2.43 (4H, m), 2.55-2.67 (1H, m), 2.70-2.82 (1H, m), 2.83-2.89 (4H, m), 2.90-2.95 (1H, m), 3.14 and 3.35 (total 1H, each d, J=12.5), 3.43-3.68

(1H, m), 3.72-3.83 (1H, m), 4.70 and 4.71 (total 1H, each s), 5.56-5.66 (1H, m), 7.06-7.21 (2H, m), 7.27-7.46 (2H, m);

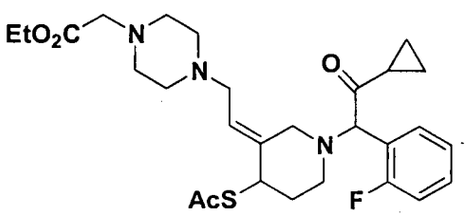
MS (FAB) m/z : 404 $(M+H)^+$.

(E)-3-[2-(4-Acetylpiperazin-1-yl)ethylidene]-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-sulfanylpiperidine having a low polarity: a colorless oil, yield 46%.

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm : 0.75-1.09 (4H, m), 1.69-1.77 (1H, m), 2.08 (3H, s), 2.12-2.26 (2H, m), 2.27-2.43 (4H, m), 2.54-2.69 (1H, m), 2.73-2.85 (1H, m), 2.87-2.97 (2H, m), 3.08 and 3.37 (total 1H, each d, J=12.5), 3.13-3.24 (1H, m), 3.41-3.67 (4H, m), 3.69-3.82 (1H, m), 4.71 and 4.73 (total 1H, each s), 5.53-5.64 (1H, m), 7.08-7.20 (2H, m), 7.28-7.44 (2H, m);

MS (FAB) m/z : 446 $(M+H)^+$.

(Example 11) (E)-4-(Acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{2-[4-(ethoxycarbonylmethyl)piperazin-1-yl]ethylidene}piperidine (Compound of Compound No. 5-46)



(a) (E)-1-[2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-hydroxy-3-[2-(piperazin-1-yl)ethylidene]piperidine trihydrochloride

The title compound was synthesized in a yield of 99% as a pale yellow powder crystal using (E)-3-{2-[4-(t-butoxycarbonyl)piperazin-1-yl]ethylidene}-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-hydroxypiperidine obtained in Example 9 (d) by conducting a reaction similar to that mentioned in Example 9 (f).

^{1}H NMR (400 MHz, DMSO-d_6) δ ppm : 0.89-1.15 (4H, m), 1.74-1.96 (2H, m), 2.00-2.15 (1H, m), 2.82-4.25 (15H, m), 5.94-6.19 (2H, m), 7.40-7.54 (2H, m), 7.64-7.84 (2H, m).

(b) (E)-1-[2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{2-[4-(ethoxycarbonylmethyl)piperazin-1-yl]ethylidene}-4-hydroxypiperidine

To a suspension of (E)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-hydroxy-3-[2-(piperazin-1-yl)ethylidene]piperidine trihydrochloride (1.14 g) obtained in (a) above in acetonitrile (35 ml) were added ethyl bromoacetate (0.31 ml) and triethylamine (1.92 ml) under ice cooling, and the resulting mixture was stirred at room temperature for 1 hour. After the reaction mixture was evaporated in vacuo, water was poured thereto and the mixture was extracted with a mixed solvent of dichloromethane and isopropanol. The organic layer was washed with a saturated aqueous sodium chloride solution and dried over anhydrous sodium sulfate. The solvent was removed in vacuo, and the residue was purified by chromatography on a silica gel column (methanol / dichloromethane = 1 / 9) to afford the title compound (0.71 g, yield 66%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 0.77-0.90 (2H, m), 0.95-1.08 (2H, m), 1.28 (3H, t, J=7.0), 1.65-1.80 (2H, m), 1.94-2.03 (1H, m), 2.16-2.25 (1H, m), 2.41-2.70 (8H, m), 2.75-2.88 (2H, m), 2.96-3.02 (2H, m), 3.20 (2H, s), 3.30 and 3.44 (total 1H, each d, J=12.5), 4.06-4.15 (1H, m), 4.19 (2H, q, J=7.0), 4.68 and 4.70 (total 1H, each s), 5.58-5.66 (1H, m), 7.07-7.21 (2H, m), 7.28-7.45 (2H, m).

(c) (E)-4-(Acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{2-[4-(ethoxycarbonylmethyl)piperazin-1-yl]ethylidene}piperidine

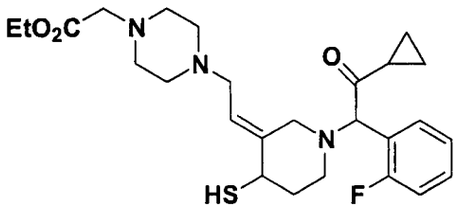
The title compound was synthesized in a yield of 23% as a pale brown oil using (E)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{2-[4-(ethoxycarbonylmethyl)piperazin-1-yl]ethylidene}-4-hydroxypiperidine obtained in (b) above by conducting a reaction similar to that mentioned in Example 1 (h).

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm : 0.77-1.09 (4H, m), 1.27 (3H, t, J=7.0), 1.75-1.83 (1H, m), 2.06-2.24 (2H, m), 2.28 (3H, s), 2.37-2.64 (8H, m), 2.65-2.81 (2H, m), 2.79 and 3.03 (total 1H, each d, J=12.5), 2.85-2.90 (1H, m), 2.92-2.98 (1H, m),

3.19 (2H, s), 3.28 and 3.34 (total 1H, each d, J=12.5), 4.19 (2H, q, J=7.0), 4.26-4.35 (1H, m), 4.66 and 4.68 (total 1H, each s), 5.61-5.67 (1H, m), 7.06-7.20 (2H, m), 7.29-7.43 (2H, m);

MS (FAB) m/z : 532 $(M+H)^+$.

(Example 12) (E)-1-[2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{2-[4-(ethoxycarbonylmethyl)piperazin-1-yl]ethylidene}-4-sulfanylpiperidine (Compound of Compound No. 5-45)

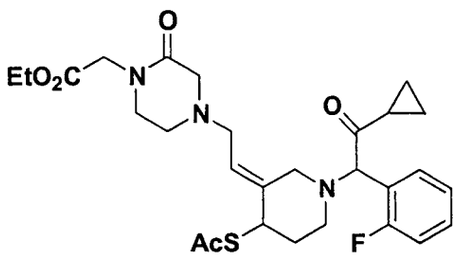


To a solution of (E)-4-(acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{2-[4-(ethoxycarbonylmethyl)piperazin-1-yl]ethylidene}piperidine (111 mg) obtained in Example 11 (c) in ethanol (3 ml) was added potassium carbonate (289 mg) under ice cooling, and the resulting mixture was stirred at room temperature for 2 hours. After the reaction mixture was poured into water and extracted with dichloromethane, the organic layer was dried over anhydrous sodium sulfate. The solvent was removed in vacuo to afford the title compound (77 mg, yield 75%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 0.75-1.09 (4H, m), 1.27 (3H, t, J=7.0), 1.66-1.76 (1H, m), 2.09-2.26 (2H, m), 2.35-2.67 (8H, m), 2.69-2.84 (1H, m), 2.86-2.91 (1H, m), 2.91-2.98 (1H, m), 3.11 and 3.35 (total 1H, each d, J=12.5), 3.18 (2H, s), 3.48 (2H, s), 3.68-3.81 (1H, m), 4.17 (2H, q, J=7.0), 4.68 and 4.69 (total 1H, each s), 5.52-5.64 (1H, m), 7.02-7.19 (2H, m), 7.23-7.43 (2H, m);

MS (FAB) m/z : 490 $(M+H)^+$.

(Example 13) (E)-4-(Acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{2-[4-(ethoxycarbonylmethyl)-3-oxopiperazin-1-yl]ethylidene}piperidine (Compound of Compound No. 5-102)



(a) (E)-4-(t-Butyldimethylsilyloxy)-3-{2-[4-(ethoxycarbonylmethyl)-3-oxopiperazin-1-yl]ethylidene}-1-(triphenylmethyl)piperidine

The title compound was synthesized in a yield of 13% as a pale yellow amorphous solid using 1-(ethoxycarbonylmethyl)-2-oxo-piperazine hydrochloride instead of morpholine by conducting a reaction similar to that mentioned in Example 1 (d).

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm : -0.01 (3H, s), -0.02 (3H, s), 0.85 (9H, s), 1.28 (3H, t, J=7.0), 1.69-2.08 (2H, m), 2.67-2.74 (2H, m), 3.00-3.20 (2H, m), 3.17 (2H, s), 3.34-3.42 (2H, m), 3.61-3.67 (2H, m), 3.73-3.81 (2H, m), 3.82-3.91 (1H, m), 4.11 (2H, s), 4.21 (2H, q, J=7.0), 5.56-5.65 (1H, m), 7.11-7.20 (3H, m), 7.21-7.32 (6H, m), 7.36-7.56 (6H, m).

(b) (E)-3-{2-[4-(Ethoxycarbonylmethyl)-3-oxopiperazin-1-yl]ethylidene}-4-hydroxy-1-(triphenylmethyl)piperidine

The title compound was synthesized in a yield of 80% as a pale yellow amorphous solid using (E)-4-(t-butyldimethylsilyloxy)-3-{2-[4-(ethoxycarbonylmethyl)-3-oxopiperazin-1-yl]ethylidene}-1-(triphenylmethyl)piperidine obtained in (a) above by conducting a reaction similar to that mentioned in Example 1 (e).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 1.28 (3H, t, J=7.0), 1.76-1.86 (1H, m), 2.02-2.12 (1H, m), 2.70-2.78 (2H, m), 3.02-3.14 (2H, m), 3.20 (2H, s), 3.37-3.44 (2H, m), 3.60-3.68 (2H, m), 3.73-3.81 (2H, m), 3.93-4.02 (1H, m), 4.12 (2H, s), 4.21 (2H, q, J=7.0), 5.60 (1H, t, J=7.0), 7.11-7.20 (3H, m), 7.21-7.31 (6H, m), 7.38-7.53 (6H, m).

(c) (E)-3-{2-[4-(Ethoxycarbonylmethyl)-3-oxopiperazin-1-yl]ethylidene}-4-hydroxypiperidine bis(hydrogen acetate)

The title compound was synthesized in a yield of 99% as a pale brown crystal using (E)-3-{2-[4-(ethoxycarbonylmethyl)-3-oxopiperazin-1-yl]ethylidene}-4-hydroxy-1-(triphenylmethyl)piperidine obtained in (b) above by conducting a reaction similar to that mentioned in Example 5 (c).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 1.28 (3H, t, J=7.0), 1.56-1.69 (1H, m), 1.94-2.06 (2H, m), 2.70-2.88 (4H, m), 3.20 (2H, s), 3.37-3.49 (2H, m), 3.70-3.79 (2H, m), 4.10 (2H, s), 4.14-4.20 (2H, m), 4.20 (2H, q, J=7.0), 5.60 (1H, t, J=7.0).

(d) (E)-1-[2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{2-[4-(ethoxycarbonylmethyl)-3-oxopiperazin-1-yl]ethylidene}-4-hydroxypiperidine

The title compound was synthesized in a yield of 68% as a pale brown amorphous solid using (E)-3-{2-[4-(ethoxycarbonylmethyl)-3-oxopiperazin-1-yl]ethylidene}-4-hydroxypiperidine bis(hydrogen acetate) obtained in (c) above by conducting a reaction similar to that mentioned in Example 1 (g).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 0.76-1.09 (4H, m), 1.28 (3H, t, J=7.0), 1.60-1.77 (2H, m), 1.94-2.04 (1H, m), 2.13-2.23 (1H, m), 2.43-2.53 (1H, m), 2.65-2.77 (2H, m), 2.79-2.90 (1H, m), 2.93-3.07 (2H, m), 3.16 (2H, s), 3.33 and 3.47 (total 1H, each d, J=12.5), 3.35-3.42 (2H, m), 4.04-4.14 (1H, m), 4.11 (2H, s), 4.21 (2H, q, J=7.0), 4.70 and 4.71 (total 1H, each s), 5.54-5.63 (1H, m), 7.05-7.21 (2H, m), 7.28-7.36 (1H, m), 7.37-7.45 (1H, m).

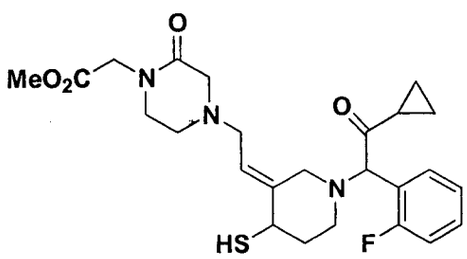
(e) (E)-4-(Acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{2-[4-(ethoxycarbonylmethyl)-3-oxopiperazin-1-yl]ethylidene}piperidine

The title compound was synthesized in a yield of 34% as a yellow oil using (E)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{2-[4-(ethoxycarbonylmethyl)-3-oxopiperazin-1-yl]ethylidene}-4-hydroxypiperidine obtained in (d) above by conducting a reaction similar to that mentioned in Example 1 (h).

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm : 0.76-1.09 (4H, m), 1.28 (3H, t, J=7.0), 1.75-1.84 (1H, m), 2.09-2.25 (2H, m), 2.29 and 2.30 (total 3H, each s), 2.48-2.59 (1H, m), 2.60-2.74 (2H, m), 2.75-2.83 (1H, m), 2.92-2.97 (1H, m), 2.99-3.03 (1H, m), 3.07 and 3.28 (total 1H, each d, J=12.5), 3.09-3.17 (2H, m), 3.34-3.41 (2H, m), 3.46-3.52 (1H, m), 4.11 (2H, s), 4.21 (2H, q, J=7.0), 4.26-4.34 (1H, m), 4.69 and 4.70 (total 1H, each s), 5.61 (1H, t, J=7.0), 7.07-7.21 (2H, m), 7.29-7.44 (2H, m);

MS (FAB) m/z : 546 $(M+H)^+$.

(Example 14) (E)-1-[2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{2-[4-(methoxycarbonylmethyl)-3-oxopiperazin-1-yl]ethylidene}-4-sulfanylpiperidine (Compound of Compound No. 5-99)

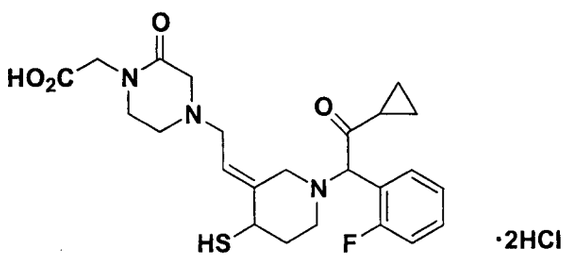


The title compound was synthesized in a yield of 93% as a yellow oil using (E)-4-(acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{2-[4-(ethoxycarbonylmethyl)-3-oxopiperazin-1-yl]ethylidene}piperidine obtained in Example 13 (e) by conducting a reaction similar to that mentioned in Example 2.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 0.76-1.09 (4H, m), 1.69-1.77 (1H, m), 2.12-2.26 (2H, m), 2.53-2.73 (3H, m), 2.74-2.85 (1H, m), 2.93-3.04 (2H, m), 3.07 and 3.38 (total 1H, each d, J=12.5), 3.12-3.22 (3H, m), 3.35-3.44 (2H, m), 3.68-3.81 (1H, m), 3.75 (3H, s), 4.13 (2H, s), 4.72 and 4.73 (total 1H, each s), 5.57 and 5.61 (total 1H, each t, J=7.0), 7.07-7.21 (2H, m), 7.29-7.44 (2H, m);

MS (FAB) m/z : 490 $(M+H)^+$.

(Example 15) (E)-3-{2-[4-(Carboxymethyl)-3-oxopiperazin-1-yl]ethylidene}-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-sulfanylpiperidine dihydrochloride (Hydrochloride of the compound of Compound No. 5-97)

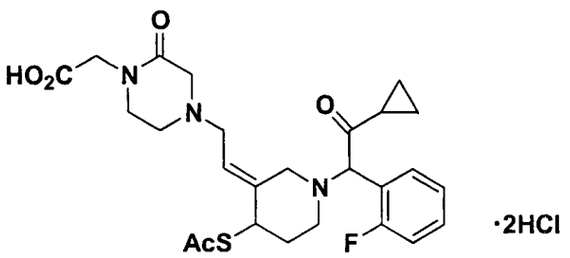


To a solution of (E)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{2-[4-(methoxycarbonylmethyl)-3-oxopiperazin-1-yl]ethylidene}-4-sulfanylpiperidine (280 mg) obtained in Example 14 in water (1 ml) was added 3N hydrochloric acid (5 ml) at room temperature, and the resulting mixture was stirred at 50°C for 2.5 hours. The reaction mixture was evaporated in vacuo, and the residue was purified using a preparative HPLC (YMC-Pack ODS-A; YMC, eluent: acetonitrile / 0.024N hydrochloric acid = 15 / 85) to afford the title compound (203 mg, yield 65%) as a colorless powder crystal.

^{1}H NMR (400 MHz, pyridine-d_5) δ ppm : 0.78-0.88 (2H, m), 0.94-1.18 (2H, m), 1.74-1.86 (1H, m), 2.14-2.28 (1H, m), 2.40-2.60 (1H, m), 2.60-2.80 (3H, m), 2.86-3.02 (1H, m), 3.02-3.15 (2H, m), 3.30-3.46 (3H, m), 3.50-3.66 (3H, m), 3.88 (1H, bs), 4.50 (2H, s), 4.94 (1H, s), 5.80 (1H, t, J=7.0), 7.18-7.36 (3H, m), 7.70-7.78 (1H, m);

MS (FAB) m/z : 476 $(M+H)^+$.

(Example 16) (E)-4-(Acetylsulfanyl)-3-{2-[4-(carboxymethyl)-3-oxopiperazin-1-yl]ethylidene}-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]piperidine dihydrochloride (Hydrochloride of the compound of Compound No. 5-98)

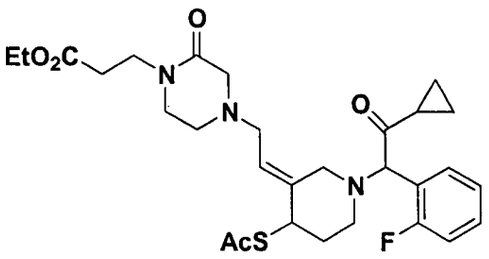


To a suspension of (E)-3-{2-[4-(carboxymethyl)-3-oxopiperazin-1-yl]ethylidene}-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-sulfanylpiperidine dihydrochloride (100 mg) obtained in Example 15 in dichloromethane (5 ml) were added acetic anhydride (259 μl) and pyridine (514 μl) under ice cooling, and the resulting mixture was stirred at room temperature for 4 hours. The reaction mixture was evaporated in vacuo, and the residue was purified by chromatography on a silica gel column (methanol / dichloromethane = 3 / 17) to afford the free form (85 mg, yield 90%) of the title compound as a brown solid. To a solution of this compound in dichloromethane (3 ml) was added a 4N solution of hydrogen chloride in dioxane (82 μl) at room temperature, and the reaction mixture was evaporated in vacuo. The residue was crystallized from ether to afford the title compound (44 mg, yield 45%) as a pale yellow amorphous solid.

^{1}H NMR (400 MHz, pyridine-d_5) δ ppm : 0.72-0.85 (2H, m), 0.98-1.05 (1H, m), 1.06-1.16 (1H, m), 1.79-1.90 (1H, m), 2.15-2.26 (1H, m), 2.23 and 2.24 (total 3H, each s), 2.35-2.49 (1H, m), 2.53-2.75 (3H, m), 2.75-2.91 (1H, m), 2.97-3.22 (3H, m), 3.30-3.38 (2H, m), 3.47-3.55 (2H, m), 3.56-3.65 (1H, m), 4.44-4.47 (2H, m), 4.51-4.55 (1H, m), 4.93 and 4.94 (total 1H, each s), 5.81 and 5.83 (total 1H, each t, J=7.0), 7.16-7.36 (3H, m), 7.64-7.72 (1H, m);

MS (FAB) m/z : 518 $(M+H)^+$.

(Example 17) (E)-4-(Acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-{4-[2-(ethoxycarbonyl)ethyl]-3-oxopiperazin-1-yl}ethylidene)piperidine (Compound of Compound No. 5-108)



(a) (E)-4-(t-Butyldimethylsilyloxy)-3-(2-{4-[2-(ethoxycarbonyl)ethyl]-3-oxopiperazin-1-yl}ethylidene)-1-(triphenylmethyl)piperidine

The title compound was synthesized in a yield of 44% as a pale yellow oil using 1-[2-(ethoxycarbonyl)-ethyl]-2-oxopiperazine hydrochloride instead of morpholine by conducting a reaction similar to that mentioned in Example 1 (d).

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm : -0.01 (3H, s), -0.02 (3H, s), 0.86 (9H, s), 1.27 (3H, t, J=7.0), 1.70-1.95 (4H, m), 2.59-2.67 (2H, m), 2.63 (2H, t, J=7.0), 2.84-2.97 (2H, m), 2.99-3.17 (2H, m), 3.11 (2H, s), 3.34-3.42 (2H, m), 3.64 (2H, t, J=7.0), 3.83-3.92 (1H, m), 4.14 (2H, q, J=7.0), 5.57-5.64 (1H, m), 7.10-7.21 (3H, m), 7.22-7.33 (6H, m), 7.37-7.57 (6H, m).

(b) (E)-3-(2-{4-[2-(Ethoxycarbonyl)ethyl]-3-oxopiperazin-1-yl}ethylidene)-4-hydroxy-1-(triphenylmethyl)piperidine

The title compound was synthesized in a yield of 96% as a pale yellow amorphous solid using (E)-4-(t-butyldimethylsilyloxy)-3-(2-{4-[2-(ethoxycarbonyl)ethyl]-3-oxopiperazin-1-yl}ethylidene)-1-(triphenylmethyl)piperidine obtained in (a) above by conducting a reaction similar to that mentioned in Example 1 (e).

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm : 1.26 (3H, t, J=7.0), 1.64-1.87 (4H, m), 2.62 (2H, t, J=7.0), 2.64-2.71 (2H, m), 2.98-3.17 (2H, m), 3.12 (2H, s), 3.35-3.43 (4H, m), 3.63 (2H, t, J=7.0), 3.91-4.01 (1H, m), 4.14 (2H, q, J=7.0), 5.58 (1H, t, J=7.0), 7.10-7.20 (3H, m), 7.21-7.33 (6H, m), 7.37-7.57 (6H, m).

(c) (E)-3-(2-{4-[2-(Ethoxycarbonyl)ethyl]-3-oxopiperazin-1-yl}ethylidene)-4-hydroxypiperidine bis(hydrogen acetate)

The title compound was synthesized in a yield of 98% as a pale brown oil using (E)-3-(2-{4-[2-(ethoxycarbonyl)ethyl]-3-oxopiperazin-1-yl}ethylidene)-4-hydroxy-1-(triphenylmethyl)piperidine obtained in (b) above by conducting a reaction similar to that mentioned in Example 5 (c).

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm : 1.26 (3H, t, J=7.0), 1.63-1.73 (2H, m), 2.61 (2H, t, J=7.0), 2.65-2.72 (2H, m), 3.07-3.15 (4H, m), 3.17-3.41 (6H, m), 3.62 (2H, t, J=7.0), 4.13 (2H, q, J=7.0), 4.17-4.22 (1H, m), 5.61 (1H, t, J=7.0).

(d) (E)-1-[2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-{4-[2-(ethoxycarbonyl)ethyl]-3-oxopiperazin-1-yl}ethylidene)-4-hydroxypiperidine

The title compound was synthesized in a yield of 77% as a pale brown oil using (E)-3-(2-{4-[2-(ethoxycarbonyl)ethyl]-3-oxopiperazin-1-yl}ethylidene)-4-hydroxypiperidine bis(hydrogen acetate) obtained in (c) above by conducting a reaction similar to that mentioned in Example 1 (g).

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm : 0.78-0.90 (2H, m), 0.95-1.09 (2H, m), 1.26 (3H, t, J=7.0), 1.52-1.65 (2H, m), 1.67-1.78 (1H, m), 1.95-2.04 (1H, m), 2.13-2.22 (1H, m), 2.44-2.52 (1H, m), 2.56-2.68 (4H, m), 2.72 and 2.96 (total 1H, each d, J=13.0), 2.79-2.90 (1H, m), 2.93-3.02 (2H, m), 3.32 and 3.47 (total 1H, each d, J=13.0), 3.35-3.41 (2H, m), 3.63 (2H, t, J=7.0), 4.05-4.12 (1H, m), 4.14 (2H, q, J=7.0), 4.70 and 4.71 (total 1H, each s), 5.53-5.60 (1H, m), 7.08-7.21 (2H, m), 7.29-7.44 (2H, m).

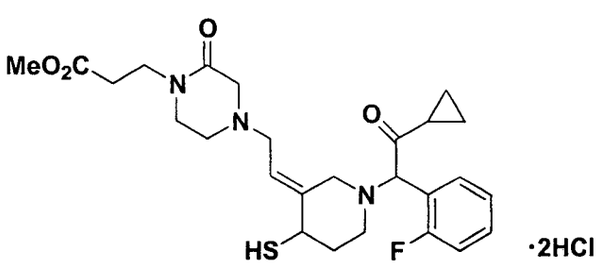
(e) (E)-4-(Acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-{4-[2-(ethoxycarbonyl)ethyl]-3-oxopiperazin-1-yl}ethylidene)piperidine

The title compound was synthesized in a yield of 22% as a pale brown oil using (E)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-{4-[2-(ethoxycarbonyl)ethyl]-3-oxopiperazin-1-yl}ethylidene)-4-hydroxypiperidine obtained in (d) above by conducting a reaction similar to that mentioned in Example 1 (h).

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm : 0.77-1.08 (4H, m), 1.26 (3H, t, J=7.0), 1.76-1.84 (1H, m), 2.08-2.24 (2H, m), 2.29 and 2.30 (total 3H, each s), 2.46-2.72 (6H, m), 2.74-2.82 (1H, m), 2.89-3.00 (2H, m), 3.01-3.09 (2H, m), 3.05 and 3.27 (total 1H, each d, J=13.0), 3.33-3.40 (2H, m), 3.63 (2H, t, J=7.0), 4.14 (2H, q, J=7.0), 4.26-4.35 (1H, m), 4.68 and 4.70 (total 1H, each s), 5.60 (1H, t, J=7.0), 7.08-7.20 (2H, m), 7.29-7.43 (2H, m);

MS (FAB) m/z : 560 $(M+H)^+$.

(Example 18) (E)-1-[2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-{4-[2-(methoxycarbonyl)ethyl]-3-oxopiperazin-1-yl}ethylidene)-4-sulfanylpiperidine dihydrochloride (Hydrochloride of the compound of Compound No. 5-105)

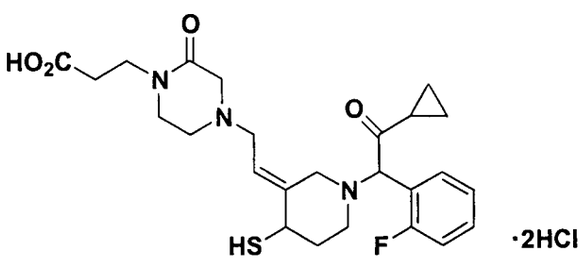


The title compound was synthesized in a yield of 71% as a white powder crystal using (E)-4-(acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-{4-[2-(ethoxycarbonyl)ethyl]-3-oxopiperazin-1-yl}ethylidene)piperidine obtained in Example 17 (e) by conducting a reaction similar to that mentioned in Example 2.

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm : 0.78-0.90 (2H, m), 0.96-1.08 (2H, m), 1.68-1.78 (1H, m), 2.12-2.26 (2H, m), 2.53-2.68 (5H, m), 2.74-2.85 (1H, m), 2.90-3.01 (2H, m), 3.03-3.10 (3H, m), 3.19 (1H, s), 3.34-3.43 (2H, m), 3.63 (2H, t, J=7.0), 3.67-3.81 (1H, m), 3.69 (3H, s), 4.71 and 4.73 (total 1H, each s), 5.55 and 5.59 (total 1H, each t, J=7.0), 7.08-7.21 (2H, m), 7.30-7.36 (1H, m), 7.38-7.43 (1H, m);

MS (FAB) m/z : 504 $(M+H)^+$.

(Example 19) (E)-3-(2-{4-[2-(Carboxyethyl)]-3-oxopiperazin-1-yl}ethylidene)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-sulfanylpiperidine dihydrochloride (Hydrochloride of the compound of Compound No. 5-103)

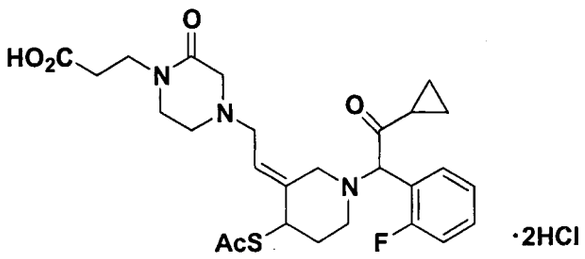


The title compound was synthesized in a yield of 48% as a white powder crystal using (E)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-{4-[2-(methoxycarbonyl)ethyl]-3-oxopiperazin-1-yl}ethylidene)-4-sulfanylpiperidine obtained in Example 18 by conducting a reaction similar to that mentioned in Example 15.

^{1}H NMR (400 MHz, pyridine-d_5) δ ppm : 0.77-1.11 (4H, m), 1.76-1.87 (1H, m), 2.14-2.27 (1H, m), 2.40-2.48 (1H, m), 2.64-2.73 (3H, m), 2.87-2.99 (3H, m), 3.04-3.13 (2H, m), 3.28-3.34 (3H, m), 3.44-3.47 (2H, m), 3.50 and 3.59 (total 1H, each d, J=12.5), 3.85-3.93 (3H, m), 4.95 (1H, s), 5.77-5.82 (1H, m), 7.21-7.37 (3H, m), 7.69-7.75 (1H, m);

MS (FAB) m/z : 490 $(M+H)^+$.

(Example 20) (E)-4-(Acetylsulfanyl)-3-(2-{4-[2-(carboxyethyl)]-3-oxopiperazin-1-yl}ethylidene)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]piperidine dihydrochloride (Hydrochloride of the compound of Compound No. 5-104)

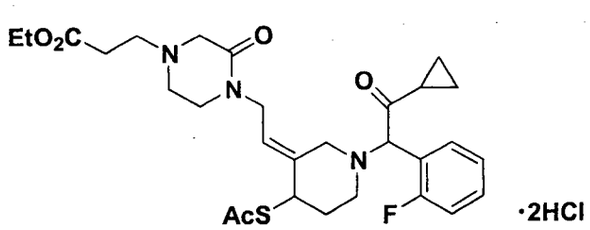


The title compound was synthesized in a yield of 35% as a pale yellow powder crystal using (E)-3-(2-{4-[2-(carboxyethyl)]-3-oxopiperazin-1-yl}ethylidene)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-sulfanylpiperidine dihydrochloride obtained in Example 19 by conducting a reaction similar to that mentioned in Example 16.

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm : 0.78-1.17 (4H, m), 1.84-1.90 (1H, m), 2.21-2.29 (1H, m), 2.25 and 2.26 (total 3H, each s), 2.39-2.46 (1H, m), 2.57-2.88 (3H, m), 2.90-2.94 (3H, m), 2.98-3.01 (2H, m), 3.19-3.28 (2H, m), 3.33-3.38 (2H, m), 3.41-3.44 (2H, m), 3.88-3.93 (2H, m), 4.54-4.55 (1H, m), 4.95 and 4.96 (total 1H, each s), 5.82-5.86 (1H, m), 7.21-7.38 (3H, m), 7.66-7.73 (1H, m);

MS (FAB) m/z : 532 $(M+H)^+$.

(Example 21) (E)-4-(Acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-{4-[2-(ethoxycarbonyl)ethyl]-2-oxopiperazin-1-yl}ethylidene)piperidine dihydrochloride (Hydrochloride of the compound of Compound No. 5-80)



(a) (E)-4-(t-Butyldimethylsilyloxy)-3-(2-{4-[2-(ethoxycarbonyl)ethyl]-2-oxopiperazin-1-yl}ethylidene)-1-(triphenylmethyl)piperidine

To a solution of sodium hydride (1.94 g) in N,N-dimethylformamide (430 ml) was added a solution of (E)-4-(t-butyldimethylsilyloxy)-3-[2-(tosyloxy)ethylidene]-1-(triphenylmethyl)piperidine (27.37 g) obtained in Example 1 (c) and 1-[2-(ethoxycarbonyl)ethyl]-3-oxopiperazine (9.70 g) in N,N-dimethylformamide (100 ml) under ice cooling, and the resulting mixture was stirred at room temperature for 3 hours. The reaction mixture was charged with a saturated aqueous sodium chloride solution and then extracted with ethyl acetate. The extract was washed with a saturated aqueous sodium chloride solution, and the organic layer was dried over anhydrous sodium sulfate. The solvent was removed in vacuo, and the residue was purified by chromatography on a silica gel column (ethyl acetate / hexane = 2 / 3 - 1 / 1) to afford the title compound (14.79 g, yield 54%) as a pale yellow amorphous solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm : -0.05 (3H, s), -0.02 (3H, s), 0.83 (9H, s), 1.26 (3H, t, J=7.5), 1.73-1.94 (2H, m), 2.48 (2H, t, J=7.5), 2.65-2.76 (4H, m), 2.84-2.93 (1H, m), 3.16 (2H, s), 3.20-3.27 (2H, m), 3.40-3.55 (1H, m), 3.81-4.18 (7H, m), 5.41-5.48 (1H, m), 7.11-7.29 (9H, m), 7.41-7.52 (6H, m).

(b) (E)-3-(2-{4-[2-(Ethoxycarbonyl)ethyl]-2-oxopiperazin-1-yl}ethylidene)-4-hydroxy-1-(triphenylmethyl)piperidine

The title compound was synthesized in a yield of 99% as a pale yellow amorphous solid using (E)-4-(t-butyldimethylsilyloxy)-3-(2-{4-[2-(ethoxycarbonyl)ethyl]-2-oxopiperazin-1-yl}ethylidene)-1-(triphenylmethyl)piperidine obtained in (a) above by conducting a reaction similar to that mentioned in Example 1 (e).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 1.26 (3H, t, J=7.0), 1.60-1.86 (2H, m), 1.98-2.11 (1H, m), 2.49 (2H, t, J=7.0), 2.65-2.77 (4H, m), 3.16 (2H, s), 3.21-3.44

(3H, m), 3.88-4.20 (7H, m), 5.44 (1H, t, J=6.5), 7.10-7.31 (9H, m), 7.39-7.53 (6H, m).

(c) (E)-3-(2-{4-[2-(Ethoxycarbonyl)ethyl]-2-oxopiperazin-1-yl}ethylidene)-4-hydroxypiperidine bis(hydrogen acetate)

The title compound was synthesized in a yield of 99% as a pale brown oil using (E)-3-(2-{4-[2-(ethoxycarbonyl)ethyl]-2-oxopiperazin-1-yl}ethylidene)-4-hydroxy-1-(triphenylmethyl)piperidine obtained in (b) above by conducting a reaction similar to that mentioned in Example 5 (c).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 1.26 (3H, t, J=7.0), 1.62-1.83 (2H, m), 2.01-2.12 (1H, m), 2.49 (2H, t, J=7.0), 2.66-2.77 (4H, m), 2.90-3.01 (1H, m), 3.15 (2H, s), 3.23-3.45 (3H, m), 3.83-4.27 (6H, m), 5.57 (1H, t, J=7.5).

(d) (E)-1-[2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-{4-[2-(ethoxycarbonyl)ethyl]-2-oxopiperazin-1-yl}ethylidene)-4-hydroxypiperidine

The title compound was synthesized in a yield of 93% as a pale yellow oil using (E)-3-(2-{4-[2-(ethoxycarbonyl)ethyl]-2-oxopiperazin-1-yl}ethylidene)-4-hydroxypiperidine bis(hydrogen acetate) obtained in (c) above by conducting a reaction similar to that mentioned in Example 1 (g).

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm : 0.78-0.91 (2H, m), 0.97-1.10 (2H, m), 1.26 (3H, t, J=7.5), 1.62-1.77 (2H, m), 1.95-2.03 (1H, m), 2.09-2.16 (1H, m), 2.43-2.54 (2H, m), 2.65-2.77 (4H, m), 2.78-2.89 (1H, m), 3.00 and 3.33 (total 1H, each d, J=12.5), 3.15 (2H, s), 3.22-3.30 (2H, m), 3.47-3.55 (1H, m), 3.88-4.19 (5H, m), 4.73 and 4.75 (total 1H, each s), 5.42-5.49 (1H, m), 7.08-7.20 (2H, m), 7.29-7.41 (2H, m).

(e) (E)-4-(Acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-{4-[2-(ethoxycarbonyl)ethyl]-2-oxopiperazin-1-yl}ethylidene)piperidine dihydrochloride

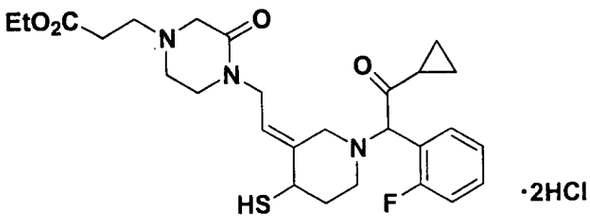
The title compound was synthesized in a yield of 4% as a pale yellow powder crystal using (E)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-{4-[2-

(ethoxycarbonyl)ethyl]-2-oxopiperazin-1-yl}ethylidene)-4-hydroxypiperidine obtained in (d) above by conducting a reaction similar to that mentioned in Example 1 (h).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 0.75-1.09 (4H, m), 1.27 (3H, t, J=7.0), 1.72-1.84 (1H, m), 2.05-2.32 (6H, m), 2.43-2.83 (7H, m), 3.04-3.42 (6H, m), 3.77-4.35 (5H, m), 4.71 and 4.74 (total 1H, each s), 5.43-5.52 (1H, m), 7.06-7.22 (2H, m), 7.29-7.41 (2H, m);

MS (FAB) m/z : 560 $(M+H)^+$.

(Example 22) (E)-1-[2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-{4-[2-(ethoxycarbonyl)ethyl]-2-oxopiperazin-1-yl}ethylidene)-4-sulfanylpiperidine dihydrochloride (Hydrochloride of the compound of Compound No. 5-79)

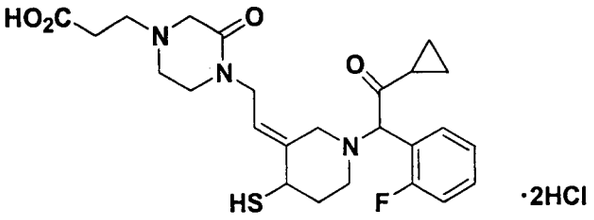


The title compound was synthesized in a yield of 80% as a white powder crystal using (E)-4-(acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-{4-[2-(ethoxycarbonyl)ethyl]-2-oxopiperazin-1-yl}ethylidene)piperidine obtained in Example 21 (e) by conducting a reaction similar to that mentioned in Example 12.

^{1}H NMR (400 MHz, pyridine-d_5) δ ppm : 0.76-0.89 (2H, m), 0.99-1.08 (2H, m), 1.13 (3H, t, J=7.5), 1.72-1.85 (1H, m), 2.12-2.26 (1H, m), 2.38-3.00 (9H, m), 3.21-3.42 (5H, m), 3.51-3.68 (1H, m), 3.81 (1H, bs), 4.06-4.21 (4H, m), 4.96 (1H, s), 5.62-5.71 (1H, m), 7.19-7.40 (3H, m), 7.66-7.76 (1H, m);

MS (FAB) m/z : 518 $(M+H)^+$.

(Example 23) (E)-3-(2-{4-[2-(Carboxyethyl)]-2-oxopiperazin-1-yl}ethylidene)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-sulfanylpiperidine dihydrochloride (Hydrochloride of the compound of Compound No. 5-75)

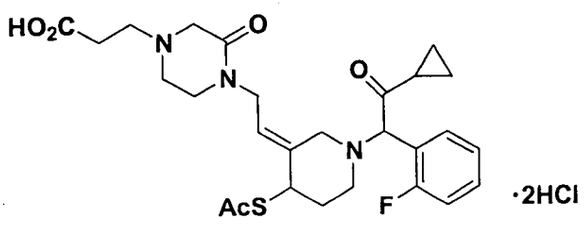


The title compound was synthesized in a yield of 88% as a white powder crystal using (E)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-{4-[2-(ethoxycarbonyl)ethyl]-2-oxopiperazin-1-yl}ethylidene)-4-sulfanylpiperidine obtained in Example 22 by conducting a reaction similar to that mentioned in Example 15.

^{1}H NMR (400 MHz, pyridine-d_5) δ ppm : 0.77-0.89 (2H, m), 0.98-1.19 (2H, m), 1.71-1.84 (1H, m), 2.10-2.28 (1H, m), 2.38-3.01 (9H, m), 3.23-3.69 (6H, m), 3.81 (1H, bs), 4.05-4.29 (2H, m), 4.96 (1H, s), 5.63-5.72 (1H, m), 7.16-7.40 (3H, m), 7.67-7.78 (1H, m);

MS (FAB) m/z : 490 $(M+H)^+$.

(Example 24) (E)-4-(Acetylsulfanyl)-3-(2-{4-[2-(carboxyethyl)]-2-oxopiperazin-1-yl}ethylidene)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]piperidine dihydrochloride (Hydrochloride of the compound of Compound No. 5-76)



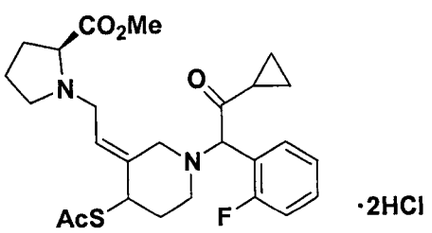
The title compound was synthesized in a yield of 44% as a pale yellow powder crystal using (E)-3-(2-{4-[2-(carboxyethyl)]-2-oxopiperazin-1-yl}ethylidene)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-sulfanylpiperidine

dihydrochloride obtained in Example 23 by conducting a reaction similar to that mentioned in Example 16.

^{1}H NMR (400 MHz, pyridine-d_5) δ ppm : 0.76-0.91 (2H, m), 1.01-1.20 (2H, m), 1.81-1.90 (1H, m), 2.14-2.29 (4H, m), 2.34-2.48 (1H, m), 2.53-2.92 (8H, m), 3.17-3.72 (6H, m), 4.00-4.31 (2H, m), 4.46-4.56 (1H, m), 4.95 and 4.97 (total 1H, each s), 5.69-5.80 (1H, m), 7.18-7.40 (3H, m), 7.62-7.75 (1H, m);

MS (FAB) m/z : 532 $(M+H)^+$.

(Example 25) (E)-4-(Acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{2-[(2S)-(methoxycarbonyl)pyrrolidin-1-yl]ethylidene}piperidine dihydrochloride (Hydrochloride of the compound of Compound No. 5-148)



(a) (E)-4-(t-Butyldimethylsilyloxy)-3-{2-[(2S)-(methoxycarbonyl)pyrrolidin-1-yl]ethylidene}-1-(triphenylmethyl)piperidine

To a solution of (E)-4-(t-butyldimethylsilyloxy)-3-[2-(tosyloxy)ethylidene]-1-(triphenylmethyl)piperidine (4.50 g) obtained in Example 1 (c) in N,N-dimethylformamide (60 ml) were added (2S)-(methoxycarbonyl)pyrrolidine hydrochloride (1.14 g) and triethylamine (2.11 ml) under ice cooling, and the resulting mixture was stirred at room temperature overnight. The reaction mixture was charged with a saturated aqueous sodium chloride solution and then extracted with ethyl acetate. The extract was washed with a saturated aqueous sodium chloride solution, and the organic layer was dried over anhydrous sodium sulfate. The solvent was removed in vacuo, and the residue was purified by chromatography on a silica gel column (ethyl acetate / hexane = 1 / 9) to afford the title compound (1.46 g, yield 35%) as a colorless amorphous solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm : -0.04 (3H, s), -0.02 (3H, s), 0.84 (9H, s), 1.69-1.98 (7H, m), 2.03-2.13 (1H, m), 2.31-2.54 (1H, m), 2.71-2.98 (1H, m), 3.03-3.29 (3H, m), 3.37-3.48 (2H, m), 3.59 and 3.62 (total 3H, each s), 3.80-3.93 (1H, m), 5.63-5.73 (1H, m), 7.08-7.19 (3H, m), 7.20-7.30 (6H, m), 7.36-7.56 (6H, m).

(b) (E)-4-Hydroxy-3-{2-[(2S)-(methoxycarbonyl)pyrrolidin-1-yl]ethylidene}-1-(triphenylmethyl)piperidine

The title compound was synthesized in a yield of 99% as a pale yellow amorphous solid using (E)-4-(t-butyldimethylsilyloxy)-3-{2-[(2S)-(methoxycarbonyl)pyrrolidin-1-yl]ethylidene}-1-(triphenylmethyl)piperidine obtained in (a) above by conducting a reaction similar to that mentioned in Example 1 (e).

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm : 1.73-1.85 (2H, m), 1.87-1.98 (2H, m), 2.01-2.18 (3H, m), 2.33-2.43 (2H, m), 2.53-2.75 (1H, m), 3.05-3.23 (4H, m), 3.26-3.37 (1H, m), 3.64 and 3.66 (total 3H, each s), 3.92-4.04 (1H, m), 5.60-5.70 (1H, m), 7.10-7.20 (3H, m), 7.21-7.32 (6H, m), 7.37-7.57 (6H, m).

(c) (E)-4-Hydroxy-3-{2-[(2S)-(methoxycarbonyl)pyrrolidin-1-yl]ethylidene}piperidine bis(hydrogen acetate)

The title compound was synthesized in a quantitative yield as a pale brown oil using (E)-4-hydroxy-3-{2-[(2S)-(methoxycarbonyl)pyrrolidin-1-yl]ethylidene}-1-(triphenylmethyl)piperidine obtained in (b) above by conducting a reaction similar to that mentioned in Example 5 (c).

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm : 1.71-1.81 (2H, m), 1.87-2.05 (3H, m), 2.09-2.19 (2H, m), 2.34-2.43 (1H, m), 2.90-2.98 (1H, m), 3.09-3.33 (4H, m), 3.37-3.45 (1H, m), 3.73 and 3.74 (total 3H, each s), 3.78 (1H, d, J=14.0), 4.18-4.25 (1H, m), 5.70 (1H, t, J=7.5).

(d) (E)-1-[2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-hydroxy-3-{2-[(2S)-(methoxycarbonyl)pyrrolidin-1-yl]ethylidene}piperidine

The title compound was synthesized in a yield of 54% as a pale brown oil using (E)-4-hydroxy-3-{2-[(2S)-(methoxycarbonyl)pyrrolidin-1-yl]ethylidene}piperidine bis(hydrogen acetate) obtained in (c) above by conducting a reaction similar to that mentioned in Example 1 (g).

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm : 0.79-0.90 (2H, m), 0.96-1.09 (2H, m), 1.66-1.84 (2H, m), 1.87-2.02 (3H, m), 2.06-2.16 (1H, m), 2.20-2.29 (1H, m), 2.31-2.39 (1H, m), 2.42-2.56 (1H, m), 2.74-2.86 (1H, m), 2.85 and 2.95 (total 1H, each d, J=12.5), 2.98 and 3.06 (total 1H, each d, J=12.5), 3.08-3.19 (2H, m), 3.21-3.45 (2H, m), 3.70 and 3.71 (total 3H, each s), 4.06-4.16 (1H, m), 4.68 and 4.69 and 4.70 (total 1H, each s), 5.61-5.70 (1H, m), 7.06-7.21 (2H, m), 7.28-7.35 (1H, m), 7.39-7.47 (1H, m).

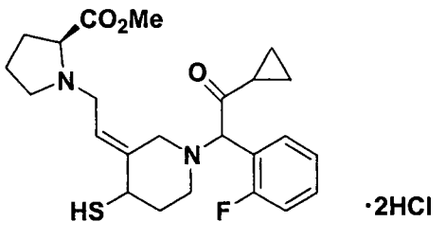
(e) (E)-4-(Acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{2-[(2S)-(methoxycarbonyl)pyrrolidin-1-yl]ethylidene}piperidine dihydrochloride

The title compound was synthesized in a yield of 22% as a pale brown powder crystal using (E)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-hydroxy-3-{2-[(2S)-(methoxycarbonyl)pyrrolidin-1-yl]ethylidene}piperidine obtained in (d) above by conducting a reaction similar to that mentioned in Example 1 (h).

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm : 0.78-0.90 (2H, m), 0.95-1.09 (2H, m), 1.72-1.82 (2H, m), 1.84-1.97 (2H, m), 2.04-2.40 (4H, m), 2.28 and 2.29 (total 3H, each s), 2.43-2.63 (1H, m), 2.65-2.78 (1H, m), 2.81-3.35 (6H, m), 3.69 and 3.70 and 3.71 and 3.72 (total 3H, each s), 4.26-4.32 (1H, m), 4.65 and 4.67 and 4.68 and 4.69 (total 1H, each s), 5.67-5.73 (1H, m), 7.07-7.19 (2H, m), 7.29-7.35 (1H, m), 7.39-7.45 (1H, m);

MS (FAB) m/z : 489 $(M+H)^+$.

(Example 26) (E)-1-[2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{2-[(2S)-(methoxycarbonyl)pyrrolidin-1-yl]ethylidene}-4-sulfanylpiperidine dihydrochloride (Hydrochloride of the compound of Compound No. 5-147)

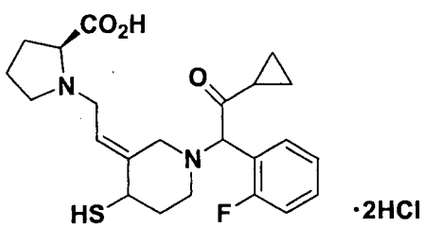


The title compound was synthesized in a yield of 46% as a pale pink powder crystal using (E)-4-(acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{2-[(2S)-(methoxycarbonyl)pyrrolidin-1-yl]ethylidene}piperidine obtained in Example 25 (e) by conducting a reaction similar to that mentioned in Example 2.

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm : 0.78-0.90 (2H, m), 0.95-1.08 (2H, m), 1.66-1.99 (4H, m), 2.05-2.38 (4H, m), 2.53-2.66 (1H, m), 2.67-2.86 (1H, m), 3.01-3.39 (6H, m), 3.65-3.79 (1H, m), 3.71 and 3.72 (total 3H, each s), 4.69 and 4.71 (total 1H, each s), 5.63-5.71 (1H, m), 7.07-7.19 (2H, m), 7.28-7.35 (1H, m), 7.40-7.46 (1H, m);

MS (FAB)m/z : 447 $(M+H)^+$.

(Example 27) (E)-3-{2-[(2S)-Carboxypyrrolidin-1-yl]ethylidene}-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-sulfanylpiperidine dihydrochloride (Hydrochloride of the compound of Compound No. 5-145)



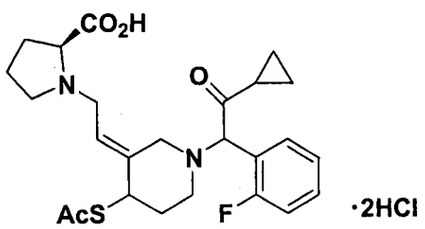
The title compound was synthesized in a yield of 76% as a pale yellow powder crystal using (E)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{2-

[(2S)-(methoxycarbonyl)pyrrolidin-1-yl]ethylidene}-4-sulfanylpiperidine obtained in Example 26 by conducting a reaction similar to that mentioned in Example 15.

^{1}H NMR (400 MHz, pyridine-d_5) δ ppm : 0.72-0.90 (2H, m), 0.95-1.20 (2H, m), 1.67-2.26 (4H, m), 2.28-2.53 (3H, m), 2.55-3.21 (3H, m), 3.37-4.38 (7H, m), 4.94-5.09 (1H, m), 6.10-6.31 (1H, m), 7.11-7.37 (3H, m), 7.62-7.83 (1H, m);

MS (FAB) m/z : 433 $(M+H)^+$.

(Example 28) (E)-4-(Acetylsulfanyl)-3-{2-[(2S)-carboxypyrrolidin-1-yl]ethylidene}-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]piperidine dihydrochloride (Hydrochloride of the compound of Compound No. 5-146)

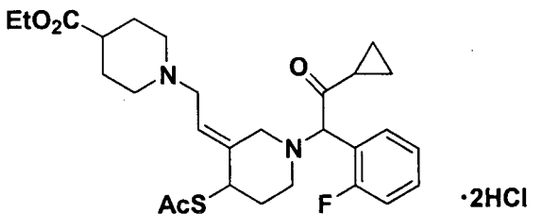


To a suspension of (E)-3-{2-[(2S)-carboxypyrrolidin-1-yl]ethylidene}-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-sulfanylpiperidine dihydrochloride (100 mg) obtained in Example 27 in dichloromethane (5 ml) were added acetic anhydride (28 μl) and triethylamine (97 μl) under ice cooling, and the resulting mixture was stirred at room temperature for 2 hours. The solvent was removed in vacuo, and the residue was purified using a preparative HPLC (YMC-Pack ODS-A; YMC, eluent: acetonitrile / water containing triethylamine (0.2%) and acetic acid (0.2%) = 3 / 7) to afford the free form (57 mg, yield 61%) of the title compound as a pale brown oil. To a solution of this compound in dichloromethane (1 ml) was added a 4N solution of hydrogen chloride in dioxane (60 μl) at room temperature, and the reaction mixture was evaporated in vacuo. The residue was crystallized from ether to afford the title compound (41 mg, yield 62%) as a pale brown powder crystal.

^{1}H NMR (400 MHz, pyridine-d_5) δ ppm : 0.72-0.92 (2H, m), 0.99-1.21 (2H, m), 1.71-2.00 (3H, m), 2.12-2.35 (2H, m), 2.25 and 2.26 and 2.27 (total 3H, each s), 2.38-2.89 (4H, m), 3.17-3.50 (3H, m), 3.55-4.06 (4H, m), 4.53 (1H, m), 4.94 and 4.97 and 4.99 (total 1H, each s), 6.10-6.21 (1H, m), 7.16-7.39 (3H, m), 7.63-7.77 (1H, m);

MS (FAB) m/z : 475 $(M+H)^+$.

(Example 29) (E)-4-(Acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{2-[4-(ethoxycarbonyl)piperidin-1-yl]ethylidene}piperidine dihydrochloride (Hydrochloride of the compound of Compound No. 5-8)



(a) (E)-4-(t-Butyldimethylsilyloxy)-3-{2-[4-(ethoxycarbonyl)piperidin-1-yl]ethylidene}-1-(triphenylmethyl)piperidine

The title compound was synthesized in a yield of 37% as a colorless amorphous solid using 4-(ethoxycarbonyl)piperidine instead of morpholine by conducting a reaction similar to that mentioned in Example 1 (d).

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm : -0.04 (3H, s), -0.02 (3H, s), 0.83 (9H, s), 1.25 (3H, t, J=7.0), 1.68-2.07 (10H, m), 2.20-2.30 (1H, m), 2.77-2.91 (3H, m), 2.93-3.10 (2H, m), 3.27-3.65 (1H, m), 3.82-3.92 (1H, m), 4.13 (2H, q, J=7.0), 5.57-5.66 (1H, m), 7.06-7.19 (3H, m), 7.20-7.30 (6H, m), 7.36-7.58 (6H, m).

(b) (E)-3-{2-[4-(Ethoxycarbonyl)piperidin-1-yl]ethylidene}-4-hydroxy-1-(triphenylmethyl)piperidine

The title compound was synthesized in a yield of 99% as a colorless oil using (E)-4-(t-butyldimethylsilyloxy)-3-{2-[4-(ethoxycarbonyl)piperidin-1-yl]ethylidene}-

1-(triphenylmethyl)piperidine obtained in (a) above by conducting a reaction similar to that mentioned in Example 1 (e).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 1.25 (3H, t, J=7.0), 1.64-2.11 (10H, m), 2.24-2.35 (1H, m), 2.83-2.94 (2H, m), 2.94-3.07 (2H, m), 3.35-3.44 (2H, m), 3.95-4.01 (1H, m), 4.14 (2H, q, J=7.0), 5.62 (1H, t, J=6.0), 7.13-7.21 (3H, m), 7.23-7.33 (6H, m), 7.41-7.55 (6H, m).

(c) (E)-3-{2-[4-(Ethoxycarbonyl)piperidin-1-yl]ethylidene}-4-hydroxypiperidine bis(hydrogen acetate)

The title compound was synthesized in a yield of 99% as a brown crystal using (E)-3-{2-[4-(ethoxycarbonyl)piperidin-1-yl]ethylidene}-4-hydroxy-1-(triphenylmethyl)piperidine obtained in (b) above by conducting a reaction similar to that mentioned in Example 5 (c).

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm : 1.25 (3H, t, J=7.0), 1.41-1.50 (1H, m), 1.60-2.12 (6H, m), 2.23-2.34 (1H, m), 2.83-3.09 (5H, m), 3.30 (2H, q, J=7.0), 3.39-3.51 (1H, m), 3.75-3.82 (1H, m), 4.13 (2H, q, J=7.0), 4.19-4.25 (1H, m), 5.58-5.75 (1H, m).

(d) (E)-1-[2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{2-[4-(ethoxycarbonyl)piperidin-1-yl]ethylidene}-4-hydroxypiperidine

The title compound was synthesized in a yield of 63% as a pale brown oil using (E)-3-{2-[4-(ethoxycarbonyl)piperidin-1-yl]ethylidene}-4-hydroxypiperidine bis(hydrogen acetate) obtained in (c) above by conducting a reaction similar to that mentioned in Example 1 (g).

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm : 0.76-1.10 (4H, m), 1.25 (3H, t, J=7.0), 1.42-1.51 (1H, m), 1.65-2.04 (8H, m), 2.08-2.23 (2H, m), 2.27-2.37 (1H, m), 2.42-2.53 (1H, m), 2.76 and 2.96 (total 1H, each d, J=12.5), 2.77-2.95 (1H, m), 3.00-3.07 (2H, m), 3.32 and 3.45 (total 1H, each d, J=12.5), 4.06-4.11 (1H, m), 4.13 (2H, q,

J=7.0), 4.69 and 4.72 (total 1H, each s), 5.61-5.70 (1H, m), 7.07-7.21 (2H, m), 7.28-7.45 (2H, m).

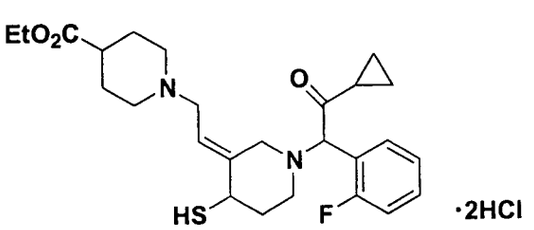
(e) (E)-4-(Acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{2-[4-(ethoxycarbonyl)piperidin-1-yl]ethylidene}piperidine dihydrochloride

The title compound was synthesized in a yield of 17% as a yellow powder crystal using (E)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{2-[4-(ethoxycarbonyl)piperidin-1-yl]ethylidene}-4-hydroxypiperidine obtained in (d) above by conducting a reaction similar to that mentioned in Example 1 (h).

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm : 0.77-1.11 (4H, m), 1.25 (3H, t, J=7.0), 1.67-1.98 (7H, m), 2.07-2.29 (3H, m), 2.28 and 2.29 (total 3H, each s), 2.47-2.62 (1H, m), 2.65-2.96 (5H, m), 2.81 and 3.02 (total 1H, each d, J=12.5), 3.26-3.39 (1H, m), 4.13 (2H, q, J=7.0), 4.27-4.36 (1H, m), 4.66 and 4.69 (total 1H, each s), 5.64 (1H, t, J=7.0), 7.07-7.20 (2H, m), 7.28-7.45 (2H, m);

MS (FAB) m/z : 517 $(M+H)^+$.

(Example 30) (E)-1-[2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{2-[4-(ethoxycarbonyl)piperidin-1-yl]ethylidene}-4-sulfanylpiperidine dihydrochloride (Hydrochloride of the compound of Compound No. 5-7)

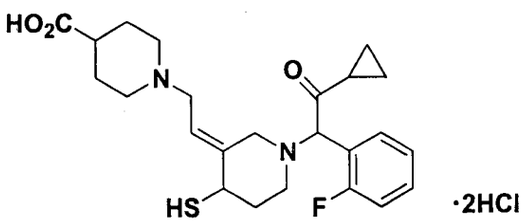


The title compound was synthesized in a yield of 97% as a pale yellow powder crystal using (E)-4-(acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{2-[4-(ethoxycarbonyl)piperidin-1-yl]ethylidene}piperidine obtained in Example 29 (e) by conducting a reaction similar to that mentioned in Example 12.

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm : 0.75-1.10 (4H, m), 1.25 (3H, t, J=7.0), 1.67-1.80 (3H, m), 1.82-1.99 (4H, m), 2.10-2.31 (3H, m), 2.54-2.68 (1H, m), 2.69-2.97 (5H, m), 3.14 and 3.35 (total 1H, each d, J=12.5), 3.16-3.23 (1H, m), 3.72-3.83 (1H, m), 4.13 (2H, q, J=7.0), 4.69 and 4.71 (total 1H, each s), 5.61 (1H, m), 7.05-7.21 (2H, m), 7.23-7.46 (2H, m);

MS (FAB) m/z : 475 $(M+H)^+$.

(Example 31) (E)-3-{2-[4-(Carboxypiperidine)-1-yl]ethylidene}-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-sulfanylpiperidine dihydrochloride (Hydrochloride of the compound of Compound No. 5-3)

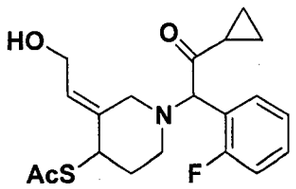


The title compound was synthesized in a yield of 90% as a pale yellow powder crystal using (E)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{2-[4-(ethoxycarbonyl)piperidin-1-yl]ethylidene}-4-sulfanylpiperidine dihydrochloride obtained in Example 30 by conducting a reaction similar to that mentioned in Example 15.

^{1}H NMR (400 MHz, pyridine-d_5) δ ppm : 0.73-0.83 (2H, m), 1.03-1.13 (2H, m), 1.73-1.81 (1H, m), 2.13-2.31 (2H, m), 2.47 (2H, br), 2.59-2.98 (7H, m), 3.04-3.27 (1H, m), 3.39 and 3.45 (total 1H, each d, J=12.0), 3.51-3.68 (2H, m), 3.80-3.89 (3H, m), 5.00 and 5.01 (total 1H, each s), 6.41 (1H, t, J=7.5), 7.22-7.25 (2H, m), 7.27-7.35 (1H, m), 7.58-7.60 (1H, m);

MS (FAB) m/z : 447 $(M+H)^+$.

(Example 32) (E)-4-(Acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-hydroxyethylidene)piperidine (Compound of Compound No. 3-2)



(a) (E)-4-(Acetylsulfanyl)-3-[(ethoxycarbonyl)methylidene]-1-(triphenylmethyl)piperidine

To a solution of (E)-3-[(ethoxycarbonyl)methylidene]-1-(triphenylmethyl)piperidin-4-ol (23.06 g) in dichloromethane (200 ml) were added methanesulfonyl chloride (4.60 ml) and triethylamine (9.77 ml) under ice cooling, and the resulting mixture was stirred at room temperature for 1 hour. After a saturated aqueous sodium hydrogen carbonate solution was poured to the reaction mixture and the resulting mixture was extracted with dichloromethane, the organic layer was dried over anhydrous magnesium sulfate. The solvent was removed in vacuo to afford a crude product of (E)-3-[(ethoxycarbonyl)methylidene]-4-mesyloxy-1-(triphenylmethyl)piperidine as a pale yellow amorphous solid. To a solution of this compound in ethanol (250 ml) was added potassium thioacetate (12.32 g) at room temperature, and the resulting mixture was stirred at 70°C for 1 hour. The reaction mixture was evaporated in vacuo. The residue was diluted with ethyl acetate and washed with water and a saturated aqueous sodium chloride solution, and the organic layer was dried over anhydrous magnesium sulfate. The solvent was removed in vacuo, and the residue was purified by chromatography on a silica gel column (ethyl acetate / hexane = 1 / 5) to afford the title compound (18.35 g, yield 70%) as a pale yellow amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 1.11(3H, t, J=7.0), 1.89-1.99 (1H, m), 2.10-2.24 (1H, m), 2.27 (3H, s), 2.30-2.40 (2H, m), 2.51-2.65 (1H, m), 3.83 (1H, m), 3.98-4.08 (2H, m), 4.30-4.37 (1H, m), 5.98 (1H, s), 7.12-7.51 (15H, m).

(b) (E)-3-(2-Hydroxyethylidene)-4-sulfanyl-1-(triphenylmethyl)piperidine

To a solution of (E)-4-(acetylsulfanyl)-3-[(ethoxycarbonyl)methylidene]-1-(triphenylmethyl)piperidine (18.35 g) obtained in (a) above in dichloromethane (300 ml) was added dropwise a 1.01N solution of diisobutylaluminum hydride in toluene (151 ml) at -78°C, and the resulting mixture was stirred at the same temperature for 1 hour. To the reaction mixture was added a saturated aqueous potassium sodium tartrate tetrahydrate solution, and the resulting mixture was stirred at room temperature for 3 hours. The reaction mixture was extracted with ethyl acetate and washed with water and a saturated aqueous sodium chloride solution, and the organic layer was dried over anhydrous sodium sulfate. The solvent was removed in vacuo, and the residue was purified by chromatography on a silica gel column (ethyl acetate / hexane / dichloromethane = 1 / 2 / 1) to afford the title compound (10.00 g, yield 66%) as a pale yellow amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 1.75-1.92 (1H, m), 2.25-2.57 (3H, m), 2.74-3.13 (2H, m), 3.53-3.72 (1H, m), 4.03-4.22 (2H, m), 5.71-5.85 (1H, m), 7.10-7.60 (15H, m).

(c) (E)-3-[2-(t-Butyldimethylsilyloxy)ethylidene]-4-sulfanyl-1-(triphenylmethyl)piperidine

To a solution of (E)-3-(2-hydroxyethylidene)-4-sulfanyl-1-(triphenylmethyl)piperidine (10.00 g) obtained in (b) above in dichloromethane (100 ml) were added t-butyldimethylsilyl chloride (5.63 g), triethylamine (5.23 ml) and 4-dimethylaminopyridine (0.15 g) under ice cooling, and the resulting mixture was stirred at room temperature for 1 hour. The reaction mixture was evaporated in vacuo. The residue was diluted with dichloromethane and washed with water and a saturated aqueous sodium chloride solution, and the organic layer was dried over anhydrous magnesium sulfate. The solvent was removed in vacuo, and the residue was purified by chromatography on a silica gel column (ethyl acetate / hexane = 1 / 10) to afford the title compound (10.66 g, yield 83%) as a colorless amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 0.01-0.05 (6H, m), 0.85-0.90 (9H, m), 1.73-1.85 (1H, m), 2.20-2.51 (3H, m), 2.86-3.20 (2H, m), 3.60-3.64 (1H, m), 4.11-4.19 (2H, m), 5.64-5.71 (1H, m), 7.12-7.53 (15H, m).

(d) (E)-4-(Acetylsulfanyl)-3-[2-(t-butyldimethylsilyloxy)ethylidene]-1-(triphenylmethyl)piperidine

To a solution of (E)-3-[2-(t-butyldimethylsilyloxy)ethylidene]-4-sulfanyl-1-(triphenylmethyl)piperidine (10.66 g) obtained in (c) above in dichloromethane (100 ml) were added acetic anhydride (2.93 ml), pyridine (5.00 ml) and 4-dimethylaminopyridine (0.13 g) under ice cooling, and the resulting mixture was stirred at room temperature for 3 hours. The reaction mixture was evaporated in vacuo. The residue was diluted with ethyl acetate and washed with water and a saturated aqueous sodium chloride solution, and the organic layer was dried over anhydrous magnesium sulfate. The solvent was removed in vacuo, and the residue was purified by chromatography on a silica gel column (ethyl acetate / hexane = 1 / 10) to afford the title compound (10.95 g, yield 95%) as a colorless amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 0.04-0.07 (6H, m), 0.83-0.92 (9H, m), 1.75-1.92 (1H, m), 2.19-2.34 (5H, m), 2.41-2.70 (1H, m), 2.90-3.13 (2H, m), 4.06-4.21 (2H, m), 4.21-4.34 (1H, m), 5.66 (1H, t, J=6.0), 7.11-7.54 (15H, m).

(e) (E)-4-(Acetylsulfanyl)-3-(2-hydroxyethylidene)piperidine hydrogen trifluoroacetate

To a solution of (E)-4-(acetylsulfanyl)-3-[2-(t-butyldimethylsilyloxy)ethylidene]-1-(triphenylmethyl)piperidine (10.95 g) obtained in (d) above in dichloromethane (10 ml) was added trifluoroacetic acid (15 ml) under ice cooling, and the resulting mixture was stirred at room temperature for 1 hour. The reaction mixture was evaporated in vacuo, and the residue was purified by chromatography on a silica gel column (methanol / dichloromethane = 1 / 10 – 1 / 1) to afford the title compound (6.90 g, quantitative yield) as a brown oil.

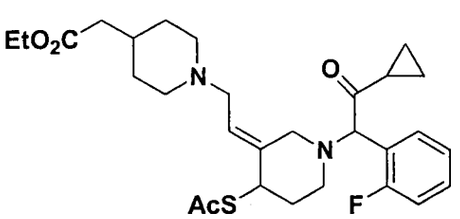
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 1.96-2.10 (1H, m), 2.26-2.43 (4H, m), 3.13-3.28 (1H, m), 3.29-3.41 (1H, m), 3.57-3.67 (1H, m), 4.02-4.11 (1H, m), 4.14-4.28 (2H, m), 4.40-4.45 (1H, m), 6.04-6.11 (1H, m).

(f) (E)-4-(Acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-hydroxyethylidene)piperidine

The title compound was synthesized in a yield of 74% as a yellow oil using (E)-4-(acetylsulfanyl)-3-(2-hydroxyethylidene)piperidine hydrogen trifluoroacetate (6.90 g) obtained in (e) above by conducting a reaction similar to that mentioned in Example 1 (g).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 0.75-0.92 (2H, m), 0.96-1.11 (2H, m), 1.59-1.87 (2H, m), 2.07-2.19 (1H, m), 2.19-2.34 (3H, m), 2.44-2.63 (1H, m), 2.64-2.79 (1H, m), 2.82 and 3.09 (total 1H, each d, J=12.5), 3.26 and 3.41 (total 1H, each d, J=12.5), 3.97-4.18 (2H, m), 4.23-4.37 (1H, m), 4.73 and 4.78 (total 1H, each s), 5.75-5.87 (1H, m), 7.70-7.24 (2H, m), 7.29-7.41 (2H, m).

(Example 33) (E)-4-(Acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{2-[4-(ethoxycarbonylmethyl)piperidin-1-yl]ethylidene}piperidine (Compound of Compound No. 5-14)



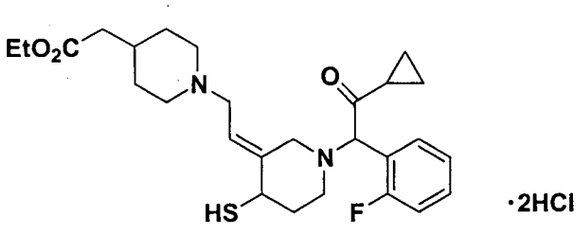
To a solution of (E)-4-(acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-hydroxyethylidene)piperidine (500 mg) obtained in Example 32 (f) and p-toluenesulfonic anhydride (580 mg) in acetonitrile (5 ml) was added triethylamine (0.22 ml) under ice cooling, the resulting mixture was stirred at room temperature for 5.5 hours. To the reaction mixture were added 4-(ethoxycarbonylmethyl)piperidine (450 mg) and triethylamine (0.37 ml), and the

204

resulting mixture was stirred at room temperature for 3 hours and then allowed to stand still for 3 days. The reaction mixture was diluted with ethyl acetate and washed with water, and the organic layer was dried over anhydrous magnesium sulfate. The solvent was removed in vacuo, and the residue was roughly purified by chromatography on a silica gel column (methanol / dichloromethane = 1 / 10) and then purified using a preparative HPLC (YMC-Pack ODS-A; YMC, eluent: acetonitrile / water containing triethylamine (0.2%) and acetic acid (0.2%) = 13 / 7). The eluted fraction was extracted with ethyl acetate and washed with a saturated aqueous sodium chloride solution, and the organic layer was dried over anhydrous magnesium sulfate. The solvent was removed in vacuo to afford the title compound (204 mg, yield 29%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 0.77-0.92 (2H, m), 0.94-1.10 (2H, m), 1.26 (3H, t, J=7.0), 1.55-1.89 (7H, m), 2.08-2.19 (2H, m), 2.21-2.26 (2H, m), 2.27-2.32 (3H, m), 2.48-2.61 (1H, m), 2.62-2.72 (1H, m), 2.72-3.40 (7H, m), 4.07-4.17 (2H, m), 4.24-4.36 (1H, m), 4.65-4.75 (1H, m), 5.69 (1H, bs), 7.08-7.22 (2H, m), 7.29-7.42 (2H, m).

(Example 34) (E)-1-[2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{2-[4-(ethoxycarbonylmethyl)piperidin-1-yl]ethylidene}-4-sulfanylpiperidine dihydrochloride (Hydrochloride of the compound of Compound No. 5-13)

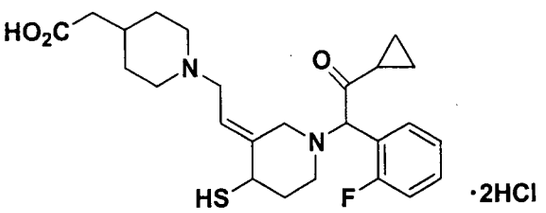


To a solution of (E)-4-(acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{2-[4-(ethoxycarbonylmethyl)piperidin-1-yl]ethylidene}piperidine (204 mg) obtained in Example 33 in ethanol (10 ml) was bubbled hydrogen chloride under ice cooling, and the resulting mixture was stirred at room temperature under

tightly sealed conditions overnight. The reaction mixture was evaporated in vacuo to afford the title compound (201 mg, yield 93%) as a colorless amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 0.71-0.86 (2H, m), 1.03-1.12 (2H, m), 1.14 (3H, t, J=7.0), 1.71-1.82 (1H, m), 1.94-2.08 (2H, m), 2.09-2.49 (6H, m), 2.57-3.02 (4H, m), 3.33-3.48 (1H, m), 3.49-3.71 (4H, m), 3.76-3.83 (2H, m), 3.83-3.92 (1H, m), 4.11 (2H, q, J=7.0), 5.03 and 5.04 (total 1H, each s), 6.31-6.43 (1H, m), 7.13-7.31 (2H, m), 7.31-7.42 (1H, m), 7.54-7.65 (1H, m).

(Example 35) (E)-3-[2-(4-Carboxymethylpiperidin-1-yl)ethylidene]-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-sulfanylpiperidine dihydrochloride (Hydrochloride of the compound of Compound No. 5-9)

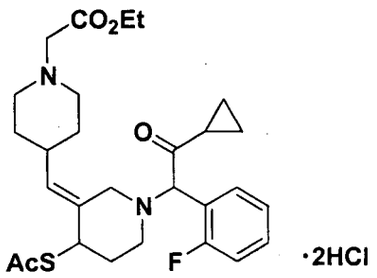


The title compound was synthesized in a yield of 57% as a colorless amorphous solid using (E)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{2-[4-(ethoxycarbonylmethyl)piperidin-1-yl]ethylidene}-4-sulfanylpiperidine dihydrochloride obtained in Example 34 by conducting a reaction similar to that mentioned in Example 15.

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm : 0.72-0.88 (2H, m), 1.04-1.17 (2H, m), 1.71-1.83 (1H, m), 1.94-2.11 (2H, m), 2.11-2.34 (5H, m), 2.46 (2H, bs), 2.65-2.76 (1H, m), 2.76-3.07 (4H, m), 3.46 (1H, d, J=12.5), 3.59 (1H, d, J=12.5), 3.62-3.75 (2H, m), 3.83-3.96 (2H, m), 5.08 (1H, s), 6.40 (1H, m), 7.22-7.31 (2H, m), 7.34-7.41 (1H, m), 7.61-7.67 (1H, m);

IR (KBr, cm^{-1}) :2556, 1714, 1493.

(Example 36) (E)-4-(Acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{[1-(ethoxycarbonylmethyl)piperidin-4-yl]methylidene}piperidine dihydrochloride (Hydrochloride of the compound of Compound No. 3-32)



(a) 3-{[1-(Ethoxycarbonylmethyl)piperidin-4-yl]hydroxymethyl}-1-(triphenylmethyl)piperidin-4-one

To a solution of 1-(triphenylmethyl)piperidin-4-one (22.99 g) in tetrahydrofuran (250 ml) was added dropwise a 1.0N solution of sodium bis(trimethylsilyl)amide in tetrahydrofuran (68 ml) at -78°C, and the resulting mixture was stirred at the same temperature for 20 minutes. To the reaction mixture was added dropwise a solution of 1-(ethoxycarbonylmethyl)piperidin-4-carbaldehyde (13.43 g) in tetrahydrofuran (35 ml) at -78°C, and the resulting mixture was stirred at the same temperature for 2 hours. The reaction mixture was charged with a saturated aqueous ammonium chloride solution and then extracted with a mixed solvent of ethyl acetate and diethyl ether. The extract was washed with water and a saturated aqueous sodium chloride solution, and the organic layer was dried over anhydrous sodium sulfate. The solvent was removed in vacuo, and the residue was purified by chromatography on a silica gel column (ethyl acetate / hexane = 1 / 4 - 1 / 0) to afford the title compound (12.32 g, yield 34%) as a pale yellow amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 1.27 (3H, t, J=7.0), 1.41-2.18 (8H, m), 2.30-2.51 (1H, m), 2.67-3.25 (8H, m), 3.45-3.71 (2H, m), 4.18 (2H, q, J=7.0), 7.11-7.60 (15H, m).

(b) (E)-3-{[1-(Ethoxycarbonylmethyl)piperidin-4-yl]methylidene}-1-(triphenylmethyl)piperidin-4-one

To a solution of 3-{[1-(ethoxycarbonylmethyl)piperidin-4-yl]hydroxymethyl}-1-(triphenylmethyl)-piperidin-4-one (9.87 g) obtained in (a) above in tetrahydrofuran (150 ml) were added methanesulfonyl chloride (7.0 ml), 1,8-diazabicyclo[5.4.0]undec-7-ene (19 ml) and 4-dimethylaminopyridine (0.23 g) under ice cooling, and the resulting mixture was stirred at room temperature for 17 hours. The reaction mixture was diluted with a mixed solvent of ethyl acetate and diethyl ether and washed with water and a saturated aqueous sodium chloride solution, and the organic layer was dried over anhydrous sodium sulfate. The solvent was removed in vacuo, and the residue was purified by chromatography on a silica gel column (ethyl acetate / hexane = 1 / 4 – 4 / 1) to afford the title compound (3.92 g, yield 41%) as a yellow amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 1.27 (3H, t, J=7.0), 1.50-1.66 (4H, m), 1.89-2.01 (1H, m), 2.10-2.21 (2H, m), 2.50-2.69 (4H, m), 2.83-2.93 (2H, m), 3.08-3.23 (4H, m), 4.18 (2H, q, J=7.0), 6.49 (1H, d, J=10.0), 7.14-7.33 (9H, m), 7.46-7.56 (6H, m).

(c) (E)-3-{[1-(Ethoxycarbonylmethyl)piperidin-4-yl]methylidene}-1-(triphenylmethyl)piperidin-4-ol

To a solution of (E)-3-{[1-(ethoxycarbonylmethyl)piperidin-4-yl]methylidene}-1-(triphenylmethyl)piperidin-4-one (6.14 g) obtained in (b) above in a mixed solvent of ethanol (40 ml) and dichloromethane (40 ml) was added sodium borohydride (0.55 g) under ice cooling, and the resulting mixture was stirred at room temperature for 1 hour. The reaction mixture was diluted with ethyl acetate and washed with a saturated aqueous sodium hydrogen carbonate solution and a saturated aqueous sodium chloride solution, and the organic layer was dried over anhydrous sodium sulfate. The solvent was removed in vacuo, and the residue was purified by

chromatography on a silica gel column (ethyl acetate / hexane = 2 / 3) to afford the title compound (4.17 g, yield 68%) as a colorless amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 1.29 (3H, t, J=7.5), 1.44-2.18 (7H, m), 2.77-3.22 (10H, m), 3.91-4.02 (1H, m), 4.20 (2H, q, J=7.5), 5.31 (1H, d, J=10.0), 7.09-7.30 (9H, m), 7.38-7.56 (6H, m).

(d) (E)-4-(Acetylsulfanyl)-3-{[1-(ethoxycarbonylmethyl)piperidin-4-yl]methylidene}piperidine bis(hydrogen trifluoroacetate)

To a solution of (E)-3-{[1-(ethoxycarbonylmethyl)piperidin-4-yl]methylidene}-1-(triphenylmethyl)piperidin-4-ol (2.98 g) obtained in (c) above in toluene (50 ml) were added thioacetic acid (1.20 ml) and N,N-dimethylformamide dineopentyl acetal (4.80 ml) under ice cooling, and the resulting mixture was stirred at room temperature for 1.5 hours. The reaction mixture was diluted with ethyl acetate and washed with water and a saturated aqueous sodium chloride solution, and the organic layer was dried over anhydrous sodium sulfate. The solvent was removed in vacuo, and the residue was purified by chromatography on a silica gel column (ethyl acetate / hexane = 2 / 3) to afford (E)-4-(acetylsulfanyl)-3-{[1-(ethoxycarbonylmethyl)piperidin-4-yl]methylidene}-1-(triphenylmethyl)piperidine (1.97 g, containing impurities) as a pale yellow amorphous solid.

To a solution of the above mixture (1.97 g) in dichloromethane (30 ml) was added trifluoroacetic acid (0.60 ml) under ice cooling, and the resulting mixture was stirred at room temperature for 30 minutes. The solvent was removed in vacuo, and the residue was purified by chromatography on a silica gel column (ethanol / dichloromethane = 1 / 4 – 2 / 3) to afford the title compound (1.53 g, yield 48%) as a yellow amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 1.29 (3H, t, J=7.0), 1.67-2.61 (10H, m), 3.00-4.03 (10H, m), 4.25 (2H, q, J=7.0), 4.39 (1H, t, J=4.5), 5.71 (1H, d, J=10.0).

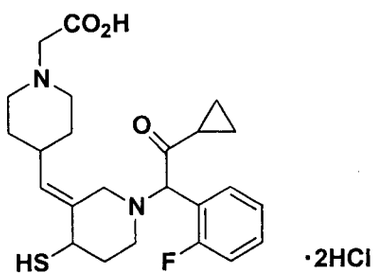
(e) (E)-4-(Acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{[1-(ethoxycarbonylmethyl)piperidin-4-yl]methylidene}piperidine dihydrochloride

The title compound was synthesized in a yield of 81% as a colorless amorphous solid using (E)-4-(acetylsulfanyl)-3-{[1-(ethoxycarbonylmethyl)piperidin-4-yl]methylidene}piperidine bis(hydrogen trifluoroacetate) obtained in (d) above by conducting a reaction similar to that mentioned in Example 1 (g).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 0.76-0.89 (2H, m), 0.90-1.12 (2H, m), 1.28 (3H, t, J=7.0), 1.39-2.34 (11H, m), 2.41-2.98 (7H, m), 3.18 and 3.19 (total 2H, each s), 3.28-3.39 (1H, m), 4.13-4.33 (3H, m), 4.63 and 4.70 (total 1H, each s), 5.38 (1H, d, J=9.0), 7.05-7.21 (2H, m), 7.27-7.37 (1H, m), 7.39-7.51 (1H, m);

IR (KBr, cm^{-1}) : 2614, 1697.

(Example 37) (E)-3-{[1-(Carboxymethyl)piperidin-4-yl]methylidene}-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-sulfanylpiperidine dihydrochloride (Hydrochloride of the compound of Compound No. 3-27)



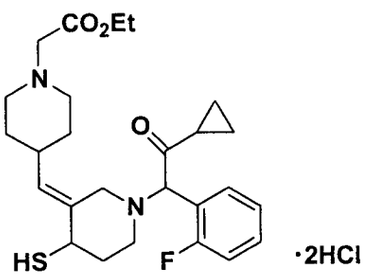
To a solution of (E)-4-(acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{[1-(ethoxycarbonylmethyl)piperidin-4-yl]methylidene}piperidine (1.13 g) obtained in Example 36 (e) in ethanol (20 ml) was bubbled hydrogen chloride under ice cooling, and the resulting mixture was stirred at room temperature under tightly sealed condition for 3 hours. After the reaction mixture was evaporated in vacuo, the obtained residue was dissolved in 3N hydrochloric acid (20

ml) and the resulting mixture was stirred at 50°C for 12.5 hours. The reaction mixture was removed in vacuo, and the residue was purified using a preparative HPLC (YMC-Pack ODS-A; YMC, eluent: acetonitrile / 0.024N hydrochloric acid = 10 / 90) to afford the title compound (0.38 g, yield 34%) as a colorless amorphous solid.

^{1}H NMR (400 MHz, pyridine-d_5) δ ppm : 0.75-0.87 (2H, m), 0.96-1.19 (2H, m), 1.62-2.54 (8H, m), 2.62-3.19 (4H, m), 3.31-3.87 (5H, m), 4.10 and 4.11 (total 2H, each s), 4.94 and 4.95 (total 1H, each s), 5.49 and 5.50 (total 1H, each d, J=9.0), 7.18-7.39 (3H, m), 7.70-7.78 (1H, m);

IR (KBr, cm^{-1}) : 2659, 1713, 1494.

(Example 38) (E)-1-[2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{[1-(ethoxycarbonylmethyl)piperidin-4-yl]methylidene}-4-sulfanylpiperidine dihydrochloride (Hydrochloride of the compound of Compound No. 3-31)

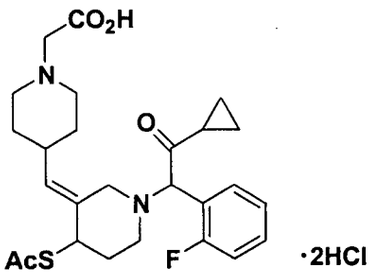


To a solution of (E)-3-{[1-(carboxymethyl)piperidin-4-yl]methylidene}-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-sulfanylpiperidine dihydrochloride (0.17 g) obtained in Example 37 in ethanol (4 ml) was bubbled hydrogen chloride under ice cooling, and the resulting mixture was stirred at room temperature under tightly sealed conditions for 7 hours. The reaction mixture was allowed to stand still at -20°C for 3 days and then stirred at room temperature for further 7 hours. The reaction mixture was evaporated in vacuo, and the residue was purified by chromatography on a silica gel column (ethanol / dichloromethane = 1 / 99 – 1 / 4) to afford the title compound (0.16 g, yield 89%) as a colorless amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 0.77-1.12 (4H, m), 1.28 (3H, t, J=7.0), 1.41-2.36 (8H, m), 2.55-3.36 (10H, m), 3.68-3.81 (1H, m), 4.19 (2H, q, J=7.0), 4.66 and 4.72 (total 1H, each s), 5.32 and 5.34 (total 1H, each d, J=9.0), 7.03-7.55 (4H, m);

IR (KBr, cm^{-1}) : 2617, 1713, 1494.

(Example 39) (E)-4-(Acetylsulfanyl)-3-{[(1-carboxymethyl)piperidin-4-yl]methylidene}-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]piperidine dihydrochloride (Hydrochloride of the compound of Compound No. 3-28)

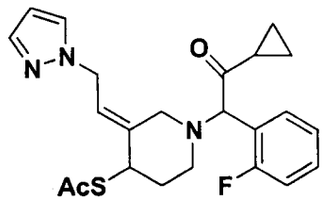


The title compound was synthesized in a yield of 52% as a colorless amorphous solid using (E)-3-{[1-(carboxymethyl)piperidin-4-yl]methylidene}-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-sulfanylpiperidine dihydrochloride obtained in Example 37 by conducting a reaction similar to that mentioned in Example 28.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 0.73-0.89 (2H, m), 0.95-1.07 (2H, m), 1.67-2.34 (11H, m), 2.47-3.42 (10H, m), 4.21 and 4.27 (total 1H, each t, J=4.5), 4.73 and 4.75 (total 1H, each s), 5.37-5.45 (1H, m), 7.09-7.20 (2H, m), 7.31-7.39 (2H, m);

IR (KBr, cm^{-1}) : 2627, 1698.

(Example 40) (E)-4-(Acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-[2-(1H-pyrazol-1-yl)ethylidene]piperidine (Compound of Compound No. 1-2)



(a) (E)-4-(t-Butyldimethylsilyloxy)-3-[2-(1H-pyrazol-1-yl)ethylidene]-1-(triphenylmethyl)piperidine

To a solution of (E)-4-(t-butyldimethylsilyloxy)-3-(2-hydroxyethylidene)-1-(triphenylmethyl)piperidine (14.7 g) obtained in Example 1 (b), 1H-pyrazole (2.0 g) and 1,1'-(azodicarbonyl)dipiperidine (8.9 g) in toluene (150 ml) under a stream of nitrogen gas was added tributylphosphine (8.8 ml) under ice cooling, and the resulting mixture was stirred at room temperature for 1 hour. The reaction mixture was evaporated in vacuo, and the residue was purified by chromatography on a silica gel column (ethyl acetate / hexane = 1 / 6) to afford the title compound (9.78 g, yield 57%) as a colorless amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 0.04 (3H, s), 0.06 (3H, s), 0.89 (9H, s), 1.82 (1H, bs), 1.90-2.03 (3H, m), 3.04 (1H, bs), 3.74 (1H, bs), 3.97 (1H, m), 4.78-4.90 (2H, m), 5.86 (1H, t, J=7.0), 6.33-6.34 (1H, m), 7.22-7.23 (5H, m), 7.28-7.32 (4H, m), 7.48-7.68 (8H, m).

(b) (E)-4-Hydroxy-3-[2-(1H-pyrazol-1-yl)ethylidene]-1-(triphenylmethyl)piperidine

The title compound was synthesized in a yield of 77% as a colorless powder crystal using (E)-4-(t-butyldimethylsilyloxy)-3-[2-(1H-pyrazol-1-yl)ethylidene]-1-(triphenylmethyl)piperidine obtained in (a) above by conducting a reaction similar to that mentioned in Example 1 (e).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 1.44-1.50 (1H, m), 1.65-1.70 (1H, m), 1.82-1.89 (1H, m), 2.08-2.12 (1H, m), 2.85 (1H, bs), 3.38-3.41 (1H, m), 4.01 (1H, bs), 4.73-4.82 (2H, m), 5.79 (1H, t, J=6.5), 6.28 (1H, m), 7.15-7.17 (5H, m), 7.24-7.27 (4H, m), 7.42 (1H, m), 7.49 (6H, bs), 7.53 (1H, m).

(c) (E)-4-(Acetylsulfanyl)-3-[2-(1H-pyrazol-1-yl)ethylidene]-1-(triphenylmethyl)piperidine

The title compound was synthesized in a yield of 56% as a yellow amorphous solid using (E)-4-hydroxy-3-[2-(1H-pyrazol-1-yl)ethylidene]-1-(triphenylmethyl)piperidine obtained in (b) above by conducting a reaction similar to that mentioned in Example 1 (h).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 1.85-1.92 (1H, m), 2.24 (3H, s), 2.26-2.34 (1H, m), 2.64-2.67 (1H, m), 2.79-2.83 (1H, m), 4.21-4.36 (3H, m), 4.65-4.78 (2H, m), 5.79 (1H, t, J=7.0), 6.26 (1H, m), 7.11-7.15 (5H, m), 7.22-7.27 (4H, m), 7.42 (1H, m), 7.45 (6H, bs), 7.62 (1H, m).

(d) (E)-4-(Acetylsulfanyl)-3-[2-(1H-pyrazol-1-yl)ethylidene]piperidine hydrogen trifluoroacetate

The title compound was synthesized in a yield of 32% as a brown oil using (E)-4-(acetylsulfanyl)-3-[2-(1H-pyrazol-1-yl)ethylidene]-1-(triphenylmethyl)piperidine obtained in (c) above by conducting a reaction similar to that mentioned in Example 3 (c).

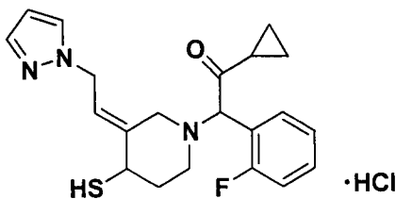
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 2.03-2.07 (1H, m), 2.35 (3H, s), 2.38-2.45 (1H, m), 3.23-3.30 (1H, m), 3.38-3.43 (1H, m), 3.73 (1H, d, J=14.0), 4.12 (1H, d, J=14.0), 4.43-4.45 (1H, m), 4.68-4.84 (2H, m), 6.03 (1H, t, J=7.0), 6.23-6.24 (1H, m), 7.39-7.40 (1H, m), 7.46 (1H, bs).

(e) (E)-4-(Acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-[2-(1H-pyrazol-1-yl)ethylidene]piperidine

The title compound was synthesized in a yield of 75% as a yellow oil using (E)-4-(acetylsulfanyl)-3-[2-(1H-pyrazol-1-yl)ethylidene]piperidine hydrogen trifluoroacetate obtained in (d) above by conducting a reaction similar to that mentioned in Example 1 (g).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 0.75-0.88 (2H, m), 0.97-1.06 (2H, m), 1.79-1.86 (1H, m), 2.10-2.21 (1H, m), 2.22-2.31 (1H, m), 2.28 and 2.29 (total 3H, each s), 2.49-2.62 (1H, m), 2.68-2.73 and 2.76-2.81 (total 1H, each m), 2.89 and 3.16 (total 1H, each d, J=12.5), 3.32 and 3.43 (total 1H, each d, J=12.5), 4.28-4.35 (1H, m), 4.67-4.75 (3H, m), 5.80 (1H, t, J=7.0), 6.22-6.24 (1H, m), 7.08-7.17 (2H, m), 7.28-7.38 (3H, m), 7.47-7.48 (1H, m).

(Example 41) (E)-1-[2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-[2-(1H-pyrazol-1-yl)ethylidene]-4-sulfanylpiperidine hydrochloride (Hydrochloride of the compound of Compound No. 1-1)

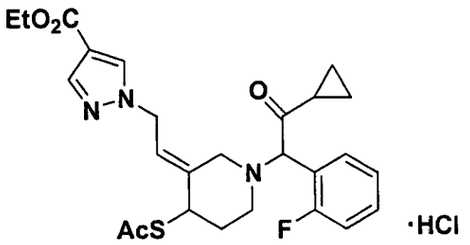


The title compound was synthesized in a yield of 27% as a colorless amorphous solid using (E)-4-(acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-[2-(1H-pyrazol-1-yl)ethylidene]piperidine obtained in Example 40 (e) by conducting a reaction similar to that mentioned in Example 2.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 0.77-0.80 (2H, m), 0.98-1.03 (1H, m), 1.06-1.13 (1H, m), 1.74-1.81 (1H, m), 2.13-2.24 (1H, m), 2.39-2.47 (1H, m), 2.51-2.54 (1H, m), 2.83-2.88 and 2.91-2.97 (total 1H, each m), 3.33-3.38 (1H, m), 3.75-3.80 (1H, m), 4.90-4.96 (3H, m), 5.94-5.98 (1H, m), 6.33 (1H, t, J=2.0), 7.17-7.22 (1H, m), 7.26-7.32 (1H, m), 7.63-7.66 (3H, m), 7.70-7.71 (2H, m);

IR (KBr, cm^{-1}) : 1712, 1495.

(Example 42) (E)-4-(Acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-[2-(4-ethoxycarbonyl-1H-pyrazol-1-yl)ethylidene]piperidine hydrochloride (Hydrochloride of the compound of Compound No. 1-26)



(a) (E)-4-(t-Butyldimethylsilyloxy)-3-[2-(4-ethoxycarbonyl-1H-pyrazol-1-yl)ethylidene]-1-(triphenylmethyl)piperidine

The title compound was synthesized in a yield of 83% as a colorless amorphous solid using (E)-4-(t-butyldimethylsilyloxy)-3-(2-hydroxyethylidene)-1-(triphenylmethyl)piperidine obtained in Example 1 (b) and 4-ethoxycarbonyl-1H-pyrazole by conducting a reaction similar to that mentioned in Example 40 (a).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 0.04 (6H, s), 0.88 (9H, s), 1.36-1.49 (2H, m), 1.40 (3H, t, J=7.0), 1.71-1.82 (1H, m), 1.90-2.00 (2H, m), 2.40 (1H, bs), 3.93-3.97 (1H, m), 4.34 (2H, q, J=7.0), 4.73-4.86 (2H, m), 5.84 (1H, t, J=7.0), 7.19-7.23 (5H, m), 7.27-7.32 (5H, m), 7.52 (5H, bs), 7.95 (1H, s), 7.97 (1H, s).

(b) (E)-3-[2-(4-Ethoxycarbonyl-1H-pyrazol-1-yl)ethylidene]-4-hydroxy-1-(triphenylmethyl)piperidine

The title compound was synthesized in a quantitative yield as a colorless amorphous solid using (E)-4-(t-butyldimethylsilyloxy)-3-[2-(4-ethoxycarbonyl-1H-pyrazol-1-yl)ethylidene]-1-(triphenylmethyl)piperidine obtained in (a) above by conducting a reaction similar to that mentioned in Example 1 (e).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 1.34 (3H, t, J=7.0), 1.81-1.90 (1H, m), 2.07-2.12 (1H, m), 2.87 (2H, bs), 3.46 (2H, bs), 3.98 (1H, bs), 4.28 (2H, q, J=7.0), 4.68-4.79 (2H, m), 5.76 (1H, t, J=7.0), 7.12-7.15 (3H, m), 7.21-7.25 (6H, m), 7.45 (6H, bs), 7.89 (2H, s).

(c) (E)-4-(Acetylsulfanyl)-3-[2-(4-ethoxycarbonyl-1H-pyrazol-1-yl)ethylidene]-1-(triphenylmethyl)piperidine

The title compound was synthesized in a yield of 88% as a yellow amorphous solid using (E)-3-[2-(4-ethoxycarbonyl-1H-pyrazol-1-yl)ethylidene]-4-hydroxy-1-(triphenylmethyl)piperidine obtained in (b) above by conducting a reaction similar to that mentioned in Example 1 (h).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 1.26 (3H, t, J=7.0), 1.86-1.94 (1H, m), 2.21-2.24 (1H, m), 2.24 (3H, s), 3.80-3.83 (1H, m), 4.11 (2H, q, J=7.0), 4.19-4.27 (6H, m), 5.77 (1H, t, J=7.0), 7.12-7.17 (5H, m), 7.22-7.26 (5H, m), 7.43-7.45 (5H, m), 7.85 (1H, s), 7.91 (1H, s).

(d) (E)-4-(Acetylsulfanyl)-3-[2-(4-ethoxycarbonyl-1H-pyrazol-1-yl)ethylidene]piperidine hydrogen trifluoroacetate

The title compound was synthesized in a yield of 23% as a brown amorphous solid using (E)-4-(acetylsulfanyl)-3-[2-(4-ethoxycarbonyl-1H-pyrazol-1-yl)ethylidene]-1-(triphenylmethyl)piperidine obtained in (c) above by conducting a reaction similar to that mentioned in Example 3 (c).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 1.33 (3H, t, J=7.0), 2.07-2.10 (1H, m), 2.36 (3H, s), 2.38-2.46 (1H, m), 3.22-3.28 (1H, m), 3.36-3.42 (1H, m), 3.73 (1H, d, J=14.0), 4.11 (1H, d, J=14.0), 4.27 (2H, q, J=7.0), 4.44-4.46 (1H, m), 4.72-4.84 (2H, m), 6.04-6.07 (1H, m), 7.85 (1H, s), 7.88 (1H, s).

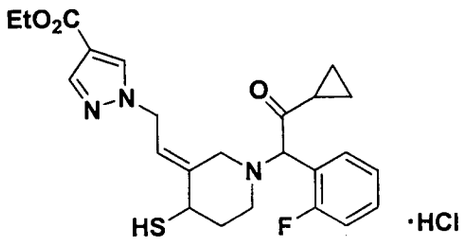
(e) (E)-4-(Acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-[2-(4-ethoxycarbonyl-1H-pyrazol-1-yl)ethylidene]piperidine hydrochloride

The title compound was synthesized in a yield of 74% as a yellow amorphous solid using (E)-4-(acetylsulfanyl)-3-[2-(4-ethoxycarbonyl-1H-pyrazol-1-yl)ethylidene]piperidine hydrogen trifluoroacetate obtained in (d) above by conducting a reaction similar to that mentioned in Example 1 (g).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 0.75-0.88 (2H, m), 1.00-1.07 (2H, m), 1.34 (3H, t, J=7.0), 1.80-1.87 (1H, m), 2.08-2.26 (2H, m), 2.28 and 2.30 (total 3H, each s), 2.50-2.60 (1H, m), 2.67-2.72 and 2.78-2.82 (total 1H, each m), 2.87 and 3.18

(total 1H, each d, J=12.5), 3.29 and 3.44 (total 1H, each d, J=12.5), 4.28 (2H, q, J=7.0), 4.33-4.35 (1H, m), 4.67-4.76 (3H, m), 5.79 (1H, t, J=7.0), 7.08-7.17 (2H, m), 7.29-7.37 (2H, m), 7.85-7.87 (2H, m).

(Example 43) (E)-1-[2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-[2-(4-ethoxycarbonyl-1H-pyrazol-1-yl)ethylidene]-4-sulfanylpiperidine hydrochloride (Hydrochloride of the compound of Compound No. 1-25)

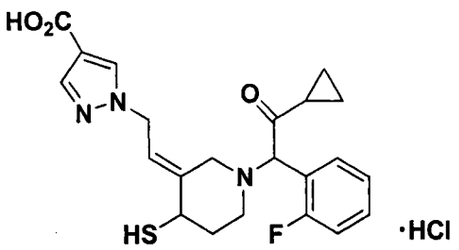


The title compound was synthesized in a yield of 46% as a yellow amorphous solid using (E)-4-(acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-[2-(4-ethoxycarbonyl-1H-pyrazol-1-yl)ethylidene]piperidine obtained in Example 42 (e) by conducting a reaction similar to that mentioned in Example 34.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 0.76-0.88 (2H, m), 1.00-1.04 (2H, m), 1.35 (3H, t, J=7.0), 1.73-1.79 (1H, m), 2.09-2.12 (1H, m), 2.17-2.28 (1H, m), 2.54-2.60 and 2.61-2.67 (total 1H, each m), 2.78-2.85 (1H, m), 3.04 and 3.24 (total 1H, each d, J=12.5), 3.31 and 3.54 (total 1H, each d, J=12.5), 3.65-3.70 and 3.73-3.77 (total 1H, each m), 4.28 (2H, q, J=7.0), 4.69-4.77 (3H, m), 5.74-5.82 (1H, m), 7.09-7.17 (2H, m), 7.29-7.38 (2H, m), 7.87-7.90 (2H, m);

IR (KBr, cm^{-1}) : 2466, 1712, 1554.

(Example 44) (E)-3-[2-(4-Carboxy-1H-pyrazol-1-yl)ethylidene]-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-sulfanylpiperidine hydrochloride (Hydrochloride of the compound of Compound No. 1-17)

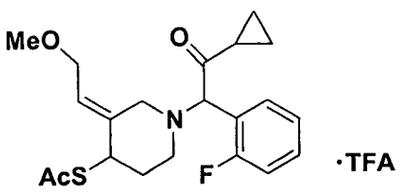


The title compound was synthesized in a yield of 14% as a colorless amorphous solid using (E)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-[2-(4-ethoxycarbonyl-1H-pyrazol-1-yl)ethylidene]-4-sulfanylpiperidine obtained in Example 43 by conducting a reaction similar to that mentioned in Example 15.

^{1}H NMR (400 MHz, pyridine-d_5) δ ppm : 0.79-0.82 (2H, m), 1.01-1.05 (1H, m), 1.09-1.13 (1H, m), 1.75-1.83 (1H, m), 2.16-2.25 (1H, m), 2.41-2.49 (1H, m), 2.62-2.68 (1H, m), 2.85-2.91 and 2.92-2.98 (total 1H, each m), 3.35 and 3.38 (total 1H, each d, J=13.0), 3.63 and 3.70 (total 1H, each d, J=13.0), 3.79-3.82 (1H, m), 4.91-5.05 (3H, m), 5.99-6.03 (1H, m), 7.19-7.27 (2H, m), 7.29-7.35 (1H, m), 7.68-7.72 (1H, m), 8.43 (1H, s), 8.53 (1H, d, J=1.5);

IR (KBr, cm^{-1}) : 2546, 1709, 1555.

(Example 45) (E)-4-(Acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-methoxyethylidene)piperidine hydrogen trifluoroacetate (Hydrogen trifluoroacetate of the compound of Compound No. 3-6)



(a) (E)-4-(t-Butyldimethylsilyloxy)-3-(2-methoxyethylidene)-1-(triphenylmethyl)piperidine

To a solution of (E)-4-(t-butyldimethylsilyloxy)-3-(2-hydroxyethylidene)-1-(triphenylmethyl)piperidine (1.85 g) obtained in Example 1 (b) in N,N-dimethylformamide (20 ml) was added sodium hydride (0.23 g) under ice cooling,

and the resulting mixture was stirred at room temperature for 15 minutes. To the reaction mixture was added methyl iodide (0.34 ml) at the same temperature, and the resulting mixture was stirred at room temperature overnight. The reaction mixture was diluted with a mixed solvent of ethyl acetate and ether and washed with a saturated aqueous sodium hydrogen carbonate solution and a saturated aqueous sodium chloride solution, and the organic layer was dried over anhydrous sodium sulfate. The solvent was removed in vacuo, and the residue was purified by chromatography on a silica gel column (ethyl acetate / hexane = 1 / 24) to afford the title compound (1.41 g, yield 74%) as a colorless oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : -0.02 (3H, s), -0.01 (3H, s), 0.86 (9H, s), 1.69-2.00 (4H, m), 2.87-2.96 (1H, m), 3.31 (3H, s), 3.49-3.61 (1H, m), 3.83-4.02 (3H, m), 5.72 (1H, t, J=8.0), 7.12-7.20 (3H, m), 7.22-7.28 (6H, m), 7.40-7.55 (6H, m).

(b) (E)-4-Hydroxy-3-(2-methoxyethylidene)-1-(triphenylmethyl)piperidine

The title compound was synthesized in a quantitative yield as a colorless amorphous solid using (E)-4-(t-butyldimethylsilyloxy)-3-(2-methoxyethylidene)-1-(triphenylmethyl)piperidine obtained in (a) above by conducting a reaction similar to that mentioned in Example 1 (e).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 1.75-2.13 (4H, m), 2.66-2.81 (2H, m), 3.35 (3H, m), 3.88-4.02 (3H, m), 5.70 (1H, t, J=7.0), 7.13-7.20 (3H, m), 7.23-7.30 (6H, m), 7.43-7.53 (6H, m).

(c) (E)-4-Hydroxy-3-(2-methoxyethylidene)piperidine bis(hydrogen trifluoroacetate)

The title compound was synthesized in a yield of 95% as a colorless oil using (E)-4-hydroxy-3-(2-methoxyethylidene)-1-(triphenylmethyl)piperidine obtained in (b) above by conducting a reaction similar to that mentioned in Example 3 (c).

^{1}H NMR (400 MHz, $CDCl_3$+DMSO-d_6) δ ppm : 1.88-2.13 (2H, m), 3.11-3.19 (1H, m), 3.32 (3H, s), 3.39-3.48 (1H, m), 3.75 (1H, d, J=13.5), 3.92 (1H, d, J=13.5), 4.01 (2H, d, J=6.0), 4.22-4.27 (1H, m), 5.87 (1H, t, J=6.0).

(d) (E)-1-[2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-hydroxy-3-(2-methoxyethylidene)piperidine

The title compound was synthesized in a yield of 78% as a brown oil using (E)-4-hydroxy-3-(2-methoxyethylidene)piperidine bis(hydrogen trifluoroacetate) obtained in (c) above by conducting a reaction similar to that mentioned in Example 1 (g).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 0.78-1.09 (4H, m), 1.68-1.79 (1H, m), 1.96-2.05 (1H, m), 2.19-2.28 (1H, m), 2.42-2.54 (1H, m), 2.76-3.00 (2H, m), 3.30 (3H, s), 3.36 and 3.47 (total 1H, each d, J=12.0), 3.92 (2H, d, J=6.0), 4.07-4.15 (1H, m), 4.69 and 4.71 (total 1H, each s), 5.68 and 5.69 (total 1H, each t, J=6.0), 7.07-7.20 (2H, m), 7.28-7.46 (2H, m).

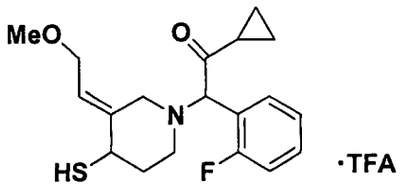
(e) (E)-4-(Acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-methoxyethylidene)piperidine hydrogen trifluoroacetate

The title compound was synthesized in a yield of 30% as a pale brown oil using (E)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-hydroxy-3-(2-methoxyethylidene)piperidine obtained in (d) above by conducting a reaction similar to that mentioned in Example 3 (e).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 0.79-0.89 (2H, m), 0.95-1.08 (2H, m), 1.77-1.85 (1H, m), 2.11-2.28 (2H, m), 2.29 and 2.30 (total 3H, each s), 2.46-3.08 (3H, m), 3.26 and 3.28 (total 3H, each s), 3.30-3.56 (1H, m), 3.81-3.92 (2H, m), 4.28-4.36 (1H, m), 4.68 and 4.71 (total 1H, each s), 5.72 (1H, t, J=6.5), 7.07-7.20 (2H, m), 7.29-7.35 (1H, m), 7.39-7.45 (1H, m);

IR (liquid film, cm^{-1}) : 1711, 1495.

(Example 46) (E)-1-[2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-methoxyethylidene)-4-sulfanylpiperidine hydrogen trifluoroacetate (Hydrogen trifluoroacetate of the compound of Compound No. 3-5)

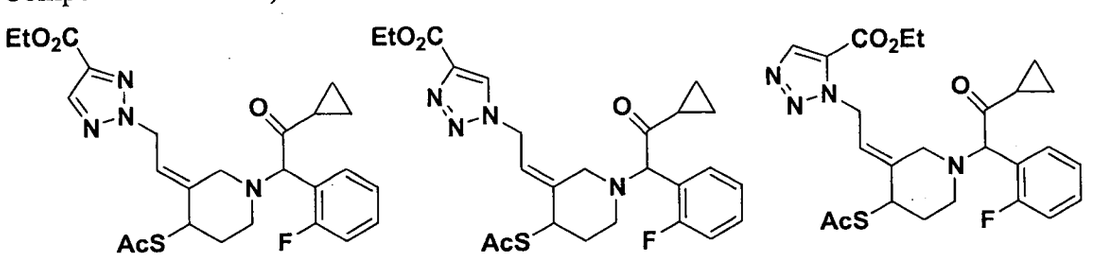


The title compound was synthesized in a yield of 60% as a colorless oil using (E)-4-(acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-methoxyethylidene)piperidine hydrogen trifluoroacetate obtained in Example 45 (e) by conducting a reaction similar to that mentioned in Example 2.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 0.79-0.90 (2H, m), 0.95-1.09 (2H, m), 1.69-1.78 (1H, m), 2.13-2.32 (2H, m), 2.51-2.87 (2H, m), 3.03-3.57 (2H, m), 3.27 and 3.29 (total 3H, each s), 3.70-3.92 (3H, m), 4.70 and 4.73 (total 1H, each s), 5.68 and 5.71 (total 1H, each t, J=6.5), 7.07-7.20 (2H, m), 7.28-7.46 (2H, m);

IR (liquid film, cm^{-1}) : 2564, 1714, 1495.

(Example 47) (E)-4-(Acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-[2-(4-ethoxycarbonyl-2H-1,2,3-triazol-2-yl)ethylidene]piperidine (Compound of Compound No. 1-592), (E)-4-(acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-[2-(4-ethoxycarbonyl-1H-1,2,3-triazol-1-yl)ethylidene]piperidine (Compound of Compound No. 1-492) and (E)-4-(acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-[2-(5-ethoxycarbonyl-1H-1,2,3-triazol-1-yl)ethylidene]piperidine (Compound of Compound No. 1-498)



To a solution of (E)-4-(acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-hydroxyethylidene)piperidine (1000 mg) obtained in Example 32

(f) and 4-ethoxycarbonyl-1H-1,2,3-triazole (449 mg) in toluene (10 ml) under a stream of nitrogen gas were added 1,1'-(azodicarbonyl)dipiperidine (802 mg) and tributylphosphine (0.79 ml) under ice cooling, and the resulting mixture was stirred at room temperature for 18 hours. To the reaction mixture were added 4-ethoxycarbonyl-1H-1,2,3-triazole (224 mg), 1,1'-(azodicarbonyl)dipiperidine (802 mg) and tributylphosphine (0.79 ml), and the resulting mixture was stirred at room temperature for 4.5 hours. To the reaction mixture were added 4-ethoxycarbonyl-1H-1,2,3-triazole (112 mg), 1,1'-(azodicarbonyl)dipiperidine (200 mg) and tributylphosphine (0.20 ml), and the resulting mixture was further stirred at room temperature for 2 hours. The reaction mixture was evaporated in vacuo, and the residue was roughly purified by chromatography on a silica gel column (ethyl acetate / hexane = 1 / 2 – 1 / 1) and then purified using a preparative HPLC (YMC-Pack ODS-A; YMC, eluent: acetonitrile / 0.024N hydrochloric acid = 15 / 85) to afford the hydrochlorides of the three title compounds. Each of the obtained hydrochlorides was neutralized with a saturated aqueous sodium hydrogen carbonate solution and extracted with ethyl acetate. The extract was washed with a saturated aqueous sodium chloride solution, and the organic layer was dried over anhydrous magnesium sulfate. The solvent was removed in vacuo to afford the three title compounds.

(E)-4-(Acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-[2-(4-ethoxycarbonyl-1H-1,2,3-triazol-1-yl)ethylidene]piperidine having the highest polarity: a colorless oil, yielded amount 120 mg, yield 9%

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 0.76-0.90 (2H, m), 1.02-1.05 (2H, m), 1.42 (3H, t, J=7.0), 1.80-1.86 (1H, m), 1.98-2.04 (1H, m), 2.09-2.19 and 2.20-2.28 (total 1H, each m), 2.29 and 2.31 (total 3H, each s), 2.53-2.59 (1H, m), 2.66-2.71 and 2.78-2.84 (total 1H, each m), 2.90 and 3.51 (total 1H, each d, J=12.5), 3.28 (1H, bs), 4.25-4.27 and 4.32-4.34 (total 1H, each m), 4.44 (2H, q, J=7.0), 4.80 and 4.81 (total

1H, each s), 4.98-5.04 (2H, m), 5.80 (1H, t, J=7.5), 7.12-7.21 (2H, m), 7.31-7.39 (2H, m), 8.19 and 8.22 (total 1H, each s).

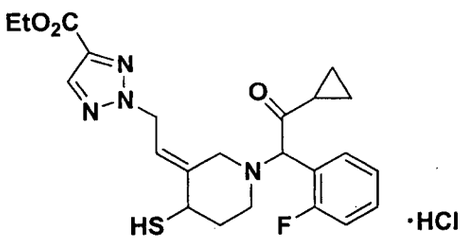
(E)-4-(Acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-[2-(5-ethoxycarbonyl-1H-1,2,3-triazol-1-yl)ethylidene]piperidine having the second highest polarity: a yellow oil, yielded amount 219 mg, yield 17%

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 0.81-0.91 (2H, m), 1.00-1.11 (2H, m), 1.39 and 1.40 (total 3H, each t, J=7.0), 1.77-1.84 (1H, m), 2.14-2.24 (2H, m), 2.25 (3H, s), 2.44-2.51 and 2.57-2.63 (total 1H, each m), 2.68-2.77 (1H, m), 3.01 and 3.19 (total 1H, each d, J=12.5), 3.48 and 3.53 (total 1H, each d, J=12.5), 4.24-4.29 (1H, m), 4.37 and 4.38 (total 2H, each q, J=7.0), 4.76 and 4.78 (total 1H, each s), 5.27-5.35 (2H, m), 5.72-5.77 (1H, m), 7.09-7.20 (2H, m), 7.28-7.44 (2H, m), 8.07 (1H, s).

(E)-4-(Acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-[2-(4-ethoxycarbonyl-2H-1,2,3-triazol-2-yl)ethylidene]piperidine having the lowest polarity: a colorless oil, yielded amount 236 mg, yield 18%

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 0.82-0.89 (2H, m), 1.00-1.08 (2H, m), 1.41 (3H, t, J=7.0), 1.79-1.86 (1H, m), 2.12-2.30 (2H, m), 2.27 and 2.28 (total 3H, each s), 2.50-2.63 (1H, m), 2.68-2.80 (1H, m), 2.95 and 3.22 (total 1H, each d, J=13.0), 3.34 and 3.68 (total 1H, each d, J=13.0), 4.28-4.35 (1H, m), 4.43 (2H, q, J=7.0), 4.75 and 4.78 (total 1H, each s), 5.05-5.13 (2H, m), 5.86 (1H, t, J=7.0), 7.11-7.22 (2H, m), 7.32-7.43 (2H, m), 8.03 (1H, s).

(Example 48) (E)-1-[2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-[2-(4-ethoxycarbonyl-2H-1,2,3-triazol-2-yl)ethylidene]-4-sulfanylpiperidine hydrochloride (Hydrochloride of the compound of Compound No. 1-591)

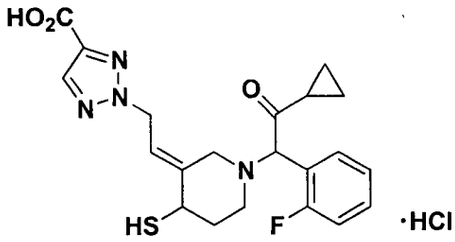


The title compound was synthesized in a quantitative yield as a pale yellow oil using (E)-4-(acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-[2-(4-ethoxycarbonyl-2H-1,2,3-triazol-2-yl)ethylidene]piperidine obtained in Example 47 by conducting a reaction similar to that mentioned in Example 34.

^{1}H NMR (400 MHz, pyridine-d_5) δ ppm : 0.84-0.91 (2H, m), 1.01-1.07 (1H, m), 1.14-1.18 (1H, m), 1.23 (3H, t, J=7.0), 1.74-1.84 (1H, m), 2.14-2.24 (1H, m), 2.48-2.64 (2H, m), 2.84-2.98 (1H, m), 3.35-3.41 (1H, m), 3.69 and 3.75 (total 1H, each d, J=12.5), 3.79-3.82 (1H, m), 4.35 (2H, q, J=7.0), 4.95 and 4.96 (total 1H, each s), 5.30-5.35 (2H, m), 6.10-6.14 (1H, m), 7.23-7.35 (3H, m), 7.69-7.75 (1H, m), 8.37 (1H, s);

IR (KBr, cm^{-1}) : 2914, 1717.

(Example 49) (E)-3-[2-(4-Carboxy-2H-1,2,3-triazol-2-yl)ethylidene]-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-sulfanylpiperidine hydrochloride (Hydrochloride of the compound of Compound No. 1-587)



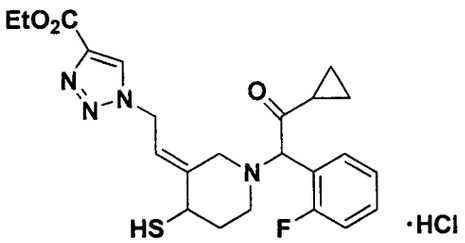
The title compound was synthesized in a yield of 74% as a colorless amorphous solid using (E)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-[2-(4-ethoxycarbonyl-2H-1,2,3-triazol-2-yl)ethylidene]-4-sulfanylpiperidine hydrochloride obtained in Example 48 by conducting a reaction similar to that mentioned in Example 15.

^{1}H NMR (400 MHz, pyridine-d_5) δ ppm : 0.80-0.94 (2H, m), 1.01-1.07 (1H, m), 1.14-1.19 (1H, m), 1.74-1.84 (1H, m), 2.14-2.25 (1H, m), 2.52-2.66 (2H, m), 2.84-2.98 (1H, m), 3.38-3.42 (1H, m), 3.70 and 3.76 (total 1H, each d, J=13.0), 3.79-

3.84 (1H, m), 4.95-4.97 (1H, m), 5.31-5.38 (2H, m), 6.12-6.17 (1H, m), 7.24-7.36 (3H, m), 7.71-7.78 (1H, m), 8.51 (1H, s);

IR (KBr, cm^{-1}) : 2927, 1712.

(Example 50) (E)-1-[2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-[2-(4-ethoxycarbonyl-1H-1,2,3-triazol-1-yl)ethylidene]-4-sulfanylpiperidine hydrochloride (Hydrochloride of the compound of Compound No. 1-491)

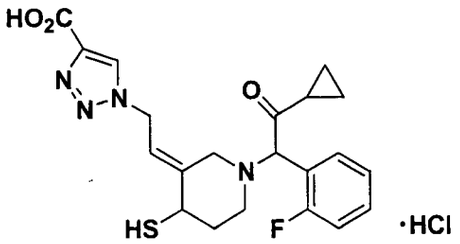


The title compound was synthesized in a quantitative yield as a colorless oil using (E)-4-(acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-[2-(4-ethoxycarbonyl-1H-1,2,3-triazol-1-yl)ethylidene]piperidine obtained in Example 47 by conducting a reaction similar to that mentioned in Example 34.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 0.77-0.90 (2H, m), 1.02-1.05 (2H, m), 1.42 (3H, t, J=7.0), 1.54-1.58 (1H, m), 1.73-1.79 (1H, m), 1.99-2.03 (1H, m), 2.15-2.29 (1H, m), 2.53-2.58 and 2.62-2.67 (total 1H, each m), 2.78-2.85 (1H, m), 3.27-3.35 (1H, m), 3.63-3.66 and 3.72-3.76 (total 1H, each m), 4.44 (2H, q, J=7.0), 4.83 (1H, s), 5.01-5.06 (2H, m), 5.76-5.85 (1H, m), 7.12-7.26 (3H, m), 7.33-7.36 (1H, m), 8.23 and 8.24 (total 1H, each s);

MS (FAB) m/z : 459 $(M+H)^+$

(Example 51) (E)-3-[2-(4-Carboxy-1H-1,2,3-triazol-1-yl)ethylidene]-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-sulfanylpiperidine hydrochloride (Hydrochloride of the compound of Compound No. 1-487)

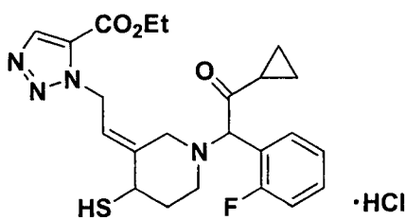


The title compound was synthesized in a yield of 71% as a colorless amorphous solid using (E)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-[2-(4-ethoxycarbonyl-1H-1,2,3-triazol-1-yl)ethylidene]-4-sulfanylpiperidine hydrochloride obtained in Example 50 by conducting a reaction similar to that mentioned in Example 15.

^{1}H NMR (400 MHz, pyridine-d_5) δ ppm : 0.77-0.81 (2H, m), 0.99-1.11 (2H, m), 1.73-1.81 (1H, m), 2.12-2.23 (1H, m), 2.29-2.36 (1H, m), 2.60-2.63 (1H, m), 2.82-2.96 (1H, m), 3.34 and 3.40 (total 1H, each d, J=12.5), 3.65 and 3.73 (total 1H, each d, J=12.5), 3.76-3.83 (1H, m), 4.96 and 4.97 (total 1H, each s), 5.21-5.27 (2H, m), 5.96-6.01 (1H, m), 7.20-7.32 (3H, m), 7.64-7.68 (1H, m), 8.88 (1H, s);

IR (KBr, cm^{-1}) : 2927, 1711.

(Example 52) (E)-1-[2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-[2-(5-ethoxycarbonyl-1H-1,2,3-triazol-1-yl)ethylidene]-4-sulfanylpiperidine hydrochloride (Hydrochloride of the compound of Compound No. 1-497)

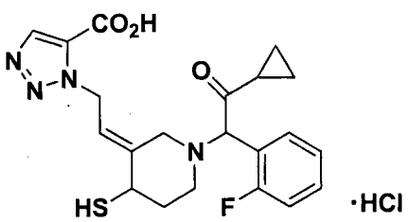


The title compound was synthesized in a yield of 90% as a colorless amorphous solid using (E)-4-(acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-[2-(5-ethoxycarbonyl-1H-1,2,3-triazol-1-yl)ethylidene]piperidine obtained in Example 47 by conducting a reaction similar to that mentioned in Example 34.

^{1}H NMR (400 MHz, pyridine-d_5) δ ppm : 0.84-0.91 (2H, m), 1.03-1.09 (1H, m), 1.15-1.22 (1H, m), 1.21 (3H, t, J=7.0), 1.75-1.83 (1H, m), 2.15-2.25 (1H, m), 2.50-2.57 (1H, m), 2.60-2.68 (1H, m), 2.84-2.89 and 2.93-2.99 (total 1H, each m), 3.46-3.54 (1H, m), 3.77-3.81 (2H, m), 4.28 (2H, q, J=7.0), 4.98 (1H, s), 5.52-5.56 (2H, m), 6.04-6.09 (1H, m), 7.21-7.35 (3H, m), 7.69-7.76 (1H, m), 8.39 (1H, s);

MS (FAB) m/z : 459 $(M+H)^+$.

(Example 53) (E)-3-[2-(5-Carboxy-1H-1,2,3-triazol-1-yl)ethylidene]-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-sulfanylpiperidine hydrochloride (Hydrochloride of the compound of Compound No. 1-493)

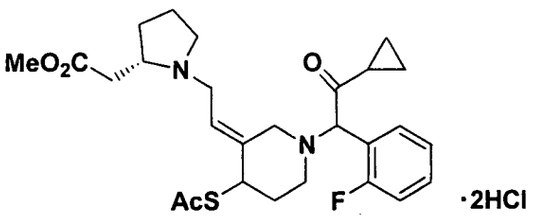


The title compound was synthesized in a yield of 68% as a colorless amorphous solid using (E)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-[2-(5-ethoxycarbonyl-1H-1,2,3-triazol-1-yl)ethylidene]-4-sulfanylpiperidine hydrochloride obtained in Example 52 by conducting a reaction similar to that mentioned in Example 15.

^{1}H NMR (400 MHz, pyridine-d_5) δ ppm : 0.77-0.91 (2H, m), 0.99-1.04 (1H, m), 1.13-1.19 (1H, m), 1.71-1.81 (1H, m), 2.10-2.21 (1H, m), 2.49-2.66 (2H, m), 2.78-2.96 (1H, m), 3.48-3.52 and 3.57-3.60 (total 1H, each m), 3.77-3.83 (2H, m), 4.95 (1H, s), 5.68-5.72 (2H, m), 6.14-6.22 (1H, m), 7.21-7.33 (3H, m), 7.70-7.78 (1H, m), 8.55 (1H, s);

MS (FAB) m/z : 431 $(M+H)^+$.

(Example 54) (E)-4-(Acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{2-[(2S)-(methoxycarbonylmethyl)pyrrolidin-1-yl]ethylidene}piperidine dihydrochloride (Hydrochloride of the compound of Compound No. 5-154)

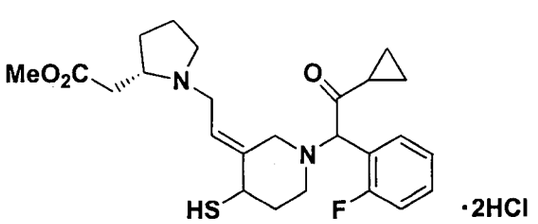


The title compound was synthesized in a yield of 17% as a yellow oil using (E)-4-(acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-hydroxyethylidene)piperidine obtained in Example 32 (f) and (2S)-(methoxycarbonylmethyl)pyrrolidine hydrochloride by conducting a reaction similar to that mentioned in Example 33.

^{1}H NMR (500 MHz, pyridine-d_5) δ ppm : 0.71-0.87 (2H, m), 1.02-1.15 (2H, m), 1.74-1.89 (2H, m), 1.89-2.04 (2H, m), 2.08-2.34 (5H, m), 2.54-2.81 (2H, m), 3.02-3.50 (5H, m), 3.53-3.69 (4H, m), 3.70-3.79 (1H, m), 3.79-3.99 (2H, m), 4.03-4.19 (1H, m), 4.42-4.51 (1H, m), 4.99-5.06 (1H, m), 6.29-6.41 (1H, m), 7.20-7.31 (2H, m), 7.32-7.41 (1H, m), 7.54-7.64 (1H, m);

IR (KBr, cm^{-1}) : 2547, 1700, 1494.

(Example 55) (E)-1-[2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{2-[(2S)-(methoxycarbonylmethyl)pyrrolidin-1-yl]ethylidene}-4-sulfanylpiperidine dihydrochloride (Hydrochloride of the compound of Compound No. 5-153)



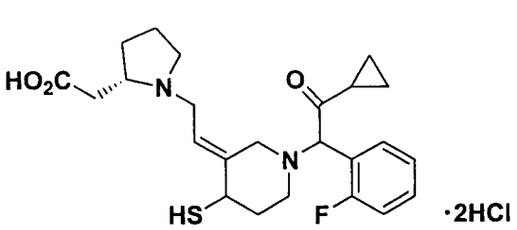
To a solution of (E)-4-(acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{2-[(2S)-(methoxycarbonylmethyl)pyrrolidin-1-yl]ethylidene}piperidine dihydrochloride (407 mg) obtained in Example 54 in methanol (10 ml) was bubbled hydrogen chloride under ice cooling, and the resulting mixture was stirred at room temperature under tightly sealed conditions overnight.

The reaction mixture was removed in vacuo, and the residue was purified using a preparative HPLC (YMC-Pack ODS-A; YMC, eluent: acetonitrile / water containing triethylamine (0.2%) and acetic acid (0.2%) = 1 / 1). The eluted fraction was extracted with ethyl acetate and washed with a saturated aqueous sodium hydrogen carbonate solution and a saturated aqueous sodium chloride solution, and the organic layer was dried over anhydrous magnesium sulfate. The solvent was removed in vacuo, and to a solution of the residue in dichloromethane (10 ml) was added a 4N solution of hydrogen chloride in dioxane (0.26 ml) at room temperature. The reaction mixture was evaporated in vacuo to afford the title compound (192 mg, yield 48%) as a pale yellow amorphous solid.

^{1}H NMR (500 MHz, pyridine-d_5) δ ppm : 0.73-0.89 (2H, m), 1.02-1.14 (2H, m), 1.69-1.82 (1H, m), 1.82-2.11 (3H, m), 2.12-2.28 (2H, m), 2.29-2.43 (1H, m), 2.59-2.73 (1H, m), 2.74-2.98 (1H, m), 3.11-3.42 (3H ,m), 3.44-3.71 (5H, m), 3.76-4.02 (4H, m), 4.13-4.28 (1H, m), 5.00-5.07 (1H, m), 6.25-6.36 (1H, m), 7.22-7.32 (2H, m), 7.34-7.44 (1H, m), 7.58-7.67 (1H, m);

IR (KBr, cm^{-1}) : 2558, 1714, 1493.

(Example 56) (E)-3-{2-[(2S)-(Carboxymethyl)pyrrolidin-1-yl]ethylidene}-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-sulfanylpiperidine dihydrochloride (Hydrochloride of the compound of Compound No. 5-151)



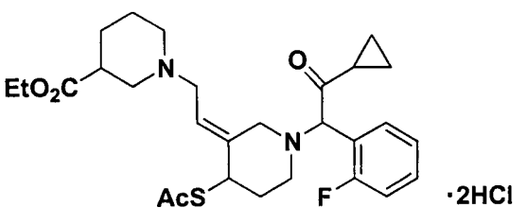
The title compound was synthesized in a yield of 46% as a colorless amorphous solid using (E)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{2-[(2S)-(methoxycarbonylmethyl)pyrrolidin-1-yl]ethylidene}-4-sulfanylpiperidine

dihydrochloride obtained in Example 55 by conducting a reaction similar to that mentioned in Example 15.

^{1}H NMR (500 MHz, pyridine-d_5) δ ppm : 0.71-0.86 (2H, m), 0.98-1.15 (2H, m), 1.71-1.90 (2H, m), 1.93-2.09 (2H, m), 2.11-2.24 (1H, m), 2.25-2.45 (2H, m), 2.56-2.75 (2H, m), 2.77-2.99 (1H, m), 3.26-4.05 (8H, m), 4.06-4.23 (1H, m), 4.95-5.02 (1H, m), 6.25-6.39 (1H, m), 7.19-7.29 (2H, m), 7.30-7.38 (1H ,m), 7.57-7.67 (1H, m);

IR (KBr, cm^{-1}) : 2562, 1713, 1493.

(Example 57) (E)-4-(Acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{2-[3-(ethoxycarbonyl)piperidin-1-yl]ethylidene}piperidine dihydrochloride (Hydrochloride of the compound of Compound No. 5-342)

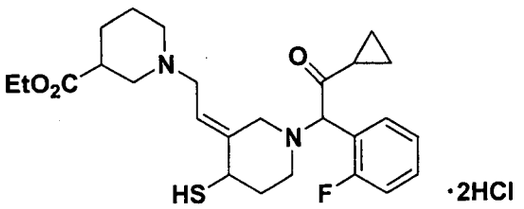


The title compound was synthesized in a yield of 61% as a brown amorphous solid using (E)-4-(acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-hydroxyethylidene)piperidine obtained in Example 32 (f) and 3-(ethoxycarbonyl)piperidine by conducting a reaction similar to that mentioned in Example 33.

^{1}H NMR (400 MHz, pyridine-d_5) δ ppm : 0.73-0.89 (2H, m), 1.02-1.14 (5H, m), 1.43-1.56 (1H, m), 1.65-1.76 (1H, m), 1.79-1.89 (1H, m), 1.98-2.09 (1H, m), 2.09-2.36 (6H, m), 2.54-2.84 (3H, m), 2.88-3.02 (1H, m), 3.17-3.66 (4H, m), 3.67-3.82 (3H, m), 4.02-4.11 (2H, m), 4.46-4.54 (1H, m), 4.99-5.05 (1H, m), 6.28-6.37 (1H, m), 7.18-7.42 (3H, m), 7.58-7.70 (1H, m);

IR (KBr, cm^{-1}) : 2526, 1710, 1493.

(Example 58) (E)-1-[2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{2-[3-(ethoxycarbonyl)piperidin}-1-yl]ethylidene}-4-sulfanylpiperidine dihydrochloride (Hydrochloride of the compound of Compound No. 5-341)

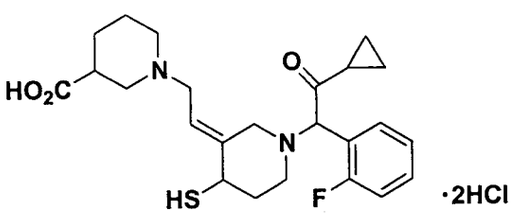


The title compound was synthesized in a yield of 49% as a pale yellow amorphous solid using (E)-4-(acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{2-[3-(ethoxycarbonyl)piperidin-1-yl]ethylidene}piperidine dihydrochloride obtained in Example 57 by conducting a reaction similar to that mentioned in Example 34.

^{1}H NMR (400 MHz, pyridine-d_5) δ ppm : 0.74-0.86 (2H, m), 1.01-1.15 (5H, m), 1.45-1.56 (1H, m), 1.64-1.82 (2H, m), 1.98-2.38 (4H, m), 2.50-3.08 (5H, m), 3.27-3.92 (7H, m), 4.00-4.12 (2H, m), 4.97-5.03 (1H, m), 6.22-6.36 (1H, m), 7.20-7.38 (3H, m), 7.60-7.72 (1H, m);

IR (KBr, cm^{-1}) : 2533, 1726, 1493.

(Example 59) (E)-3-{2-[3-(Carboxypiperidin)-1-yl]ethylidene}-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-sulfanylpiperidine dihydrochloride (Hydrochloride of the compound of Compound No. 5-337)



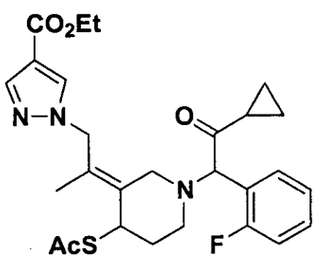
The title compound was synthesized in a yield of 72% as a colorless amorphous solid using (E)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{2-[3-(ethoxycarbonyl)piperidin}-1-yl]ethylidene}-4-sulfanylpiperidine dihydrochloride

obtained in Example 58 by conducting a reaction similar to that mentioned in Example 15.

^{1}H NMR (500 MHz, pyridine-d_5) δ ppm : 0.75-0.92 (2H, m), 1.02-1.17 (2H, m), 1.62-1.89 (3H, m), 2.11-2.38 (4H, m), 2.61-2.74 (1H, m), 2.74-3.00 (2H, m), 3.13-3.32 (1H, m), 3.37-3.54 (1H, m), 3.54-3.69 (3H, m), 3.85-4.10 (4H, m), 5.01-5.08 (1H, m), 6.27-6.37 (1H, m), 7.22-7.46 (3H, m), 7.65-7.79 (1H, m);

IR (KBr, cm^{-1}) : 2542, 1713, 1493.

(Example 60) (E)-4-(Acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{[2-(4-ethoxycarbonyl-1H-pyrazol-1-yl)-1-methyl]ethylidene}piperidine (Compound of Compound No. 1-978)



(a) (E)-3-[1-(Ethoxycarbonyl)ethylidene]-4-hydroxy-1-(triphenylmethyl)piperidine

To a solution of (E)-4-(t-butyldimethylsilyloxy)-3-[(ethoxycarbonyl)methylidene]-1-(triphenylmethyl)piperidine (1.67 g) obtained in Example 1 (a) in tetrahydrofuran (20 ml) was added dropwise a 2.0N solution of lithium diisopropylamide in heptane / tetrahydrofuran / ethyl benzene solution (2.30 ml) at -78°C, and the resulting mixture was stirred at the same temperature for 1 hour. To the reaction mixture was added dropwise methyl iodide (0.31 ml) at -78°C, and then the resulting mixture was stirred for 2 hours while gradually warmed to room temperature. The reaction mixture was charged with a saturated aqueous ammonium chloride solution and then extracted with ethyl acetate. The extract was washed with water and a saturated aqueous sodium chloride solution, and the organic layer was dried over anhydrous sodium sulfate. The solvent was removed in vacuo,

and the residue was purified by chromatography on a silica gel column (ethyl acetate / hexane = 3 / 97) to afford a 1:2 mixture (1.18 g, yield 69%) of (E)-4-(t-butyldimethylsilyloxy)-3-[(1-ethoxycarbonyl)ethylidene]-1-(triphenylmethyl)piperidine and the (Z)-isomer thereof as a pale yellow amorphous solid. To a solution of this mixture (0.97 g) in tetrahydrofuran (15 ml) was added a 75% solution of tetrabutylammonium fluoride (1.40 g) in water, and the resulting mixture was stirred at 60°C for 2 hours. The reaction mixture was diluted with ethyl acetate and washed with water and a saturated aqueous sodium chloride solution, and the organic layer was dried over anhydrous sodium sulfate. The solvent was removed in vacuo, and the residue was purified by chromatography on a silica gel column (ethyl acetate / hexane = 1 / 19 - 1 / 1) to afford the title compound (292 mg, yield 38%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 1.03 (3H, t, J=7.0), 1.78-2.50 (6H, m), 2.74-2.83 (1H, m), 3.20-3.28 (1H, m), 3.84-4.03 (3H, m), 4.79 (1H, bs), 7.08-7.32 (9H, m), 7.37-7.50 (6H, m).

(b) (E)-4-(t-Butyldimethylsilyloxy)-3-[1-(ethoxycarbonyl)ethylidene]-1-(triphenylmethyl)piperidine

To a solution of (E)-3-[1-(ethoxycarbonyl)ethylidene]-4-hydroxy-1-(triphenylmethyl)piperidine (1.05 g) obtained in (a) above in dichloromethane (20 ml) were added dropwise t-butyldimethylsilyl trifluoromethanesulfonate (0.60 ml) and 2,6-lutidine (0.83 ml) under ice cooling, and the resulting mixture was stirred at the same temperature for 10 minutes. The reaction mixture was charged with a saturated aqueous sodium hydrogen carbonate solution and then extracted with ethyl acetate. The extract was washed with a saturated aqueous sodium chloride solution, and the organic layer was dried over anhydrous sodium. The solvent was removed in vacuo, and the residue was purified by chromatography on a silica gel column

(toluene / hexane = 1 / 9 – 1 / 4, then ethyl acetate / hexane = 1 / 9 – 1 / 4) to afford the title compound (1.05 g, yield 79%) as a pale yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : -0.16 (3H, s), -0.06 (3H, s), 0.63 (9H, s), 0.99 (3H, t, J=7.5), 1.64-2.32 (7H, m), 2.75-2.83 (1H, m), 3.83-4.02 (3H, m), 4.68 (1H, bs), 7.07-7.34 (9H, m), 7.38-7.52 (6H, m).

(c) (E)-4-(t-Butyldimethylsilyloxy)-3-[(2-hydroxy-1-methyl)ethylidene]-1-(triphenylmethyl)piperidine

To a suspension of (E)-4-(t-butyldimethylsilyloxy)-3-[1-(ethoxycarbonyl)ethylidene]-1-(triphenylmethyl)piperidine (1.05 g) obtained in (b) above in dichloromethane (15 ml) was added dropwise a 1.01N solution of diisobutylaluminum hydride in toluene (5.7 ml) at -78°C, and the resulting mixture was stirred at the same temperature for 30 minutes. To the reaction mixture was added an aqueous potassium sodium tartrate solution, and then the resulting mixture was stirred at room temperature for 2 hours. The reaction mixture was diluted with ethyl acetate and washed with a saturated aqueous sodium chloride solution, and the organic layer was dried over anhydrous sodium sulfate. The solvent was removed in vacuo, and the residue was purified by chromatography on a silica gel column (ethyl acetate / hexane = 1 / 19 - 1 / 4) to afford the title compound (0.72 g, yield 74%) as a colorless amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : -0.20 (3H, s), -0.07 (3H, s), 0.61 (9H, s), 1.62-2.20 (7H, m), 2.76-2.84 (1H, m), 3.57 (1H, d, J=12.0), 4.03-4.08 (2H, m), 4.70 (1H, bs), 7.08-7.28 (9H, m), 7.40-7.54 (6H, m).

(d) (E)-4-(t-Butyldimethylsilyloxy)-3-{[2-(4-ethoxycarbonyl-1H-pyrazol-1-yl)-1-methyl]ethylidene}-1-(triphenylmethyl)piperidine

The title compound was synthesized in a yield of 94% as a pale yellow amorphous solid using (E)-4-(t-butyldimethylsilyloxy)-3-[(2-hydroxy-1-

methyl)ethylidene]-1-(triphenylmethyl)piperidine obtained in (c) above by conducting a reaction similar to that mentioned in Example 40 (a).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : -0.20 (3H, s), -0.08 (3H, s), 0.62 (9H, s), 1.34 (3H, t, J=7.5), 1.62-2.08 (6H, m), 2.30-2.36 (1H, m), 2.83-2.90 (1H, m), 3.60-3.67 (1H, m), 4.22-4.35 (2H, m), 4.67-4.75 (3H, m), 7.07-7.33 (9H, m), 7.43-7.57 (6H, m), 7.77 (1H, s), 7.92 (1H, s).

(e) (E)-3-{[2-(4-Ethoxycarbonyl-1H-pyrazol-1-yl)-1-methyl]ethylidene}-4-hydroxy-1-(triphenylmethyl)piperidine

The title compound was synthesized in a yield of 69% as a yellow amorphous solid using (E)-4-(t-butyldimethylsilyloxy)-3-{[2-(4-ethoxycarbonyl-1H-pyrazol-1-yl)-1-methyl]ethylidene}-1-(triphenylmethyl)piperidine obtained in (d) above by conducting a reaction similar to that mentioned in Example 1 (e).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 1.36 (3H, t, J=7.5), 1.69 (3H, s), 1.86-2.35 (4H, m), 2.88-2.97 (1H, m), 3.75 (1H, d, J=13.5), 4.31 (2H, q, J=7.5), 4.62-4.73 (2H, m), 4.83 (1H, bs), 7.10-7.30 (9H, m), 7.40-7.56 (6H, m), 7.80 (1H, s), 7.92 (1H, s).

(f) (E)-4-(Acetylsulfanyl)-3-{[2-(4-ethoxycarbonyl-1H-pyrazol-1-yl)-1-methyl]ethylidene}piperidine hydrogen trifluoroacetate

The title compound was synthesized in a yield of 67% as a colorless oil using (E)-3-{[2-(4-ethoxycarbonyl-1H-pyrazol-1-yl)-1-methyl]ethylidene}-4-hydroxy-1-(triphenylmethyl)piperidine obtained in (e) above by conducting a reaction similar to that mentioned in Example 36 (d).

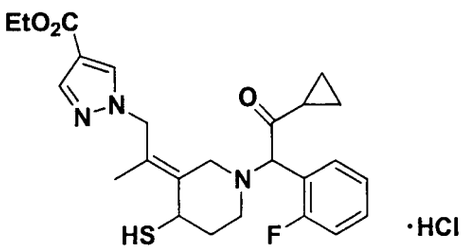
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 1.33 (3H, t, J=7.0), 1.80 (3H, s), 2.01-2.12 (1H, m), 2.37 (3H, s), 3.16-3.56 (4H, m), 4.28 (2H, q, J=7.0), 4.47 (1H, d, J=13.5), 4.72 (2H, s), 4.89 (1H, bs), 7.86 (1H, s), 7.88 (1H, s).

(g) (E)-4-(Acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{[2-(4-ethoxycarbonyl-1H-pyrazol-1-yl)-1-methyl]ethylidene}piperidine

The title compound was synthesized in a yield of 78% as a colorless amorphous solid using (E)-4-(acetylsulfanyl)-3-{[2-(4-ethoxycarbonyl-1H-pyrazol-1-yl)-1-methyl]ethylidene}piperidine hydrogen trifluoroacetate obtained in (f) above by conducting a reaction similar to that mentioned in Example 1 (g).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 0.65-1.08 (4H, m), 1.35 (3H, t, J=7.0), 1.70 and 1.73 (total 3H, each s), 1.76-1.91 (1H, m), 2.02-2.99 (7H, m), 3.80-3.93 (1H, m), 4.24-4.34 (2H, m), 4.56-4.88 (5H, m), 7.08-7.23 (2H, m), 7.27-7.47 (2H, m), 7.77-7.91 (2H, m).

(Example 61) (E)-1-[2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{[2-(4-ethoxycarbonyl-1H-pyrazol-1-yl)-1-methyl]ethylidene}-4-sulfanylpiperidine hydrochloride (Hydrochloride of the compound of Compound No. 1-977)

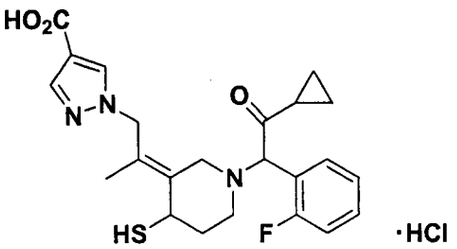


The title compound was synthesized in a yield of 64% as a colorless amorphous solid using (E)-4-(acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{[2-(4-ethoxycarbonyl-1H-pyrazol-1-yl)-1-methyl]ethylidene}piperidine obtained in Example 60 (g) above by conducting a reaction similar to that mentioned in Example 34.

^{1}H NMR (400 MHz, pyridine-d_5) δ ppm : 0.69-0.87 (2H, m), 0.96-1.16 (2H, m), 1.22 (3H, t, J=7.0), 1.70-2.80 (7H, m), 2.89-3.00 (1H, m), 3.19 and 3.36 (total 1H, each d, J=13.5), 4.01-4.48 (4H, m), 4.75-5.04 (3H, m), 7.14-7.37 (3H, m), 7.71-7.81 (1H, m), 8.25 (1H, s), 8.38 and 8.48 (total 1H, each s);

IR (KBr, cm^{-1}) : 2611, 1713, 1494.

(Example 62) (E)-3-{[2-(4-Carboxy-1H-pyrazol-1-yl)-1-methyl]ethylidene}-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-sulfanylpiperidine hydrochloride (Hydrochloride of the compound of Compound No. 1-973)

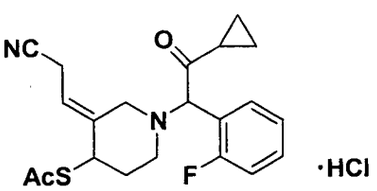


The title compound was synthesized in a yield of 75% as a colorless amorphous solid using (E)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{[2-(4-ethoxycarbonyl-1H-pyrazol-1-yl)-1-methyl]ethylidene}-4-sulfanylpiperidine hydrochloride obtained in Example 61 by conducting a reaction similar to that mentioned in Example 15.

^{1}H NMR (400 MHz, pyridine-d_5) δ ppm : 0.72-0.88 (2H, m), 0.97-1.17 (2H, m), 1.57-3.03 (8H, m), 3.20 and 3.37 (total 1H, each d, J=12.5), 4.06 and 4.18 (total 1H, each d, J=12.5), 4.37-4.47 (1H, m), 4.77-5.04 (3H, m), 7.16-7.35 (3H, m), 7.74-7.84 (1H, m), 8.41 (1H, s), 8.47 and 8.57 (total 1H, each s);

IR (KBr, cm^{-1}) : 2630, 1711, 1494.

(Example 63) (E)-4-(Acetylsulfanyl)-3-(2-cyanoethylidene)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]piperidine hydrochloride (Hydrochloride of the compound of Compound No. 3-47)



(a) (E)-4-(t-Butyldimethylsilyloxy)-3-(2-cyanoethylidene)-1-(triphenylmethyl)piperidine

To a solution of sodium cyanide (13.7 g) in a mixed solvent of N,N-dimethylformamide (250 ml) and water (25 ml) was added (E)-4-(t-

butyldimethylsilyloxy)-3-[2-(tosyloxy)ethylidene]-1-(triphenylmethyl)piperidine (34.4 g) obtained in Example 1 (c) at room temperature, and the resulting mixture was stirred for 30 minutes. The reaction mixture was charged with water and then extracted with ethyl acetate. The extract was washed with water and a saturated aqueous sodium chloride solution, and the organic layer was dried over anhydrous magnesium sulfate. The solvent was removed in vacuo to afford the title compound (26.8 g, quantitative yield) as a brown oil.

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm : 0.01 (3H, s), 0.02 (3H, s), 0.88 (9H, s), 1.64-1.98 (4H, m), 2.94-3.16 (3H, m), 3.45-3.61 (1H, m), 3.82-3.89 (1H, m), 5.57 (1H, t, J=7.5), 7.12-7.36 (9H, m), 7.39-7.56 (6H, m).

(b) (E)-3-(2-Cyanoethylidene)-1-(triphenylmethyl)piperidin-4-ol

The title compound was synthesized in a yield of 65% as a pale yellow amorphous solid using (E)-4-(t-butyldimethylsilyloxy)-3-(2-cyanoethylidene)-1-(triphenylmethyl)piperidine obtained in (a) above by conducting a reaction similar to that mentioned in Example 1 (e).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 1.75-2.28 (4H, m), 2.75-2.95 (1H, m), 3.07 (2H, m), 3.19-3.41 (1H, m), 3.91-4.02 (1H, m), 5.58 (1H, t, J=7.5), 7.14-7.35 (9H, m), 7.39-7.55 (6H, m).

(c) (E)-4-(Acetylsulfanyl)-3-(2-cyanoethylidene)piperidine hydrogen trifluoroacetate

The title compound was synthesized in a yield of 12% as a colorless solid using (E)-3-(2-cyanoethylidene)-1-(triphenylmethyl)piperidin-4-ol obtained in (b) above by conducting a reaction similar to that mentioned in Example 36 (d).

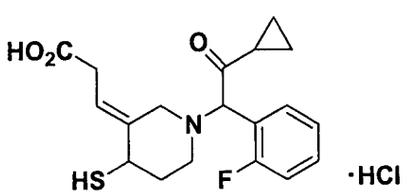
^{1}H NMR (400 MHz, DMSO-d_6) δ ppm : 1.82-1.93 (1H, m), 2.11-2.23 (1H, m), 2.37 (3H, s), 3.05-3.17 (1H, m), 3.25-3.43 (1H, m), 3.47 (2H, d, J=7.0), 3.60-3.68 (1H, m), 3.90-3.97 (1H, m), 4.40 (1H, m), 5.77 (1H, t, J=7.0).

(d) (E)-4-(Acetylsulfanyl)-3-(2-cyanoethylidene)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]piperidine hydrochloride

The title compound was synthesized in a yield of 58% as a yellow oil using (E)-4-(acetylsulfanyl)-3-(2-cyanoethylidene)piperidine hydrogen trifluoroacetate obtained in (c) above by conducting a reaction similar to that mentioned in Example 1 (g).

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm : 0.79-0.92 (2H, m), 0.99-1.09 (2H, m), 1.77-1.85 (1H, m), 2.05-2.27 (2H, m), 2.29 and 2.31 (total 3H, each s), 2.46-2.58 (1H, m), 2.64-2.71 and 2.75-2.81 (total 1H, each m), 2.76 and 3.08 (total 1H, each d, J=12.5), 3.02-3.11 (2H, m), 3.15 and 3.33 (total 1H, each d, J=12.5), 4.27 and 4.32 (total 1H, each m), 4.74 and 4.77 (total 1H, each s), 5.57 (1H, t, J=7.0), 7.11-7.23 (2H, m), 7.32-7.39 (2H, m).

(Example 64) (E)-3-(2-Carboxyethylidene)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-sulfanylpiperidine hydrochloride (Hydrochloride of the compound of Compound No. 3-13)

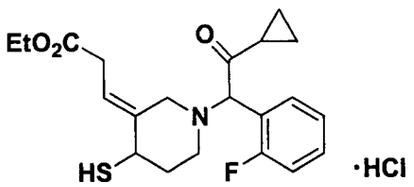


The title compound was synthesized in a yield of 39% as a colorless amorphous solid using (E)-4-(acetylsulfanyl)-3-(2-cyanoethylidene)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]piperidine obtained in Example 63 (d) by conducting a reaction similar to that mentioned in Example 37.

^{1}H NMR (500 MHz, pyridine-d_5) δ ppm : 0.77-0.94 (2H, m), 0.97-1.04 (1H, m), 1.10-1.20 (1H, m), 1.75-1.85 (1H, m), 2.17-2.29 (1H, m), 2.51-2.60 (1H, m), 2.62-2.69 (1H, m), 2.87 and 2.97 (total 1H, each m), 3.32-3.44 (3H, m), 3.59 (1H, m), 3.88-3.95 (1H, m), 4.91 and 4.93 (total 1H, each s), 6.18-6.24 (1H, m), 7.17-7.26 (2H, m), 7.27-7.34 (1H, m), 7.70-7.75 (1H, m).

MS (FAB) m/z : 364 $(M+H)^+$.

(Example 65) (E)-1-[2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-[2-(ethoxycarbonyl)ethylidene]-4-sulfanylpiperidine hydrochloride (Hydrochloride of the compound of Compound No. 3-17)

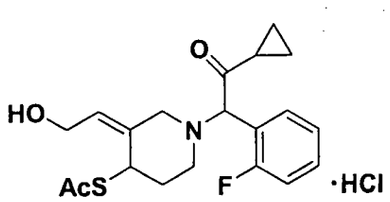


The title compound was synthesized in a yield of 81% as a colorless amorphous solid using (E)-3-(2-carboxyethylidene)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-sulfanylpiperidine hydrochloride obtained in Example 64 by conducting a reaction similar to that mentioned in Example 38.

^{1}H NMR (400 MHz, pyridine-d_5) δ ppm : 0.76-0.88 (2H, m), 0.97-1.04 (1H, m), 1.11-1.17 (1H, m), 1.11 (3H, t, J=7.0), 1.73-1.84 (1H, m), 2.12-2.26 (1H, m), 2.44-2.53 (1H, m), 2.60-2.69 (1H, m), 2.80-2.99 (1H, m), 3.20-3.35(3H, m), 3.53 (1H, m), 3.87 (1H, m), 4.10 (2H, q, J=7.0), 4.91 and 4.92 (total 1H, each s), 5.98-6.05 (1H, m), 7.17-7.26 (2H, m), 7.28-7.36 (1H, m), 7.66-7.72 (1H, m).

MS (FAB) m/z : 392 $(M+H)^+$.

(Example 66) (Z)-4-(Acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-hydroxyethylidene)piperidine hydrochloride (Hydrochloride of the compound of Compound No. 4-2)



(a) (E)-3-(2-Hydroxyethylidene)-1-(triphenylmethyl)piperidin-4-ol

The title compound was synthesized in a yield of 86% as a colorless amorphous solid using (E)-4-(t-butyldimethylsilyloxy)-3-(2-hydroxyethylidene)-1-

(triphenylmethyl)piperidine obtained in Example 1 (b) by conducting a reaction similar to that mentioned in Example 1 (e).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 1.75-1.87 (2H, m), 2.02-2.04 (2H, m), 2.78 (1H, bs), 3.33 (1H, bs), 3.97 (1H, bs), 4.10-4.22 (2H, m), 5.74 (1H, t, J=7.0), 7.13-7.31 (15H, m).

(b) (E)-3-[2-(t-Butyldiphenylsilyloxy)ethylidene]-1-(triphenylmethyl)piperidin-4-ol

To a solution of (E)-3-(2-hydroxyethylidene)-1-(triphenylmethyl)piperidin-4-ol (5.50 g) obtained in (a) above in dichloromethane (120 ml) were added t-butyldiphenylsilyl chloride (6.30 g), triethylamine (4.00 ml) and 4-dimethylaminopyridine (0.35 g) under ice cooling, and the resulting mixture was stirred at room temperature for 24 hours. The reaction mixture was evaporated in vacuo and then diluted with dichloromethane. The resulting mixture was washed with water and a saturated aqueous sodium chloride solution, and the organic layer was dried over anhydrous magnesium sulfate. The solvent was removed in vacuo, and the residue was purified by chromatography on a silica gel column (ethyl acetate / hexane = 1 / 4) to afford the title compound (7.54 g, yield 85%) as a colorless amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 1.03 (9H, s), 1.68-1.81 (2H, m), 1.97-2.09 (2H, m), 2.64 (1H, bs), 3.03 (1H, bs), 3.89 (1H, bs), 4.22-4.35 (2H, m), 5.66 (1H, t, J=7.0), 7.04-7.50 (20H, m), 7.60-7.75 (5H, m).

(c) (E)-4-Acetoxy-3-[2-(t-butyldiphenylsilyloxy)ethylidene]-1-(triphenylmethyl)piperidine

To a solution of (E)-3-[2-(t-butyldiphenylsilyloxy)ethylidene]-1-(triphenylmethyl)piperidin-4-ol (512 mg) obtained in (b) above in dichloromethane (8 ml) were added acetic anhydride (0.10 ml), triethylamine (0.17 ml) and 4-dimethylaminopyridine (10 mg) under ice cooling, and the resulting mixture was stirred at room temperature overnight. The reaction mixture was diluted with ethyl

acetate and washed with a saturated aqueous sodium chloride solution, and the organic layer was dried over anhydrous sodium sulfate. The solvent was removed in vacuo, and the residue was purified by chromatography on a silica gel column (ethyl acetate / hexane = 1 / 19 - 3 / 17) to afford the title compound (527 mg, yield 96%) as a colorless amorphous solid.

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm : 1.03 (9H, s), 1.76-1.89 (1H, m), 1.94-2.10 (4H, m), 2.40-2.76 (2H, m), 2.80-3.18 (1H, m), 3.39-3.64 (1H, m), 4.26 (2H, t, J=6.0), 4.99-5.11 (1H, m), 5.61 (1H, t, J=6.0), 7.03-7.48 (21H, m), 7.59-7.70 (4H, m).

(d) (Z)-4-(Acetylsulfanyl)-3-(2-hydroxyethylidene)-1-(triphenylmethyl)piperidine and (E)-4-(acetylsulfanyl)-3-(2-hydroxyethylidene)-1-(triphenylmethyl)piperidine

Palladium chloride (7 mg) and 1,1'-bis(diphenylphosphino)ferrocene (44 mg) were dissolved in 1,4-dioxane (4 ml) under a nitrogen gas stream, and the resulting mixture was stirred at room temperature for 30 minutes. To the resulting mixture were added a solution of (E)-4-acetoxy-3-[2-(t-butyldiphenylsilyloxy)ethylidene]-1-(triphenylmethyl)piperidine (527 mg) obtained in (c) above in 1,4-dioxane (2 ml) and a solution of potassium thioacetate (283 mg) in water (1.5 ml), and the resulting mixture was stirred at 100°C for 6 hours. The reaction mixture was diluted with ethyl acetate and washed with a saturated aqueous sodium chloride solution, and the organic layer was dried over anhydrous sodium sulfate. The solvent was removed in vacuo, and the residue was purified by chromatography on a silica gel column (ethyl acetate / hexane = 1 / 19 - 3 / 17) to afford a 1:7 mixture (479 mg, yield 89%) of (Z)-4-(acetylsulfanyl)-3-[2-(t-butyldiphenylsilyloxy)ethylidene]-1-(triphenylmethyl)piperidine and the (E)-isomer thereof as a colorless oil.

To a solution of this 1:7 mixture (374 mg) in tetrahydrofuran (5 ml) were added acetic acid (0.12 ml) and a 75% solution of tetrabutylammonium fluoride (750 mg) in water at room temperature, and the resulting mixture was stirred at the same temperature for 3 hours and at 50°C for further 2 hours. The reaction mixture was

diluted with ethyl acetate and washed with a saturated aqueous sodium chloride solution, and the organic layer was dried over anhydrous sodium sulfate. The solvent was removed in vacuo, and the residue was purified by chromatography on a silica gel column (ethyl acetate / hexane = 1 / 19 - 1 / 3) to afford the (Z) form of the title compound (25 mg, yield 11%) as a colorless amorphous solid and the (E) form (178 mg, yield 74%) as a white crystal.

(Z)-4-(Acetylsulfanyl)-3-(2-hydroxyethylidene)-1-(triphenylmethyl)piperidine:

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 1.60 (1H, dd, J=12.0, 2.0), 1.77-1.83 (1H, m), 2.13 (1H, d, J=12.0), 2.20 (3H, s), 2.31-2.42 (1H, m), 3.03-3.10 (1H, m), 3.37 (1H, dd, J=12.0, 2.0), 4.19-4.28 (1H, m), 4.40-4.48 (1H, m), 4.86 (1H, d, J=4.0), 5.51 (1H, t, J=7.0), 7.11-7.54 (15H, m).

(E)-4-(Acetylsulfanyl)-3-(2-hydroxyethylidene)-1-(triphenylmethyl)piperidine:

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 1.83-1.96 (1H, m), 2.21-2.42 (1H, m), 2.37 (3H, s), 2.95-3.16 (2H, m), 3.36-3.48 (1H, m), 3.60-3.79 (3H, m), 4.40 (1H, m), 5.98 (1H, t, J=6.0), 7.19-7.31 (9H, m), 7.36-7.40 (6H, m).

(e) (Z)-4-(Acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-hydroxyethylidene)piperidine hydrochloride

To a solution of (Z)-4-(acetylsulfanyl)-3-(2-hydroxyethylidene)-1-(triphenylmethyl)piperidine (130 mg) obtained in (d) above in dichloromethane (5 ml) was added trifluoroacetic acid (0.30 ml) under ice cooling, and the resulting mixture was stirred at room temperature for 1 hour. The solvent was removed in vacuo, and the residue was purified by chromatography on a silica gel column (methanol / dichloromethane = 1 / 5) to afford (Z)-4-(acetylsulfanyl)-3-(2-hydroxyethylidene)piperidine hydrogen trifluoroacetate as a colorless amorphous solid.

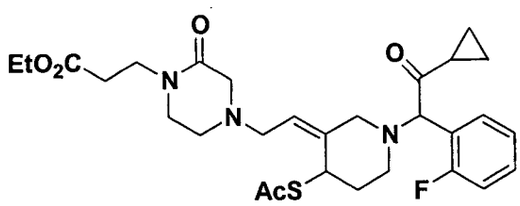
To a solution of the above amorphous solid and 2-bromo-2-(2-fluorophenyl)-1-cyclopropylethanone (150 mg) in acetonitrile (2 ml) was added triethylamine (0.10

ml) under ice cooling, and the resulting mixture was stirred at room temperature for 15 minutes. The reaction mixture was diluted with ethyl acetate and washed with water and a saturated aqueous sodium chloride solution, and the organic layer was dried over anhydrous sodium sulfate. The solvent was removed in vacuo, and the residue was purified by chromatography on a silica gel column (ethyl acetate / hexane = 1 / 1) to afford the free form (54 mg, yield 49%) of the title compound as a colorless amorphous solid. To a solution of this compound in dioxane (3 ml) was added a 4N solution of hydrogen chloride in dioxane (0.11 ml) at room temperature, and the solvent was removed in vacuo to afford the title compound (61 mg, quantitative yield) as a colorless amorphous solid.

^{1}H NMR (500 MHz, pyridine-d_5) δ ppm : 0.70-0.84 (2H, m), 0.94-1.13 (2H, m), 1.75-1.89 (1H, m), 2.13-2.61 (3H, m), 2.19 (3H, s), 2.87-3.11 (1H, m), 2.91 and 3.07 (total 1H, each d, J=12.0), 3.37 and 3.54 (total 1H, each d, J=12.0), 4.54-4.64 (1H, m), 4.71-4.81 (1H, m), 4.83 and 4.88 (total 1H, each s), 5.12 (1H, bs), 5.81 and 5.91 (total 1H, each t, J=6.5), 7.17-7.24 (2H, m), 7.27-7.33 (1H, m), 7.61-7.68 (1H, m).

MS (FAB) m/z : 378 $(M+H)^+$.

(Example 67) (Z)-4-(Acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-{4-[2-(ethoxycarbonyl)ethyl]-3-oxopiperazin-1-yl}ethylidene)piperidine (Compound of Compound No. 6-108)



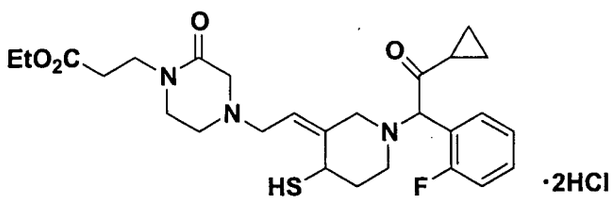
The title compound was synthesized in a yield of 50% as a colorless amorphous solid using (Z)-4-(acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-hydroxyethylidene)piperidine obtained in Example 66 (e) and 1-[2-

(ethoxycarbonyl)ethyl]-2-oxopiperazine hydrochloride by conducting a reaction similar to that mentioned in Example 33.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 0.79-0.90 (2H, m), 0.94-1.07 (2H, m), 1.26 and 1.27 (total 3H, each t, J=7.0), 1.71-1.84 (1H, m), 2.06-2.50 (3H, m), 2.30 (3H, s), 2.57-2.72 (6H, m), 2.77-3.33 (5H, m), 3.34-3.42 (2H, m), 3.58-3.66 (2H, m), 4.13 and 4.15 (total 2H, each q, J=7.0), 4.63 and 4.67 (total 1H, each s), 4.78 (1H, bs), 5.27 and 5.36 (total 1H, each t, J=7.0), 7.07-7.20 (2H, m), 7.28-7.44 (2H, m).

MS (FAB) m/z : 560 $(M+H)^+$.

(Example 68) (Z)-1-[2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-{4-[2-(ethoxycarbonyl)ethyl]-3-oxopiperazin-1-yl}ethylidene)-4-sulfanylpiperidine dihydrochloride (Hydrochloride of the compound of Compound No. 6-107)

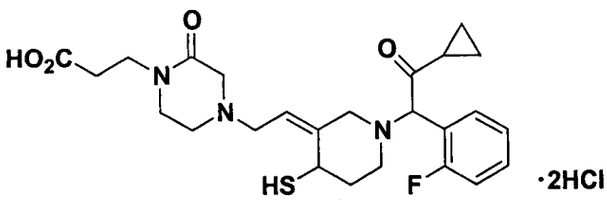


The title compound was synthesized in a yield of 66% as a colorless amorphous solid using (Z)-4-(acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-{4-[2-(ethoxycarbonyl)ethyl]-3-oxopiperazin-1-yl}ethylidene)piperidine obtained in Example 67 by conducting a reaction similar to that mentioned in Example 34.

^{1}H NMR (400 MHz, pyridine-d_5) δ ppm : 0.71-0.83 (2H, m), 0.95-1.02 (1H, m), 1.05-1.11 (4H, m), 1.69-1.80 (1H, m), 2.15-2.30 (1H, m), 2.40-2.48 (1H, m), 2.64-3.00 (6H, m), 3.10-3.18 (2H, m), 3.19-3.51 (6H, m), 3.72-3.78 (2H, m), 4.07 and 4.08 (total 2H, each q, J=7.0), 4.43 (1H, bs), 4.90 and 4.92 (total 1H, each s), 5.35 and 5.43 (total 1H, each t, J=7.0), 7.16-7.23 (2H, m), 7.27-7.33 (2H, m).

MS (FAB) m/z : 518 $(M+H)^+$.

(Example 69) (Z)-3-(2-{4-[2-(Carboxyethyl)]-3-oxopiperazin-1-yl}ethylidene)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-sulfanylpiperidine dihydrochloride (Hydrochloride of the compound of Compound No. 6-103)

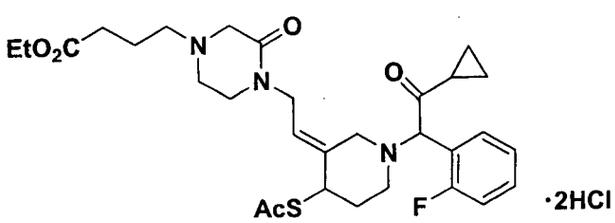


The title compound was synthesized in a yield of 95% as a colorless amorphous solid using (Z)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-{4-[2-(ethoxycarbonyl)ethyl]-3-oxopiperazin-1-yl}ethylidene)-4-sulfanylpiperidine dihydrochloride obtained in Example 68 by conducting a reaction similar to that mentioned in Example 15.

^{1}H NMR (400 MHz, pyridine-d_5) δ ppm : 0.69-0.85 (2H, m), 0.94-1.13 (2H, m), 1.66-1.82 (1H, m), 2.12-2.33 (1H, m), 2.39-2.50 (1H, m), 2.60-3.04 (6H, m), 3.08-3.43 (6H, m), 3.43-3.54 (2H, m), 3.83-3.94 (2H, m), 4.44 (1H, bs), 4.90 and 4.92 (total 1H, each s), 5.33 and 5.44 (total 1H, each t, J=7.0), 7.16-7.33 (3H, m), 7.64-7.72 (1H, m).

MS (FAB) m/z : 490 $(M+H)^+$.

(Example 70) (E)-4-(Acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-{4-[3-(ethoxycarbonyl)propyl]-2-oxopiperazin-1-yl}ethylidene)piperidine dihydrochloride (Hydrochloride of the compound of Compound No. 5-86)



(a) (E)-4-(t-Butyldimethylsilyloxy)-3-(2-{4-[3-(ethoxycarbonyl)propyl]-2-oxopiperazin-1-yl}ethylidene)-1-(triphenylmethyl)piperidine

The title compound was synthesized in a yield of 62% as a yellow oil using (E)-4-(t-butyldimethylsilyloxy)-3-[2-(tosyloxy)ethylidene]-1-(triphenylmethyl)piperidine obtained in Example 1 (c) and 1-[3-(ethoxycarbonyl)propyl]-3-oxopiperazine by conducting a reaction similar to that mentioned in Example 21 (a).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : -0.05 (3H, s), -0.02 (3H, s), 0.83 (9H, s), 1.25 (3H, t, J=7.0), 1.75-1.94 (3H, m), 1.81 (2H, t, J=7.0), 2.35 (2H, t, J=7.0), 2.41 (2H, t, J=7.0), 2.63 (2H, t, J=5.5), 2.80-2.95 (1H, m), 3.12 (2H, s), 3.18-3.27 (2H, m), 3.50 (1H, m), 3.81-3.89 (1H, m), 3.94-4.10 (3H, m), 4.12 (2H, q, J=7.0), 5.44 (1H, t, J=6.5), 7.10-7.19 (3H, m), 7.21-7.31 (6H, m), 7.37-7.56 (6H, m).

(b) (E)-3-(2-{4-[3-(Ethoxycarbonyl)propyl]-2-oxopiperazin-1-yl}ethylidene)-4-hydroxy-1-(triphenylmethyl)piperidine

The title compound was synthesized in a yield of 98% as a yellow amorphous solid using (E)-4-(t-butyldimethylsilyloxy)-3-(2-{4-[3-(ethoxycarbonyl)propyl]-2-oxopiperazin-1-yl}ethylidene)-1-(triphenylmethyl)piperidine obtained in (a) above by conducting a reaction similar to that mentioned in Example 1 (e).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 1.24 (3H, t, J=7.0), 1.74-1.84 (1H, m), 1.80 (2H, t, J=7.0), 1.91-2.11 (3H, m), 2.34 (2H, t, J=7.0), 2.40 (2H, t, J=7.0), 2.65 (2H, t, J=6.0), 2.74 (1H, m), 3.12 (2H, s), 3.19-3.40 (1H, m), 3.25 (2H, t, J=5.5), 3.90-4.01 (2H, m), 4.02-4.09 (1H, m), 4.11 (2H, q, J=7.0), 5.43 (1H, t, J=6.5), 7.06-7.32 (9H, m), 7.35-7.58 (6H, m).

(c) (E)-4-(Acetylsulfanyl)-3-(2-{4-[3-(ethoxycarbonyl)propyl]-2-oxopiperazin-1-yl}ethylidene)-1-(triphenylmethyl)piperidine

The title compound was synthesized in a yield of 10% as a yellow amorphous solid using (E)-3-(2-{4-[3-(ethoxycarbonyl)propyl]-2-oxopiperazin-1-yl}ethylidene)-

4-hydroxy-1-(triphenylmethyl)piperidine obtained in (b) above by conducting a reaction similar to that mentioned in Example 1 (h).

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm : 1.26 (3H, t, J=7.0), 1.74-1.88 (1H, m), 1.82 (2H, t, J=7.0), 2.15-2.39 (2H, m), 2.24 (3H, s), 2.36 (2H, t, J=7.5), 2.41 (2H, t, J=7.0), 2.49-2.70 (4H, m), 2.98-3.33 (1H, m), 3.13 (2H, s), 3.20 (2H, t, J=5.5), 3.92-4.07 (2H, m), 4.11 (2H, q, J=7.0), 4.25 (1H, bs), 5.44 (1H, t, J=6.5), 7.12-7.21 (3H, m), 7.23-7.32 (6H, m), 7.38-7.56 (6H, m).

(d) (E)-4-(Acetylsulfanyl)-3-(2-{4-[3-(ethoxycarbonyl)propyl]-2-oxopiperazin-1-yl}ethylidene)piperidine bis(hydrogen trifluoroacetate)

The title compound was synthesized in a quantitative yield as a pale orange amorphous solid using (E)-4-(acetylsulfanyl)-3-(2-{4-[3-(ethoxycarbonyl)propyl]-2-oxopiperazin-1-yl}ethylidene)-1-(triphenylmethyl)piperidine obtained in (c) above by conducting a reaction similar to that mentioned in Example 3 (c).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 1.26 (3H, t, J=7.0), 1.93-2.05 (3H, m), 2.32-2.44 (1H, m), 2.35 (3H, s), 2.41 (2H, t, J=7.0), 2.99 (2H, t, J=7.5), 3.16-3.42 (4H, m), 3.50-3.82 (4H, m), 3.79 (2H, t, J=7.5), 4.13 (2H, q, J=7.0), 4.26-4.36 (2H, m), 4.42 (1H, m), 5.92 (1H, t, J=7.5).

(e) (E)-4-(Acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-{4-[3-(ethoxycarbonyl)propyl]-2-oxopiperazin-1-yl}ethylidene)piperidine dihydrochloride

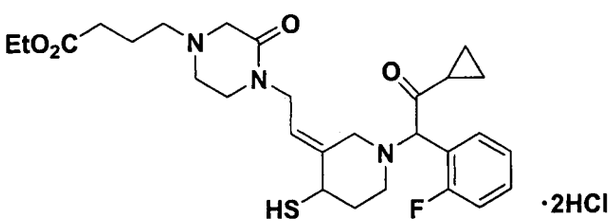
The title compound was synthesized in a yield of 70% as a pale brown amorphous solid using (E)-4-(acetylsulfanyl)-3-(2-{4-[3-(ethoxycarbonyl)propyl]-2-oxopiperazin-1-yl}ethylidene)piperidine bis(hydrogen trifluoroacetate) obtained in (d) above by conducting a reaction similar to that mentioned in Example 1 (g).

^{1}H NMR (500 MHz, pyridine-d_5) δ ppm : 0.76-0.88 (2H, m), 1.04-1.09 (1H, m), 1.10-1.18 (1H, m), 1.15 (3H, t, J=7.0), 1.77-1.91 (1H, m), 1.81 (2H, t, J=7.0), 2.15-2.35 (3H, m), 2.24 and 2.26 (total 3H, each s), 2.38 (2H, t, J=7.0), 2.40-2.47

(1H, m), 2.48-2.75 (3H, m), 2.77-2.83 and 2.85-2.91 (total 1H, each m), 3.06-3.32 (3H, m), 3.24 (2H, s), 3.64-3.70 (1H, m), 4.06-4.22 (1H, m), 4.13 (2H, q, J=7.0), 4.24-4.31 (1H, m), 4.52 (1H, m), 4.96 and 4.98 (total 1H, each s), 5.73-5.81 (1H, m), 7.20-7.39 (3H, m), 7.65-7.73 (1H, m).

IR (KBr, cm^{-1}) : 1727, 1662, 1495.

(Example 71) (E)-1-[2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-{4-[3-(ethoxycarbonyl)propyl]-2-oxopiperazin-1-yl}ethylidene)-4-sulfanylpiperidine dihydrochloride (Hydrochloride of the compound of Compound No. 5-85)

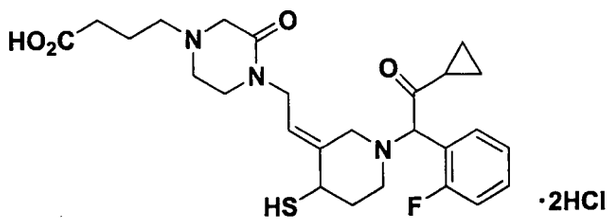


The title compound was synthesized in a yield of 35% as a pale yellow amorphous solid using (E)-4-(acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-{4-[3-(ethoxycarbonyl)propyl]-2-oxopiperazin-1-yl}ethylidene)piperidine dihydrochloride obtained in Example 70 (e) by conducting a reaction similar to that mentioned in Example 34.

^{1}H NMR (400 MHz, pyridine-d_5) δ ppm : 0.79-0.88 (2H, m), 1.00-1.08 (1H, m), 1.10-1.19 (1H, m), 1.15 (3H, t, J=7.0), 1.74-1.88 (1H, m), 1.83 (2H, t, J=7.0), 2.14-2.27 (1H, m), 2.29-2.57 (3H, m), 2.33 (2H, t, J=7.0), 2.39 (2H, t, J=7.0), 2.61-2.74 (1H, m), 2.85-3.04 (1H, m), 3.24-3.32 (2H, m), 3.27 (2H, s), 3.39 (1H, dd, J=12.0, 3.5), 3.53-3.68 (1H, m), 3.80-3.86 (1H, m), 4.13 (2H, q, J=7.0), 4.17-4.29 (2H, m), 4.97 (1H, s), 5.68-5.75 (1H, m), 7.21-7.42 (3H, m), 7.68-7.75 (1H, m).

IR (KBr, cm^{-1}) : 2536, 1727, 1661, 1495.

(Example 72) (E)-3-(2-{4-[3-(Carboxypropyl)]-2-oxopiperazin-1-yl}ethylidene)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-sulfanylpiperidine dihydrochloride (Hydrochloride of the compound of Compound No. 5-81)

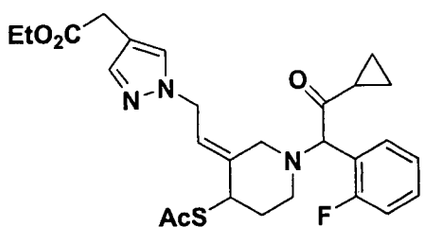


The title compound was synthesized in a yield of 57% as a colorless amorphous solid using (E)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-{4-[3-(ethoxycarbonyl)propyl]-2-oxopiperazin-1-yl}ethylidene)-4-sulfanylpiperidine dihydrochloride obtained in Example 71 by conducting a reaction similar to that mentioned in Example 15.

^{1}H NMR (500 MHz, pyridine-d_5) δ ppm : 0.76-0.88 (2H, m), 1.01-1.08 (1H, m), 1.10-1.18 (1H, m), 1.74-1.84 (1H, m), 1.96 (2H, t, J=7.0), 2.13-2.28 (1H, m), 2.38-2.60 (5H, m), 2.42 (2H, t, J=7.0), 2.61-2.74 (1H, m), 2.84-3.00 (1H, m), 3.27 (2H, t, J=5.5), 3.30 (2H, s), 3.34-3.42 (1H, m), 3.55 and 3.64 (total 1H, each d, J=12.5), 3.79-3.86 (1H, m), 4.10-4.28 (2H, m), 4.96 (1H, s), 5.67-5.74 (1H, m), 7.19-7.37 (3H, m), 7.68-7.76 (1H, m).

IR (KBr, cm^{-1}) : 2576, 1713, 1659, 1495.

(Example 73) (E)-4-(Acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{2-[4-(ethoxycarbonylmethyl)-1H-pyrazol-1-yl]ethylidene}piperidine (Compound of Compound No. 1-62)



(a) (E)-4-(t-Butyldimethylsilyloxy)-3-{2-[4-(ethoxycarbonylmethyl)-1H-pyrazol-1-yl]ethylidene}-1-(triphenylmethyl)piperidine

The title compound was synthesized in a yield of 45% as a colorless amorphous solid using (E)-4-(t-butyldimethylsilyloxy)-3-[2-(tosyloxy)ethylidene]-1-

(triphenylmethyl)piperidine obtained in Example 1 (c) and 4-(ethoxycarbonylmethyl)-1H-pyrazole by conducting a reaction similar to that mentioned in Example 21 (a).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 0.06 (6H, s), 0.88 (9H, s), 1.29 (3H, t, J=7.0), 1.89-2.04 (4H, m), 3.03 (1H, bs), 3.55 (2H, s), 3.69 (1H, bs), 3.93-3.98 (1H, m), 4.19 (2H, q, J=7.0), 4.73-4.84 (2H, m), 5.84 (1H, t, J=7.5), 7.17-7.37 (15H, m), 7.44 (1H, s), 7.49 (1H, s).

(b) (E)-3-{2-[4-(Ethoxycarbonylmethyl)-1H-pyrazol-1-yl]ethylidene}-4-hydroxy-1-(triphenylmethyl)piperidine

The title compound was synthesized in a yield of 63% as a colorless amorphous solid using (E)-4-(t-butyldimethylsilyloxy)-3-{2-[4-(ethoxycarbonylmethyl)-1H-pyrazol-1-yl]ethylidene}-1-(triphenylmethyl)piperidine obtained in (a) above by conducting a reaction similar to that mentioned in Example 1 (e).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 1.26 (3H, t, J=7.0), 1.58-1.61 (1H, m), 1.81-1.89 (1H, m), 2.00 (1H, bs), 2.08-2.14 (1H, m), 2.84 (1H, bs), 3.45 (1H, bs), 3.50 (2H, s), 4.00 (1H, bs), 4.16 (2H, q, J=7.0), 4.68-4.79 (2H, m), 5.77 (1H, t, J=7.0), 7.14-7.18 (3H, m), 7.24-7.28 (12H, m), 7.41 (1H, s), 7.44 (1H, s).

(c) (E)-4-(Acetylsulfanyl)-3-{2-[4-(ethoxycarbonylmethyl)-1H-pyrazol-1-yl]ethylidene}-1-(triphenylmethyl)piperidine

The title compound was synthesized in a yield of 60% as a yellow oil using (E)-3-{2-[4-(ethoxycarbonylmethyl)-1H-pyrazol-1-yl]ethylidene}-4-hydroxy-1-(triphenylmethyl)piperidine obtained in (b) above by conducting a reaction similar to that mentioned in Example 1 (h).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 1.25 (3H, t, J=7.0), 1.79-1.92 (1H, m), 2.24 (3H, s), 2.29-2.33 (2H, m), 3.10-3.14 (1H, m), 3.41 (2H, s), 3.98 (1H, bs), 4.13

(2H, q, J=7.0), 4.25-4.36 (2H, m), 4.61-4.73 (2H, m), 5.78 (1H, t, J=7.0), 7.12-7.20 (3H, m), 7.21-7.31 (6H, m), 7.40-7.56 (8H, m).

(d) (E)-4-(Acetylsulfanyl)-3-{2-[4-(ethoxycarbonylmethyl)-1H-pyrazol-1-yl]ethylidene}piperidine hydrogen trifluoroacetate

The title compound was synthesized in a yield of 20% as a colorless oil using (E)-4-(acetylsulfanyl)-3-{2-[4-(ethoxycarbonylmethyl)-1H-pyrazol-1-yl]ethylidene}-1-(triphenylmethyl)piperidine obtained in (c) above by conducting a reaction similar to that mentioned in Example 3 (c).

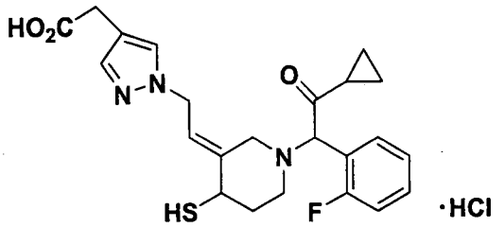
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 1.28 (3H, t, J=7.0), 2.03-2.08 (1H, m), 2.36 (3H, s), 2.37-2.41 (1H, m), 3.24-3.31 (1H, m), 3.39-3.44 (1H, m), 3.47 (2H, s), 3.73 (1H, d, J=14.0), 4.10 (1H, d, J=14.0), 4.16 (2H, q, J=7.0), 4.44 (1H, t, J=4.0), 4.63-4.68 (1H, m), 4.73-4.80 (1H, m), 6.05 (1H, t, J=7.0), 7.41 (2H, s).

(e) (E)-4-(Acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{2-[4-(ethoxycarbonylmethyl)-1H-pyrazol-1-yl]ethylidene}piperidine

The title compound was synthesized in a yield of 57% as a pale yellow oil using (E)-4-(acetylsulfanyl)-3-{2-[4-(ethoxycarbonylmethyl)-1H-pyrazol-1-yl]ethylidene}piperidine hydrogen trifluoroacetate obtained in (d) above by conducting a reaction similar to that mentioned in Example 1 (g).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 0.75-0.88 (2H, m), 0.97-1.07 (2H, m), 1.27 (3H, t, J=7.0), 1.78-1.86 (1H, m), 2.12-2.22 (2H, m), 2.28 and 2.29 (total 3H, each s), 2.49-2.62 (1H, m), 2.68-2.73 and 2.76-2.81 (total 1H, each m), 2.88 and 3.15 (total 1H, each d, J=12.5), 3.30 and 3.41 (total 1H, each d, J=12.5), 3.46 (2H, s), 4.15 (2H, q, J=7.0), 4.28-4.34 (1H, m), 4.62-4.64 and 4.67-4.70 (total 2H, each m), 4.71 and 4.74 (total 1H, each s), 5.78 (1H, t, J=7.0), 7.07-7.17 (2H, m), 7.19-7.27 (1H, m), 7.28-7.37 (1H, m), 7.33 and 7.34 (total 1H, each s), 7.39 (1H, s).

(Example 74) (E)-3-{2-[4-(Carboxymethyl)-1H-pyrazol-1-yl]ethylidene}-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-sulfanylpiperidine hydrochloride (Hydrochloride of the compound of Compound No. 1-53)

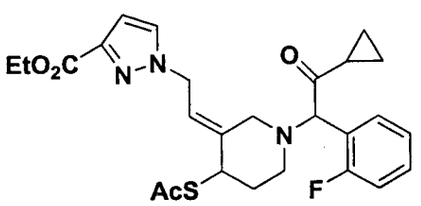


The title compound was synthesized in a yield of 28% as a colorless amorphous solid using (E)-4-(acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{2-[4-(ethoxycarbonylmethyl)-1H-pyrazol-1-yl]ethylidene}piperidine obtained in Example 73 (e) by conducting a reaction similar to that mentioned in Example 15.

^{1}H NMR (400 MHz, pyridine-d_5) δ ppm : 0.78-0.83 (2H, m), 0.98-1.04 (1H, m), 1.09-1.15 (1H, m), 1.74-1.83 (1H, m), 2.14-2.24 (1H, m), 2.46-2.55 (1H, m), 2.61-2.67 (1H, m), 2.82-2.98 (1H, m), 3.36 and 3.67 (total 2H, each d, J=12.5), 3.79 (3H, bs), 4.85-4.93 (3H, m), 5.98 (1H, t, J=7.0), 7.23-7.26 (2H, m), 7.29-7.35 (1H, m), 7.69-7.74 (1H, m), 7.81 (1H, s), 7.84 (1H, s).

MS (FAB) m/z : 444 $(M+H)^+$.

(Example 75) (E)-4-(Acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-[2-(3-ethoxycarbonyl-1H-pyrazol-1-yl)ethylidene]piperidine (Compound of Compound No. 1-14)

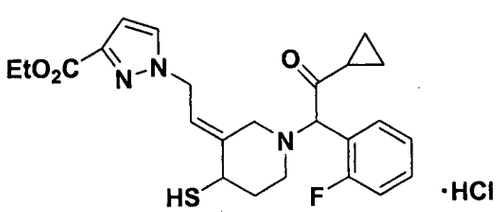


The title compound was synthesized in a yield of 12% as a yellow oil using (E)-4-(acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-

hydroxyethylidene)piperidine obtained in Example 32 (f) and 3-ethoxycarbonyl-1H-pyrazole instead of 4-ethoxycarbonyl-1H-1,2,3-triazole by conducting a reaction similar to that mentioned in Example 47.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 0.80-0.91 (2H, m), 0.99-1.11 (2H, m), 1.37 (3H, t, J=7.0), 1.76-1.84 (1H, m), 2.12-2.35 (2H, m), 2.26 (3H, s), 2.47 and 2.62 (total 1H, each m), 2.73 (1H, m), 3.01 and 3.11 (total 1H, each d, J=12.5), 3.48 and 3.51 (total 1H, each d, J=12.5), 4.28-4.36 (3H, m), 4.75 and 4.77 (total 1H, each s), 5.13-5.21 (2H, m), 5.70-5.74 (1H, m), 6.81-6.82 (1H, m), 7.09-7.21 (2H, m), 7.33 (1H, m), 7.43-7.49 (2H, m).

(Example 76) (E)-1-[2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-[2-(3-ethoxycarbonyl-1H-pyrazol-1-yl)ethylidene]-4-sulfanylpiperidine hydrochloride (Hydrochloride of the compound of Compound No. 1-13)

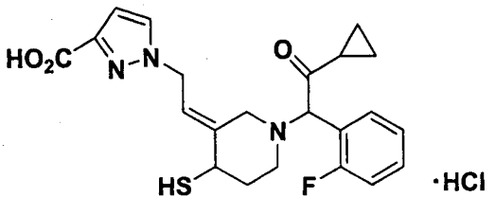


The title compound was synthesized in a yield of 39% as a colorless amorphous solid using (E)-4-(acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-[2-(3-ethoxycarbonyl-1H-pyrazol-1-yl)ethylidene]piperidine obtained in Example 75 by conducting a reaction similar to that mentioned in Example 34.

^{1}H NMR (400 MHz, pyridine-d_5) δ ppm : 0.84-0.92 (2H, m), 1.03-1.09 (1H, m), 1.16-1.24 (1H, m), 1.20 and 1.21 (total 3H, each t, J=7.0), 1.74-1.82 (1H, m), 2.14-2.24 (1H, m), 2.55-2.68 (2H, m), 2.83-2.90 and 2.93-2.99 (total 1H, each m), 3.46 and 3.54 (total 1H, each t, d=12.0), 3.69-3.82 (2H, m), 4.26 (2H, q, J=7.0), 4.97 (1H, s), 5.43-5.46 (2H, m), 6.08 (1H, m), 6.99-7.00 (1H, m), 7.23-7.36 (3H, m), 7.68-7.69 (1H, m), 7.74-7.80 (1H, m).

MS (FAB) m/z : 458 $(M+H)^+$.

(Example 77) (E)-3-[2-(3-Carboxy-1H-pyrazol-1-yl)ethylidene]-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-sulfanylpiperidine hydrochloride (Hydrochloride of the compound of Compound No. 1-5)

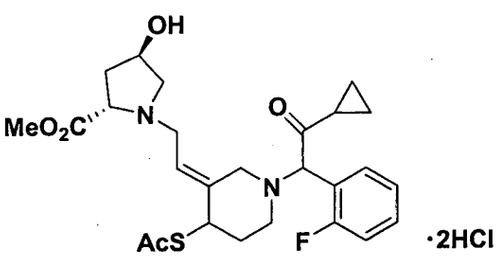


The title compound was synthesized in a yield of 34% as a colorless amorphous solid using (E)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-[2-(3-ethoxycarbonyl-1H-pyrazol-1-yl)ethylidene]-4-sulfanylpiperidine hydrochloride obtained in Example 76 by conducting a reaction similar to that mentioned in Example 15.

^{1}H NMR (400 MHz, pyridine-d_5) δ ppm : 0.81-0.95 (2H, m), 1.02-1.06 (1H, m), 1.16-1.21 (1H, m), 1.74-1.81 (1H, m), 2.14-2.22 (1H, m), 2.59-2.67 (2H, m), 2.85 and 2.95 (total 1H, each m), 3.50 and 3.61 (total 1H, each d, J=12.5), 3.77-3.84 (2H, m), 4.96 (1H, s), 5.59-5.63 (2H, m), 6.17-6.21 (1H, m), 7.19-7.34 (4H, m), 7.73 (1H, s), 7.75-7.81 (1H, m).

MS (FAB) m/z : 430 $(M+H)^+$.

(Example 78) (E)-4-(Acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{2-[(2S,4R)-4-hydroxy-2-(methoxycarbonyl)pyrrolidin-1-yl]ethylidene}piperidine dihydrochloride (Hydrochloride of the compound of Compound No. 5-388)

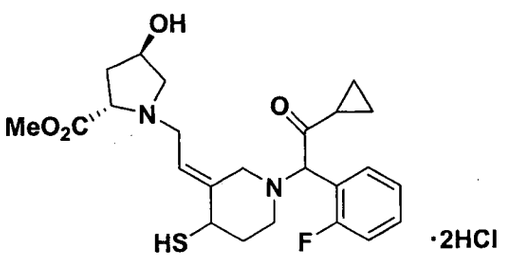


The title compound was synthesized in a yield of 57% as a yellow amorphous solid using (E)-4-(acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-hydroxyethylidene)piperidine obtained in Example 32 (f) and (2S,4R)-4-hydroxy-2-(methoxycarbonyl)pyrrolidine instead of 4-(ethoxycarbonylmethyl)piperidine by conducting a reaction similar to that mentioned in Example 33.

^{1}H NMR (400 MHz, pyridine-d_5) δ ppm : 0.79-0.88 (2H, m), 1.00-1.07 (1H, m), 1.10-1.21 (1H, m), 1.82-1.93 (1H, m), 2.17-2.27 (1H, m), 2.25 and 2.26 (total 3H, each s), 2.31-2.60 (4H, m), 2.67-2.92 (3H, m), 3.14-3.25 (1H, m), 3.36-3.53 (2H, m), 3.58-3.75 (1H, m), 3.69 and 3.71 (total 3H, each s), 3.80-3.90 (1H, m), 4.53-4.58 (1H, m), 4.71-4.77 (1H, m), 4.92 and 4.95 (total 1H, each s), 6.01-6.08 (1H, m), 7.20-7.34 (3H, m), 7.67-7.78 (1H, m).

IR (KBr, cm^{-1}) : 1747, 1702, 1494.

(Example 79) (E)-1-[2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{2-[(2S,4R)-4-hydroxy-2-(methoxycarbonyl)pyrrolidin-1-yl]ethylidene}-4-sulfanylpiperidine dihydrochloride (Hydrochloride of the compound of Compound No. 5-387)

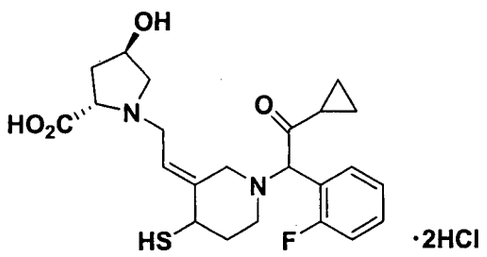


The title compound was synthesized in a yield of 58% as a pale yellow amorphous solid using (E)-4-(acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{2-[(2S,4R)-4-hydroxy-2-(methoxycarbonyl)pyrrolidin-1-yl]ethylidene}piperidine dihydrochloride obtained in Example 78 by conducting a reaction similar to that mentioned in Example 55.

^{1}H NMR (400 MHz, pyridine-d_5) δ ppm : 0.77-0.97 (2H, m), 0.98-1.08 (1H, m), 1.09-1.21 (1H, m), 1.74-1.85 (1H, m), 2.13-2.29 (1H, m), 2.35-2.60 (4H, m), 2.61-2.71 (1H, m), 2.81-3.04 (2H, m), 3.34-3.61 (3H, m), 3.65-3.80 (1H, m), 3.72 and 3.73 and 3.74 (total 3H, each s), 3.82-4.06 (2H, m), 4.72-4.80 (1H, m), 4.94 and 4.95 and 4.96 (total 1H, each s), 5.95-6.06 (1H, m), 7.19-7.37 (3H, m), 7.71-7.81 (1H, m).

IR (KBr, cm^{-1}) : 2545, 1746, 1712, 1494.

(Example 80) (E)-3-{2-[(2S,4R)-2-Carboxy-4-hydroxypyrrolidin-1-yl]ethylidene}-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-sulfanylpiperidine dihydrochloride (Hydrochloride of the compound of Compound No. 5-385)

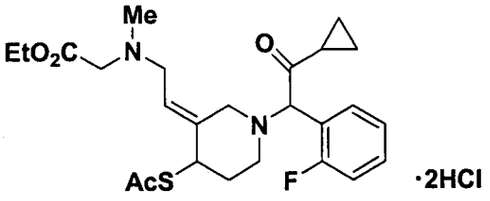


The title compound was synthesized in a yield of 75% as a colorless amorphous solid using (E)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{2-[(2S,4R)-4-hydroxy-2-(methoxycarbonyl)pyrrolidin-1-yl]ethylidene}-4-sulfanylpiperidine dihydrochloride obtained in Example 79 by conducting a reaction similar to that mentioned in Example 15.

^{1}H NMR (500 MHz, pyridine-d_5) δ ppm : 0.76-0.95 (2H, m), 0.99-1.06 (1H, m), 1.11-1.20 (1H, m), 1.73-1.84 (1H, m), 2.15-2.26 (1H, m), 2.45-2.55 (1H, m), 2.56-2.86 (3H, m), 2.93-3.03 (1H, m), 3.34-4.03 (4H, m), 4.05-4.35 (3H, m), 4.53-4.66 (1H, m), 4.84-4.90 (1H, m), 4.97 and 4.99 and 5.00 and 5.02 (total 1H, each s), 6.18-6.29 (1H, m), 7.16-7.34 (3H, m), 7.70-7.80 (1H, m).

IR (KBr, cm^{-1}) : 2559, 1738, 1711, 1494.

(Example 81) (E)-4-(Acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{2-[N-(ethoxycarbonylmethyl)-N-methylamino]ethylidene}piperidine dihydrochloride (Hydrochloride of the compound of Compound No. 3-55)

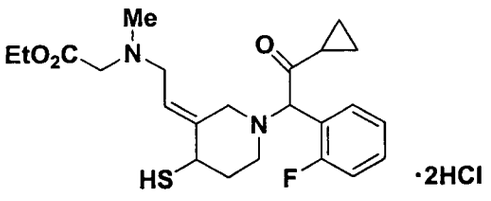


The title compound was synthesized in a yield of 56% as a pale yellow amorphous solid using (E)-4-(acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-hydroxyethylidene)piperidine obtained in Example 32 (f) and N-(ethoxycarbonylmethyl)-N-methylamine hydrochloride instead of 4-(ethoxycarbonylmethyl)piperidine by conducting a reaction similar to that mentioned in Example 33.

^{1}H NMR (500 MHz, pyridine-d_5) δ ppm : 0.76-0.92 (2H, m), 0.99-1.06 (1H, m), 1.11-1.22 (1H, m), 1.13 and 1.14 (total 3H, each t, J=7.0), 1.81-1.93 (1H, m), 2.16-2.30 (1H, m), 2.25 and 2.26 (total 3H, each s), 2.39-2.51 (1H, m), 2.45 and 2.47 (total 3H, each s), 2.52-2.60 and 2.67-2.75 (total 1H, each m), 2.77-2.90 (1H, m), 3.13 and 3.22 (total 1H, each d, J=13.0), 3.27-3.51 (4H, m), 3.56-3.72 (1H, m), 4.13 (2H, q, J=7.0), 4.52-4.58 (1H, m), 4.94 and 4.96 (total 1H, each s), 5.90-6.00 (1H, m), 7.20-7.30 (2H, m), 7.31-7.39 (1H, m), 7.66-7.74 (1H, m).

IR (KBr, cm^{-1}) : 1745, 1700, 1494.

(Example 82) (E)-1-[2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{2-[N-(ethoxycarbonylmethyl)-N-methylamino]ethylidene}-4-sulfanylpiperidine dihydrochloride (Hydrochloride of the compound of Compound No. 3-54)



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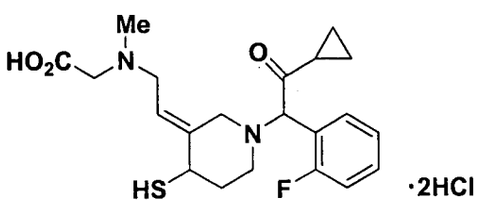
The title compound was synthesized in a yield of 63% as a pale yellow amorphous solid using (E)-4-(acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{2-[N-(ethoxycarbonylmethyl)-N-methylamino]ethylidene}piperidine dihydrochloride obtained in Example 81 by conducting a reaction similar to that mentioned in Example 34.

^{1}H NMR (500 MHz, pyridine-d_5) δ ppm : 0.79-0.88 (2H, m), 1.01-1.07 (1H, m), 1.11-1.20 (1H, m), 1.14 and 1.15 (total 3H, each t, J=7.0), 1.74-1.83 (1H, m), 2.16-2.27 (1H, m), 2.43-2.54 (1H, m), 2.47 and 2.49 (total 3H, each s), 2.63-2.72 (1H, m), 2.81-2.90 and 2.93-3.00 (total 1H, each m), 3.30-3.61 (6H, m), 3.84-3.89 (1H, m), 4.14 and 4.15 (total 2H, each q, J=7.0), 4.94 and 4.95 (total 1H, each s), 5.86-5.91 (1H, m), 7.21-7.28 (2H, m), 7.31-7.37 (1H, m), 7.70-7.75 (1H, m).

IR (KBr, cm^{-1}) : 2536, 1745, 1713, 1494.

(Example 83) (E)-3-{2-[N-(Carboxymethyl)-N-methylamino]ethylidene}-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-sulfanylpiperidine dihydrochloride (Hydrochloride of the compound of Compound No. 3-50)



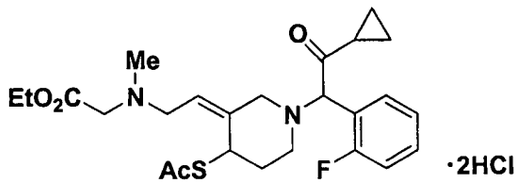
The title compound was synthesized in a yield of 17% as a colorless amorphous solid using (E)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{2-[N-(ethoxycarbonylmethyl)-N-methylamino]ethylidene}-4-sulfanylpiperidine dihydrochloride obtained in Example 82 by conducting a reaction similar to that mentioned in Example 15.

^{1}H NMR (500 MHz, pyridine-d_5) δ ppm : 0.79-0.92 (2H, m), 1.00-1.08 (1H, m), 1.12-1.21 (1H, m), 1.74-1.86 (1H, m), 2.15-2.28 (1H, m), 2.44-2.60 (1H, m), 2.63-2.75 (1H, m), 2.71 and 2.73 (total 3H, each s), 2.80-2.89 and 2.93-3.02 (total

1H, each m), 3.38-3.69 (4H, m), 3.72-3.93 (3H, m), 4.94 and 4.96 (total 1H, each s), 5.99-6.06 (1H, m), 7.17-7.35 (3H, m), 7.69-7.76 (1H, m).

IR (KBr, cm^{-1}) : 2630, 1741, 1712, 1494.

(Example 84) (Z)-4-(Acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{2-[N-(ethoxycarbonylmethyl)-N-methylamino]ethylidene}piperidine dihydrochloride (Hydrochloride of the compound of Compound No. 4-55)



(a) (Z)-4-(Acetylsulfanyl)-3-{2-[N-(ethoxycarbonylmethyl)-N-methylamino]ethylidene}-1-(triphenylmethyl)piperidine

The title compound was synthesized in a yield of 38% as a colorless amorphous solid using (Z)-4-(acetylsulfanyl)-3-(2-hydroxyethylidene)-1-(triphenylmethyl)piperidine obtained in Example 66 (d) instead of (E)-4-(acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-hydroxyethylidene)piperidine and N-(ethoxycarbonylmethyl)-N-methylamine hydrochloride instead of 4-(ethoxycarbonylmethyl)piperidine by conducting a reaction similar to that mentioned in Example 33.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 1.29 (3H, t, J=7.0), 1.73-1.85 (1H, m), 1.94-2.05 (1H, m), 2.15-2.52 (4H, m), 2.20 (3H, s), 2.41 (3H, s), 3.00-3.47 (4H, m), 4.21 (2H, q, J=7.0), 4.82 (1H, bs), 5.39 (1H, t, J=6.5), 7.03-7.75 (15H, m).

(b) (Z)-4-(Acetylsulfanyl)-3-{2-[N-(ethoxycarbonylmethyl)-N-methylamino]ethylidene}piperidine bis(hydrogen trifluoroacetate)

The title compound was synthesized in a yield of 90% as a colorless amorphous solid using (Z)-4-(acetylsulfanyl)-3-{2-[N-(ethoxycarbonylmethyl)-N-

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methylamino]ethylidene}-1-(triphenylmethyl)piperidine obtained in (a) above by conducting a reaction similar to that mentioned in Example 3 (c).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 1.30 (3H, t, J=7.0), 1.99-2.10 (1H, m), 2.35 (3H, s), 2.35-2.50 (1H, m), 2.88 (3H, s), 3.07-3.20 (1H, m), 3.36-3.49 (1H, m), 3.65-3.98 (5H, m), 4.25 (2H, q, J=7.0), 4.28-4.38 (1H, m), 4.78 (1H, bs), 5.78-5.86 (1H, m).

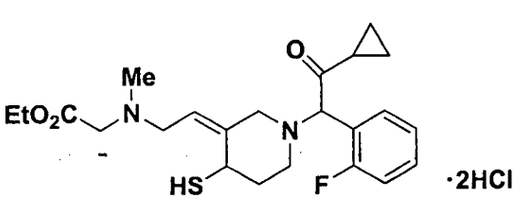
(c) (Z)-4-(Acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{2-[N-(ethoxycarbonylmethyl)-N-methylamino]ethylidene}piperidine dihydrochloride

The title compound was synthesized in a yield of 50% as a colorless amorphous solid using (Z)-4-(acetylsulfanyl)-3-{2-[N-(ethoxycarbonylmethyl)-N-methylamino]ethylidene}piperidine bis(hydrogen trifluoroacetate) obtained in (b) above by conducting a reaction similar to that mentioned in Example 1 (g).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 0.75-0.92 (2H, m), 0.93-1.09 (2H, m), 1.23-1.35 (3H, m), 1.70-1.87 (1H, m), 2.06-2.56 (2H, m), 2.29 (3H, s), 2.35 and 2.36 (total 3H, each s), 2.65-3.00 (2H, m), 3.08-3.36 (6H, m), 4.14-4.25 (2H, m), 4.62 and 4.67 (total 1H, each s), 4.79 (1H, bs), 5.35 and 5.45 (total 1H. each t, J=6.5), 7.04-7.22 (2H, m), 7.26-7.48 (2H, m).

IR (KBr, cm^{-1}) : 1745, 1699, 1494.

(Example 85) (Z)-1-[2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{2-[N-(ethoxycarbonylmethyl)-N-methylamino]ethylidene}-4-sulfanylpiperidine dihydrochloride (Hydrochloride of the compound of Compound No. 4-54)



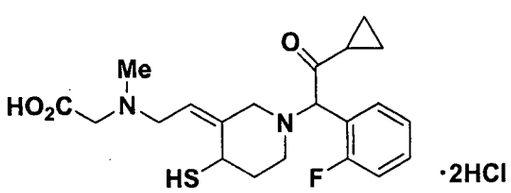
The title compound was synthesized in a yield of 90% as a colorless amorphous solid using (Z)-4-(acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-

oxoethyl]-3-{2-[N-(ethoxycarbonylmethyl)-N-methylamino]ethylidene}piperidine dihydrochloride obtained in Example 84 by conducting a reaction similar to that mentioned in Example 34.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 0.75-0.91 (2H, m), 0.94-1.09 (2H, m), 1.22-1.33 (3H, m), 1.65-1.79 (1H, m), 2.07-2.28 (2H, m), 2.37 and 2.39 (total 3H, each s), 2.44-3.35 (8H, m), 4.12-4.24 (2H, m), 4.30 (1H, bs), 4.68 and 4.73 (total 1H, each s), 5.23 and 5.33 (total 1H, each t, J=7.0), 7.05-7.21 (2H, m), 7.26-7.48 (2H, m).

IR (KBr, cm^{-1}) : 2626, 2560, 1745, 1712, 1494.

(Example 86) (Z)-3-{2-[N-(Carboxymethyl)-N-methylamino]ethylidene}-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-sulfanylpiperidine dihydrochloride (Hydrochloride of the compound of Compound No. 4-50)

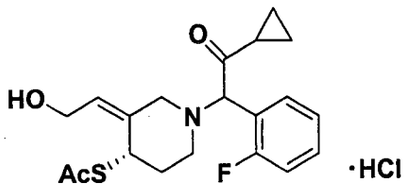


The title compound was synthesized in a yield of 50% as a colorless amorphous solid using (Z)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{2-[N-(ethoxycarbonylmethyl)-N-methylamino]ethylidene}-4-sulfanylpiperidine dihydrochloride obtained in Example 85 by conducting a reaction similar to that mentioned in Example 15.

^{1}H NMR (400 MHz, pyridine-d_5) δ ppm : 0.71-0.94 (2H, m), 0.96-1.17 (2H, m), 1.71-1.87 (1H, m), 2.21-2.42 (1H, m), 2.43-2.56 (1H, m), 2.60-3.07 (2H, m), 2.98 and 3.02 (total 3H, each s), 3.25-3.62 (2H, m), 4.00-4.26 (4H, m), 4.71 (1H, bs), 4.90 and 4.96 (total 1H, each s), 5.76 and 5.87 (total 1H, each t, J=7.0), 7.10-7.36 (3H, m), 7.62-7.72 (1H, m).

IR (KBr, cm^{-1}) : 2558, 1740, 1712, 1494.

(Example 87) (4S)-(Z)-4-(Acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-hydroxyethylidene)piperidine hydrochloride (Hydrochloride of the (4S) form of the compound of Compound No. 4-2)



(a) (4S)-(Z)-4-(Acetylsulfanyl)-3-(2-hydroxyethylidene)-1-(triphenylmethyl)piperidine and (4R)-(Z)-4-(acetylsulfanyl)-3-(2-hydroxyethylidene)-1-(triphenylmethyl)piperidine

(Z)-4-(Acetylsulfanyl)-3-(2-hydroxyethylidene)-1-(triphenylmethyl)piperidine (102 mg) obtained in Example 66 (d) was separated using a preparative HPLC (Daicel, Chiralcel OD-H, eluent: hexane / ethanol / diethylamine = 90 / 10 / 0.1) to afford (4S)-(Z)-4-(acetylsulfanyl)-3-(2-hydroxyethylidene)-1-(triphenylmethyl)piperidine (41 mg) having a shorter retention time and (4R)-(Z)-4-(acetylsulfanyl)-3-(2-hydroxyethylidene)-1-(triphenylmethyl)piperidine (43 mg) having a longer retention time as colorless amorphous solids, respectively.

The ^{1}H NMR was the same as that of (Z)-4-(acetylsulfanyl)-3-(2-hydroxyethylidene)-1-(triphenylmethyl)piperidine of Example 66 (d).

[α]D of (4S) form: -15.2° (c=1.00, MeOH)

[α]D of (4R) form: +11.5° (c=0.50, MeOH)

(b) (4S)-(Z)-4-(Acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-hydroxyethylidene)piperidine hydrochloride

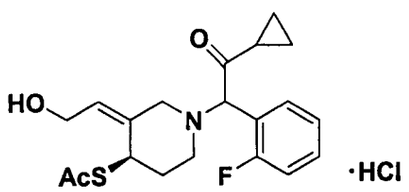
The title compound was synthesized in a yield of 67% as a colorless amorphous solid using (4S)-(Z)-4-(acetylsulfanyl)-3-(2-hydroxyethylidene)-1-

(triphenylmethyl)piperidine obtained in (a) above by conducting a reaction similar to that mentioned in Example 66 (e).

The ^{1}H NMR was the same as in Example 66 (e).

IR(KBr, cm^{-1}): 3345, 1696, 1494.

(Example 88) (4R)-(Z)-4-(Acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-hydroxyethylidene)piperidine hydrochloride (Hydrochloride of the (4R) form of the compound of Compound No. 4-2)

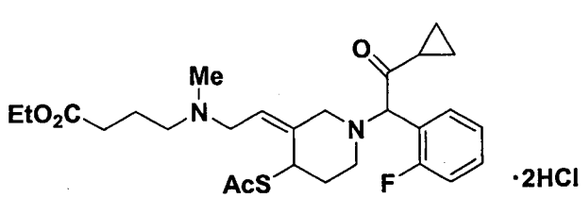


The title compound was synthesized in a yield of 70% as a colorless amorphous solid using (4R)-(Z)-4-(acetylsulfanyl)-3-(2-hydroxyethylidene)-1-(triphenylmethyl)piperidine obtained in Example 87 (a) by conducting a reaction similar to that mentioned in Example 66 (e).

The ^{1}H NMR was the same as in Example 66 (e).

IR(KBr, cm^{-1}): 3350, 1696, 1494.

(Example 89) (Z)-4-(Acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-{N-[3-(ethoxycarbonyl)propyl]-N-methylamino}ethylidene)piperidine dihydrochloride (Hydrochloride of the compound of Compound No. 4-67)



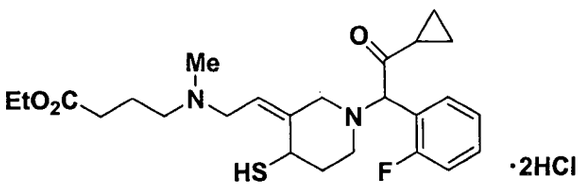
The title compound was synthesized in a yield of 43% as a pale orange amorphous solid using (Z)-4-(acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-

oxoethyl]-3-(2-hydroxyethylidene)piperidine obtained in Example 66 (e) instead of (E)-4-(acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-hydroxyethylidene)piperidine and N-[3-(ethoxycarbonyl)propyl]-N-methylamine hydrochloride instead of 4-(ethoxycarbonylmethyl)piperidine by conducting a reaction similar to that mentioned in Example 33.

^{1}H NMR (500 MHz, pyridine-d_5) δ ppm : 0.76-0.85 (1H, m), 0.99-1.08 (2H, m), 1.09-1.18 (1H, m), 1.11 and 1.12 (total 3H, each t, J=7.0), 1.81-1.89 (1H, m), 2.23-2.42 (3H, m), 2.25 and 2.26 (total 3H, each s), 2.47-2.61 (1H, m), 2.51 (2H, t, J=7.0), 2.77 and 2.78 (total 3H, each s), 2.96-3.13 (2H, m), 3.15-3.26 (2H, m), 3.35 and 3.55 (total 1H, each d, J=12.0), 3.60-3.67 (1H, m), 3.98-4.12 (1H, m), 4.08 and 4.09 (total 2H, each q, J=7.0), 4.13-4.23 (1H, m), 4.86 and 4.96 (total 1H, each s), 4.89-4.94 (1H, m), 6.10 and 6.21 (total 1H, each t, J=7.0), 7.19-7.38 (3H, m), 7.57-7.66 (1H, m).

IR (KBr, cm^{-1}) : 1725, 1712, 1495.

(Example 90) (Z)-1-[2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-{N-[3-(ethoxycarbonyl)propyl)]-N-methylamino}ethylidene)-4-sulfanylpiperidine dihydrochloride (Hydrochloride of the compound of Compound No. 4-66)

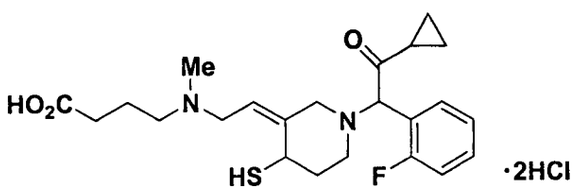


The title compound was synthesized in a yield of 76% as a yellow amorphous solid using (Z)-4-(acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-{N-[3-(ethoxycarbonyl)propyl]-N-methylamino}ethylidene)piperidine dihydrochloride obtained in Example 89 by conducting a reaction similar to that mentioned in Example 34.

^{1}H NMR (500 MHz, pyridine-d_5) δ ppm : 0.74-0.85 (1H, m), 0.87-0.96 (1H, m), 0.99-1.06 (1H, m), 1.07-1.15 (1H, m), 1.10 and 1.11 (total 3H, each t, J=7.0), 1.74-1.85 (1H, m), 2.25-2.40 (3H, m), 2.43-2.54 (3H, m), 2.65-2.72 (1H, m), 2.81 and 2.83 (total 3H, each s), 2.93-2.98 (1H, m), 3.19-3.64 (4H, m), 3.89-4.00 (2H, m), 4.07 and 4.09 (total 2H, each q, J=7.0), 4.54-4.59 (1H, m), 4.89 and 4.95 (total 1H, each s), 5.85 and 5.96 (total 1H, each t, J=7.0), 7.17-7.25 (2H, m), 7.26-7.34 (1H, m), 7.57-7.68 (1H, m).

IR (KBr, cm^{-1}) : 2550, 1728, 1495.

(Example 91) (Z)-3-(2-{N-[3-(Carboxy)propyl]-N-methylamino}ethylidene)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-sulfanylpiperidine dihydrochloride (Hydrochloride of the compound of Compound No. 4-62)

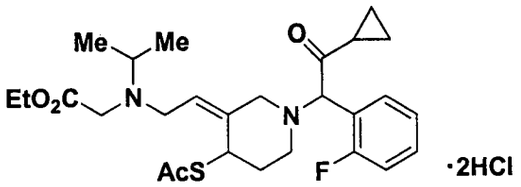


The title compound was synthesized in a yield of 50% as a colorless amorphous solid using (Z)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-{N-[3-(ethoxycarbonyl)propyl]-N-methylamino}ethylidene)-4-sulfanylpiperidine dihydrochloride obtained in Example 90 by conducting a reaction similar to that mentioned in Example 15.

^{1}H NMR (500 MHz, pyridine-d_5) δ ppm : 0.73-0.83 (1H, m), 0.86-0.97 (1H, m), 0.98-1.06 (1H, m), 1.07-1.17 (1H, m), 1.71-1.85 (1H, m), 2.25-2.54 (4H, m), 2.58-2.89 (3H, m), 2.81 and 2.83 (total 3H, each s), 2.90-3.01 (1H, m), 3.21-3.37 (2H, m), 3.39-3.48 (1H, m), 3.50-3.56 (1H, m), 3.86-4.00 (2H, m), 4.53-4.60 (1H, m), 4.89 and 4.97 (total 1H, each s), 5.86 and 5.97 (total 1H, each t, J=7.0), 7.16-7.24 (2H, m), 7.25-7.34 (1H, m), 7.62-7.68 (1H, m).

IR (KBr, cm^{-1}) : 2553, 1713, 1494.

(Example 92) (Z)-4-(Acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{2-[N-(ethoxycarbonylmethyl)-N-isopropylamino]ethylidene}piperidine dihydrochloride (Hydrochloride of the compound of Compound No. 4-79)

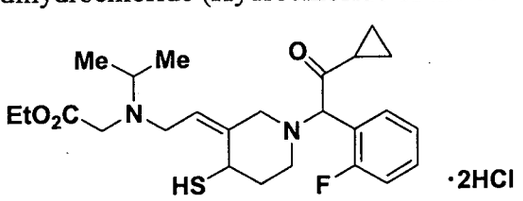


The title compound was synthesized in a yield of 33% as a brown amorphous solid using (Z)-4-(acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-hydroxyethylidene)piperidine obtained in Example 66 (e) instead of (E)-4-(acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-hydroxyethylidene)piperidine and N-(ethoxycarbonylmethyl)-N-isopropylamine instead of 4-(ethoxycarbonylmethyl)piperidine by conducting a reaction similar to that mentioned in Example 33.

^{1}H NMR (400 MHz, pyridine-d_5) δ ppm : 0.74-0.86 (2H, m), 0.98-1.13 (2H, m), 1.04 and 1.06 (total 3H, each d, J=6.5), 1.07 and 1.09 (total 3H, each d ,J=6.5), 1.17 and 1.19 (total 3H, each t, J=7.0), 1.85-1.96 (1H, m), 2.28 (3H, s), 2.30-2.41 (1H, m), 2.42-2.52 (1H, m), 2.59-2.68 (1H, m), 2.90-3.01 (1H, m), 3.03-3.12 (1H, m), 3.13-3.22 (1H, m), 3.36-3.70 (5H, m), 4.18 and 4.20 (total 2H, each q, J=7.0), 4.87 and 4.92 (total 1H, each s), 5.14 (1H, bs), 5.63 and 5.72 (total 1H, each t, J=7.0), 7.19-7.27 (2H, m), 7.29-7.36 (1H, m), 7.64-7.70 (1H, m).

IR (KBr, cm^{-1}) : 1745, 1696, 1495.

(Example 93) (Z)-1-[2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{2-[N-(ethoxycarbonylmethyl)-N-isopropylamino]ethylidene}-4-sulfanylpiperidine dihydrochloride (Hydrochloride of the compound of Compound No. 4-78)

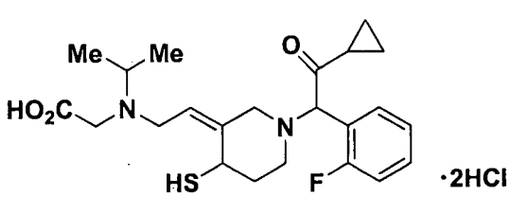


The title compound was synthesized in a yield of 41% as a colorless amorphous solid using (Z)-4-(acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{2-[N-(ethoxycarbonylmethyl)-N-isopropylamino]ethylidene}piperidine dihydrochloride obtained in Example 92 by conducting a reaction similar to that mentioned in Example 34.

^{1}H NMR (400 MHz, pyridine-d_5) δ ppm : 0.75-0.83 (2H, m), 0.97-1.13 (2H, m), 1.03 (3H, d, J=6.5), 1.06 (3H, d, J=6.5), 1.16 and 1.18 (total 3H, each t, J=7.0), 1.73-1.85 (1H, m), 2.22-2.37 (1H, m), 2.45-2.54 (1H, m), 2.66-2.75 (1H, m), 2.81-3.27 (3H, m), 3.36-3.55 (5H, m), 4.17 and 4.18 (total 2H, each q, J=7.0), 4.61 (1H, bs), 4.89 and 4.93 (total 1H, each s), 5.44 and 5.55 (total 1H, each t, J=7.0), 7.18-7.24 (2H, m), 7.27-7.34 (1H, m), 7.67-7.74 (1H, m).

IR (KBr, cm^{-1}) : 2545, 1745, 1712, 1494.

(Example 94) (Z)-3-{2-[N-(Carboxymethyl)-N-isopropylamino]ethylidene}-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-sulfanylpiperidine dihydrochloride (Hydrochloride of the compound of Compound No. 4-74)



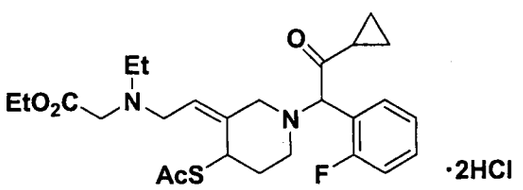
The title compound was synthesized in a yield of 40% as a colorless amorphous solid using (Z)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{2-[N-(ethoxycarbonylmethyl)-N-isopropylamino]ethylidene}-4-sulfanylpiperidine dihydrochloride obtained in Example 93 by conducting a reaction similar to that mentioned in Example 15.

^{1}H NMR (400 MHz, pyridine-d_5) δ ppm : 0.70-0.87 (2H, m), 0.94-1.04 (1H, m), 1.05-1.19 (1H, m), 1.13 and 1.14 (total 3H, each d, J=6.5), 1.15 and 1.16 (total 3H, each d, J=6.5), 1.71-1.84 (1H, m), 2.22-2.41 (1H, m), 2.48-2.57 (1H, m), 2.64-

3.02 (2H, m), 3.21-3.44 (2H, m), 3.49-3.69 (5H, m), 4.67 (1H, bs), 4.87 and 4.92 (total 1H, each s), 5.55 and 5.67 (total 1H, each t, J=7.0), 7.16-7.23 (2H, m), 7.25-7.32 (1H, m), 7.66-7.73 (1H, m).

IR (KBr, cm^{-1}) : 2554, 1740, 1712, 1494.

(Example 95) (Z)-4-(Acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{2-[N-(ethoxycarbonylmethyl)-N-ethylamino]ethylidene}piperidine dihydrochloride (Hydrochloride of the compound of Compound No. 4-73)



The title compound was synthesized in a yield of 38% as a brown amorphous solid using (Z)-4-(acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-hydroxyethylidene)piperidine obtained in Example 66 (e) instead of (E)-4-(acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-hydroxyethylidene)piperidine and N-(ethoxycarbonylmethyl)-N-ethylamine instead of 4-(ethoxycarbonylmethyl)piperidine by conducting a reaction similar to that mentioned in Example 33.

^{1}H NMR (500 MHz, pyridine-d_5) δ ppm : 0.74-0.88 (2H, m), 0.99-1.05 (1H, m), 1.07-1.15 (1H, m), 1.10 and 1.12 (total 3H, each t, J=7.5), 1.17 and 1.18 (total 3H, each t, J=7.0), 1.84-1.94 (1H, m), 2.27 (3H, s), 2.30-2.68 (3H, m), 2.83 and 2.86 (total 2H, each d, J=7.5), 2.92-3.01 (1H, m), 3.05-3.12 (1H, m), 3.40 and 3.55 (total 1H, each d, J =13.0), 3.52-3.67 (3H, m), 3.72-3.81 (1H, m), 4.15-4.22 (2H, m), 4.89 and 4.94 (total 1H, each s), 5.12 (1H, bs), 5.63 and 5.73 (total 1H, each t, J=7.0), 7.20-7.26 (2H, m), 7.30-7.36 (1H, m), 7.64-7.69 (1H, m).

IR (KBr, cm^{-1}) : 1745, 1697, 1494.

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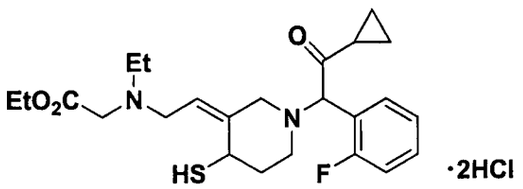
(Example 96) (Z)-1-[2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{2-[N-(ethoxycarbonylmethyl)-N-ethylamino]ethylidene}-4-sulfanylpiperidine dihydrochloride (Hydrochloride of the compound of Compound No. 4-72)

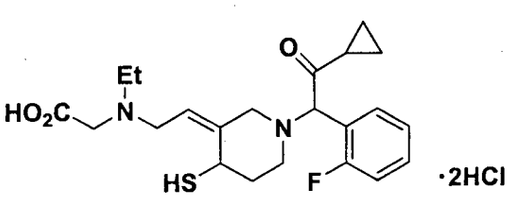


The title compound was synthesized in a yield of 64% as a colorless amorphous solid using (Z)-4-(acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{2-[N-(ethoxycarbonylmethyl)-N-ethylamino]ethylidene}piperidine dihydrochloride obtained in Example 95 by conducting a reaction similar to that mentioned in Example 34.

^{1}H NMR (400 MHz, pyridine-d_5) δ ppm : 0.71-0.86 (2H, m), 0.96-1.04 (1H, m), 1.06-1.20 (1H, m), 1.09 (3H, t, J=7.0), 1.15 and 1.16 (total 3H, each t, J=7.0), 1.70-1.85 (1H, m), 2.17-2.36 (1H, m), 2.44-2.54 (1H, m), 2.64-3.04 (4H, m), 3.25 and 3.40 (total 1H, each d, J=12.5), 3.37-3.62 (5H, m), 4.16 and 4.17 (total 2H, each q, J=7.0), 4.57 (1H, bs), 4.90 and 4.94 (total 1H, each s), 5.46 and 5.57 (total 1H, each t, J=7.0), 7.16-7.26 (2H, m), 7.27-7.36 (1H, m), 7.64-7.76 (1H, m).

IR (KBr, cm^{-1}) : 2558, 1744, 1712, 1494.

(Example 97) (Z)-3-{2-[N-(Carboxymethyl)-N-ethylamino]ethylidene}-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-sulfanylpiperidine dihydrochloride (Hydrochloride of the compound of Compound No. 4-68)

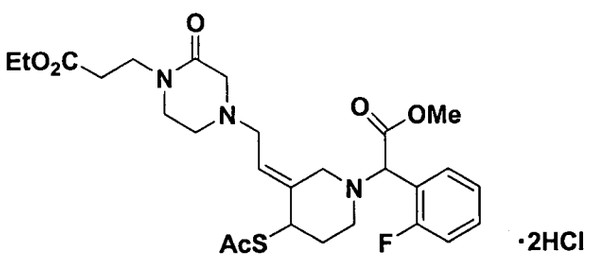


The title compound was synthesized in a yield of 53% as a colorless amorphous solid using (Z)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{2-[N-(ethoxycarbonylmethyl)-N-ethylamino]ethylidene}-4-sulfanylpiperidine dihydrochloride obtained in Example 96 by conducting a reaction similar to that mentioned in Example 15.

^{1}H NMR (400 MHz, pyridine-d_5) δ ppm : 0.72-0.92 (2H, m), 0.97-1.05 (1H, m), 1.06-1.15 (1H, m), 1.33 and 1.35 (total 3H, each t, J=7.0), 1.72-1.84 (1H, m), 2.23-2.41 (1H, m), 2.46-2.56 (1H, m), 2.62-2.98 (2H, m), 3.22-3.58 (4H, m), 3.71-4.12 (4H, m), 4.68 (1H, bs), 4.89 and 4.95 (total 1H, each s), 5.17 and 5.89 (total 1H, each t, J=7.0), 7.16-7.24 (2H, m), 7.25-7.34 (1H, m), 7.64-7.72 (1H, m).

IR (KBr, cm^{-1}) : 2556, 1740, 1713, 1494.

(Example 98) (E)-4-(Acetylsulfanyl)-3-(2-{4-[2-(ethoxycarbonyl)ethyl]-3-oxopiperazin-1-yl}ethylidene)-1-[1-(2-fluorophenyl)-2-methoxy-2-oxoethyl]piperidine dihydrochloride (Hydrochloride of the compound of Compound No. 11-108)



(a) (E)-4-(Acetylsulfanyl)-3-(2-{4-[2-(ethoxycarbonyl)ethyl]-3-oxopiperazin-1-yl}ethylidene)-1-(triphenylmethyl)piperidine

The title compound was synthesized in a yield of 40% as a yellow powder crystal using (E)-3-(2-{4-[2-(ethoxycarbonyl)ethyl]-3-oxopiperazin-1-yl}ethylidene)-4-hydroxy-1-(triphenylmethyl)piperidine obtained in Example 17 (b) by conducting a reaction similar to that mentioned in Example 1 (h).

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^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 1.27 (3H, t, J=7.0), 1.79-1.91 (1H, m), 2.14-2.32 (2H, m), 2.24 (3H, s), 2.51-2.66 (6H, m), 2.93-3.06 (3H, m), 3.09 (2H, s), 3.38 (2H, t, J=5.0), 3.63 (2H, t, J=7.0), 4.15 (2H, q, J=7.0), 4.25 (1H, m), 5.59 (1H, t, J=7.0), 7.13-7.22 (3H, m), 7.23-7.34 (6H, m), 7.40-7.54 (6H, m).

(b) (E)-4-(Acetylsulfanyl)-3-(2-{4-[2-(ethoxycarbonyl)ethyl]-3-oxopiperazin-1-yl}ethylidene)piperidine bis(hydrogen trifluoroacetate)

The title compound was synthesized in a yield of 81% as a brown oil using (E)-4-(acetylsulfanyl)-3-(2-{4-[2-(ethoxycarbonyl)ethyl]-3-oxopiperazin-1-yl}ethylidene)-1-(triphenylmethyl)piperidine obtained in (a) above by conducting a reaction similar to that mentioned in Example 3 (c).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 1.26 (3H, t, J=7.0), 2.00-2.09 (1H, m), 2.36 (3H, s), 2.38-2.45 (1H, m), 2.62 (2H, t, J=6.5), 2.86-2.95 (1H, m), 2.97-3.06 (1H, m), 3.17-3.26 (1H, m), 3.28-3.45 (5H, m), 3.50-3.54 (2H, m), 3.63 (2H, t, J=7.0), 3.67 (1H, d, J=13.0), 4.13 (2H, q, J=7.0), 4.16 (1H, d, J=13.0), 4.43-4.47 (1H, m), 5.59 (1H, t, J=7.0).

(c) (E)-4-(Acetylsulfanyl)-3-(2-{4-[2-(ethoxycarbonyl)ethyl]-3-oxopiperazin-1-yl}ethylidene)-1-[1-(2-fluorophenyl)-2-methoxy-2-oxoethyl]piperidine dihydrochloride

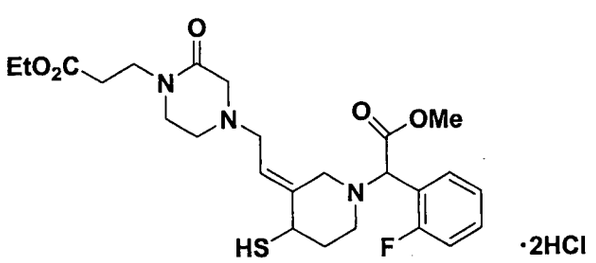
To a solution of (E)-4-(acetylsulfanyl)-3-(2-{4-[2-(ethoxycarbonyl)ethyl]-3-oxopiperazin-1-yl}ethylidene)piperidine bis(hydrogen trifluoroacetate) (0.76 g) obtained in (b) above and methyl bromo(2-fluorophenyl)acetate (0.45 g) in acetonitrile (10 ml) was added triethylamine (0.51 ml) under ice cooling, and the resulting mixture was stirred at room temperature for 30 minutes. The reaction mixture was diluted with ethyl acetate and washed with water and a saturated aqueous sodium chloride solution, and the organic layer was dried over anhydrous magnesium sulfate. The solvent was removed in vacuo, and the residue was purified by chromatography on a silica gel column (methanol / dichloromethane = 1 /

20) to afford the free form (0.50 g, yield 74%) of the title compound as a pale yellow oil. To a solution of this compound in dichloromethane (8 ml) was added a 4N solution of hydrogen chloride in dioxane (0.69 ml) at room temperature, and the reaction mixture was evaporated in vacuo to afford the title compound (0.66 g, quantitative yield) as a pale brown amorphous solid.

^{1}H NMR (400 MHz, pyridine-d_5) δ ppm : 1.12 (3H, t, J=7.0), 1.80-1.89 (1H, m), 2.14-2.24 (1H, m), 2.25 and 2.27 (total 3H, each s), 2.45-2.65 (2H, m), 2.73 (2H, t, J=7.0), 2.77-3.02 (5H, m), 3.19 and 3.37 (total 1H, each d, J=12.5), 3.23 and 3.25 (total 2H, each s), 3.29-3.36 (2H, m), 3.68 (3H, s), 3.76 (2H, t, J=7.0), 4.10 (2H, q, J=7.0), 4.50-4.57 (1H, m), 4.95 and 4.97 (total 1H, each s), 5.81 (1H, t, J=7.0), 7.20-7.28 (2H, m), 7.31-7.38 (1H, m), 7.73-7.80 (1H, m).

IR (KBr, cm^{-1}) : 1752, 1730, 1697, 1664, 1497.

(Example 99) (E)-3-(2-{4-[2-(Ethoxycarbonyl)ethyl]-3-oxopiperazin-1-yl}ethylidene)-1-[1-(2-fluorophenyl)-2-methoxy-2-oxoethyl]-4-sulfanylpiperidine dihydrochloride (Hydrochloride of the compound of Compound No. 11-107)



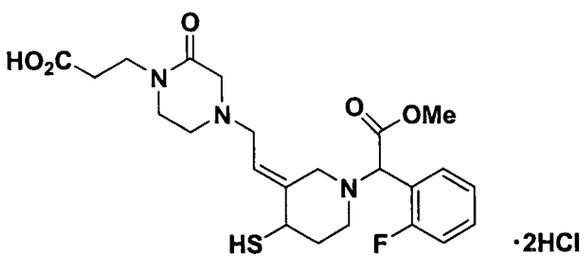
The title compound was synthesized in a yield of 65% as a colorless amorphous solid using (E)-4-(acetylsulfanyl)-3-(2-{4-[2-(ethoxycarbonyl)ethyl]-3-oxopiperazin-1-yl}ethylidene)-1-[1-(2-fluorophenyl)-2-methoxy-2-oxoethyl]piperidine dihydrochloride obtained in Example 98 by conducting a reaction similar to that mentioned in Example 34.

^{1}H NMR (400 MHz, pyridine-d_5) δ ppm : 1.12 (3H, t, J=7.0), 1.71-1.83 (1H, m), 2.11-2.24 (1H, m), 2.54-2.65 (2H, m), 2.67-2.82 (1H, m), 2.74 (2H, t, J=7.0),

2.96-3.09 (1H, m), 3.01 (2H, t, J=6.5), 3.26 (2H, s), 3.34 (2H, t, J=5.0), 3.37 and 3.48 (total 1H, each d, J=12.5), 3.60 and 3.73 (total 1H, each d, J=12.5), 3.67 (3H, s), 3.77 (2H, t, J=7.0), 3.80-3.89 (1H, m), 4.10 (2H, q, J=7.0), 4.94 and 4.95 (total 1H, each s), 5.69-5.78 (1H, m), 7.18-7.28 (2H, m), 7.30-7.38 (1H, m), 7.75-7.83 (1H, m).

IR (KBr, cm^{-1}) : 2522, 1752, 1730, 1661, 1496.

(Example 100) (E)-3-(2-{4-[2-(Carboxyethyl)]-3-oxopiperazin-1-yl}ethylidene)-1-[1-(2-fluorophenyl)-2-methoxy-2-oxoethyl]-4-sulfanylpiperidine dihydrochloride (Hydrochloride of the compound of Compound No. 11-103)

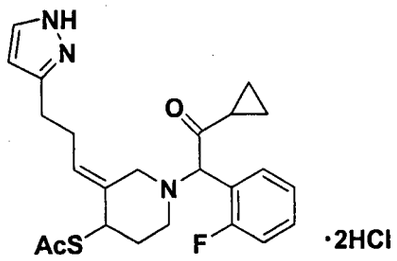


The title compound was synthesized in a quantitative yield as a colorless amorphous solid using (E)-3-(2-{4-[2-(ethoxycarbonyl)ethyl]-3-oxopiperazin-1-yl}ethylidene)-1-[1-(2-fluorophenyl)-2-methoxy-2-oxoethyl]-4-sulfanylpiperidine dihydrochloride obtained in Example 99 by conducting a reaction similar to that mentioned in Example 15.

^{1}H NMR (400 MHz, pyridine-d_5) δ ppm : 1.71-1.83 (1H, m), 2.12-2.24 (1H, m), 2.53-2.64 (2H, m), 2.67-2.84 (1H, m), 2.92 (2H, t, J=7.0), 2.95-3.09 (1H, m), 2.99 (2H, t, J=6.5), 3.26 and 3.27 (total 2H, each s), 3.34-3.46 (2H, m), 3.37 and 3.47 (total 1H, each d, J=12.5), 3.60 and 3.72 (total 1H, each d, J=12.5), 3.67 (3H, s), 3.80-3.88 (1H, m), 3.91 (2H, t, J=7.0), 4.94 and 4.95 (total 1H, each s), 5.69-5.78 (1H, m), 7.18-7.26 (2H, m), 7.29-7.36 (1H, m), 7.75-7.82 (1H, m).

IR (KBr, cm^{-1}) : 2570, 1750, 1659, 1496.

(Example 101) (E)-4-(Acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{3-[1H-pyrazol-3(5)-yl]propylidene}piperidine dihydrochloride (Hydrochloride of the compound of Compound No. 1-264)



(a) (E)-3-{3-[1-(t-Butoxycarbonyl)-1H-pyrazole-3-yl]-1-hydroxypropyl}-1-(triphenylmethyl)piperidin-4-one

The title compound was synthesized in a yield of 45% as a colorless amorphous solid using 3-[1-(t-butoxycarbonyl)-1H-pyrazol-3-yl]propanal instead of 1-(ethoxycarbonylmethyl)piperidin-4-carbaldehyde by conducting a reaction similar to that mentioned in Example 36 (a).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 1.63 (9H, s), 1.66-1.80 (2H, m), 1.84-2.01 (1H, m), 2.37-2.45 (1H, m), 2.68-2.95 (4H, m), 3.11-3.32 (2H, m), 3.73-3.84 (2H, m), 6.16 (1H, d, J=2.5), 7.14-7.21 (3H, m), 7.23-7.34 (6H, m), 7.41-7.59 (6H, m), 7.94 (1H, d, J=2.5).

(b) (E)-3-{3-[1-(t-Butoxycarbonyl)-1H-pyrazole-3-yl]propylidene}-1-(triphenylmethyl)piperidin-4-one

To a solution of (E)-3-{3-[1-(t-butoxycarbonyl)-1H-pyrazole-3-yl]-1-hydroxypropyl}-1-(triphenylmethyl)piperidin-4-one (1.92 g) obtained in (a) above in dichloromethane (45 ml) were added methanesulfonyl chloride (0.29 ml) and triethylamine (0.61 ml) under ice cooling, and the resulting mixture was stirred at the same temperature for 2.5 hours. The reaction mixture was diluted with ethyl acetate and washed with a saturated aqueous sodium chloride solution, and the organic layer was dried over anhydrous sodium sulfate. The solvent was removed in vacuo to

afford a mesyl compound (2.14 g) as a colorless amorphous solid. To a solution of this compound in tetrahydrofuran (50 ml) was added 1,8-diazabicyclo[5.4.0]undeca-7-ene (0.98 ml), the resulting mixture was refluxed for 2 hours. The reaction mixture was diluted with ethyl acetate and washed with a saturated aqueous ammonia solution and a saturated aqueous sodium chloride solution, and the organic layer was dried over anhydrous sodium sulfate. The solvent was removed in vacuo, and the residue was purified by chromatography on a silica gel column (ethyl acetate / hexane = 7 / 13) to afford the title compound (1.20 g, yield 65%) as a colorless amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 1.64 (9H, s), 2.28-2.35 (2H, m), 2.58 (2H, bs), 2.66 (2H, t, J=6.0), 2.79 (2H, t, J=7.5), 3.12 (2H, bs), 6.12 (1H, d, J=2.5), 6.68 (1H, t, J=7.5), 7.12-7.21 (3H, m), 7.22-7.32 (6H, m), 7.41-7.56 (6H, m), 7.94 (1H, d, J=2.5).

(c) (E)-3-{3-[1-(t-Butoxycarbonyl)-1H-pyrazole-3-yl]propylidene}-4-hydroxy-1-(triphenylmethyl)piperidine

The title compound was synthesized in a yield of 68% as a colorless solid using (E)-3-{3-[1-(t-butoxycarbonyl)-1H-pyrazole-3-yl]propylidene}-1-(triphenylmethyl)piperidin-4-one obtained in (b) above by conducting a reaction similar to that mentioned in Example 36 (c).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 1.63 (9H, s), 1.72-1.83 (1H, m), 2.01-2.25 (2H, m), 2.31-2.42 (2H, m), 2.59 (2H, bs), 2.78 (2H, t, J=7.5), 3.06 (1H, bs), 3.98 (1H, bs), 5.52 (1H, t, J=7.5), 6.15 (1H, d, J=2.5), 7.09-7.19 (3H, m), 7.20-7.31 (6H, m), 7.36-7.56 (6H, m), 7.97 (1H, d, J=2.5).

(d) (E)-3-{3-[1-(t-Butoxycarbonyl)-1H-pyrazole-3-yl]propylidene}-4-hydroxypiperidine hydrogen trifluoroacetate

The title compound was synthesized in a yield of 65% as a colorless oil using (E)-3-{3-[1-(t-butoxycarbonyl)-1H-pyrazole-3-yl]propylidene}-4-hydroxy-1-

(triphenylmethyl)piperidine obtained in (c) above by conducting a reaction similar to that mentioned in Example 3 (c).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 1.60 (9H, s), 1.91-2.05 (2H, m), 2.39-2.50 (1H, m), 2.53-2.65 (1H, m), 2.75-2.92 (2H, m), 3.27-3.38 (1H, m), 3.58-3.70 (1H, m), 3.88-3.96 (1H, m), 3.97-4.06 (1H, m), 4.37 (1H, m), 5.73 (1H, t, J=8.0), 6.18 (1H, d, J=2.5), 7.85 (1H, d, J=2.5).

(e) (E)-3-{3-[1-(t-Butoxycarbonyl)-1H-pyrazole-3-yl]propylidene}-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-hydroxypiperidine

The title compound was synthesized in a yield of 93% as a colorless amorphous solid using (E)-3-{3-[1-(t-butoxycarbonyl)-1H-pyrazole-3-yl]propylidene}-4-hydroxypiperidine hydrogen trifluoroacetate obtained in (d) above by conducting a reaction similar to that mentioned in Example 1 (g).

^{1}H NMR (400 MHz, $CDCl_3$ + D_2O) δ ppm : 0.77-0.89 (2H, m), 0.92-1.08 (2H, m), 1.64 (9H, s), 1.66-1.77 (1H, m), 1.89-2.10 (1H, m), 2.17-2.27 (1H, m), 2.29-2.39 (2H, m), 2.41-2.55 (1H, m), 2.69-2.82 (3H, m), 2.84 and 2.93 (total 1H, each d, J=12.5), 3.16 and 3.26 (total 1H, each d, J=12.5), 4.08 (1H, m), 4.67 and 4.68 (total 1H, each s), 5.52 (1H, m), 6.18 and 6.19 (total 1H, each d, J=2.5), 7.06-7.22 (2H, m), 7.25-7.34 (1H, m), 7.38-7.46 (1H, m), 7.95 and 7.96 (total 1H, each d, J=2.5).

(f) (E)-4-(Acetylsulfanyl)-3-{3-[1-(t-butoxycarbonyl)-1H-pyrazole-3-yl]propylidene}-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]piperidine

The title compound was synthesized in a yield of 17% as a colorless oil using (E)-3-{3-[1-(t-butoxycarbonyl)-1H-pyrazole-3-yl]propylidene}-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-hydroxypiperidine obtained in (e) above by conducting a reaction similar to that mentioned in Example 1 (h).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 0.77-0.91 (2H, m), 0.92-1.09 (2H, m), 1.65 (9H, s), 1.71-1.84 (1H, m), 2.06-2.62 (5H, m), 2.28 and 2.29 (total 3H, each s), 2.65-2.92 (4H, m), 3.28-3.39 (1H, m), 4.32 (1H, m), 4.63 and 4.69 (total 1H, each s),

5.59 (1H, m), 6.15 and 6.19 (total 1H, each d, J=2.5), 7.06-7.22 (2H, m), 7.25-7.47 (2H, m), 7.95 and 7.96 (total 1H, each d, J=2.5).

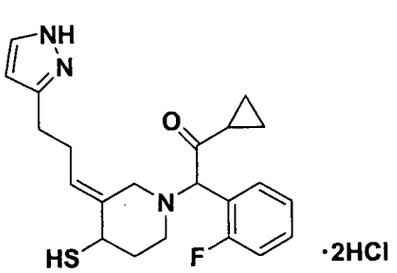
(g) (E)-4-(Acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{3-[1H-pyrazol-3(5)-yl]propylidene}piperidine dihydrochloride

The title compound was synthesized in a quantitative yield as a colorless amorphous solid using (E)-4-(acetylsulfanyl)-3-{3-[1-(t-butoxycarbonyl)-1H-pyrazole-3-yl]propylidene}-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]piperidine obtained in (f) above by conducting a reaction similar to that mentioned in Example 9 (f).

^{1}H NMR (400 MHz, pyridine-d_5) δ ppm : 0.75-0.90 (2H, m), 0.95-1.05 (1H, m), 1.08-1.17 (1H, m), 1.81-1.92 (1H, m), 2.17-2.32 (1H, m), 2.25 and 2.27 (total 3H, each s), 2.42-2.74 (4H, m), 2.76-2.95 (3H, m), 3.00 and 3.07 (total 1H, each d, J=12.5), 3.58 and 3.67 (total 1H, each d, J=12.5), 4.56 (1H, m), 4.87 and 4.92 (total 1H, each s), 5.85 (1H, m), 6.30 and 6.31 (total 1H, each d, J=2.0), 7.18-7.36 (3H, m), 7.64-7.74 (1H, m), 7.81 and 7.82 (total 1H, each d, J=2.0).

MS (FAB) m/z : 442 $(M+H)^+$.

(Example 102) (E)-1-[2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{3-[1H-pyrazol-3(5)-yl]propylidene}-4-sulfanylpiperidine dihydrochloride (Hydrochloride of the compound of Compound No. 1-263)



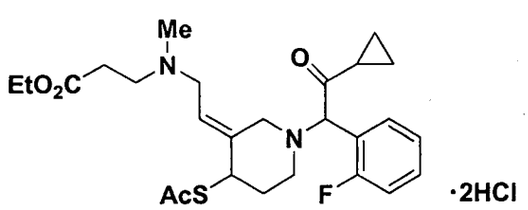
The title compound was synthesized in a yield of 82% as a colorless amorphous solid using (E)-4-(acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{3-[1H-pyrazol-3(5)-yl]propylidene}piperidine dihydrochloride

obtained in Example 101 (g) by conducting a reaction similar to that mentioned in Example 34.

^{1}H NMR (400 MHz, pyridine-d_5) δ ppm : 0.73-0.89 (2H, m), 0.94-1.04 (1H, m), 1.06-1.17 (1H, m), 1.71-1.82 (1H, m), 2.13-2.28 (1H, m), 2.44-2.61 (3H, m), 2.62-2.72 (1H, m), 2.79-3.01 (1H, m), 2.91 and 2.92 (total 2H, each t, J=7.5), 3.32 and 3.41 (total 1H, each d, J=12.5), 3.48 and 3.49 (total 1H, each d, J=12.5), 3.85 (1H, m), 4.90 and 4.92 (total 1H, each s), 5.75 and 5.76 (total 1H, each t, J=7.5), 6.31 and 6.32 (total 1H, each d, J=2.0), 7.16-7.35 (3H, m), 7.69-7.76 (1H, m), 7.82 and 7.83 (total 1H, each d, J=2.0).

MS (FAB) m/z : 400 $(M+H)^+$.

(Example 103) (E)-4-(Acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-{N-[2-(ethoxycarbonyl)ethyl]-N-methylamino}ethylidene)piperidine dihydrochloride (Hydrochloride of the compound of Compound No. 3-61)



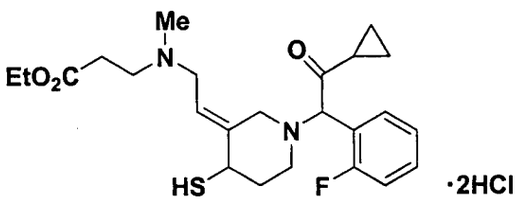
The title compound was synthesized in a yield of 35% as a colorless amorphous solid using (E)-4-(acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-hydroxyethylidene)piperidine obtained in Example 32 (f) and N-[2-(ethoxycarbonyl)ethyl]-N-methylamine instead of 4-(ethoxycarbonylmethyl)piperidine by conducting a reaction similar to that mentioned in Example 33.

^{1}H NMR (500 MHz, pyridine-d_5 + D_2O) δ ppm : 0.79-0.96 (2H, m), 1.06-1.16 (2H, m), 1.16 (3H, t, J=7.0), 1.81-1.90 (1H, m), 2.17-2.37 (2H, m), 2.31 and 2.34 (total 3H, each s), 2.50-2.57 and 2.67-2.74 (total 1H, each m), 2.73 and 2.75 (total 3H, each s), 2.79-2.89 (1H, m), 2.94-3.02 (2H, m), 3.11 and 3.24 (total 1H, each d,

J=12.5), 3.26-3.41 (2H, m), 3.62-3.68 (2H, m), 3.70-3.75 (1H, m), 4.14 (2H, q, J=7.0), 4.46-4.51 (1H, m), 5.03 and 5.04 (total 1H, each s), 6.07 and 6.09 (total 1H, each t, J=7.5), 7.28-7.40 (2H, m), 7.45-7.52 (1H, m), 7.67-7.73 (1H, m).

IR (KBr, cm^{-1}) : 1730, 1709, 1495.

(Example 104) (E)-1-[2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-{N-[2-(ethoxycarbonyl)ethyl]-N-methylamino}ethylidene)-4-sulfanylpiperidine dihydrochloride (Hydrochloride of the compound of Compound No. 3-60)

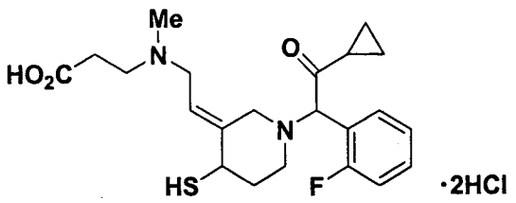


The title compound was synthesized in a yield of 31% as a colorless amorphous solid using (E)-4-(acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-{N-[2-(ethoxycarbonyl)ethyl)-N-methylamino}ethylidene)piperidine dihydrochloride obtained in Example 103 by conducting a reaction similar to that mentioned in Example 34.

^{1}H NMR (400 MHz, pyridine-d_5 + D_2O) δ ppm : 0.79-0.98 (2H, m), 1.05-1.17 (2H, m), 1.17 (3H, t, J=7.0), 1.75-1.86 (1H, m), 2.19-2.34 (2H, m), 2.63-2.73 (1H, m), 2.80 and 2.83 (total 3H, each s), 2.76-2.84 and 2.89-2.97 (total 1H, each m), 3.01 and 3.03 (total 2H, each t, J=7.0), 3.35-3.47 (3H, m), 3.52 and 3.60 (total 1H, each d, J=12.5), 3.66-3.80 (2H, m), 3.89-3.95 (1H, m), 4.15 (2H, q, J=7.0), 5.01 and 5.03 (total 1H, each s), 6.05-6.12 (1H, m), 7.29-7.39 (2H, m), 7.45-7.53 (1H, m), 7.67-7.73 (1H, m).

IR (KBr, cm^{-1}) : 2463, 1730, 1495.

(Example 105) (E)-3-(2-{N-[2-(Carboxy)ethyl]-N-methylamino}ethylidene)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-sulfanylpiperidine dihydrochloride (Hydrochloride of the compound of Compound No. 3-56)

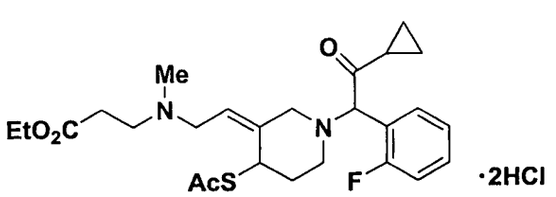


(E)-4-(Acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-{N-[2-(ethoxycarbonyl)ethyl)-N-methylamino}ethylidene)piperidine (365 mg) obtained in Example 103 was treated with 3N hydrochloric acid (10 ml) and then the resulting mixture was stirred at 60°C for 3 hours. The reaction mixture was evaporated in vacuo, and the residue was purified using a preparative HPLC (YMC-Pack ODS-A; YMC, eluent: acetonitrile / 0.012N hydrochloric acid = 15 / 85) to afford the title compound (271 mg, yield 74%) as a colorless amorphous solid.

^{1}H NMR (500 MHz, pyridine-d_5 + D_2O) δ ppm : 0.77-0.86 (1H, m), 0.87-0.94 (1H, m), 1.07-1.15 (2H, m), 1.75-1.84 (1H, m), 2.20-2.31 (2H, m), 2.64-2.71 (1H, m), 2.76-2.83 and 2.89-2.96 (total 1H, each m), 2.98 and 2.99 (total 3H, each s), 3.21 and 3.22 (total 2H, each t, J=7.0), 3.44 and 3.45 (total 1H, each d, J=12.0), 3.55 and 3.62 (total 1H, each d, J=12.0), 3.59-3.68 (2H, m), 3.88-3.94 (2H, m), 3.93-4.02 (1H, m), 5.03 and 5.05 (total 1H, each s), 6.15 (1H, t, J=7.5), 7.27-7.38 (2H, m), 7.43-7.50 (1H, m), 7.66-7.72 (1H, m).

IR (KBr, cm^{-1}) : 2553, 1713, 1494.

(Example 106) (Z)-4-(Acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-{N-[2-(ethoxycarbonyl)ethyl]-N-methylamino}ethylidene)piperidine dihydrochloride (Hydrochloride of the compound of Compound No. 4-61)

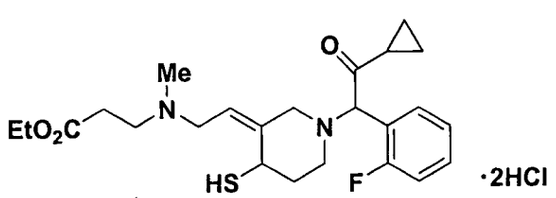


The title compound was synthesized in a yield of 36% as a colorless amorphous solid using (Z)-4-(acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-hydroxyethylidene)piperidine obtained in Example 66 (e) instead of (E)-4-(acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-hydroxyethylidene)piperidine and N-[2-(ethoxycarbonyl)ethyl)-N-methylamine instead of 4-(ethoxycarbonylmethyl)piperidine by conducting a reaction similar to that mentioned in Example 33.

^{1}H NMR (400 MHz, pyridine-d_5) δ ppm : 0.76-0.84 (1H, m), 0.96-1.18 (3H, m), 1.07 and 1.08 (total 3H, each t, J=7.0), 1.80-1.91 (1H, m), 2.23-2.42 (1H, m), 2.26 and 2.27 (total 3H, each s), 2.46-2.65 (2H, m), 2.77 and 2.79 (total 3H, each s), 2.95-3.13 (2H, m), 3.22-3.32 (2H, m), 3.40-3.57 (3H, m), 3.93-4.20 (2H, m), 4.07 and 4.08 (total 2H, each q, J=7.0), 4.87 and 4.95 (total 1H, each s), 4.93-4.99 (1H, m), 6.02 and 6.13 (total 1H, each t, J=7.0), 7.20-7.39 (3H, m), 7.58-7.67 (1H, m).

IR (KBr, cm^{-1}) : 1731, 1711, 1494.

(Example 107) (Z)-1-[2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-{N-[2-(ethoxycarbonyl)ethyl]-N-methylamino}ethylidene)-4-sulfanylpiperidine dihydrochloride (Hydrochloride of the compound of Compound No. 4-60)

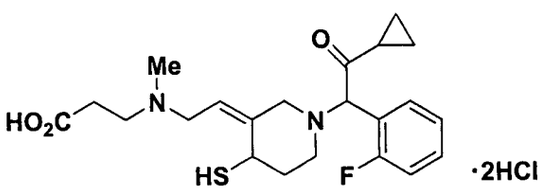


The title compound was synthesized in a yield of 60% as a colorless amorphous solid using (Z)-4-(acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-{N-[2-(ethoxycarbonyl)ethyl]-N-methylamino}ethylidene)piperidine dihydrochloride obtained in Example 106 by conducting a reaction similar to that mentioned in Example 34.

^{1}H NMR (400 MHz, pyridine-d_5 + D_2O) δ ppm : 0.77-0.89 (1H, m), 0.90-0.98 (1H, m), 0.99-1.06 (1H, m), 1.07-1.15 (1H, m), 1.12 and 1.13 (total 3H, each t, J=7.0), 1.75-1.88 (1H, m), 2.25-2.50 (2H, m), 2.58-3.01 (2H, m), 2.86 and 2.90 (total 3H, each s), 3.08-3.18 (2H, m), 3.31 and 3.37 (total 1H, each d, J=12.5), 3.42-3.57 (3H, m), 3.86-4.02 (2H, m), 4.10 and 4.12 (total 2H, each q, J=7.0), 4.61-4.66 (1H, m), 4.87 and 4.94 (total 1H, each s), 5.71 and 5.84 (total 1H, each t, J=7.5), 7.22-7.30 (2H, m), 7.34-7.43 (1H, m), 7.63-7.70 (1H, m).

IR (KBr, cm^{-1}) : 2550, 1730, 1714, 1494.

(Example 108) (Z)-3-(2-{N-[2-(Carboxy)ethyl)-N-methylamino}ethylidene)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-sulfanylpiperidine dihydrochloride (Hydrochloride of the compound of Compound No. 4-56)

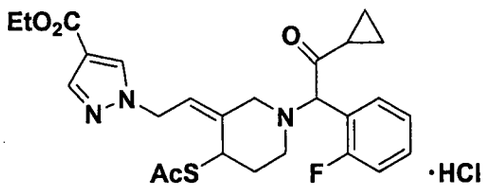


The title compound was synthesized in a yield of 42% as a colorless amorphous solid using (Z)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-{N-[2-(ethoxycarbonyl)ethyl]-N-methylamino}ethylidene)-4-sulfanylpiperidine dihydrochloride obtained in Example 107 by conducting a reaction similar to that mentioned in Example 15.

^{1}H NMR (500 MHz, pyridine-d_5 + D_2O) δ ppm : 0.79-0.96 (2H, m), 0.99-1.05 (1H, m), 1.06-1.13 (1H, m), 1.76-1.87 (1H, m), 2.28-2.48 (2H, m), 2.60-2.99 (2H, m), 2.83 and 2.87 (total 3H, each s), 3.13 and 3.16 (total 2H, each t, J=7.0), 3.30 and 3.36 (total 1H, each d, J=12.0), 3.42-3.56 (3H, m), 3.80-3.97 (2H, m), 4.60-4.64 (1H, m), 4.87 and 4.93 (total 1H, each s), 5.65 and 5.78 (total 1H, each t, J=7.0), 7.23-7.30 (2H, m), 7.36-7.44 (1H, m), 7.64-7.70 (1H, m).

MS (FAB) m/z : 421 $(M+H)^+$.

(Example 109) (Z)-4-(Acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-[2-(4-ethoxycarbonyl-1H-pyrazol-1-yl)ethylidene]piperidine hydrochloride (Hydrochloride of the compound of Compound No. 2-26)

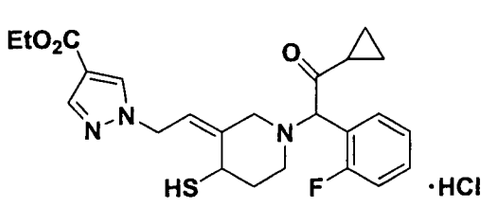


The title compound was synthesized in a yield of 11% as a pale yellow amorphous solid using (Z)-4-(acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-hydroxyethylidene)piperidine obtained in Example 66 (e) and 4-ethoxycarbonyl-1H-pyrazole by conducting a reaction similar to that mentioned in Example 40 (a).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 0.77-0.89 (2H, m), 0.96-1.06 (2H, m), 1.33 and 1.34 (total 3H, each t, J=7.0), 1.81-1.89 (1H, m), 2.10-2.21 (2H, m), 2.30-2.38 (1H, m), 2.32 (3H, s), 2.79 and 2.97 (total 1H, each d, J=12.0), 2.83-2.85 and 2.98-3.00 (total 1H, each m), 3.15 and 3.30 (total 1H, each d, J=12.0), 4.28 and 4.29 (total 2H, each q, J=7.0), 4.67 and 4.71 (total 1H, each s), 4.83 (1H, bs), 4.90-5.05 (2H, m), 5.47 and 5.56 (total 1H, each t, J=7.0), 7.09-7.18 (2H, m), 7.30-7.39 (2H, m), 7.86 and 7.87 (total 1H, each s), 7.88 and 7.90 (total 1H, each s).

IR (KBr, cm^{-1}) : 1713, 1495.

(Example 110) (Z)-1-[2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-[2-(4-ethoxycarbonyl-1H-pyrazol-1-yl)ethylidene]-4-sulfanylpiperidine hydrochloride (Hydrochloride of the compound of Compound No. 2-25)

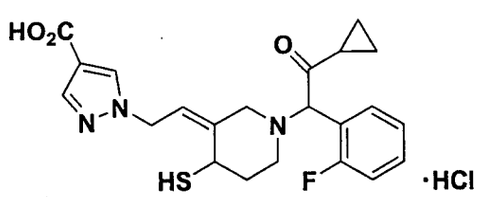


The title compound was synthesized in a yield of 88% as a colorless amorphous solid using (Z)-4-(acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-[2-(4-ethoxycarbonyl-1H-pyrazol-1-yl)ethylidene]piperidine hydrochloride obtained in Example 109 by conducting a reaction similar to that mentioned in Example 34.

^{1}H NMR (400 MHz, pyridine-d_5) δ ppm : 0.73-0.83 (2H, m), 0.97-1.04 (1H, m), 1.06-1.13 (1H, m), 1.18-1.25 (3H, m), 1.75-1.84 (1H, m), 2.20-2.36 (1H, m), 2.65-2.71 and 2.97-3.01 (total 1H, each m), 2.82-2.93 (2H, m), 3.23 and 3.40 (total 1H, each d, J=12.0), 3.37 and 3.53 (total 1H, each d, J=12.0), 4.25-4.34 (2H, m), 4.68 (1H, bs), 4.91 and 4.93 (total 1H, each s), 5.02 and 5.05 (total 2H, each d, J=7.0), 5.52 and 5.63 (total 1H, each t, J=7.0), 7.17-7.25 (2H, m), 7.29-7.34 (1H, m), 7.64-7.68 (1H, m), 8.28 and 8.29 (total 1H, each s), 8.41 and 8.44 (total 1H, each s).

IR (KBr, cm^{-1}) : 2541, 1713, 1494.

(Example 111) (Z)-3-[2-(4-Carboxy-1H-pyrazol-1-yl)ethylidene]-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-sulfanylpiperidine hydrochloride (Hydrochloride of the compound of Compound No. 2-17)



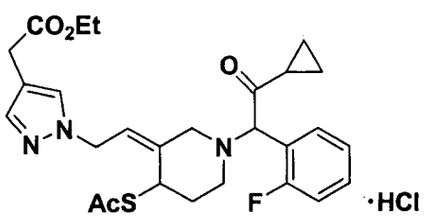
The title compound was synthesized in a yield of 49% as a colorless amorphous solid using (Z)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-[2-(4-ethoxycarbonyl-1H-pyrazol-1-yl)ethylidene]-4-sulfanylpiperidine hydrochloride obtained in Example 110 by conducting a reaction similar to that mentioned in Example 15.

^{1}H NMR (400 MHz, pyridine-d_5) δ ppm : 0.71-0.84 (2H, m), 0.96-1.04 (1H, m), 1.06-1.15 (1H, m), 1.72-1.89 (1H, m), 2.17-2.36 (1H, m), 2.62-3.02 (3H, m),

3.22 and 3.39 (total 1H, each d, J=12.0), 3.37 and 3.53 (total 1H, each d, J=12.5), 4.68 (1H, bs), 4.90 and 4.92 (total 1H, each s), 4.98-5.09 (2H, m), 5.52 and 5.63 (total 1H, each t, J=7.0), 7.16-7.35 (3H, m), 7.66 (1H, m), 8.43 and 8.45 (total 1H, each s), 8.52 and 8.55 (total 1H, each s).

IR (KBr, cm^{-1}) : 3399, 2547, 1710, 1494.

(Example 112) (Z)-4-(Acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{2-[4-(ethoxycarbonylmethyl) -1H-pyrazol-1-yl]ethylidene}piperidine hydrochloride (Hydrochloride of the compound of Compound No. 2-62)



(a) (Z)-4-Acetoxy-3-[2-(t-butyldiphenylsilyloxy)ethylidene]-1-(triphenylmethyl)piperidine

To a solution of (E)-4-acetoxy-3-[2-(t-butyldiphenylsilyloxy)ethylidene]-1-(triphenylmethyl)piperidine (200 mg) obtained in Example 66 (c) and 1,1'-bis(diphenylphosphino)ferrocene (33 mg) in toluene (2 ml) were added a solution of potassium acetate (147 mg) in water (1 ml) at room temperature and then palladium acetate (7 mg) at 50°C, and the resulting mixture was stirred at the same temperature for 1.5 hours. The reaction mixture was diluted with ethyl acetate and washed with water and a saturated aqueous sodium chloride solution, and the organic layer was dried over anhydrous sodium sulfate. The solvent was removed in vacuo, and the residue was purified by chromatography on a silica gel column (ethyl acetate / hexane = 1 / 19 - 1 / 9) to afford a 1:11 mixture (143 mg) of the title compound and the (E)-isomer thereof as a colorless amorphous solid. This mixture was further purified using a preparative HPLC (YMC-Pack ODS-A; YMC, eluent: acetonitrile /

water = 19 / 1) to afford the title compound (3 mg, yield 2%) and the (E) form (73 mg, yield 37%) thereof as a colorless amorphous solid, respectively.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 1.10 (9H, s), 1.67-1.80 (1H, m), 1.77 (3H, s), 1.84-1.96 (2H, m), 2.25-2.37 (1H, m), 2.69-2.81 (1H, m), 3.07-3.16 (1H, m), 4.38 (1H, dd, J=14.0, 4.5), 4.54 (1H, dd, J=14.0, 7.0), 5.42 (1H, bs), 5.55 (1H, dd, J=7.0, 4.5), 7.14-7.20 (3H, m), 7.23-7.30 (6H, m), 7.37-7.50 (12H, m), 7.71-7.77 (4H, m).

(b) (Z)-3-[2-(t-Butyldiphenylsilyloxy)ethylidene]-1-(triphenylmethyl)piperidin-4-ol

To a solution of (Z)-4-acetoxy-3-[2-(t-butyldiphenylsilyloxy)ethylidene]-1-(triphenylmethyl)piperidine (3.00 g) obtained in (a) above in methanol (60 ml) was added potassium carbonate (2.00 g) under ice cooling, and the resulting mixture was stirred at room temperature for 4 hours. Insolubles in the reaction mixture were removed by filtration, and the solvent was evaporated in vacuo. The obtained residue was diluted with ethyl acetate and washed with a saturated aqueous sodium chloride solution, and the organic layer was dried over anhydrous sodium sulfate. The solvent was removed in vacuo, and the residue was purified by chromatography on a silica gel column (ethyl acetate / hexane = 1 / 10) to afford the title compound (2.02 g, yield 72%) as a colorless amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 1.06 (9H, s), 1.72-1.83 (1H, m), 1.89-2.01 (1H, m), 2.06-2.27 (1H, m), 2.40-2.65 (2H, m), 2.77-2.95 (1H, m), 4.30-4.41 (3H, m), 5.50 (1H, t, J=6.5), 7.12-7.20 (3H, m), 7.22-7.31 (6H, m), 7.34-7.53 (12H, m), 7.64-7.77 (4H, m).

(c) (Z)-3-(2-Hydroxyethylidene)-1-(triphenylmethyl)piperidin-4-ol

The title compound was synthesized in a yield of 96% as a colorless amorphous solid using (Z)-3-[2-(t-butyldiphenylsilyloxy)ethylidene]-1-(triphenylmethyl)piperidin-4-ol obtained in (b) above by conducting a reaction similar to that mentioned in Example 1 (e).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 1.78-1.89 (1H, m), 1.97-2.09 (1H, m), 2.11-2.67 (3H, m), 2.79-2.95 (1H, m), 4.21 (1H, dd, J=12.5, 6.5), 4.31 (1H, dd, J=12.5, 7.5), 4.55 (1H, bs), 5.52 (1H, dd, J=7.5, 6.5), 7.11-7.18 (3H, m), 7.21-7.30 (6H, m), 7.41-7.55 (6H, m).

(d) (Z)-3-(2-Acetoxyethylidene)-1-(triphenylmethyl)piperidin-4-ol

To a suspension of (Z)-3-(2-hydroxyethylidene)-1-(triphenylmethyl)piperidin-4-ol (33.0 g) obtained in (c) above in dichloromethane (500 ml) were added a solution of acetic anhydride (8.0 ml) in dichloromethane (60 ml) and triethylamine (24.0 ml) under ice cooling, and the resulting mixture was stirred at room temperature for 20 hours. The reaction mixture was diluted with dichloromethane and washed with water and a saturated aqueous sodium chloride solution, and the organic layer was dried over anhydrous sodium sulfate. The solvent was removed in vacuo, and the residue was purified by chromatography on a silica gel column (ethyl acetate / hexane = 1 / 2) to afford the title compound (30.9 g, yield 84%) as a colorless amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 1.85-2.17 (5H, m), 2.36-2.45 (1H, m), 2.50-2.59 (1H, m), 2.62-2.74 (1H, m), 2.97-3.09 (1H, m), 4.53 (1H, dd, J=12.0, 6.0), 4.74 (1H, bs), 5.05 (1H, dd, J=12.0, 9.0), 5.35 (1H, dd, J=9.0, 6.0), 7.11-7.19 (3H, m), 7.21-7.29 (6H, m), 7.40-7.52 (6H, m).

(e) (Z)-4-(t-Butyldimethylsilyloxy)-3-(2-acetoxyethylidene)-1-(triphenylmethyl)piperidine

The title compound was synthesized in a yield of 68% as a colorless amorphous solid using (Z)-3-(2-acetoxyethylidene)-1-(triphenylmethyl)piperidin-4-ol obtained in (d) above by conducting a reaction similar to that mentioned in Example 1 (a).

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm : -0.13 (3H, s), -0.05 (3H, s), 0.67 (9H, s), 1.69-1.78 (1H, m), 1.84-1.93 (1H, m), 2.08 (3H, s), 2.12-2.30 (1H, m), 2.43-2.68 (2H,

m), 2.79-2.98 (1H, m), 4.40 (1H, bs), 4.66-4.85 (2H, m), 5.35 (1H, t, J=7.5), 7.08-7.18 (3H, m), 7.20-7.29 (6H, m), 7.39-7.54 (6H, m).

(f) (Z)-4-(t-Butyldimethylsilyloxy)-3-(2-hydroxyethylidene)-1-(triphenylmethyl)piperidine

The title compound was synthesized in a yield of 94% as a colorless amorphous solid using (Z)-4-(t-butyldimethylsilyloxy)-3-(2-acetoxyethylidene)-1-(triphenylmethyl)piperidine obtained in (e) above by conducting a reaction similar to that mentioned in Example 112 (b).

^{1}H NMR (500 MHz, $CDCl_3$) δ ppm : -0.09 (3H, s), -0.03 (3H, s), 0.72 (9H, s), 1.71-1.94 (2H, m), 2.21-2.85 (4H, m), 4.16-4.36 (2H, m), 4.46 (1H, bs), 5.50 (1H, t, J=7.0), 7.09-7.18 (3H, m), 7.20-7.29 (6H, m), 7.39-7.56 (6H, m).

(g) (Z)-4-(t-Butyldimethylsilyloxy)-3-{2-[4-(ethoxycarbonylmethyl)-1H-pyrazol-1-yl]ethylidene}-1-(triphenylmethyl)piperidine

To a solution of (Z)-4-(t-butyldimethylsilyloxy)-3-(2-hydroxyethylidene)-1-(triphenylmethyl)piperidine (5.80 g) obtained in (f) above and p-toluenesulfonic anhydride (3.80 g) in acetonitrile (60 ml) was added triethylamine (1.94 ml) at room temperature, and the resulting mixture was stirred at the same temperature for 2.5 hours. The reaction mixture was diluted with ethyl acetate and washed with water and a saturated aqueous sodium chloride solution, and the organic layer was dried over anhydrous sodium sulfate. The solvent was removed in vacuo to afford (Z)-4-(t-butyldimethylsilyloxy)-3-[2-(tosyloxy)ethylidene]-1-(triphenylmethyl)piperidine (9.08 g, quantitative yield) as a brown oil.

To a solution of 4-(ethoxycarbonylmethyl)-1H-pyrazole (1.80 g) in N,N-dimethylformamide (40 ml) was added sodium hydride (0.56 g) under ice cooling, and the resulting mixture was stirred at the same temperature for 20 minutes. To the reaction mixture was added a solution of (Z)-4-(t-butyldimethylsilyloxy)-3-[2-(tosyloxy)ethylidene]-1-(triphenylmethyl)piperidine obtained above in N,N-

dimethylformamide (10 ml), and then the resulting mixture was stirred at room temperature for 1.5 hours and at 60°C for further 30 minutes. The reaction mixture was diluted with ethyl acetate and washed with water and a saturated aqueous sodium chloride solution, and the organic layer was dried over anhydrous sodium sulfate. The solvent was removed in vacuo, and the residue was purified by chromatography on a silica gel column (ethyl acetate / hexane = 1 / 5 - 1 / 4) to afford the title compound (3.83 g, yield 52%) as a yellow oil.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : -0.11 (3H, s), -0.04 (3H, s), 0.70 (9H, s), 1.22-1.31 (3H, m), 1.72-1.99 (4H, m), 2.15-2.40 (1H, m), 2.53-2.79 (1H, m), 3.51 (2H, s), 4.16 (2H, q, J=7.5), 4.51-4.57 (1H, m), 4.88-4.98 (2H, m), 5.46 (1H, t, J=7.0), 7.09-7.28 (15H, m), 7.42 (1H, s), 7.45 (1H, s).

(h) (Z)-3-{2-[4-(Ethoxycarbonylmethyl)-1H-pyrazol-1-yl]ethylidene}-4-hydroxy-1-(triphenylmethyl)piperidine

The title compound was synthesized in a yield of 67% as a colorless amorphous solid using (Z)-4-(t-butyldimethylsilyloxy)-3-{2-[4-(ethoxycarbonylmethyl)-1H-pyrazol-1-yl]ethylidene}-1-(triphenylmethyl)piperidine obtained in (g) above by conducting a reaction similar to that mentioned in Example 1 (e).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 1.26 (3H, t, J=7.0), 1.92-2.00 (1H, m), 2.08-2.23 (2H, m), 2.57-2.69 (2H, m), 2.91-3.03 (1H, m), 3.44 (2H, s), 4.14 (2H, q, J=7.0), 4.59-4.68 (1H, m), 4.75 (1H, m), 4.97-5.06 (1H, m), 5.48 (1H, t, J=8.0), 7.10-7.29 (15H, m), 7.36 (1H, s), 7.37 (1H, s).

(i) (Z)-4-(Acetylsulfanyl)-3-{2-[4-(ethoxycarbonylmethyl)-1H-pyrazol-1-yl]ethylidene}-1-(triphenylmethyl)piperidine

The title compound was synthesized in a yield of 88% as a brown amorphous solid using (Z)-3-{2-[4-(ethoxycarbonylmethyl)-1H-pyrazol-1-yl]ethylidene}-4-

hydroxy-1-(triphenylmethyl)piperidine obtained in (h) above by conducting a reaction similar to that mentioned in Example 1 (h).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 1.26 (3H, t, J=7.0), 1.62-1.69 (1H, m), 1.80-1.87 (1H, m), 2.06-2.12 (1H, m), 2.23 (3H, s), 2.36-2.49 (1H, m), 3.06-3.14 (1H, m), 3.38-3.44 (1H, m), 3.47 (2H, s), 4.15 (2H, q, J=7.0), 4.85-4.89 (1H, m), 4.95 (2H, d, J=6.5), 5.50 (1H, t, J=6.5), 7.12-7.30 (15H, m), 7.37 (1H, s), 7.42 (1H, s).

(j) (Z)-4-(Acetylsulfanyl)-3-{2-[4-(ethoxycarbonylmethyl)-1H-pyrazol-1-yl]ethylidene}piperidine hydrogen trifluoroacetate

The title compound was synthesized in a yield of 87% as a brown oil using (Z)-4-(acetylsulfanyl)-3-{2-[4-(ethoxycarbonylmethyl)-1H-pyrazol-1-yl]ethylidene}-1-(triphenylmethyl)piperidine obtained in (i) above by conducting a reaction similar to that mentioned in Example 3 (c).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 1.26 (3H, t, J=7.0), 2.06-2.10 (1H, m), 2.39 (3H, s), 2.39-2.51 (1H, m), 3.10-3.21 (1H, m), 3.38-3.46 (1H, m), 3.47 (2H, s), 3.62-3.77 (2H, m), 4.12 (2H, q, J=7.0), 4.86 (1H, m), 4.89-5.04 (2H, m), 5.80 (1H, t, J=6.5), 7.42 (1H, s), 7.43 (1H, s).

(k) (Z)-4-(Acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{2-[4-(ethoxycarbonylmethyl)-1H-pyrazol-1-yl]ethylidene}piperidine hydrochloride

The title compound was synthesized in a yield of 80% as a pale yellow amorphous solid using (Z)-4-(acetylsulfanyl)-3-{2-[4-(ethoxycarbonylmethyl)-1H-pyrazol-1-yl]ethylidene}piperidine hydrogen trifluoroacetate obtained in (j) above by conducting a reaction similar to that mentioned in Example 1 (g).

^{1}H NMR (400 MHz, pyridine-d_5) δ ppm : 0.70-0.83 (2H, m), 0.96-1.12 (2H, m), 1.11 and 1.12 (total 3H, each t, J=7.0), 1.81-1.93 (1H, m), 2.04-2.15 (1H, m), 2.26-2.44 (2H, m), 2.26 (3H, s), 2.48-2.59 (1H, m), 2.90-2.98 and 3.04-3.12 (total 1H, each m), 3.31 and 3.46 (total 1H, each d, J=12.0), 3.61 (2H, s), 4.11 and 4.12 (total 2H, each q, J=7.0), 4.87 and 4.90 (total 1H, each s), 5.05-5.23 (3H, m), 5.65 and 5.74

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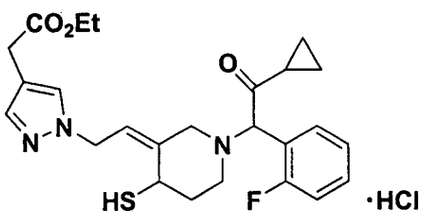
(total 1H, each t, J=6.5), 7.16-7.27 (2H, m), 7.28-7.36 (1H, m), 7.57-7.65 (1H, m), 7.69 and 7.72 (total 1H, each s), 7.73 and 7.75 (total 1H, each s).

MS (FAB) m/z : 514 $(M+H)^+$.

(Example 113) (Z)-1-[2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{2-[4-(ethoxycarbonylmethyl)-1H-pyrazol-1-yl]ethylidene}-4-sulfanylpiperidine hydrochloride (Hydrochloride of the compound of Compound No. 2-61)

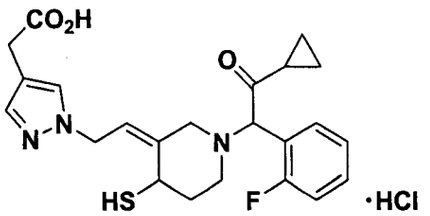


The title compound was synthesized in a yield of 45% as a colorless amorphous solid using (Z)-4-(acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{2-[4-(ethoxycarbonylmethyl)-1H-pyrazol-1-yl]ethylidene}piperidine hydrochloride obtained in Example 112 (k) by conducting a reaction similar to that mentioned in Example 34.

^{1}H NMR (400 MHz, pyridine-d_5) δ ppm : 0.71-0.81 (2H, m), 0.95-1.13 (2H, m), 1.11 and 1.12 (total 3H, each t, J=7.0), 1.71-1.83 (1H, m), 2.16-2.36 (1H, m), 2.38-2.47 (1H, m), 2.61-3.02 (3H, m), 3.18 and 3.36 (total 1H, each d, J=12.5), 3.51 and 3.61 (total 1H, each d, J=12.5), 3.64 (2H, s), 4.11 and 4.12 (total 2H, each q, J=7.0), 4.63 (1H, m), 4.87-4.97 (2H, m), 5.46 and 5.58 (total 1H, each t, J=6.5), 7.15-7.35 (3H, m), 7.56-7.78 (3H, m).

MS (FAB) m/z : 472 $(M+H)^+$.

(Example 114) (Z)-3-{2-[4-(Carboxymethyl)-1H-pyrazol-1-yl]ethylidene}-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-sulfanylpiperidine hydrochloride (Hydrochloride of the compound of Compound No. 2-53)

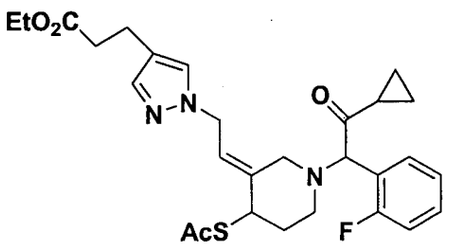


The title compound was synthesized in a yield of 23% as a colorless amorphous solid using (Z)-4-(acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-{2-[4-(ethoxycarbonylmethyl)-1H-pyrazol-1-yl]ethylidene}piperidine hydrochloride obtained in Example 112 (k) by conducting a reaction similar to that mentioned in Example 105.

^{1}H NMR (400 MHz, pyridine-d_5) δ ppm : 0.71-0.83 (2H, m), 0.96-1.12 (2H, m), 1.73-1.82 (1H, m), 2.19-2.35 (1H, m), 2.40-2.48 (1H, m), 2.80-3.00 (2H, m), 3.18 and 3.35 (total 1H, each d, J=11.5), 3.35 and 3.51 (total 1H, each d, J=11.5), 3.79 and 3.80 (total 2H, each s), 4.64 (1H, bs), 4.86-5.01 (2H, m), 4.88 and 4.91 (total 1H, each s), 5.47 and 5.59 (total 1H, each t, J=7.0), 7.16-7.33 (3H, m), 7.65 (1H, m), 7.78 and 7.81 (total 1H, each s), 7.83 and 7.85 (total 1H, each s).

MS (FAB) m/z : 444 $(M+H)^+$.

(Example 115) (E)-4-(Acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-{4-[2-(ethoxycarbonyl)ethyl)-1H-pyrazol-1-yl}ethylidene)piperidine (Compound of Compound No. 1-88)



(a) (E)-4-(t-Butyldimethylsilyloxy)-3-(2-{4-[2-(ethoxycarbonyl)ethyl]-1H-pyrazol-1-yl}ethylidene)-1-(triphenylmethyl)piperidine

The title compound was synthesized in a yield of 64% as a colorless oil using (E)-4-(t-butyldimethylsilyloxy)-3-[2-(tosyloxy)ethylidene]-1-

(triphenylmethyl)piperidine obtained in Example 1 (c) and 4-[2-(ethoxycarbonyl)ethyl]-1H-pyrazole by conducting a reaction similar to that mentioned in Example 21 (a).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 0.06 (6H, s), 0.88 (9H, s), 1.27 (3H, t, J=7.0), 1.82 (1H, m), 1.90-2.03 (3H, m), 2.60 (2H, t, J=7.0), 2.86 (2H, t, J=7.0), 3.03 (1H, bs), 3.70 (1H, bs), 3.91-3.98 (1H, m), 4.16 (2H, q, J=7.0), 4.71-4.81 (2H, m), 5.81-5.84 (1H, m), 7.21 (3H, m), 7.28-7.33 (9H, m), 7.40 (1H, s), 7.53 (4H, m).

(b) (E)-3-(2-{4-[2-(Ethoxycarbonyl)ethyl]-1H-pyrazol-1-yl}ethylidene)-4-hydroxy-1-(triphenylmethyl)piperidine

The title compound was synthesized in a yield of 58% a colorless amorphous solid using (E)-4-(t-butyldimethylsilyloxy)-3-(2-{4-[2-(ethoxycarbonyl)ethyl]-1H-pyrazol-1-yl}ethylidene)-1-(triphenylmethyl)piperidine obtained in (a) above by conducting a reaction similar to that mentioned in Example 1 (e).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 1.23 (3H, t, J=7.0), 1.57-1.63 (1H, m), 1.81-1.90 (1H, m), 2.10-2.14 (1H, m), 2.34 (1H, bs), 2.56 (2H, t, J=7.0), 2.80 (2H, t, J=7.0), 2.84 (1H, bs), 3.42 (1H, bs), 4.01 (1H, m), 4.12 (2H, q, J=7.0), 4.65-4.76 (2H, m), 5.75 (1H, t, J=7.0), 7.14-7.27 (10H, m), 7.35 (1H, s), 7.48 (6H, m).

(c) (E)-4-(Acetylsulfanyl)-3-(2-{4-[2-(ethoxycarbonyl)ethyl]-1H-pyrazol-1-yl}ethylidene)-1-(triphenylmethyl)piperidine

The title compound was synthesized in a yield of 65% as a colorless oil using (E)-3-(2-{4-[2-(ethoxycarbonyl)ethyl]-1H-pyrazol-1-yl}ethylidene)-4-hydroxy-1-(triphenylmethyl)piperidine obtained in (b) above by conducting a reaction similar to that mentioned in Example 1 (h).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 1.24 (3H, t, J=7.0), 1.86-1.94 (1H, m), 2.25 (3H, s), 2.31 (2H, m), 2.56 (2H, t, J=7.0), 2.81 (2H, t, J=7.0), 2.86 (1H, m), 4.12 (2H, q, J=7.0), 4.16-4.34 (3H, m), 4.58-4.71 (2H, m), 5.77 (1H, t, J=7.0), 7.15-7.29 (10H, m), 7.36 (1H, s), 7.60 (6H, m).

(d) (E)-4-(Acetylsulfanyl)-3-(2-{4-[2-(ethoxycarbonyl)ethyl]-1H-pyrazol-1-yl}ethylidene)piperidine hydrogen trifluoroacetate

The title compound was synthesized in a yield of 23% as a colorless oil using (E)-4-(acetylsulfanyl)-3-(2-{4-[2-(ethoxycarbonyl)ethyl]-1H-pyrazol-1-yl}ethylidene)-1-(triphenylmethyl)piperidine obtained in (c) above by conducting a reaction similar to that mentioned in Example 3 (c).

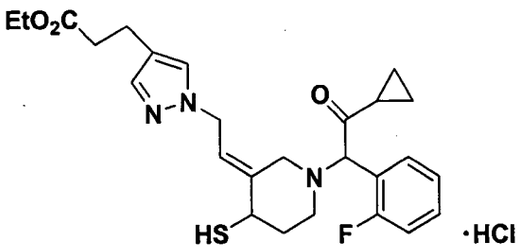
^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 1.25 (3H, t, J=7.0), 2.03-2.09 (1H, m), 2.36 (3H, s), 2.39-2.47 (1H, m), 2.55 (2H, t, J=7.0), 2.79 (2H, t, J=7.0), 3.24-3.31 (1H, m), 3.41-3.49 (1H, m), 3.75 (1H, d, J=14.0), 4.11-4.17 (3H, m), 4.44 (1H, m), 4.63 (1H, dd, J=15.5, 5.5), 4.83 (1H, dd, J=15.5, 9.0), 5.93-5.96 (1H, m), 7.31 (1H, s), 7.39 (1H, s).

(e) (E)-4-(Acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-{4-[2-(ethoxycarbonyl)ethyl]-1H-pyrazol-1-yl}ethylidene)piperidine

The title compound was synthesized in a yield of 67% as a colorless oil using (E)-4-(acetylsulfanyl)-3-(2-{4-[2-(ethoxycarbonyl)ethyl]-1H-pyrazol-1-yl}ethylidene)piperidine hydrogen trifluoroacetate obtained in (d) above by conducting a reaction similar to that mentioned in Example 1 (g).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 0.77-0.89 (2H, m), 0.99-1.07 (2H, m), 1.25 (3H, t, J=7.0), 1.83 (1H, m), 2.15 (2H, m), 2.29 and 2.30 (total 3H, each s), 2.54 (2H, t, J=7.0), 2.55-2.64 (1H, m), 2.68-2.76 (1H, m), 2.78 (2H, t, J=7.0), 2.84-2.92 and 3.12-3.18 (total 1H, each m), 3.26-3.35 and 3.39-3.46 (total 1H, each m), 4.14 (2H, q, J=7.0), 4.28-4.35 (1H, m), 4.60-4.76 (3H, m), 5.77 (1H, m), 7.09-7.22 (2H, m), 7.27-7.42 (4H, m).

(Example 116) (E)-1-[2-Cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-{4-[2-(ethoxycarbonyl)ethyl]-1H-pyrazol-1-yl}ethylidene)-4-sulfanylpiperidine hydrochloride (Hydrochloride of the compound of Compound No. 1-87)

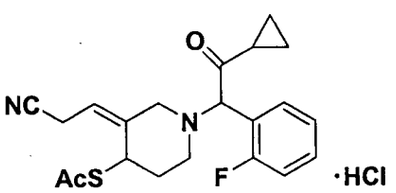


The title compound was synthesized in a yield of 74% as a colorless amorphous solid using (E)-4-(acetylsulfanyl)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-3-(2-{4-[2-(ethoxycarbonyl)ethyl]-1H-pyrazol-1-yl}ethylidene)piperidine obtained in Example 115 (e) by conducting a reaction similar to that mentioned in Example 34.

^{1}H NMR (400 MHz, pyridine-d_5) δ ppm : 0.77-0.83 (2H, m), 0.99-1.06 (1H, m), 1.09-1.16 (1H, m), 1.12 (3H, t, J=7.0), 1.74-1.83 (1H, m), 2.14-2.24 (1H, m), 2.47-2.52 (1H, m), 2.62 (2H, t, J=7.0), 2.65 (1H, m), 2.86 (2H, t, J=7.0), 2.83-2.99 (1H, m), 3.34 and 3.36 (total 1H, each d, J=12.5), 3.77-3.81 (1H, m), 4.12 (2H, q, J=7.0), 4.84-4.92 (3H, m), 4.93 and 4.95 (total 1H, each s), 5.95-5.99 (1H, m), 7.19-7.27 (2H, m), 7.28-7.36 (1H, m), 7.58 (1H, s), 7.62 (1H, s), 7.66-7.73 (1H, m).

MS (FAB) m/z : 486 $(M+H)^+$.

(Example 117) (Z)-4-(Acetylsulfanyl)-3-(2-cyanoethylidene)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]piperidine hydrochloride (Hydrochloride of the compound of Compound No. 4-47)



(a) (Z)-4-(t-Butyldimethylsilyloxy)-3-(2-cyanoethylidene)-1-(triphenylmethyl)piperidine

To a solution of (Z)-4-(t-butyldimethylsilyloxy)-3-(2-hydroxyethylidene)-1-(triphenylmethyl)piperidine (10.00 g) obtained in Example 112 (f) in benzene (500 ml) were added tributylphosphine (6.10 g), acetone cyanohydrin (3.60 g) and 1,1'-azobis(N,N-dimethylformamide) (5.20 g), and the resulting mixture was stirred at room temperature for 2 hours. The reaction mixture was diluted with ethyl acetate and washed with a saturated aqueous sodium chloride solution, and the organic layer was dried over anhydrous magnesium sulfate. The solvent was removed in vacuo, and the residue was purified by chromatography on a silica gel column (ethyl acetate / hexane = 1 / 6) to afford the title compound (9.27 g, yield 91%) as a colorless amorphous solid.

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 0.00-0.10 (6H, m), 0.81 (9H, s), 1.82-2.01 (2H, m), 2.15-3.02 (4H, m), 3.35-3.60 (2H, m), 4.40 (1H, bs), 5.29 (1H, t, J=7.5), 7.18-7.25 (3H, m), 7.28-7.36 (5H, m), 7.46-7.59 (7H, m).

(b) (Z)-3-(2-Cyanoethylidene)-1-(triphenylmethyl)piperidin-4-ol

The title compound was synthesized in a quantitative yield as a colorless amorphous solid using (Z)-4-(t-butyldimethylsilyloxy)-3-(2-cyanoethylidene)-1-(triphenylmethyl)piperidine obtained in (a) above by conducting a reaction similar to that mentioned in Example 1 (e).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 1.86-1.97 (1H, m), 1.99-2.10 (1H, m), 2.23-2.54 (2H, m), 2.64-2.88 (2H, m), 3.37 (2H, d, J=7.5), 4.50 (1H, bs), 5.30 (1H, t, J=7.5), 7.13-7.20 (1H, m), 7.23-7.31 (7H, m), 7.42-7.52 (7H, m).

(c) (Z)-4-(Acetylsulfanyl)-3-(2-cyanoethylidene)-1-(triphenylmethyl)piperidine

The title compound was synthesized in a yield of 83% as a colorless amorphous solid using (Z)-3-(2-cyanoethylidene)-1-(triphenylmethyl)piperidin-4-ol obtained in (b) above by conducting a reaction similar to that mentioned in Example 1 (h).

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^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 1.54-1.64 (1H, m), 1.78-1.85 (1H, m), 2.08 (1H, d, J=13.0), 2.22 (3H, s), 2.34-2.45 (1H, m), 3.06-3.13 (1H, m), 3.28 (1H, dd, J=18.0, 7.0), 3.41 (1H, d, J=13.0), 3.47 (1H, dd, J=18.0, 7.0), 4.68 (1H, m), 5.24 (1H, t, J=7.0), 7.13-7.32 (7H, m), 7.39-7.53 (8H, m).

(d) (Z)-4-(Acetylsulfanyl)-3-(2-cyanoethylidene)piperidine hydrogen trifluoroacetate

The title compound was synthesized in a yield of 54% as a colorless amorphous solid using (Z)-4-(acetylsulfanyl)-3-(2-cyanoethylidene)-1-(triphenylmethyl)piperidine obtained in (c) above by conducting a reaction similar to that mentioned in Example 3 (c).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 2.02-2.12 (1H, m), 2.36-2.47 (1H, m), 2.39 (3H, s), 3.04-3.17 (1H, m), 3.33-3.77 (5H, m), 4.70 (1H, bs), 5.59 (1H, t, J=7.0).

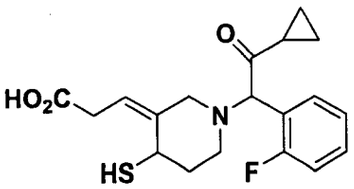
(e) (Z)-4-(Acetylsulfanyl)-3-(2-cyanoethylidene)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]piperidine hydrochloride

The title compound was synthesized in a yield of 80% as a colorless amorphous solid using (Z)-4-(acetylsulfanyl)-3-(2-cyanoethylidene)piperidine hydrogen trifluoroacetate obtained in (d) above by conducting a reaction similar to that mentioned in Example 1 (g).

^{1}H NMR (400 MHz, $CDCl_3$) δ ppm : 0.75-0.88 (2H, m), 0.97-1.07 (2H, m), 1.27 (3H, t, J=7.0), 1.78-1.86 (1H, m), 2.12-2.22 (2H, m), 2.28 and 2.29 (total 3H, each s), 2.49-2.62 (1H, m), 2.68-2.73 and 2.76-2.81 (total 1H, each m), 2.88 and 3.15 (total 1H, each d, J=12.5), 3.30 and 3.41 (total 1H, each d, J=12.5), 3.46 (2H, s), 4.15 (2H, q, J=7.0), 4.28-4.34 (1H, m), 4.62-4.64 and 4.67-4.70 (total 2H, each m), 4.71 and 4.74 (total 1H, each s), 5.78 (1H, t, J=7.0), 7.07-7.17 (2H, m), 7.19-7.27 (1H, m), 7.28-7.37 (1H, m), 7.33 and 7.34 (total 1H, each s), 7.39 (1H, s).

MS (FAB) m/z : 387 $(M+H)^+$.

(Example 118) (Z)-3-(2-Carboxyethylidene)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]-4-sulfanylpiperidine (Compound of Compound No. 4-13)



(Z)-4-(Acetylsulfanyl)-3-(2-cyanoethylidene)-1-[2-cyclopropyl-1-(2-fluorophenyl)-2-oxoethyl]piperidine hydrochloride (48 mg) obtained in Example 117 (e) was treated with 6N hydrochloric acid (6 ml) at room temperature and then the resulting mixture was stirred at 60°C for 3 hours. The reaction mixture was evaporated in vacuo, and the residue was purified using a preparative HPLC (YMC-Pack ODS-A; YMC, eluent: acetonitrile / water / acetic acid / triethylamine = 1 / 1 / 0.05 / 0.05) to afford the title compound (22 mg, yield 56%) as a colorless oil.

^{1}H NMR (400 MHz, pyridine-d_5) δ ppm : 0.72-0.86 (2H, m), 0.96-1.04 (1H, m), 1.07-1.15 (1H, m), 1.70-1.84 (1H, m), 2.19-2.38 (1H, m), 2.46-2.54 (1H, m), 2.61-3.09 (2H, m), 3.30 and 3.39 (total 1H, each d, J=14.0), 3.41-3.58 (3H, m), 4.55 (1H, bs), 4.89 and 4.93 (total 1H, each s), 5.72 and 5.83 (total 1H, each t, J=7.5), 7.15-7.25 (2H, m), 7.26-7.34 (1H, m), 7.67-7.73 (1H, m).

MS (FAB) m/z : 364 $(M+H)^+$.

(Test Example 1) Test for confirming in vitro platelet aggregation inhibitory effect

Male Sprague-Dawley rats (8-week old, Japan SLC, Inc.), 3 to 4 animals per group, were used for the test. The platelet aggregation was measured with an automatic platelet aggregometer (MCM Hema Tracer 313M, MC Medical, Inc.) by a partially modified method of Born et al., The Journal of Physiology, Vol. 168, Section 178 (1963). 6.3 ml of blood was sampled from the ventral aorta of a rat anesthetized with pentobarbital (40 mg/kg) using 3.8% (w/v) sodium citrate solution (0.7 ml) as an anticoagulant. The obtained blood containing citrate was centrifuged (230 g, 15 minutes, room temperature) to separate a platelet-rich plasma (hereinbelow abbreviated as PRP). The blood after the separation of PRP was

further centrifuged (2,000 g, 10 minutes, room temperature) to separate a platelet-poor plasma (hereinbelow abbreviated as PPP). After the number of blood platelet in PRP was measured with a multi-item automatic blood corpuscle counter (KX-21N, Sysmex Corporation), PPP was added thereto to adjust the blood platelet count to 5×10^8/ml. After PRP (239 μl) was pipetted into cuvettes, test compounds (1 μl) dissolved in dimethylsulfoxide (DMSO) were added to PRP and the cuvettes were set in the automatic platelet aggregometer. DMSO (1 μl) was added in place of the test compounds for the control group. After preliminary warming (37°C) for 1.5 minutes, 10 μl of adenosine 5'-diphosphate (ADP) solution (final concentration at 10 μM) was added to cause platelet aggregation. Platelet aggregation was measured for 5 minutes and the maximum platelet aggregation ratio was determined. The results are shown in Table 7.

(Table 7)

Test Compound	Test Example 1 (% inhibition) 10 μg/ml
Compound of Example 15	90
Compound of Example 18	73
Compound of Example 19	77
Compound of Example 22	67
Compound of Example 23	77
Compound of Example 44	81
Compound of Example 50	79
Compound of Example 51	81
Compound of Example 74	80
Compound of Example 83	68
Compound of Example 86	82
Compound of Example 91	74
Compound of Example 111	82

The compounds of the present invention showed a remarkable platelet aggregation inhibitory effect. The compounds of the present invention are useful as an antithrombotic drug.

(Test Example 2) Test for confirming ex vivo platelet aggregation inhibitory effect

Male Sprague-Dawley rats (8-week old, Japan SLC, Inc.), 3 to 4 animals per group, were used for the test. The platelet aggregation was measured with an automatic platelet aggregometer (MCM Hema Tracer 313M, MC Medical, Inc.) by a partially modified method of Born et al., The Journal of Physiology, Vol. 168, Section 178 (1963). Test compounds suspended in 5% Arabian gum solution or 10% dimethylacetamide/64% polyethylene glycol 400/16% Tween 80 solution were orally administered in a dose ratio of 1 mL/kg 4 hours before blood sampling. Vehicle was orally administered 4 hours in a dose ratio of 1 mL/kg before the sampling of the blood for the control group. 6.3 ml of blood was sampled from the ventral aorta of a rat anesthetized with pentobarbital (40 mg/kg) using 3.8% (w/v) sodium citrate solution (0.7 ml) as an anticoagulant. The obtained blood containing citrate was centrifuged (230 g, 15 minutes, room temperature) to separate PRP. The blood after the separation of PRP was further centrifuged (2,000 g, 10 minutes, room temperature) to separate PPP. After the number of blood platelet in PRP was measured with a multi-item automatic blood corpuscle counter (KX-21N, Sysmex Corporation), PPP was added thereto to adjust the blood platelet to 5×10^8/ml. After PRP (240 μl) was pipetted into cuvettes, the cuvettes were set in the automatic platelet aggregometer. After preliminary warming (37°C) for 1.5 minutes, 10 μl of ADP solution (final concentration 3 μM) was added to cause platelet aggregation. Platelet aggregation was measured for 5 minutes and the maximum platelet aggregation ratio was determined. The results are shown in Table 8.

(Table 8)

Test Compound	Test Example 1 (% inhibition)	
	3 mg/kg	10 mg/kg
Compound of Example 13	-	63
Compound of Example 17	-	92
Compound of Example 18	-	74
Compound of Example 19	-	60
Compound of Example 21	-	90

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Compound of Example 22	-	79
Compound of Example 23	-	72
Compound of Example 24	-	85
Compound of Example 25	-	92
Compound of Example 26	-	92
Compound of Example 29	-	89
Compound of Example 30	-	93
Compound of Example 31	-	82
Compound of Example 32	-	86
Compound of Example 36	-	80
Compound of Example 38	-	66
Compound of Example 44	61	-
Compound of Example 62	-	94
Compound of Example 64	-	94
Compound of Example 66	-	87
Compound of Example 72	-	76
Compound of Example 74	-	100
Compound of Example 78	-	75
Compound of Example 81	-	83
Compound of Example 82	-	81
Compound of Example 84	-	82
Compound of Example 85	-	82
Compound of Example 89	-	83
Compound of Example 111	-	82

The compounds of the present invention showed a remarkable platelet aggregation inhibitory effect. The compounds of the present invention are useful as an antithrombotic drug.

(Preparation Example 1) Hard capsules

Each standard two-part hard gelatine capsule is filled with 100 mg of powdered compound of Example 1, 150 mg of lactose, 50 mg of cellulose and 6 mg of magnesium stearate to prepare single unit capsules, which are washed and then dried.

(Preparation Example 2) Soft capsules

A mixture of the compound of Example 2 in digestible oil such as soybean oil, cottonseed oil and olive oil is prepared and injected into gelatine with a direct exchange pump to obtain soft capsules containing 100 mg of an active substance, which are washed and then dried.

(Preparation Example 3) Tablets

Tablets are prepared according to a common method using 100 mg of the compound of Example 3, 0.2 mg of colloidal silicon dioxide, 5 mg of magnesium stearate, 275 mg of microcrystalline cellulose, 11 mg of starch and 98.8 mg of lactose.

A tablet coating is applied, if desired.

(Preparation Example 4) Suspension

A suspension is prepared such that 5 ml of the suspension contains 100 mg of finely powdered compound of Example 4, 100 mg of sodium carboxymethyl cellulose, 5 mg of sodium benzoate, 1.0 g of sorbitol solution (Japan Pharmacopoeia) and 0.025 ml of vanillin.

(Preparation Example 5) Cream

A cream is prepared by mixing 100 mg of finely powdered compound of Example 5 into 5 g of a cream containing 40% white petrolatum, 3% microcrystalline wax, 10% lanolin, 5% Span 20, 0.3% Tween 20 and 41.7% water.

(Preparation Example 6) Injection agent

1.5% by weight of the compound of Example 6 was the resultant mixture was stirred in 10% by weight of propylene glycol and after the volume was adjusted to a predetermined volume with water for injection, the mixture was sterilized to prepare an injectable preparation.

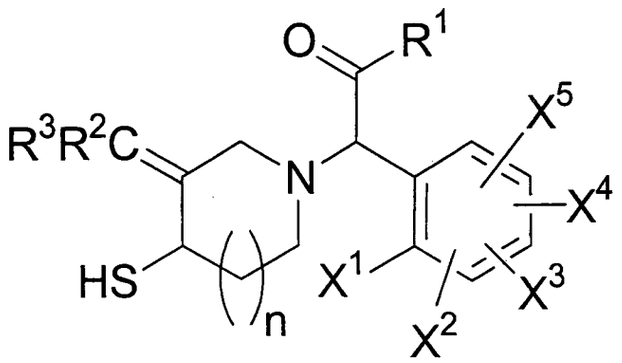
Industrial Applicability

The compounds according to the present invention are chemically stable and have excellent platelet activation-inhibiting activity and thrombosis-inhibiting activity, and also the responses thereof are quick and the toxicities thereof are low. Therefore, the compounds are useful as drugs for prophylaxis, recurrence prevention, or therapy (in particular, for therapy) of thromboembolism or diseases induced by

activation of platelets such as platelet aggregation or platelet release reaction, for example, restenosis after percutaneous coronary intervention (PCI), angioplasty, endarterectomy, or stenting; acute coronary syndromes; stable or unstable angina; myocardial infarction; atrial fibrillation; cerebral ischemic attack; cerebral infarction; atherosclerosis; cardiovascular and cerebrovascular diseases associated with diabetes mellitus, such as thromboembolism; peripheral arterial diseases; heparin-induced thrombocytopenia (HIT); thrombotic thrombocytopenic purpura (TTP); antiphospholipid antibody syndromes; venous thrombosis; and septicemia.

CLAIMS

1. A compound having the general formula (I) shown below,



(I)

[where R^1 represents a hydrogen atom, a C1-C6 alkyl group which may be substituted (said substituent group represents a halogen atom or a C1-C6 alkoxy group), a C3-C6 cycloalkyl group which may be substituted (said substituent group represents a halogen atom or a C1-C6 alkoxy group), a C1-C6 alkoxy group which may be substituted (said substituent group represents a halogen atom or a C1-C6 alkoxy group), or a C6-C10 aryl group which may be substituted (said substituent group represents a halogen atom, a C1-C6 alkyl group, a C1-C6 alkoxy group, a cyano group, or a nitro group);

R^2 represents a hydrogen atom, a halogen atom, a carboxy group, a C2-C7 alkoxycarbonyl group, a carbamoyl group, a cyano group, a C1-C6 alkyl group, a halogeno C1-C6 alkyl group, a C1-C6 alkyl group substituted by a heteroaryl group, a C1-C6 alkoxy group, a halogeno C1-C6 alkoxy group, a hydroxy C1-C6 alkyl group, a C2-C12 alkoxyalkyl group, a formyl group, a C2-C7 alkanoyl group, a C4-C7 cycloalkylcarbonyl group, a C2-C7 alkylcarbamoyl group, a di(C1-C6 alkyl)carbamoyl group, a group of formula R^4-CO-CR^5R^6-$(CH_2)_m$ {wherein R^4 represents a hydroxyl group, an amino group, a C1-C6 alkyl group, a C1-C6 alkylamino group, a di(C1-C6 alkyl)amino group, a hydroxyamino group, a C1-C6 alkoxyamino group or a C1-C6 alkoxy group; R^5 and R^6 are the same or different and

each represents a hydrogen atom or a C1-C6 alkyl group; and m represents an integer of from 0 to 5}, a group of formula R^7-CO-$(CH_2)_l$-N(R^8) {wherein R^7 represents a hydroxyl group, an amino group, a C1-C6 alkyl group, a C1-C6 alkylamino group, a di(C1-C6 alkyl)amino group, a hydroxyamino group, a C1-C6 alkoxyamino group or a C1-C6 alkoxy group; R^8 represents a hydrogen atom or a C1-C6 alkyl group; and l represents an integer of from 0 to 5} or a sulfamoyl C1-C6 alkyl group;

R^3 represents a substituted C1-C6 alkyl group {said substituent group represents a C6-C10 aryl group or a C6-C10 aryl group substituted with from 1 to 5 substituents selected from <Substituent group α>; a heterocyclyl group or a heterocyclyl group substituted with from 1 to 5 substituents selected from <Substituent group α> (said heterocyclyl groups may be substituted by from 1 to 4 oxo groups); a heteroaryl group or a heteroaryl group substituted with from 1 to 5 substituents selected from <Substituent group α>; or a substituent selected from <Substituent group β>}, or a heterocyclyl group or a heterocyclyl group substituted with from 1 to 5 substituents selected from <Substituent group α> (said heterocyclyl groups may be substituted by from 1 to 4 oxo groups);

X^1, X^2, X^3, X^4 and X^5 each independently represents a hydrogen atom, a halogen atom, an amino group, a carboxy group, a carbamoyl group, a cyano group, a nitro group, a C1-C6 alkyl group, a halogeno C1-C6 alkyl group, a C1-C6 alkoxy group or a halogeno C1-C6 alkoxy group;

n represents an integer of from 0 to 2,

<Substituent group α> is defined by a halogen atom, an amino group, a carboxy group, a C2-C7 alkoxycarbonyl group, a carbamoyl group, a cyano group, a hydroxyl group, a nitro group, a C1-C6 alkyl group, a halogeno C1-C6 alkyl group, a C1-C6 alkyl group substituted with heteroaryl group(s), a C1-C6 alkoxy group, a halogeno C1-C6 alkoxy group, a hydroxy C1-C6 alkyl group, a C2-C12 alkoxyalkyl group, a formyl group, a C2-C7 alkanoyl group, a C4-C7 cycloalkylcarbonyl group,

a C1-C6 alkylamino group, a di(C1-C6 alkyl)amino group, a C2-C7 alkylcarbamoyl group, a di(C1-C6 alkyl)carbamoyl group, a group of formula R^4-CO-CR^5R^6-$(CH_2)_m$- {wherein R^4 represents a hydroxyl group, an amino group, a C1-C6 alkyl group, a C1-C6 alkylamino group, a di(C1-C6 alkyl)amino group, a hydroxyamino group, a C1-C6 alkoxyamino group or a C1-C6 alkoxy group; R^5 and R^6 are the same or different and each represents a hydrogen atom or a C1-C6 alkyl group; and m represents an integer of from 0 to 5} and a sulfamoyl C1-C6 alkyl group; and

<Substituent group β> is defined by a halogen atom, an amino group, a carboxy group, a C2-C7 alkoxycarbonyl group, a carbamoyl group, a cyano group, a hydroxyl group, a nitro group, a C1-C6 alkoxy group, a halogeno C1-C6 alkoxy group, a formyl group, a C2-C7 alkanoyl group, a C4-C7 cycloalkylcarbonyl group, a C1-C6 alkylamino group, a di(C1-C6 alkyl)amino group, a C2-C7 alkylcarbamoyl group, a di(C1-C6 alkyl)carbamoyl group, a hydroxyaminocarbonyl group, a (C1-C6 alkoxy)aminocarbonyl group, a group of formula R^9-CO-$(CH_2)_k$-N(R^{10})- {wherein R^9 represents a hydroxyl group, an amino group, a C1-C6 alkyl group, a C1-C6 alkylamino group, a di(C1-C6 alkyl)amino group, a hydroxyamino group, a C1-C6 alkoxyamino group or a C1-C6 alkoxy group; R^{10} represents a hydrogen atom or a C1-C6 alkyl group; and k represents an integer of from 0 to 5} and a sulfamoyl C1-C6 alkyl group], pharmacologically acceptable salts thereof or prodrugs thereof..

2. A compound according to claim 1 wherein R^1 represents a C1-C6 alkyl group, a halogeno C1-C6 alkyl group, a C3-C6 cycloalkyl group, a halogeno C3-C6 cycloalkyl group or a C1-C6 alkoxy group, pharmacologically acceptable salts thereof or prodrugs thereof.

3. A compound according to claim 1 wherein R^1 represents a C3-C6 cycloalkyl group, a halogeno C3-C6 cycloalkyl group or a C1-C6 alkoxy group, pharmacologically acceptable salts thereof or prodrugs thereof.

4. A compound according to claim 1 wherein R^1 represents a C3-C6 cycloalkyl group or a C1-C6 alkoxy group, pharmacologically acceptable salts thereof or prodrugs thereof.

5. A compound according to claim 1 wherein R^1 represents a cyclopropyl group or a methoxy group, pharmacologically acceptable salts thereof or prodrugs thereof.

6. A compound according to claim 1 wherein R^1 is a cyclopropyl group, pharmacologically acceptable salts thereof or prodrugs thereof.

7. A compound according to any one of claims 1 to 6 wherein R^2 represents a hydrogen atom or a C1-C6 alkyl group, pharmacologically acceptable salts thereof or prodrugs thereof.

8. A compound according to any one of claims 1 to 6, wherein R^2 represents a hydrogen atom or a methyl group, pharmacologically acceptable salts thereof or prodrugs thereof.

9. A compound according to any one of claims 1 to 6, wherein R^2 represents a hydrogen atom, pharmacologically acceptable salts thereof or prodrugs thereof.

10. A compound according to any one of claims 1 to 9, wherein R^3 represents a substituted C1-C6 alkyl group {said substituent group represents a heterocyclyl group or a heterocyclyl group substituted with 1 or 2 substituents selected from <Substituent group α> (said heterocyclyl groups may be substituted by 1 or 2 oxo groups), a heteroaryl group or a heteroaryl group substituted with 1 or 2 substituents selected from <Substituent group α> or a substituent selected from <Substituent group β>}, or a heterocyclyl group or a heterocyclyl group substituted with 1 or 2 substituents selected from <Substituent group α> (said heterocyclyl groups may be substituted by 1 or 2 oxo groups), pharmacologically acceptable salts thereof or prodrugs thereof.

11. A compound according to any one of claims 1 to 9, wherein R^3 represents a substituted C1-C6 alkyl group {said substituent group represents a 4- to 7-membered

heterocyclyl group containing at least one nitrogen atom which may be substituted with 1 or 2 substituents selected from <Substituent group α1> (said heterocyclyl group may be substituted by one oxo group), a heteroaryl group containing at least one nitrogen atom which may be substituted with 1 or 2 substituents selected from <Substituent group α1>, a carboxy group, a C2-C7 alkoxycarbonyl group, a cyano group, a hydroxyl group, a C1-C6 alkoxy group or a group of formula R^9-CO-$(CH_2)_k$-N(R^{10})- (wherein R^9 represents a hydroxyl group or a C1-C6 alkoxy group; R^{10} represents a C1-C6 alkyl group; and k represents an integer of from 1 to 5)}, or a 4- to 7-membered heterocyclyl group containing at least one nitrogen atom which may be substituted with one substituent selected from <Substituent group α1> (said heterocyclyl group may be substituted by one oxo group), and

<Substituent group α1> is a group consisting of a carboxy group, a C2-C7 alkoxycarbonyl group and a group of formula R^4-CO-CR^5R^6-$(CH_2)_m$- (wherein R^4 represents a hydroxyl group, an amino group, a C1-C6 alkylamino group, a di(C1-C6 alkyl)amino group, a hydroxyamino group, a C1-C6 alkoxyamino group or a C1-C6 alkoxy group; R^5 and R^6 each represents a hydrogen atom; and m represents an integer of from 0 to 5), pharmacologically acceptable salts thereof or prodrugs thereof.

12. A compound according to any one of claims 1 to 9, wherein R^3 represents a substituted C1-C3 alkyl group {said substituent group represents a pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl, piperazinyl, pyrazolyl, triazolyl or tetrazolyl group which may be substituted with 1 or 2 substituents selected from <Substituent group α2> (said pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl or piperazinyl group may be substituted by one oxo group), a carboxy group, a C2-C4 alkoxycarbonyl group, a hydroxyl group or a group of formula R^9-CO-$(CH_2)_k$-N(R^{10})- (wherein R^9 represents a hydroxyl group or a C1-C3 alkoxy group; R^{10} represents a C1-C3 alkyl group; and k represents an integer of from 1 to 3)}, or a

pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl or piperazinyl group which may be substituted one substituent selected from <Substituent group α2> (said pyrrolidinyl, piperidinyl, morpholinyl, thiomorpholinyl or piperazinyl group may be substituted by one oxo group), and

<Substituent group α2> is a group consisting of a carboxy group, a C2-C4 alkoxycarbonyl group and a group of formula R^4-CO-CR^5R^6-$(CH_2)_m$- (wherein R^4 represents a hydroxyl group or a C1-C3 alkoxy group, R^5 and R^6 each represents a hydrogen atom, and m represents an integer of from 0 to 2), pharmacologically acceptable salts thereof or prodrugs thereof.

13. A compound according to any one of claims 1 to 9, wherein R^3 represents a substituted methyl or ethyl group {said substituent group represents a pyrrolidinyl, piperidinyl, piperazinyl or pyrazolyl group which may be substituted with 1 or 2 substituents selected from <Substituent group α3> (said pyrrolidinyl, piperidinyl or piperazinyl group may be substituted by one oxo group), a carboxy group or a group of formula R^9-CO-$(CH_2)_k$-N(R^{10})- (wherein R^9 represents a hydroxyl group, a methoxy group or an ethoxy group; R^{10} represents a methyl group, an ethyl group or an isopropyl group; and k represents an integer of from 1 to 3), and

<Substituent group α3> is a group consisting of a carboxy group, a methoxycarbonyl group, an ethoxycarbonyl group, a carboxymethyl group, a methoxycarbonylmethyl group, an ethoxycarbonylmethyl group, a 2-(carboxy)ethyl group, a 2-(methoxycarbonyl)ethyl group and a 2-(ethoxycarbonyl)ethyl group, pharmacologically acceptable salts thereof or prodrugs thereof.

14. A compound according to any one of claims 1 to 13 wherein X^1, X^2, X^3, X^4 and X^5 represent independently a hydrogen atom or a halogen atom, pharmacologically acceptable salts thereof or prodrugs thereof.

15. A compound according to any one of claims 1 to 13 wherein X^1 and X^2 represent independently a hydrogen atom or a halogen atom; and X^3, X^4 and X^5

represent a hydrogen atom, pharmacologically acceptable salts thereof or prodrugs thereof.

16. A compound according to any one of claims 1 to 13 wherein X^1 represents a halogen atom; and X^2, X^3, X^4 and X^5 represent a hydrogen atom, pharmacologically acceptable salts thereof or prodrugs thereof.

17. A compound according to any one of claims 1 to 13 wherein X^1 represents a fluorine atom; and X^2, X^3, X^4 and X^5 represent a hydrogen atom, pharmacologically acceptable salts thereof or prodrugs thereof.

18. A compound according to any one of claims 1 to 17 wherein n represents 0 or 1, pharmacologically acceptable salts thereof or prodrugs thereof.

19. A compound according to any one of claims 1 to 17 wherein n represents 1, pharmacologically acceptable salts thereof or prodrugs thereof.

20. A compound according to any one of claims 1 to 19 wherein a prodrug which is a pharmacologically acceptable ester is formed on the sulfanyl moiety, pharmacologically acceptable salts thereof, or prodrugs thereof.

21. The compound according to claim 20 wherein a functional group forming the pharmacologically acceptable ester with a sulfanyl group is a C1-C6 alkanoyl group or an arylcarbonyl group, pharmacologically acceptable salts thereof or prodrugs thereof.

22. The compound according to claim 20 wherein a functional group forming the pharmacologically acceptable ester with a sulfanyl group is a C1-C3 alkanoyl group or a benzoyl group, pharmacologically acceptable salts thereof or prodrugs thereof.

23. The compound according to claim 20 wherein a functional group forming the pharmacologically acceptable ester with a sulfanyl group is an ester formed with an acetyl group, pharmacologically acceptable salts thereof or prodrugs thereof.

24. A pharmaceutical composition containing a compound according to any one of claims 1 to 23, pharmacologically acceptable salts thereof or prodrugs thereof as an active ingredient.

25. A pharmaceutical composition according to claim 24 wherein the pharmaceutical composition is a composition for prophylactic or therapeutic agents for diseases related to thrombus or embolus formation.

26. Use of a compound according to any one of claims 1 to 23, pharmacologically acceptable salts thereof or prodrugs thereof to manufacture a pharmaceutical composition.

27. Use according to claim 26 wherein the pharmaceutical composition is a composition for prophylactic or therapeutic agents for diseases related to thrombus or embolus formation.

28. Use of a compound according to any one of claims 1 to 23, pharmacologically acceptable salts thereof or prodrugs thereof for prophylactic or therapeutic agents for diseases related to thrombus or embolus formation.

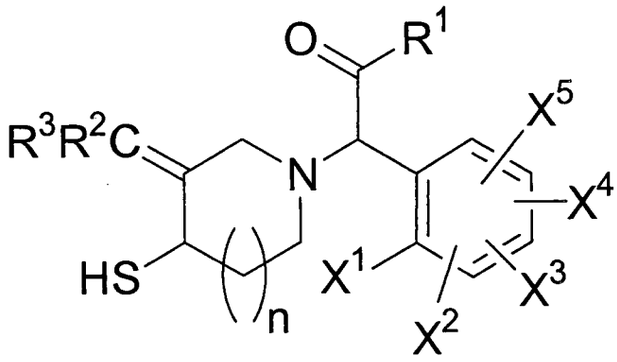
29. A prophylactic or therapeutic method for diseases by administration of a compound according to any one of claims 1 to 23, pharmacologically acceptable salts thereof or prodrugs thereof to warm-blooded animals at pharmacologically effective doses.

30. A method according to claim 29 wherein the diseases are diseases related to thrombus or embolus formation.

31. A method according to claim 29 or 30 wherein the warm-blooded animals are humans.

ABSTRACT

A compound having the general formula (I), pharmacologically acceptable salts thereof or prodrugs thereof:



(I)

[wherein R^1 represents a hydrogen atom, a C1-C6 alkyl group which may be substituted, a C3-C6 cycloalkyl group which may be substituted, a C1-C6 alkoxy group which may be substituted or a C6-C10 aryl group which may be substituted;

R^2 represents a hydrogen atom, a halogen atom, a carboxy group, a C2-C7 alkoxycarbonyl group, a carbamoyl group, a cyano group, a C1-C6 alkyl group, a halogeno C1-C6 alkyl group, a C1-C6 alkyl group substituted by a heteroaryl group, a C1-C6 alkoxy group, a halogeno C1-C6 alkoxy group, a hydroxy C1-C6 alkyl group, a C2-C12 alkoxyalkyl group, a formyl group, a C2-C7 alkanoyl group, a C4-C7 cycloalkylcarbonyl group, a C2-C7 alkylcarbamoyl group, a di(C1-C6 alkyl)carbamoyl group, a group of formula R^4-CO-CR^5R^6-$(CH_2)_m$-, a group of formula R^7-CO-$(CH_2)_l$-N(R^8) - or a sulfamoyl C1-C6 alkyl group;

R^3 represents a substituted C1-C6 alkyl group, a heterocyclyl group or a heterocyclyl group substituted with 1 to 5 substituents;

X^1, X^2, X^3, X^4 and X^5 each independently represents a hydrogen atom, a halogen atom, an amino group, a carboxy group, a carbamoyl group, a cyano group, a nitro group, a C1-C6 alkyl group, a halogeno C1-C6 alkyl group, a C1-C6 alkoxy group, or a halogeno C1-C6 alkoxy group; and

n represents an integer of 0 to 2].

DERIVADO DE AMINA CÍCLICA CON GRUPO ALQUILO SUSTITUIDO

Campo técnico

La presente invención se refiere a compuestos que muestran actividad en la inhibición de la agregación de plaquetas, sales de ellos aceptables farmacológicamente, y profármacos de ellos.

Antecedentes de la invención

Recientemente, la cantidad de pacientes con enfermedades cardiovasculares asociadas con el envejecimiento de la población y con los cambios de hábitos de alimentación y estilo de vida, ha aumentado marcadamente. Dado que las enfermedades trombóticas tales como infarto cerebral, infarto al miocardio y trastornos circulatorios periféricos no sólo tienen alta morbilidad sino que también producen un pronóstico deficiente y limitación de actividades de la vida diaria, el paciente con estos trastornos tiene una carga indebida de discapacidad personal y social. Es bien conocido que las causas directas de estas enfermedades son angioestenosis producidas por trombos inducidos por la activación de plaquetas (adhesión a áreas dañadas de los vasos sanguíneos, liberación de sustancias activas fisiológicamente, formación de coágulos y similares) e isquemia asociada con angioestenosis. Así, los agentes antitrombóticos que inhiben la activación de plaquetas juegan papeles importantes en la prevención de la aparición y recurrencia de estas enfermedades, así como también en su tratamiento. Adicionalmente, se considera que estos agentes se hacen más y más importantes en el futuro a medida que la cantidad de pacientes con enfermedades trombóticas aumenta.

Varias sustancias biológicas relacionadas con la agregación de plaquetas, tales como 5'-difosfato de adenosina (ADP), tromboxano A_2 (TXA_2), colágeno, serotonina (5-hidroxitriptamina, 5-HT) y

similares, son conocidas. Más aún, los receptores de $P2Y_1$ y los receptores de $P2Y_{12}$ se conocen como receptores de ADP. Algunos agentes antitrombóticos existentes actúan ejerciendo acción antagónica contra estos receptores. Ejemplos de estos agentes antitrombóticos son la ticlopidina y el clopidogrel, los cuales tienen estructuras de tienopiridina.

Además, los compuestos descritos en documentos de patente 1 y 2 se conocen como compuestos con estructuras que no son de tienopiridina y con acción antagónica contra receptores de ADP. Sin embargo, hay ciertos problemas en que estos compuestos son inestables químicamente o son débilmente activos.

Documento de patente 1: WO98/08811

Documento de patente 2: WO99/43648

Descripción de la invención

Problemas que va a resolver la invención

Los inventores de la presente, con el fin de crear agentes antitrombóticos novedosos, han explorado diligentemente compuestos estables que tienen estructuras que no son de tienopiridina y que tienen actividad en la inhibición de agregación de plaquetas, y encontraron que los compuestos que tienen la fórmula general (I) de la presente invención, sales de ellos aceptables farmacológicamente y profármacos de ellos tienen características deseables, y de esta manera realizaron la presente invención.

La presente invención proporciona compuestos que tienen la fórmula general (I), sales de él o profármacos de él aceptables farmacológicamente; composiciones farmacéuticas que contienen compuestos que tienen la fórmula general (I), sales de él o profármacos de él aceptables farmacológicamente, como ingredientes activos (particularmente composiciones farmacéuticas para agentes profilácticos o terapéuticos para enfermedades relacionadas con formación de trombos o émbolos); uso del

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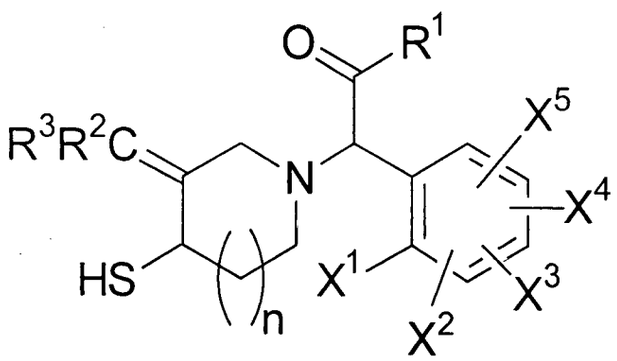
compuesto que tiene la fórmula general (I), sales de él o profármacos de él aceptables farmacológicamente para fabricar composiciones farmacéuticas (particularmente composiciones farmacéuticas para agentes profilácticos o terapéuticos para enfermedades relacionadas con formación de trombos o émbolos); use del compuestos que tienen la fórmula general (I), sales de él o profármacos de él aceptables farmacológicamente para agentes profilácticos o terapéuticos para enfermedades relacionadas con formación de trombos o émbolos; y métodos profilácticos o terapéuticos para enfermedades (particularmente enfermedades relacionadas con formación de trombos o émbolos) mediante la administración de dosis efectiva farmacológicamente del compuestos que tienen la fórmula general (I), sales de él o profármacos de él aceptables farmacológicamente a animales de sangre caliente (especialmente humanos).

Medios para resolver los problemas

La presente invención se refiere al compuesto que tiene la fórmula general (I) que se muestra a continuación,



(I)

[en donde R^1 representa un átomo de hidrógeno, un grupo alquilo de 1 a 6 átomos de carbono que puede estar sustituido (dicho grupo sustituyente representa un átomo de halógeno o un grupo alcoxi de 1 a 6 átomos de carbono), un grupo cicloalquilo de 3 a 6 átomos de carbono que puede estar sustituido (dicho grupo sustituyente representa un átomo de halógeno o un grupo alcoxi de 1 a 6 átomos de carbono), un grupo alcoxi de 1 a 6 átomos de carbono

que puede estar sustituido (dicho grupo sustituyente representa un átomo de halógeno o un grupo alcoxi de 1 a 6 átomos de carbono), o un grupo arilo de 6 a 10 átomos de carbono que puede estar sustituido (dicho grupo sustituyente representa un átomo de halógeno, un grupo alquilo de 1 a 6 átomos de carbono, un grupo alcoxi de 1 a 6 átomos de carbono, un grupo ciano o un grupo nitro);

R^2 representa un átomo de hidrógeno, un átomo de halógeno, un grupo carboxi, un grupo alcoxicarbonilo de 2 a 7 átomos de carbono, un grupo carbamoilo, un grupo ciano, un grupo alquilo de 1 a 6 átomos de carbono, un grupo alquilo halogenado de 1 a 6 átomos de carbono, un grupo alquilo de 1 a 6 átomos de carbono sustituido por un grupo heteroarilo, un grupo alcoxi de 1 a 6 átomos de carbono, un grupo alcoxi halogenado de 1 a 6 átomos de carbono, un grupo hidroxi alquilo de 1 a 6 átomos de carbono, un grupo alcoxialquilo de 2 a 12 átomos de carbono, un grupo formilo, un grupo alcanoilo de 2 a 7 átomos de carbono, un grupo cicloalquilcarbonilo de 4 a 7 átomos de carbono, un grupo alquilcarbamoilo de 2 a 7 átomos de carbono, un grupo di(alquilo de 1 a 6 átomos de carbono)carbamoilo, un grupo de la fórmula R^4-CO-CR^5R^6-$(CH_2)_m$- {en donde R^4 representa un grupo hidroxilo, un grupo amino, un grupo alquilo de 1 a 6 átomos de carbono, un grupo alquilamino de 1 a 6 átomos de carbono, un grupo di(alquil de 1 a 6 átomos de carbono)amino, un grupo hidroxiamino, un grupo alcoxiamino de 1 a 6 átomos de carbono o un grupo alcoxi de 1 a 6 átomos de carbono; R^5 y R^6 son iguales o diferentes y representan cada uno un átomo de hidrógeno o un grupo alquilo de 1 a 6 átomos de carbono; y m representa un entero desde 0 hasta 5}, un grupo de la fórmula R^7-CO-$(CH_2)_l$-N(R^8)- {en donde R^7 representa un grupo hidroxilo, un grupo amino, un grupo alquilo de 1 a 6 átomos de carbono, un grupo alquilamino de 1 a 6 átomos de carbono, un grupo di(alquil de 1 a 6 átomos de carbono)amino, un grupo hidroxiamino,

un grupo alcoxiamino de 1 a 6 átomos de carbono o un grupo alcoxi de 1 a 6 átomos de carbono; R^8 representa un átomo de hidrógeno o un grupo alquilo de 1 a 6 átomos de carbono; y l representa un entero desde 0 hasta 5} o un grupo sulfamoil alquilo de 1 a 6 átomos de carbono;

R^3 representa un grupo alquilo sustituido de 1 a 6 átomos de carbono {dicho grupo sustituyente representa un grupo arilo de 6 a 10 átomos de carbono o un grupo arilo de 6 a 10 átomos de carbono sustituido con desde 1 hasta 5 sustituyentes seleccionados del <Grupo sustituyente α>; un grupo heterociclilo o un grupo heterociclilo sustituido con desde 1 hasta 5 sustituyentes seleccionados del <Grupo sustituyente α> (dichos grupos heterociclilo pueden estar sustituidos con desde 1 hasta 4 grupos oxo); un grupo heteroarilo o un grupo heteroarilo sustituido con desde 1 hasta 5 sustituyentes seleccionados del <Grupo sustituyente α>; o un sustituyente seleccionado del <Grupo sustituyente β>}, o un grupo heterociclilo o un grupo heterociclilo sustituido con desde 1 hasta 5 sustituyentes seleccionados del <Grupo sustituyente α> (dichos grupos heterociclilo pueden estar sustituidos con desde 1 hasta 4 grupos oxo);

X^1, X^2, X^3, X^4 y X^5 representan cada uno independientemente un átomo de hidrógeno, un átomo de halógeno, un grupo amino, un grupo carboxi, un grupo carbamoilo, un grupo ciano, un grupo nitro, un grupo alquilo de 1 a 6 átomos de carbono, un grupo alquilo halogenado de 1 a 6 átomos de carbono, un grupo alcoxi de 1 a 6 átomos de carbono o un grupo alcoxi halogenado de 1 a 6 átomos de carbono;

n representa un entero desde 0 hasta 2,

El <Grupo sustituyente α> está definido por un átomo de halógeno, un grupo amino, un grupo carboxi, un grupo

alcoxicarbonilo de 2 a 7 átomos de carbono, un grupo carbamoilo, un grupo ciano, un grupo hidroxilo, un grupo nitro, un grupo alquilo de 1 a 6 átomos de carbono, un grupo alquilo halogenado de 1 a 6 átomos de carbono, un grupo alquilo de 1 a 6 átomos de carbono sustituido con grupo(s) heteroarilo, un grupo alcoxi de 1 a 6 átomos de carbono, un grupo alcoxi halogenado de 1 a 6 átomos de carbono, un grupo hidroxi alquilo de 1 a 6 átomos de carbono, un grupo alcoxialquilo de 2 a 12 átomos de carbono, un grupo formilo, un grupo alcanoilo de 2 a 7 átomos de carbono, un grupo cicloalquilcarbonilo de 4 a 7 átomos de carbono, un grupo alquilamino de 1 a 6 átomos de carbono, un grupo di(alquil de 1 a 6 átomos de carbono)amino, un grupo alquilcarbamoilo de 2 a 7 átomos de carbono, un grupo di(alquilo de 1 a 6 átomos de carbono)carbamoilo, un grupo de la fórmula R^4-CO-CR^5R^6-$(CH_2)_m$- {en donde R^4 representa un grupo hidroxilo, un grupo amino, un grupo alquilo de 1 a 6 átomos de carbono, un grupo alquilamino de 1 a 6 átomos de carbono, un grupo di(alquil de 1 a 6 átomos de carbono)amino, un grupo hidroxiamino, un grupo alcoxiamino de 1 a 6 átomos de carbono o un grupo alcoxi de 1 a 6 átomos de carbono; R^5 y R^6 son iguales o diferentes y representan cada uno un átomo de hidrógeno o un grupo alquilo de 1 a 6 átomos de carbono; y m representa un entero desde 0 hasta 5} y un grupo sulfamoil alquilo de 1 a 6 átomos de carbono; y

El <Grupo sustituyente β> está definido por un átomo de halógeno, un grupo amino, un grupo carboxi, un grupo alcoxicarbonilo de 2 a 7 átomos de carbono, un grupo carbamoilo, un grupo ciano, un grupo hidroxilo, un grupo nitro, un grupo alcoxi de 1 a 6 átomos de carbono, un grupo alcoxi halogenado de 1 a 6 átomos de carbono, un grupo formilo, un grupo alcanoilo de 2 a 7 átomos de carbono, un grupo cicloalquilcarbonilo de 4 a 7 átomos de carbono, un grupo alquilamino de 1 a 6 átomos de carbono, un grupo di(alquil

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de 1 a 6 átomos de carbono)amino, un grupo alquilcarbamoilo de 2 a 7 átomos de carbono, un grupo di(alquilo de 1 a 6 átomos de carbono)carbamoilo, un grupo hidroxiaminocarbonilo, un grupo (alcoxi de 1 a 6 átomos de carbono)aminocarbonilo, un grupo de la fórmula R^9-CO-$(CH_2)_k$-N(R^{10})- {en donde R^9 representa un grupo hidroxilo, un grupo amino, un grupo alquilo de 1 a 6 átomos de carbono, un grupo alquilamino de 1 a 6 átomos de carbono, un grupo di(alquil de 1 a 6 átomos de carbono)amino, un grupo hidroxiamino, un grupo alcoxiamino de 1 a 6 átomos de carbono o un grupo alcoxi de 1 a 6 átomos de carbono; R^{10} representa un átomo de hidrógeno o un grupo alquilo de 1 a 6 átomos de carbono; y k representa un entero desde 0 hasta 5} y un grupo sulfamoil alquilo de 1 a 6 átomos de carbono], sales de él o profármacos de él aceptables farmacológicamente.

Un compuesto que tiene la fórmula general (I) que se muestra arriba, una sal de él aceptable farmacológicamente o un profármaco de él, preferiblemente es

(1) un compuesto en donde R^1 representa un grupo alquilo de 1 a 6 átomos de carbono, un grupo alquilo halogenado de 1 a 6 átomos de carbono, un grupo cicloalquilo de 3 a 6 átomos de carbono, un grupo cicloalquilo halogenado de 3 a 6 átomos de carbono o un grupo alcoxi de 1 a 6 átomos de carbono, sales de él o profármacos de él aceptables farmacológicamente;

(2) un compuesto en donde R^1 representa un grupo cicloalquilo de 3 a 6 átomos de carbono, un grupo cicloalquilo halogenado de 3 a 6 átomos de carbono o un grupo alcoxi de 1 a 6 átomos de carbono, sales de él o profármacos de él aceptables farmacológicamente;

(3) un compuesto en donde R^1 representa un grupo cicloalquilo de 3 a 6 átomos de carbono o un grupo alcoxi de 1 a 6 átomos de carbono, sales de él o profármacos de él aceptables farmacológicamente;

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(4) un compuesto en donde R^1 representa un grupo ciclopropilo o un grupo metoxi, sales de él o profármacos de él aceptables farmacológicamente;

(5) un compuesto en donde R^1 representa un grupo ciclopropilo, sales de él o profármacos de él aceptables farmacológicamente;

(6) un compuesto en donde R^2 representa un átomo de hidrógeno o un grupo alquilo de 1 a 6 átomos de carbono, sales de él o profármacos de él aceptables farmacológicamente;

(7) un compuesto en donde R^2 representa un átomo de hidrógeno o un grupo metilo, sales de él o profármacos de él aceptables farmacológicamente;

(8) un compuesto en donde R^2 representa un átomo de hidrógeno, sales de él o profármacos de él aceptables farmacológicamente;

(9) un compuesto en donde R^3 representa un grupo alquilo sustituido de 1 a 6 átomos de carbono {dicho grupo sustituyente representa un grupo heterociclilo o un grupo heterociclilo sustituido con 1 o 2 sustituyentes seleccionados del <Grupo sustituyente α> (dichos grupos heterociclilo pueden estar sustituidos por 1 o 2 grupos oxo), un grupo heteroarilo o un grupo heteroarilo sustituido con 1 o 2 sustituyentes seleccionados del <Grupo sustituyente α> o un sustituyente seleccionado del <Grupo sustituyente β>}, o un grupo heterociclilo o un grupo heterociclilo sustituido con 1 o 2 sustituyentes seleccionados del <Grupo sustituyente α> (dichos grupos heterociclilo pueden estar sustituidos por 1 o 2 grupos oxo), sales de él o profármacos de él aceptables farmacológicamente;

(10) un compuesto en donde R^3 representa un grupo alquilo sustituido de 1 a 6 átomos de carbono {dicho grupo sustituyente representa un grupo heterociclilo de 4 a 7 miembros que contiene al menos un átomo de nitrógeno que puede estar sustituido con 1 o 2

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sustituyentes seleccionados del <Grupo sustituyente α1> (dicho grupo heterociclilo puede estar sustituido por un grupo oxo), un grupo heteroarilo que contiene al menos un átomo de nitrógeno que puede estar sustituido con 1 o 2 sustituyentes seleccionados del <Grupo sustituyente α1>, un grupo carboxi, un grupo alcoxicarbonilo de 2 a 7 átomos de carbono, un grupo ciano, un grupo hidroxilo, un grupo alcoxi de 1 a 6 átomos de carbono o un grupo de la fórmula R^9-CO-$(CH_2)_k$-N(R^{10})- (en donde R^9 representa un grupo hidroxilo o un grupo alcoxi de 1 a 6 átomos de carbono; R^{10} representa un grupo alquilo de 1 a 6 átomos de carbono; y k representa un entero desde 1 hasta 5)}, o un grupo heterociclilo de 4 a 7 miembros que contiene al menos un átomo de nitrógeno que puede estar sustituido con un sustituyente seleccionado del <Grupo sustituyente α1> (dicho grupo heterociclilo puede estar sustituido por un grupo oxo), y

El <Grupo sustituyente α1> es un grupo que consiste en un grupo carboxi, un grupo alcoxicarbonilo de 2 a 7 átomos de carbono y un grupo de la fórmula R^4-CO-CR^5R^6-$(CH_2)_m$- (en donde R^4 representa un grupo hidroxilo, un grupo amino, un grupo alquilamino de 1 a 6 átomos de carbono, un grupo di(alquil de 1 a 6 átomos de carbono)amino, un grupo hidroxiamino, un grupo alcoxiamino de 1 a 6 átomos de carbono o un grupo alcoxi de 1 a 6 átomos de carbono; R^5 y R^6 representan cada uno un átomo de hidrógeno; y m representa un entero desde 0 hasta 5), sales de él o profármacos de él aceptables farmacológicamente;

(11) un compuesto en donde R^3 representa un grupo alquilo sustituido de 1 a 3 átomos de carbono {dicho grupo sustituyente representa un grupo pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo, piperazinilo, pirazolilo, triazolilo o tetrazolilo que puede estar sustituido con 1 o 2 sustituyentes seleccionados del <Grupo sustituyente α2> (dicho grupo pirrolidinilo, piperidinilo,

morfolinilo, tiomorfolinilo o piperazinilo puede estar sustituido por un grupo oxo), un grupo carboxi, un grupo alcoxicarbonilo de 2 a 4 átomos de carbono, un grupo hidroxilo o un grupo de la fórmula R^9-CO-$(CH_2)_k$-N(R^{10})- (en donde R^9 representa un grupo hidroxilo o un grupo alcoxi de 1 a 3 átomos de carbono; R^{10} representa un grupo alquilo de 1 a 3 átomos de carbono y k representa un entero desde 1 hasta 3)}, o un grupo pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo o piperazinilo que puede estar sustituido con un sustituyente seleccionado del <Grupo sustituyente α2> (dicho grupo pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo o piperazinilo puede estar sustituido por un grupo oxo), y

El <Grupo sustituyente α2> es un grupo que consiste en un grupo carboxi, un grupo alcoxicarbonilo de 2 a 4 átomos de carbono y un grupo de la fórmula R^4-CO-CR^5R^6-$(CH_2)_m$- (en donde R^4 representa un grupo hidroxilo o un grupo alcoxi de 1 a 3 átomos de carbono, R^5 y R^6 representan cada uno un átomo de hidrógeno, y m representa un entero desde 0 hasta 2), sales de ellos aceptables farmacológicamente,o profármacos de ellos;

(12) un compuesto en donde R^3 representa un grupo metilo o etilo sustituido {dicho grupo sustituyente representa un grupo pirrolidinilo, piperidinilo, piperazinilo o pirazolilo que puede estar sustituido con 1 o 2 sustituyentes seleccionados del <Grupo sustituyente α3> (dicho grupo pirrolidinilo, piperidinilo o piperazinilo puede estar sustituido por un grupo oxo), un grupo carboxi o un grupo de la fórmula R^9-CO-$(CH_2)_k$-N(R^{10})- (en donde R^9 representa un grupo hidroxilo, un grupo metoxi o un grupo etoxi; R^{10} representa un grupo metilo, un grupo etilo o un grupo isopropilo; y k representa un entero desde 1 hasta 3), y

El <Grupo sustituyente α3> es un grupo que consiste en un grupo carboxi, un grupo metoxicarbonilo, un grupo etoxicarbonilo, un grupo carboximetilo, un grupo metoxicarbonilmetilo, un grupo

etoxicarbonilmetilo, un grupo 2-(carboxi)etilo, un grupo 2-(metoxicarbonil)etilo y un grupo 2-(etoxicarbonil)etilo, sales de él o profármacos de él aceptables farmacológicamente;

(13) un compuesto en donde X^1, X^2, X^3, X^4 y X^5 representan independientemente un átomo de hidrógeno o un átomo de halógeno, sales de él o profármacos de él aceptables farmacológicamente;

(14) un compuesto en donde X^1 y X^2 representan independientemente un átomo de hidrógeno o un átomo de halógeno; y X^3, X^4 y X^5 representan un átomo de hidrógeno, sales de él o profármacos de él aceptables farmacológicamente;

(15) un compuesto en donde X^1 representa un átomo de halógeno; y X^2, X^3, X^4 y X^5 representan un átomo de hidrógeno, sales de él o profármacos de él aceptables farmacológicamente;

(16) un compuesto en donde X^1 representa un átomo de flúor; y X^2, X^3, X^4 y X^5 representan un átomo de hidrógeno, sales de él o profármacos de él aceptables farmacológicamente;

(17) un compuesto en donde n representa 0 o 1, sales de él o profármacos de él aceptables farmacológicamente; y

(18) un compuesto en donde n representa 1, sales de él o profármacos de él aceptables farmacológicamente.

Adicionalmente, en cada grupo de (1) - (5), (6) - (8), (9) - (12), (13) - (16) y (17) - (18) descrito anteriormente, se muestra un compuesto más preferible a medida que el número aumenta [el mismo concepto se aplica a cada grupo de (19) - (22) descrito más adelante]. Un compuesto obtenido seleccionando R^1 de cada grupo de (1) - (5); R^2 de cada grupo de (6) - (8); R^3 de cada grupo de (9) - (12); X^1, X^2, X^3, X^4 y X^5 de cada grupo de (13) - (16); y n de cada grupo de (17) - (18), respectivamente, seguido por la combinación arbitraria de estos grupos seleccionados, también es preferible, y puede ser, por ejemplo, el siguiente:

(19) un compuesto en donde R^1 representa un grupo

cicloalquilo de 3 a 6 átomos de carbono o un grupo alcoxi de 1 a 6 átomos de carbono;

R^2 representa un átomo de hidrógeno o un grupo alquilo de 1 a 6 átomos de carbono;

R^3 representa un grupo alquilo sustituido de 1 a 6 átomos de carbono {dicho grupo sustituyente representa un grupo heterociclilo o un grupo heterociclilo sustituido con 1 o 2 sustituyentes seleccionados del <Grupo sustituyente α> (dichos grupos heterociclilo pueden estar sustituidos por 1 o 2 grupos oxo), un grupo heteroarilo o un grupo heteroarilo sustituido con 1 o 2 sustituyentes seleccionados del <Grupo sustituyente α>, o un sustituyente seleccionado del <Grupo sustituyente β>}, o un grupo heterociclilo o un grupo heterociclilo sustituido con 1 o 2 sustituyentes seleccionados del <Grupo sustituyente α> (dichos grupos heterociclilo pueden estar sustituidos por 1 o 2 grupos oxo);

X^1 y X^2 representan independientemente un átomo de hidrógeno o un átomo de halógeno;

X^3, X^4, y X^5 representan un átomo de hidrógeno; y

n es 0 o 1, una sal de él aceptable farmacológicamente, o un profármaco de él;

(20) un compuesto en donde R^1 representa un grupo ciclopropilo o un grupo metoxi;

R^2 representa un átomo de hidrógeno o un grupo metilo;

R^3 representa un grupo alquilo sustituido de 1 a 6 átomos de carbono {dicho grupo sustituyente representa un grupo heterociclilo de 4 a 7 miembros que contiene al menos un átomo de nitrógeno que puede estar sustituido con 1 o 2 sustituyentes seleccionados del <Grupo sustituyente α1> (dicho grupo heterociclilo puede estar sustituido por un grupo oxo), un grupo heteroarilo que contiene al menos un átomo de nitrógeno que puede estar sustituido con 1 o 2

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sustituyentes seleccionados del <Grupo sustituyente α1>, un grupo carboxi, un grupo alcoxicarbonilo de 2 a 7 átomos de carbono, un grupo ciano, un grupo hidroxilo, un grupo alcoxi de 1 a 6 átomos de carbono o un grupo de la fórmula R^9-CO-$(CH_2)_k$-N(R^{10})- (en donde R^9 representa un grupo hidroxilo o un grupo alcoxi de 1 a 6 átomos de carbono; R^{10} representa un grupo alquilo de 1 a 6 átomos de carbono; y k representa un entero desde 1 hasta 5)}, o un grupo heterociclilo de 4 a 7 miembros que contiene al menos un átomo de nitrógeno que puede estar sustituido con un sustituyente seleccionado del <Grupo sustituyente α1> (dicho grupo heterociclilo puede estar sustituido por un grupo oxo), y

El <Grupo sustituyente α1> es un grupo que consiste en un grupo carboxi, un grupo alcoxicarbonilo de 2 a 7 átomos de carbono, y un grupo de la fórmula R^4-CO-CR^5R^6-$(CH_2)_m$- (en donde R^4 representa un grupo hidroxilo, un grupo amino, un grupo alquilamino de 1 a 6 átomos de carbono, un grupo di(alquil de 1 a 6 átomos de carbono)amino, un grupo hidroxiamino, un grupo alcoxiamino de 1 a 6 átomos de carbono o un grupo alcoxi de 1 a 6 átomos de carbono; R^5 y R^6 representan cada uno un átomo de hidrógeno; y m representa un entero desde 0 hasta 5);

X^1 representa un átomo de halógeno;

X^2, X^3, X^4 y X^5 representan un átomo de hidrógeno; y

n representa 1, sales de él o profármacos de él aceptables farmacológicamente;

(21) un compuesto en donde R^1 representa un grupo ciclopropilo;

R^2 representa un átomo de hidrógeno;

R^3 representa un grupo alquilo sustituido de 1 a 3 átomos de carbono {dicho grupo sustituyente representa un grupo pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo, piperazinilo, pirazolilo, triazolilo o tetrazolilo que puede estar sustituido con 1 o 2

sustituyentes seleccionados del <Grupo sustituyente α2> (dicho grupo pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo o piperazinilo puede estar sustituido por un grupo oxo), un grupo carboxi, un grupo alcoxicarbonilo de 2 a 4 átomos de carbono, un grupo hidroxilo o un grupo de la fórmula R^9-CO-$(CH_2)_k$-N(R^{10})- (en donde R^9 representa un grupo hidroxilo o un grupo alcoxi de 1 a 3 átomos de carbono; R^{10} representa un grupo alquilo de 1 a 3 átomos de carbono y k representa un entero desde 1 hasta 3)}, o un grupo pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo o piperazinilo que puede estar sustituido con un sustituyente seleccionado del <Grupo sustituyente α2> (dicho grupo pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo, o piperazinilo puede estar sustituido por un grupo oxo), y

El <Grupo sustituyente α2> es un grupo que consiste en un grupo carboxi, un grupo alcoxicarbonilo de 2 a 4 átomos de carbono, y un grupo de la fórmula R^4-CO-CR^5R^6-$(CH_2)_m$- (en donde R^4 representa un grupo hidroxilo o un grupo alcoxi de 1 a 3 átomos de carbono, R^5 y R^6 representan cada uno un átomo de hidrógeno, y m representa un entero desde 0 hasta 2);

X^1 representa un átomo de flúor;

X^2, X^3, X^4 y X^5 representan un átomo de hidrógeno; y

n representa 1, sales de él o profármacos de él aceptables farmacológicamente, y

(22) un compuesto en donde R^1 representa un grupo ciclopropilo;

R^2 representa un átomo de hidrógeno;

R^3 representa un grupo metilo o etilo sustituido {dicho grupo sustituyente representa un grupo pirrolidinilo, piperidinilo, piperazinilo o pirazolilo que puede estar sustituido con 1 o 2 sustituyentes seleccionados del <Grupo sustituyente α3> (dicho grupo pirrolidinilo, piperidinilo o piperazinilo puede estar sustituido

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por un grupo oxo), un grupo carboxi o un grupo de la fórmula R^9-CO-$(CH_2)_k$-N(R^{10})- (en donde R^9 representa un grupo hidroxilo, un grupo metoxi o un grupo etoxi; R^{10} representa un grupo metilo, un grupo etilo o un grupo isopropilo; y k representa un entero desde 1 hasta 3), y

<Grupo sustituyente α3> es un grupo que consiste en un grupo carboxi, un grupo metoxicarbonilo, un grupo etoxicarbonilo, un grupo carboximetilo, un grupo metoxicarbonilmetilo, un grupo etoxicarbonilmetilo, un grupo 2-(carboxi)etilo, un grupo 2-(metoxicarbonil)etilo y un grupo 2-(etoxicarbonil)etilo;

X^1 representa un átomo de flúor;

X^2, X^3, X^4 y X^5 representan un átomo de hidrógeno; y

n representa 1, sales de él o profármacos de él aceptables farmacológicamente.

Además, otro aspecto de la presente invención se refiere a un medicamento que contiene el compuesto, sales de él o profármacos de él aceptables farmacológicamente descritos en (1) - (22) anterior (preferiblemente un agente antitrombótico); uso del compuesto, sales de él o profármacos de él aceptables farmacológicamente para fabricar composiciones farmacéuticas; uso del compuesto, sales de él o profármacos de él aceptables farmacológicamente para agentes profilácticos o terapéuticos para enfermedades relacionadas con formación de trombos o émbolos; y métodos profilácticos o terapéuticos para enfermedades (particularmente enfermedades relacionadas con formación de trombos o émbolos) mediante administración de dosis efectiva farmacológicamente del compuesto, sales de él o profármacos de él aceptables farmacológicamente a animales de sangre caliente (especialmente humanos).

El "grupo alquilo de 1 a 6 átomos de carbono" en la fórmula general (I) que se muestra arriba puede ser, por ejemplo, un grupo alquilo de cadena recta o ramificada que tiene desde 1 hasta 6

átomos de carbono tal como un grupo metilo, etilo, propilo, isopropilo, butilo, isobutilo, s-butilo, t-butilo, pentilo, isopentilo, 2-metilbutilo, neopentilo, 1-etilpropilo, hexilo, 4-metilpentilo, 3-metilpentilo, 2-metilpentilo, 1-metilpentilo, 3,3-dimetilbutilo, 2,2-dimetilbutilo, 1,1-dimetilbutilo, 1,2-dimetilbutilo, 1,3-dimetilbutilo, 2,3-dimetilbutilo o 2-etilbutilo, y preferiblemente es un grupo alquilo de cadena recta o ramificada que tiene desde 1 hasta 4 átomos de carbono, más preferiblemente un grupo alquilo de cadena recta o ramificada que tiene desde 1 hasta 3 átomos de carbono, más preferiblemente un grupo metilo o etilo, y mucho más preferiblemente un grupo metilo.

El "átomo de halógeno" en la fórmula general (I) que se muestra arriba puede ser, por ejemplo, un átomo de flúor, un átomo de cloro, un átomo de bromo o un átomo de yodo, y preferiblemente es un átomo de flúor o un átomo de cloro, y más preferiblemente un átomo de flúor.

El "Grupo alcoxi de 1 a 6 átomos de carbono" en la fórmula general (I) que se muestra arriba indica un grupo en donde dicho "grupo alquilo de 1 a 6 átomos de carbono" está unido a un átomo de oxígeno, y puede ser, por ejemplo, un grupo alcoxi de cadena recta o ramificada que tiene desde 1 hasta 6 átomos de carbono tal como un grupo metoxi, etoxi, n-propoxi, isopropoxi, n-butoxi, isobutoxi, s-butoxi, t-butoxi, n-pentiloxi, isopentiloxi, 2-metilbutoxi, neopentiloxi, n-hexiloxi, 4-metilpentiloxi, 3-metilpentiloxi, 2-metilpentiloxi, 3,3-dimetilbutoxi, 2,2-dimetilbutoxi, 1,1-dimetilbutoxi, 1,2-dimetilbutoxi, 1,3-dimetilbutoxi o 2,3-dimetilbutoxi, y preferiblemente es un grupo alcoxi de cadena recta o ramificada que tiene desde 1 hasta 4 átomos de carbono, más preferiblemente un grupo alcoxi de cadena recta o ramificada que tiene desde 1 hasta 3 átomos de carbono, y mucho más preferiblemente un grupo metoxi o etoxi.

El "grupo cicloalquilo de 3 a 6 átomos de carbono" en la

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fórmula general (I) que se muestra arriba puede ser, por ejemplo, un grupo hidrocarburo cíclico saturado de 3 a 6 miembros tal como un grupo ciclopropilo, ciclobutilo, ciclopentilo o ciclohexilo, y preferiblemente es un grupo ciclopropilo.

El "grupo arilo de 6 a 10 átomos de carbono" en la fórmula general (I) que se muestra arriba puede ser, por ejemplo, un grupo hidrocarburo aromático que tiene desde 6 hasta 10 átomos de carbono tal como un grupo fenilo o naftilo, y preferiblemente es un grupo fenilo.

El "grupo alcoxicarbonilo de 2 a 7 átomos de carbono" en la fórmula general (I) que se muestra arriba puede ser, por ejemplo, un grupo alcoxicarbonilo de cadena recta o ramificada que tiene desde 2 hasta 7 átomos de carbono tal como un grupo metoxicarbonilo, etoxicarbonilo, n-propoxicarbonilo, isopropoxicarbonilo, n-butoxicarbonilo, isobutoxicarbonilo, s-butoxicarbonilo, t-butoxicarbonilo, n-pentiloxicarbonilo, isopentiloxicarbonilo, 2-metilbutoxicarbonilo, neopentiloxicarbonilo, n-hexiloxicarbonilo, 4-metilpentiloxicarbonilo, 3-metilpentiloxicarbonilo, 2-metilpentiloxicarbonilo, 3,3-dimetilbutoxicarbonilo, 2,2-dimetilbutoxicarbonilo, 1,1-dimetilbutoxicarbonilo, 1,2-dimetilbutoxicarbonilo, 1,3-dimetilbutoxicarbonilo o 2,3-dimetilbutoxicarbonilo, y preferiblemente es un grupo alcoxicarbonilo de cadena recta o ramificada que tiene desde 2 hasta 5 átomos de carbono, más preferiblemente un grupo alcoxicarbonilo de cadena recta o ramificada que tiene desde 2 hasta 4 átomos de carbono, y aún más preferiblemente un grupo metoxicarbonilo o etoxicarbonilo.

El "grupo alquilo halogenado de 1 a 6 átomos de carbono" en la fórmula general (I) que se muestra arriba indica un grupo en donde dicho "grupo alquilo de 1 a 6 átomos de carbono" está sustituido con átomo(s) de halógeno, y puede ser, por ejemplo, un grupo trifluorometilo, triclorometilo, difluorometilo, diclorometilo,

dibromometilo, fluorometilo, 2,2,2-trifluoroetilo, 2,2,2-tricloroetilo, 2-bromoetilo, 2-cloroetilo, 2-fluoroetilo, 2-iodoetilo, 3-cloropropilo, 4-fluorobutilo, 6-yodohexilo o 2,2-dibromoetilo, y preferiblemente es un grupo trifluorometilo.

El "grupo heteroarilo" en la fórmula general (I) que se muestra arriba puede ser, por ejemplo, un grupo heterocíclico aromático de 5 a 7 miembros que contiene desde 1 hasta 4 átomo(s) de azufre, átomo(s) de oxígeno y/o átomo(s) de nitrógeno tal como un grupo furilo, tienilo, pirrolilo, pirazolilo, imidazolilo, oxazolilo, isoxazolilo, tiazolilo, isotiazolilo, triazolilo, tetrazolilo, tiadiazolilo, oxadiazolilo, piranilo, piridilo, piridazinilo, pirimidinilo o pirazinilo, o un grupo heterocíclico aromático fusionado con otros grupos cíclicos tal como un grupo isoindolilo, indolilo, isoquinolilo y quinolilo, y preferiblemente es un grupo heterocíclico aromático de 5 a 7 miembros que contiene al menos un átomo de nitrógeno, y más preferiblemente un grupo pirazolilo, triazolilo o tetrazolilo.

El "grupo alcoxi halogenado de 1 a 6 átomos de carbono" en la fórmula general (I) que se muestra arriba indica un grupo en donde dicho "grupo alcoxi de 1 a 6 átomos de carbono" está sustituido con átomo(s) de halógeno, y puede ser, por ejemplo, un grupo trifluorometoxi, triclorometoxi, difluorometoxi, diclorometoxi, dibromometoxi, fluorometoxi, 2,2,2-tricloroetoxi, 2,2,2-trifluoroetoxi, 2-bromoetoxi, 2-cloroetoxi, 2-fluoroetoxi o 2,2-dibromoetoxi, y preferiblemente es un grupo 2-bromoetoxi, 2-cloroetoxi o 2-fluoroetoxi.

El "grupo hidroxi alquilo de 1 a 6 átomos de carbono" en la fórmula general (I) que se muestra arriba indica un grupo en donde dicho "grupo alquilo de 1 a 6 átomos de carbono" está sustituido con grupo(s) hidroxilo, y puede ser, por ejemplo, un grupo hidroximetilo, 1-hidroxietilo, 2-hidroxietilo, 1-hidroxi-2-metiletilo, 2-hidroxi-2-metiletilo, 1-hidroxipropilo, 2-hidroxipropilo, 3-hidroxipropilo, 1-

hidroxibutilo, 2-hidroxibutilo, 3-hidroxibutilo, 4-hidroxibutilo, 5-hidroxipentilo o 6-hidroxihexilo, y preferiblemente es un grupo hidroximetilo, 2-hidroxietilo o 3-hidroxipropilo.

El "grupo alcoxialquilo de 2 a 12 átomos de carbono" en la fórmula general (I) que se muestra arriba indica un grupo en donde dicho "grupo alcoxi de 1 a 6 átomos de carbono" está unido a dicho "grupo alquilo de 1 a 6 átomos de carbono", y puede ser, por ejemplo, un grupo metoximetilo, etoximetilo, n-propoximetilo, isopropoximetilo, n-butoximetilo, isobutoximetilo, s-butoximetilo, t-butoximetilo, n-pentiloximetilo, isopentiloximetilo, 2-metilbutoximetilo, neopentiloximetilo, n-hexiloximetilo, 4-metilpentiloximetilo, 3-metilpentiloximetilo, 2-metilpentiloximetilo, 3,3-dimetilbutoximetilo, 2,2-dimetilbutoximetilo, 1,1-dimetilbutoximetilo, 1,2-dimetilbutoximetilo, 1,3-dimetilbutoximetilo, 2,3-dimetilbutoximetilo, 2-metoxietilo, 2-etoxietilo, 2-(n-propoxi)etilo, 2-(isopropoxi)etilo, 2-(n-butoxi)etilo, 2-(isobutoxi)etilo, 2-(s-butoxi)etilo, 2-(t-butoxi)etilo, 2-(n-pentiloxi)etilo, 2-(isopentiloxi)etilo, 2-(2-metilbutoxi)etilo, 2-(neopentiloxi)etilo, 2-(n-hexiloxi)etilo, 2-(4-metilpentiloxi)etilo, 2-(3-metilpentiloxi)etilo, 2-(2-metilpentiloxi)etilo, 2-(3,3-dimetilbutoxi)etilo, 2,2-dimetilbutoxietilo, 1,1-dimetilbutoxietilo, 1,2-dimetilbutoxietilo, 1,3-dimetilbutoxietilo o 2,3-dimetilbutoxietilo, y preferiblemente es un grupo alcoxialquilo de cadena recta o ramificada que tiene desde 2 hasta 4 átomos de carbono, y más preferiblemente un grupo metoximetilo o metoxietilo.

El "grupo alcanoilo de 2 a 7 átomos de carbono" en la fórmula general (I) que se muestra arriba puede ser, por ejemplo, un grupo alcanoilo de cadena recta o ramificada que tiene desde 2 hasta 7 átomos de carbono tal como un grupo acetilo, propionilo, butirilo, isobutirilo, pentanoilo, pivaloilo, valerilo, isovalerilo, hexanoilo o heptanoilo, y preferiblemente es un grupo alcanoilo de cadena recta o ramificada que tiene desde 2 hasta 5 átomos de carbono, más

preferiblemente un grupo alcanoilo de cadena recta o ramificada que tiene desde 2 hasta 4 átomos de carbono, y aún más preferiblemente un grupo acetilo.

El "grupo cicloalquilcarbonilo de 4 a 7 átomos de carbono" en la fórmula general (I) que se muestra arriba indica un grupo en donde dicho "grupo cicloalquilo de 3 a 6 átomos de carbono" está unido a un grupo carbonilo, y puede ser, por ejemplo, un grupo ciclopropilcarbonilo, ciclobutilcarbonilo, ciclopentilcarbonilo o ciclohexilcarbonilo, y preferiblemente es un grupo ciclopropilcarbonilo.

El "grupo alquilcarbamoilo de 2 a 7 átomos de carbono" en la fórmula general (I) que se muestra arriba indica un grupo en donde un "grupo alquilo de 1 a 6 átomos de carbono" está unido a un grupo carbamoilo, y puede ser, por ejemplo, un grupo metilcarbamoilo, etilcarbamoilo, propilcarbamoilo, isopropilcarbamoilo, butilcarbamoilo, isobutilcarbamoilo, s-butilcarbamoilo, t-butilcarbamoilo, pentilcarbamoilo, isopentilcarbamoilo, 2-metilbutilcarbamoilo, neopentilcarbamoilo, 1-etilpropilcarbamoilo, hexilcarbamoilo, 4-metilpentilcarbamoilo, 3-metilpentilcarbamoilo, 2-metilpentilcarbamoilo, 1-metilpentilcarbamoilo, 3,3-dimetilbutilcarbamoilo, 2,2-dimetilbutilcarbamoilo, 1,1-dimetilbutilcarbamoilo, 1,2-dimetilbutilcarbamoilo, 1,3-dimetilbutilcarbamoilo, 2,3-dimetilbutilcarbamoilo o 2-etilbutilcarbamoilo, y preferiblemente es un grupo alquilcarbamoilo que tiene desde 2 hasta 5 átomos de carbono, y más preferiblemente un grupo metilcarbamoilo o etilcarbamoilo.

El "grupo di(alquil de 1 a 6 átomos de carbono)carbamoilo " en la fórmula general (I) que se muestra arriba indica un grupo en donde un grupo carbamoilo está disustituido con dos "grupos alquilo de 1 a 6 átomos de carbono", y puede ser, por ejemplo, un grupo dimetilcarbamoilo, metiletilcarbamoilo, dietilcarbamoilo, di-n-

propilcarbamoilo, diisopropilcarbamoilo, N-(n-propil)-N-etilcarbamoilo, di-n-butilcarbamoilo, diisobutilcarbamoilo, di-s-butilcarbamoilo, di-t-butilcarbamoilo, di-n-pentilcarbamoilo, diisopentilcarbamoilo, di-2-metilbutilcarbamoilo, dineopentilcarbamoilo, di-1-etilpropilcarbamoilo, di-n-hexilcarbamoilo, di-4-metilpentilcarbamoilo, di-3-metilpentilcarbamoilo, di-2-metilpentilcarbamoilo, di-1-metilpentilcarbamoilo, di-3,3-dimetilbutilcarbamoilo, di-2,2-dimetilbutilcarbamoilo, di-1,1-dimetilbutilcarbamoilo, di-1,2-dimetilbutilcarbamoilo, di-1,3-dimetilbutilcarbamoilo, di-2,3-dimetilbutilcarbamoilo o di-2-etilbutilcarbamoilo, y preferiblemente es un grupo dimetilcarbamoilo, metiletilcarbamoilo o dietilcarbamoilo.

El "Grupo alquilamino de 1 a 6 átomos de carbono" en la fórmula general (I) que se muestra arriba indica un grupo en donde un "grupo alquilo de 1 a 6 átomos de carbono" está unido a un grupo amino, y puede ser, por ejemplo, un grupo alquilamino de cadena recta o ramificada que tiene desde 1 hasta 6 átomos de carbono tal como un grupo metilamino, etilamino, propilamino, isopropilamino, butilamino, isobutilamino, s-butilamino, t-butilamino, pentilamino, isopentilamino, 2-metilbutilamino, neopentilamino, 1-etilpropilamino, hexilamino, 4-metilpentilamino, 3-metilpentilamino, 2-metilpentilamino, 1-metilpentilamino, 3,3-dimetilbutilamino, 2,2-dimetilbutilamino, 1,1-dimetilbutilamino, 1,2-dimetilbutilamino, 1,3-dimetilbutilamino, 2,3-dimetilbutilamino o 2-etilbutilamino, y preferiblemente es un grupo alquilamino de cadena recta o ramificada que tiene desde 1 hasta 4 átomos de carbono, más preferiblemente un grupo alquilamino de cadena recta o ramificada que tiene desde 1 hasta 3 átomos de carbono, y aún más preferiblemente un grupo metilamino.

El "grupo di(alquil de 1 a 6 átomos de carbono)amino " en la fórmula general (I) que se muestra arriba indica un grupo en donde

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un grupo amino está sustituido con dos "grupos alquilo de 1 a 6 átomos de carbono", y puede ser, por ejemplo, un grupo dimetilamino, metiletilamino, dietilamino, di-n-propilamino, diisopropilamino, N-(n-propil)-N-etilamino, di-n-butilamino, diisobutilamino, di-s-butilamino, di-t-butilamino, di-n-pentilamino, diisopentilamino, di-2-metilbutilamino, dineopentilamino, di-1-etilpropilamino, di-n-hexilamino, di-4-metilpentilamino, di-3-metilpentilamino, di-2-metilpentilamino, di-1-metilpentilamino, di-3,3-dimetilbutilamino, di-2,2-dimetilbutilamino, di-1,1-dimetilbutilamino, di-1,2-dimetilbutilamino, di-1,3-dimetilbutilamino, di-2,3-dimetilbutilamino o di-2-etilbutilamino, y preferiblemente es un grupo dimetilamino, metiletilamino o dietilamino.

El "grupo alcoxiamino de 1 a 6 átomos de carbono" en la fórmula general (I) que se muestra arriba indica un grupo en donde el átomo de oxígeno de un grupo hidroxiamino está sustituido con dicho "grupo alquilo de 1 a 6 átomos de carbono", y puede ser, por ejemplo, un grupo metoxiamino, etoxiamino, n-propoxiamino, isopropoxiamino, n-butoxiamino, isobutoxiamino, s-butoxiamino, t-butoxiamino, n-pentiloxiamino, isopentiloxiamino, 2-metilbutoxiamino, neopentiloxiamino, n-hexiloxiamino, 4-metilpentiloxiamino, 3-metilpentiloxiamino, 2-metilpentiloxiamino, 3,3-dimetilbutoxiamino, 2,2-dimetilbutoxiamino, 1,1-dimetilbutoxiamino, 1,2-dimetilbutoxiamino, 1,3-dimetilbutoxiamino o 2,3-dimetilbutoxiamino, y preferiblemente es un grupo alcoxiamino de cadena recta o ramificada que tiene desde 1 hasta 4 átomos de carbono, más preferiblemente un grupo alcoxiamino de cadena recta o ramificada que tiene desde 1 hasta 3 átomos de carbono, y aún más preferiblemente un grupo metoxiamino.

El "grupo sulfamoil alquilo de 1 a 6 átomos de carbono" en la fórmula general (I) que se muestra arriba indica un grupo en donde dicho "grupo alquilo de 1 a 6 átomos de carbono" está sustituido con

grupo(s) sulfamoilo, y puede ser, por ejemplo, un grupo sulfamoilmetilo, 1-sulfamoiletilo, 2-sulfamoiletilo, 1-sulfamoil-2-metiletilo, 2-sulfamoil-2-metiletilo, 1-sulfamoilpropilo, 2-sulfamoilpropilo, 3-sulfamoilpropilo, 1-sulfamoilbutilo, 2-sulfamoilbutilo, 3-sulfamoilbutilo, 4-sulfamoilbutilo, 5-sulfamoilpentilo o 6-sulfamoilhexilo, y preferiblemente es un grupo sulfamoil alquilo que tiene desde 1 hasta 4 átomos de carbono, más preferiblemente un grupo sulfamoil alquilo que tiene desde 1 hasta 3 átomos de carbono, y aún más preferiblemente un grupo sulfamoilmetilo, 2-sulfamoiletilo o 3-sulfamoilpropilo.

El "grupo heterociclilo" en la fórmula general (I) que se muestra arriba puede ser, por ejemplo, un grupo heterocíclico de 4 a 7 miembros reducido parcial o completamente que contiene desde 1 hasta 3 átomo(s) de azufre, átomo(s) de oxígeno y/o átomo(s) de nitrógeno tal como un grupo morfolinilo, tiomorfolinilo, azetidinilo, pirrolidinilo, pirrolinilo, imidazolidinilo, imidazolinilo, pirrazolidinilo, pirrazolinilo, piperidilo, piperazinilo, homopiperazinilo o homopiperidinilo, y preferiblemente es un grupo heterociclilo de 4 a 7 miembros que contiene al menos un átomo de nitrógeno, más preferiblemente un grupo morfolinilo, tiomorfolinilo, pirrolidinilo, pirrolinilo, imidazolidinilo, imidazolinilo, pirrazolidinilo, pirrazolinilo, piperidilo o piperazinilo, y más preferiblemente un grupo pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo o piperazinilo.

El "grupo heterociclilo (dicho grupo heterociclilo puede estar sustituido con desde 1 hasta 4 grupos oxo)" en la fórmula general (I) que se muestra arriba puede ser un grupo oxopiperazinilo o dioxopiperazinilo, además de dicho "grupo heterociclilo"; y preferiblemente es un grupo 2-oxo-1-piperazino, 3-oxo-1-piperazino o 2,5-dioxo-1-piperazino; y más preferiblemente un grupo 2-oxo-1-piperazino o 3-oxo-1-piperazino.

El grupo sustituyente α en la fórmula general (I) que se

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muestra arriba, preferiblemente es un grupo que consiste en un grupo carboxi, un grupo alcoxicarbonilo de 2 a 7 átomos de carbono, y un grupo de la fórmula R^4-CO-CR^5R^6-$(CH_2)_m$- (en donde R^4 representa un grupo hidroxilo, un grupo amino, un grupo alquilamino de 1 a 6 átomos de carbono, un grupo di(alquil de 1 a 6 átomos de carbono)amino, un grupo hidroxiamino, un grupo alcoxiamino de 1 a 6 átomos de carbono o un grupo alcoxi de 1 a 6 átomos de carbono; R^5 y R^6 representan cada uno un átomo de hidrógeno; y m representa un entero desde 0 hasta 5), más preferiblemente un grupo que consiste en un grupo carboxi, un grupo alcoxicarbonilo de 2 a 4 átomos de carbono y un grupo de la fórmula R^4-CO-CR^5R^6-$(CH_2)_m$- (en donde R^4 representa un grupo hidroxilo o un grupo alcoxi de 1 a 3 átomos de carbono; R^5 y R^6 representan cada uno un átomo de hidrógeno; y m representa un entero desde 0 hasta 2), y aún más preferiblemente un grupo que consiste en un grupo carboxi, un grupo metoxicarbonilo, un grupo etoxicarbonilo, un grupo carboximetilo, un grupo metoxicarbonilmetilo, un grupo etoxicarbonilmetilo, un grupo 2-(carboxi)etilo, un grupo 2-(metoxicarbonil)etilo y un grupo 2-(etoxicarbonil)etilo.

El grupo sustituyente β en la fórmula general (I) que se muestra arriba, preferiblemente es un grupo que consiste en un grupo carboxi, un grupo alcoxicarbonilo de 2 a 7 átomos de carbono, un grupo ciano, un grupo hidroxilo, un grupo alcoxi de 1 a 6 átomos de carbono y un grupo de la fórmula R^9-CO-$(CH_2)_k$-N(R^{10})- (en donde R^9 representa un grupo hidroxilo o un grupo alcoxi de 1 a 6 átomos de carbono; R^{10} representa un grupo alquilo de 1 a 6 átomos de carbono; y k representa un entero desde 1 hasta 5), más preferiblemente un grupo que consiste en un grupo carboxi, un grupo alcoxicarbonilo de 2 a 4 átomos de carbono, un grupo hidroxilo y un grupo de la fórmula R^9-CO-$(CH_2)_k$-N(R^{10})- (en donde R^9 representa un grupo hidroxilo o un grupo alcoxi de 1 a 3 átomos de carbono; R^{10}

representa un grupo alquilo de 1 a 3 átomos de carbono y k representa un entero desde 1 hasta 3), y más preferiblemente un grupo que consiste en un grupo carboxi y un grupo de la fórmula R^9-CO-$(CH_2)_k$-N(R^{10})- (en donde R^9 representa un grupo hidroxilo, un grupo metoxi o un grupo etoxi; R^{10} representa un grupo metilo, un grupo etilo o un grupo isopropilo; y k representa un entero desde 1 hasta 3).

En los compuestos (I) de la presente invención, pueden estar presente isómeros ópticos debido a los átomos de carbono asimétricos en sus estructuras (incluyendo diaestereómeros), y adicionalmente, también pueden estar presentes isómeros geométricos debido al doble enlace carbono-carbono en el mismo compuesto. La presente invención comprende todos estos isómeros.

Como algunos compuestos (I) de la presente invención tienen varios grupos, tales como un grupo sulfanilo, un grupo carboxi, un grupo hidroxilo o un grupo amino en su estructura, el "profármaco de él" significa un derivado en el cual cualquiera de estos grupos está modificado por un grupo funcional apropiado que puede ser segmentado mediante un proceso biológico tal como hidrólisis in vivo. En estos casos, se puede determinar si el derivado es "un grupo funcional apropiado que puede ser segmentado mediante un proceso biológico tal como hidrólisis in vivo" o no, de acuerdo con si el compuesto original o una sal de él aceptable farmacológicamente puede ser detectado, administrando el derivado a un animal experimental tal como una rata o un ratón mediante una inyección intravenosa, inyección subcutánea o administración oral, y midiendo un fluido corporal del animal después de ello.

Cuando los compuestos (I) de la presente invención contienen un grupo sulfanilo en sus estructuras, el grupo funcional empleado para formar un profármaco de él no está restringido particularmente, y puede ser, por ejemplo, un "grupo acilo alifático", incluyendo un

grupo alcanoilo tal como un grupo formilo, acetilo, propionilo, butirilo, isobutirilo, pentanoilo, pivaloilo, valerilo, isovalerilo, octanoilo, nonanoilo, decanoilo, 3-metilnonanoilo, 8-metilnonanoilo, 3-etiloctanoilo, 3,7-dimetiloctanoilo, undecanoilo, dodecanoilo, tridecanoilo, tetradecanoilo, pentadecanoilo, hexadecanoilo, 1-metilpentadecanoilo, 14-metilpentadecanoilo, 13,13-dimetiltetradecanoilo, heptadecanoilo, 15-metilhexadecanoilo, octadecanoilo, 1-metilheptadecanoilo, nonadecanoilo, icosanoilo o henicosanoilo; un grupo alquilcarbonilo sustituido con un grupo carboxi tal como un grupo succinoilo, glutaroilo o adipoilo; un grupo carbonilo sustituido con un grupo alquilo inferior halogenado tal como un grupo cloroacetilo, dicloroacetilo, tricloroacetilo o trifluoroacetilo; un grupo hidrocarburo cíclico saturado-carbonilo tal como un grupo ciclopropilcarbonilo, ciclobutilcarbonilo, ciclopentilcarbonilo, ciclohexilcarbonilo, cicloheptilcarbonilo o ciclooctilcarbonilo; un grupo alquilcarbonilo sustituido con grupo(s) alcoxi inferiores tal como un grupo metoxiacetilo; y un grupo alquilcarbonilo insaturado tal como un grupo (E)-2-metil-2-butenoilo (preferiblemente un grupo alcanoilo de 1 a 6 átomos de carbono); un "grupo carboniloxialquilo", incluyendo un grupo oxodioxolenilmetilo tal como un grupo (5-metil-2-oxo-1,3-dioxolen-4-il)metilo o a (5-fenil-2-oxo-1,3-dioxolen-4-il)metilo; un "grupo acilo aromático", incluyendo un grupo arilcarbonilo tal como un grupo benzoilo, α-naftoilo, β-naftoilo, piridoilo, tienoilo o furoilo; un grupo arilcarbonilo halogenado tal como un grupo 2-bromobenzoilo o 4-clorobenzoilo; un grupo arilcarbonilo sustituido con grupo(s) alquilo inferior tal como un grupo 2,4,6-trimetilbenzoilo o 4-toluoilo; un grupo arilcarbonilo inferior alcoxilado tal como un grupo 4-anisoilo; un grupo arilcarbonilo sustituido con grupo(s) carboxi tal como un grupo 2-carboxibenzoilo, 3-carboxibenzoilo o 4-carboxibenzoilo; un grupo arilcarbonilo nitrado tal como un grupo 4-nitrobenzoilo o 2-

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nitrobenzoilo; un grupo arilcarbonilo sustituido con grupo(s) alcoxicarbonilo inferior tal como un grupo 2-(metoxicarbonil)benzoilo; y un grupo arilcarbonilo sustituido con grupo(s) arilo tal como un grupo 4-fenilbenzoilo (preferiblemente un grupo arilcarbonilo); un "grupo aralquilcarbonilo", incluyendo un grupo carbonilo sustituido con un grupo alquilo inferior que está sustituido con desde 1 hasta 3 grupos arilo tal como un grupo fenilacetilo, α-naftilpropionilo, β-naftilbutirilo, difenilisobutirilo, trifenilacetilo, α-naftildifenilisobutirilo o 9-antrilpentanoilo; y un grupo alquilcarbonilo inferior sustituido con desde 1 hasta 3 grupos arilo, de los cuales un anillo arilo está sustituido con grupo(s) alquilo inferior, grupo(s) alcoxi inferiores, grupo(s) nitro, átomo(s) de halógeno o grupo(s) ciano, tal como un grupo 4-metilfenilacetilo, 2,4,6-trimetilfenilformilo, 3,4,5-trimetilfenilbutirilo, 4-metoxifenilisobutirilo, 4-metoxifenildifenilpivaloilo, 2-nitrofenilacetilo, 4-nitrofenilpropionilo, 4-clorofenilbutirilo, 4-bromofenilacetilo o 4-cianofenilpentanoilo; un "grupo tetrahidropiranilo o tetrahidrotiopiranilo" tal como un grupo tetrahidropiran-2-ilo, 3-bromotetrahidropiran-2-ilo, 4-metoxitetrahidropiran-4-ilo, tetrahidrotiopiran-2-ilo o 4-metoxitetrahidrotiopiran-4-ilo; un "grupo tetrahidrofuranilo o tetrahidrotiofuranilo" tal como un grupo tetrahidrofurano-2-ilo o tetrahidrotiofuran-2-ilo; un "grupo alcoximetilo", incluyendo un grupo alcoximetilo inferior tal como un grupo metoximetilo, 1,1-dimetil-1-metoximetilo, etoximetilo, propoximetilo, isopropoximetilo, butoximetilo o t-butoximetilo; un grupo alcoximetilo inferior sustituido con grupo(s) alcoxi inferiores tal como un grupo 2-metoxietoximetilo; y un grupo alcoximetilo inferior halogenado tal como un grupo 2,2,2-tricloroetoximetilo o bis(2-cloroetoxi)metilo; un "grupo etilo sustituido", incluyendo un grupo etilo inferior alcoxilado tal como un grupo 1-etoxietilo o 1-(isopropoxi)etilo; y un grupo etilo halogenado tal como un grupo 2,2,2-tricloroetilo; un "grupo aralquilo", incluyendo

un grupo alquilo inferior sustituido con desde 1 hasta 3 grupos arilo tal como un grupo bencilo, α-naftilmetilo, β-naftilmetilo, difenilmetilo, trifenilmetilo, α-naftildifenilmetilo o 9-antrilmetilo; y un grupo alquilo inferior sustituido con desde 1 hasta 3 grupos arilo, de los cuales un anillo arilo está sustituido con grupo(s) alquilo inferior, grupo(s) alcoxi inferiores, grupo(s) nitro, átomo(s) de halógeno o grupo(s) ciano, tal como un grupo 4-metilbencilo, 2,4,6-trimetilbencilo, 3,4,5-trimetilbencilo, 4-metoxibencilo, 4-metoxifenildifenilmetilo, 2-nitrobencilo, 4-nitrobencilo, 4-clorobencilo, 4-bromobencilo o 4-cianobencilo; un "grupo alcoxicarbonilo", incluyendo un grupo alcoxicarbonilo inferior tal como un grupo metoxicarbonilo, etoxicarbonilo, t-butoxicarbonilo o isobutoxicarbonilo; y un grupo alcoxicarbonilo inferior sustituido con átomo(s) de halógeno o grupo(s) tri-alquilsililo inferior tal como un grupo 2,2,2-tricloroetoxicarbonilo o 2-trimetilsililetoxicarbonilo; un "grupo alqueniloxicarbonilo" tal como un grupo viniloxicarbonilo y aliloxicarbonilo; un "grupo aralquiloxicarbonilo", de los cuales un anillo arilo puede estar sustituido con 1 o 2 sustituyentes seleccionados de grupo(s) alcoxi inferiores o grupo(s) nitro, tal como un grupo benciloxicarbonilo, 4-metoxibenciloxicarbonilo, 3,4-dimetoxibenciloxicarbonilo, 2-nitrobenciloxicarbonilo o 4-nitrobenciloxicarbonilo; un grupo alquilsulfanilo de cadena recta o ramificada que tiene desde 1 hasta 6 átomos de carbono tal como un grupo metilsulfanilo, etilsulfanilo, n-propilsulfanilo, isopropilsulfanilo, n-butilsulfanilo, isobutilsulfanilo, s-butilsulfanilo, t-butilsulfanilo, n-pentilsulfanilo, isopentilsulfanilo, 2-metilbutilsulfanilo, neopentilsulfanilo, 1-etilpropilsulfanilo, n-hexilsulfanilo, 4-metilpentilsulfanilo, 3-metilpentilsulfanilo, 2-metilpentilsulfanilo, 1-metilpentilsulfanilo, 3,3-dimetilbutilsulfanilo, 2,2-dimetilbutilsulfanilo, 1,1-dimetilbutilsulfanilo, 1,2-dimetilbutilsulfanilo, 1,3-dimetilbutilsulfanilo, 2,3-dimetilbutilsulfanilo o 2-etilbutilsulfanilo; o

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un "grupo aminoacilo de un α-amino ácido" tal como una fenilalanina, y preferiblemente es un grupo que forma un éster aceptable farmacológicamente tal como un "grupo acilo alifático" o un "grupo acilo aromático", o "grupo alquilsulfanilo de 1 a 6 átomos de carbono" tal como un grupo metilsulfanilo, etilsulfanilo, n-propilsulfanilo, isopropilsulfanilo, n-butilsulfanilo, isobutilsulfanilo, s-butilsulfanilo o t-butilsulfanilo; más preferiblemente un grupo que forma un éster aceptable farmacológicamente; aún más preferiblemente un "grupo alcanoilo de 1 a 6 átomos de carbono" tal como un grupo formilo, acetilo, propionilo, butirilo, isobutirilo, pentanoilo o pivaloilo o un "grupo arilcarbonilo" tal como un grupo benzoilo; en particular preferiblemente un "grupo alcanoilo de 1 a 3 átomos de carbono" o un grupo benzoilo; y mucho más preferiblemente un grupo acetilo.

Cuando los compuestos (I) de la presente invención contienen un grupo carboxi en sus estructuras, el grupo funcional empleado para formar un profármaco de él puede ser, por ejemplo, un "grupo alquilo inferior" tal como un grupo metilo, etilo, n-propilo, isopropilo, n-butilo, isobutilo, s-butilo, tert-butilo, n-pentilo, isopentilo, 2-metilbutilo, neopentilo, 1-etilpropilo, n-hexilo, 4-metilpentilo, 3-metilpentilo, 2-metilpentilo, 1-metilpentilo, 3,3-dimetilbutilo, 2,2-dimetilbutilo, 1,1-dimetilbutilo, 1,2-dimetilbutilo, 1,3-dimetilbutilo, 2,3-dimetilbutilo o 2-etilbutilo (preferiblemente un grupo alquilo de 1 a 6 átomos de carbono); un "grupo alcoxi alquilo inferior", incluyendo un grupo alcoxi inferior alquilo inferior, tal como un grupo metoximetilo, 1-etoxietilo, 1-metil-1-metoxietilo, 1-(isopropoxi)etilo, 2-metoxietilo, 2-etoxietilo, 1,1-dimetil-1-metoximetilo, etoximetilo, n-propoximetilo, isopropoximetilo, n-butoximetilo o tert-butoximetilo; un grupo alcoxi inferior alquilo inferior alcoxilado inferior tal como un grupo 2-metoxietoximetilo; un "aril"oxi "grupo alquilo inferior" tal como un grupo fenoximetilo; y un grupo alcoxi inferior alquilo inferior

halogenado tal como un grupo 2,2,2-tricloroetoximetilo o bis(2-cloroetoxi)metilo; un "alcoxi inferior" carbonil "grupo alquilo inferior" tal como un grupo metoxicarbonilmetilo; un ciano "grupo alquilo inferior" tal como un grupo cianometilo o 2-cianoetilo; un grupo "alquilo inferior" tiometilo tal como un grupo metiltiometilo o etiltiometilo; un grupo "aril" tiometilo tal como un grupo feniltiometilo o naftiltiometilo; un "alquilo inferior" sulfonil "grupo alquilo inferior", que puede estar sustituido con átomo(s) de halógeno, tal como un grupo 2-metanosulfoniletilo o 2-trifluorometanosulfoniletilo; un grupo "aril" sulfonil "grupo alquilo inferior" tal como un grupo 2-bencenosulfoniletilo o 2-toluenosulfoniletilo; un aciloxi "grupo alquilo inferior", incluyendo un "acil alifático"oxi "grupo alquilo inferior" tal como un grupo formiloximetilo, acetoximetilo, propioniloximetilo, butiriloximetilo, pivaloiloximetilo, valeriloximetilo, isovaleriloximetilo, hexanoiloximetilo, 1-formiloxietilo, 1-acetoxietilo, 1-propioniloxietilo, 1-butiriloxietilo, 1-pivaloiloxietilo, 1-valeriloxietilo, 1-isovaleriloxietilo, 1-hexanoiloxietilo, 2-formiloxietilo, 2-acetoxietilo, 2-propioniloxietilo, 2-butiriloxietilo, 2-pivaloiloxietilo, 2-valeriloxietilo, 2-isovaleriloxietilo, 2-hexanoiloxietilo, 1-formiloxipropilo, 1-acetoxipropilo, 1-propioniloxipropilo, 1-butiriloxipropilo, 1-pivaloiloxipropilo, 1-valeriloxipropilo, 1-isovaleriloxipropilo, 1-hexanoiloxipropilo, 1-acetoxibutilo, 1-propioniloxibutilo, 1-butiriloxibutilo, 1-pivaloiloxibutilo, 1-acetoxipentilo, 1-propioniloxipentilo, 1-butiriloxipentilo, 1-pivaloiloxipentilo o 1-pivaloiloxihexilo; un "cicloalquil" carboniloxi "grupo alquilo inferior" tal como un grupo ciclopentanoiloximetilo, ciclohexanoiloximetilo, 1-ciclopentanoiloxietilo, 1-ciclohexanoiloxietilo, 1-ciclopentanoiloxipropilo, 1-ciclohexanoiloxipropilo, 1-ciclopentanoiloxibutilo o 1-ciclohexanoiloxibutilo; y un "acil aromático"oxi "grupo alquilo inferior" tal como un grupo benzoiloximetilo; un "grupo (alcoxicarboniloxi)alquilo" tal como un

grupo metoxicarboniloximetilo, etoxicarboniloximetilo, propoxicarboniloximetilo, isopropoxicarboniloximetilo, butoxicarboniloximetilo, isobutoxicarboniloximetilo, pentiloxicarboniloximetilo, hexiloxicarboniloximetilo, ciclohexiloxicarboniloximetilo, ciclohexiloxicarboniloxi(ciclohexil)metilo, 1-(metoxicarboniloxi)etilo, 1-(etoxicarboniloxi)etilo, 1-propoxicarboniloxietilo, 1-(isopropoxicarboniloxi)etilo, 1-butoxicarboniloxietilo, 1-isobutoxicarboniloxietilo, 1-(tert-butoxicarboniloxi)etilo, 1-pentiloxicarboniloxietilo, 1-hexiloxicarboniloxietilo, 1-ciclopentiloxicarboniloxietilo, 1-ciclopentiloxicarboniloxipropilo, 1-ciclohexiloxicarboniloxipropilo, 1-ciclopentiloxicarboniloxibutilo, 1-ciclohexiloxicarboniloxibutilo, 1-(ciclohexiloxicarboniloxi)etilo, 1-(etoxicarboniloxi)propilo, 2-metoxicarboniloxietilo, 2-etoxicarboniloxietilo, 2-propoxicarboniloxietilo, 2-isopropoxicarboniloxietilo, 2-butoxicarboniloxietilo, 2-isobutoxicarboniloxietilo, 2-pentiloxicarboniloxietilo, 2-hexiloxicarboniloxietilo, 1-metoxicarboniloxipropilo, 1-etoxicarboniloxipropilo, 1-propoxicarboniloxipropilo, 1-isopropoxicarboniloxipropilo, 1-butoxicarboniloxipropilo, 1-isobutoxicarboniloxipropilo, 1-pentiloxicarboniloxipropilo, 1-hexiloxicarboniloxipropilo, 1-metoxicarboniloxibutilo, 1-etoxicarboniloxibutilo, 1-propoxicarboniloxibutilo, 1-isopropoxicarboniloxibutilo, 1-butoxicarboniloxibutilo, 1-isobutoxicarboniloxibutilo, 1-metoxicarboniloxipentilo, 1-etoxicarboniloxipentilo, 1-metoxicarboniloxihexilo o 1-etoxicarboniloxihexilo; un "grupo carboniloxialquilo", incluyendo un grupo oxodioxolenilmetilo tal como un grupo (5-fenil-2-oxo-1,3-dioxolen-4-il)metilo, [5-(4-metilfenil)-2-oxo-1,3-dioxolen-4-il]metilo, [5-(4-metoxifenil)-2-oxo-1,3-dioxolen-4-il]metilo, [5-(4-fluorofenil)-2-oxo-1,3-dioxolen-4-il]metilo, [5-(4-clorofenil)-2-oxo-1,3-dioxolen-4-

il]metilo, (2-oxo-1,3-dioxolen-4-il)metilo, (5-metil-2-oxo-1,3-dioxolen-4-il)metilo, (5-etil-2-oxo-1,3-dioxolen-4-il)metilo, (5-propil-2-oxo-1,3-dioxolen-4-il)metilo, (5-isopropil-2-oxo-1,3-dioxolen-4-il)metilo o (5-butil-2-oxo-1,3-dioxolen-4-il)metilo; un "grupo ftalidilo" tal como un grupo ftalidilo, dimetilftalidilo o dimetoxi ftalidilo; un "grupo arilo" tal como un grupo fenilo e indanilo; un "grupo carboxialquilo" tal como un grupo carboximetilo; o un "grupo residual que forma una amida de aminoácido" tal como una fenilalanina, y preferiblemente es un grupo que forma ésteres aceptables farmacológicamente tal como un "grupo alquilo", "grupo alcoxialquilo", "grupo carboniloxialquilo" o grupo (alcoxicarboniloxi)alquilo; más preferiblemente un "grupo alquilo de 1 a 6 átomos de carbono" tal como un grupo metilo, etilo, n-propilo, isopropilo, n-butilo, isobutilo, s-butilo, tert-butilo, n-pentilo, isopentilo, 2-metilbutilo, neopentilo, 1-etilpropilo, n-hexilo, 4-metilpentilo, 3-metilpentilo, 2-metilpentilo o 1-metilpentil; y en particular preferiblemente metilo o etilo.

Cuando los compuestos (I) de la presente invención contienen un grupo hidroxilo en sus estructuras, el grupo funcional empleado para formar un profármaco de él puede ser, por ejemplo, un "grupo acilo alifático", incluyendo un grupo alquilcarbonilo tal como un grupo formilo, acetilo, propionilo, butirilo, isobutirilo, pentanoilo, pivaloilo, valerilo, isovalerilo, octanoilo, nonanoilo, decanoilo, 3-metilnonanoilo, 8-metilnonanoilo, 3-etiloctanoilo, 3,7-dimetiloctanoilo, undecanoilo, dodecanoilo, tridecanoilo, tetradecanoilo, pentadecanoilo, hexadecanoilo, 1-metilpentadecanoilo, 14-metilpentadecanoilo, 13,13-dimetiltetradecanoilo, heptadecanoilo, 15-metilhexadecanoilo, octadecanoilo, 1-metilheptadecanoilo, nonadecanoilo, icosanoilo o henicosanoilo; un grupo alquilcarbonilo carboxilado tal como un grupo succinoilo, glutaroilo o adipoilo; un grupo alquilcarbonilo inferior halogenado tal como un grupo cloroacetilo, dicloroacetilo, tricloroacetilo o trifluoroacetilo; un grupo

alcoxi inferior alquilcarbonilo inferior tal como un grupo metoxiacetilo; y un grupo alquilcarbonilo insaturado tal como un grupo (E)-2-metil-2-butenoilo (preferiblemente un grupo alcanoilo de 1 a 6 átomos de carbono); un "grupo acilo aromático", incluyendo un grupo arilcarbonilo tal como un grupo benzoilo, α-naftoilo o β-naftoilo; un grupo arilcarbonilo halogenado tal como un grupo 2-bromobenzoilo o 4-clorobenzoilo group; un grupo arilcarbonilo inferior alquilado tal como un grupo 2,4,6-trimetilbenzoilo o 4-toluoilo; un grupo arilcarbonilo inferior alcoxilado tal como un grupo 4-anisoilo; un grupo arilcarbonilo carboxilado tal como un grupo 2-carboxibenzoilo, 3-carboxibenzoilo o 4-carboxibenzoilo; un grupo arilcarbonilo nitrado tal como un grupo 4-nitrobenzoilo o 2-nitrobenzoilo; un grupo arilcarbonilo inferior alcoxicarbonilado tal como un grupo 2-(metoxicarbonil)benzoilo; y un grupo arilcarbonilo arilado tal como un grupo 4-fenilbenzoilo; un "grupo carboniloxialquilo", incluyendo un grupo aciloxialquilo tal como un grupo etilcarboniloximetilo, pivaloiloximetilo, dimetilaminoacetiloximetilo o 1-acetoxietilo; un grupo 1-(alcoxicarboniloxi)alquilo tal como un grupo 1-(metoxicarboniloxi)etilo, 1-(etoxicarboniloxi)etilo, etoxicarboniloximetilo, 1-(isopropoxicarboniloxi)etilo, 1-(t-butoxicarboniloxi)etilo, 1-(etoxicarboniloxi)propilo o 1-(ciclohexiloxicarboniloxi)etilo; un grupo ftalidilo; y un grupo oxodioxolenilmetilo tal como un grupo 4-metil-oxodioxolenilmetilo, 4-fenil-oxodioxolenilmetilo o oxodioxolenilmetilo; un "grupo residual de una sal de un semi éster de ácido succínico"; un "grupo residual de una sal de un semi éster de ácido fosfórico"; un "grupo residual que forma un éster de aminoácido"; un grupo carbamoilo; un grupo carbamoilo sustituido con 1 o 2 grupos alquilo inferior; o un "grupo carboniloxialquiloxicarbonilo" tal como un grupo pivaloiloximetiloxicarbonilo, y preferiblemente es un grupo que forma

un éster aceptable farmacológicamente tal como un "grupo acilo alifático" o un "grupo acilo aromático", más preferiblemente un "grupo alcanoilo de 1 a 6 átomos de carbono" tal como un grupo acetilo, propionilo, butirilo, isobutirilo, pentanoilo o pivaloilo; y en particular preferiblemente un grupo acetilo.

Cuando los compuestos (I) de la presente invención contienen un grupo amino en sus estructuras, el grupo funcional empleado para formar un profármaco de él puede ser, por ejemplo, un grupo acilo alifático, incluyendo un grupo alcanoilo tal como un grupo formilo, acetilo, propionilo, butirilo, isobutirilo, pentanoilo, pivaloilo, valerilo, isovalerilo, octanoilo, lauroilo, palmitoilo o estearoilo; un grupo alquilcarbonilo inferior halogenado tal como un grupo cloroacetilo, dicloroacetilo, tricloroacetilo o trifluoroacetilo; un grupo alcoxi inferior alquilcarbonilo inferior tal como un grupo metoxiacetilo; y un grupo alquilcarbonilo insaturado tal como un grupo (E)-2-metil-2-butenoilo (preferiblemente un grupo alcanoilo de 1 a 6 átomos de carbono); un grupo acilo aromático, incluyendo un grupo arilcarbonilo tal como un grupo benzoilo, α-naftoilo o β-naftoilo, un grupo arilcarbonilo halogenado tal como un grupo 2-bromobenzoilo o 4-clorobenzoilo, un grupo arilcarbonilo inferior alquilado tal como un grupo 2,4,6-trimetilbenzoilo o 4-toluoilo, un grupo arilcarbonilo inferior alcoxilado tal como un grupo 4-anisoilo, un grupo arilcarbonilo nitrado tal como a 4-nitrobenzoilo o 2-nitrobenzoilo group, un grupo arilcarbonilo inferior alcoxicarbonilado tal como un grupo 2-(metoxicarbonil)benzoilo, y un grupo arilcarbonilo arilado tal como un grupo 4-fenilbenzoilo; un grupo alcoxicarbonilo, incluyendo un grupo alcoxicarbonilo inferior tal como un grupo metoxicarbonilo, etoxicarbonilo, t-butoxicarbonilo o isobutoxicarbonilo, y un grupo alcoxicarbonilo inferior sustituido con átomo(s) de halógeno o grupo(s) tri-alquilsililo inferior, tal como un grupo 2,2,2-tricloroetoxicarbonilo o 2-trimetilsililetoxicarbonilo; un grupo

alqueniloxicarbonilo tal como un grupo viniloxicarbonilo o aliloxicarbonilo; o un grupo ariloxicarbonilo, de los cuales un anillo arilo puede estar sustituido con 1 o 2 grupo(s) alcoxi inferiores, grupo(s) nitro o átomo(s) de halógeno, tal como un grupo fenoxicarbonilo, 4-metoxifenoxicarbonilo, 3,4-dimetoxifenoxicarbonilo, 2-nitrofenoxicarbonilo, 4-nitrofenoxicarbonilo o 4-fluorofenoxicarbonilo, y preferiblemente es un grupo alcanoilo de 1 a 6 átomos de carbono.

El "profármaco" de los compuestos de la fórmula (I) preferiblemente es un éster aceptable farmacológicamente de ellos, que se prepara convirtiendo el grupo sulfanilo, el grupo carboxi o el grupo hidroxilo contenido en dichos compuestos, respectivamente.

Las "sales de ellos aceptables farmacológicamente" significan una sal que se prepara a partir de los compuestos (I) de la presente invención. Esta sal preferiblemente es una sal metálica, incluyendo una sal de metal alcalino tal como sal de sodio, sal de potasio o sal de litio, una sal de metal alcalino térreo tal como sal de calcio o sal de magnesio, una sal de aluminio, una sal de hierro, una sal de zinc, una sal de cobre, una sal de níquel y una sal de cobalto; una sal de amina, incluyendo una sal inorgánica tal como sal de aluminio, una sal orgánica tal como una sal de t-octilamina, sal de dibencilamina, sal de morfolina, sal de glucosamina, sal de éster alquílico de fenilglicina, sal de etilendiamina, sal de N-meitilglucamina, sal de guanidina, sal de dietilamina, sal de trietilamina, sal de diciclohexilamina, sal de N,N'-dibenciletilenodiamina, sal de cloroprocaína, sal de procaína, sal de dietanolamina, sal de N-bencil-fenetilamina, sal de piperazina, sal de tetrametilamonio o sal de tris(hidroximetil)aminometano; una sal de ácido inorgánico, incluyendo una sal hidrohalógena tal como fluorhidrato, clorhidrato, bromhidrato o yodhidrato, un nitrato, un perclorato, un sulfato y un fosfato; una sal de ácido orgánico, incluyendo un alcanosulfonato

inferior tal como metanosulfonato, trifluorometanosulfonato o etanosulfonato, un arilsulfonato tal como un bencenosulfonato o p-toluenosulfonato, un acetato, un malato, un fumarato, un succinato, un citrato, un tartrato, un oxalato, un maleato y un trifluoroacetato; o una sal de aminoácido tal como sal de glicina, sal de lisina, sal de arginina, sal de ornitina, glutamato o aspartato, y más preferiblemente una sal de ácido inorgánico o una sal de ácido orgánico. Además, los compuestos (I) de la presente invención pueden existir como un hidrato o un solvato de ellos.

Los ejemplos preferidos de los compuestos de la fórmula general (I) pueden ser los que se muestran específicamente en las tablas 1-6, pero el alcance de la presente invención no debe ser limitado a estos compuestos.

El significado de las abreviaturas en las siguientes Tablas es el que se muestra a continuación.

Ac:	grupo acetilo,
Me:	grupo metilo,
Et:	grupo etilo,
iPr:	grupo isopropilo,
1-Pyza:	grupo pirazol-1-ilo,
3-Pyza:	grupo pirazol-3-ilo,
4-Pyza:	grupo pirazol-4-ilo,
5-Pyza:	grupo pirazol-5-ilo,
1-Triz:	grupo 1,2,3-triazol-1-ilo,
2-Triz:	grupo 1,2,3-triazol-2-ilo,
4-Triz:	grupo 1,2,3-triazol-4-ilo,
5-Triz:	grupo 1,2,3-triazol-5-ilo,
1-Tez:	grupo tetrazol-1-ilo,
2-Tez:	grupo tetrazol-2-ilo,
5-Tez:	grupo tetrazol-5-ilo,
1-Pird:	grupo pirrolidino,

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1-Pip: grupo piperidino,

4-Pip: grupo piperidin-4-ilo,

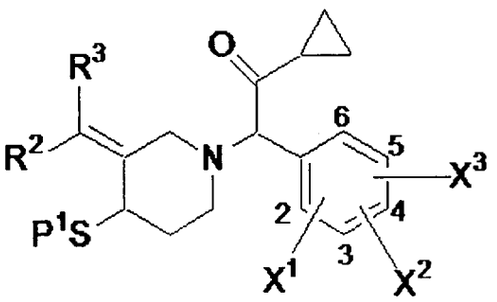
Mor: grupo morfolino,

Thim: grupo tiomorfolino,

1-Piz: grupo piperazino, y

2,5-dioxo-1-Pip: grupo 2,5-dioxo-1-piperidino.

(Tabla 1)



Comp. No.	P^1	R^2	R^3	X^1	X^2	X^3
1-1	H	H	CH_2-1-Pyza	2-F	H	H
1-2	Ac	H	CH_2-1-Pyza	2-F	H	H
1-3	H	H	CH_2-1-Pyza	2-F	4-F	H
1-4	Ac	H	CH_2-1-Pyza	2-F	4-F	H
1-5	H	H	CH_2-(3-CO_2H-1-Pyza)	2-F	H	H
1-6	Ac	H	CH_2-(3-CO_2H-1-Pyza)	2-F	H	H
1-7	H	H	CH_2-(3-CO_2H-1-Pyza)	2-F	4-F	H
1-8	Ac	H	CH_2-(3-CO_2H-1-Pyza)	2-F	4-F	H
1-9	H	H	CH_2-(3-CO_2Me-1-Pyza)	2-F	H	H
1-10	Ac	H	CH_2-(3-CO_2Me-1-Pyza)	2-F	H	H
1-11	H	H	CH_2-(3-CO_2Me-1-Pyza)	2-F	4-F	H
1-12	Ac	H	CH_2-(3-CO_2Me-1-Pyza)	2-F	4-F	H
1-13	H	H	CH_2-(3-CO_2Et-1-Pyza)	2-F	H	H
1-14	Ac	H	CH_2-(3-CO_2Et-1-Pyza)	2-F	H	H
1-15	H	H	CH_2-(3-CO_2Et-1-Pyza)	2-F	4-F	H
1-16	Ac	H	CH_2-(3-CO_2Et-1-Pyza)	2-F	4-F	H

1-17	H	H	CH_2-(4-CO_2H-1-Pyza)	2-F	H	H
1-18	Ac	H	CH_2-(4-CO_2H-1-Pyza)	2-F	H	H
1-19	H	H	CH_2-(4-CO_2H-1-Pyza)	2-F	4-F	H
1-20	Ac	H	CH_2-(4-CO_2H-1-Pyza)	2-F	4-F	H
1-21	H	H	CH_2-(4-CO_2Me-1-Pyza)	2-F	H	H
1-22	Ac	H	CH_2-(4-CO_2Me-1-Pyza)	2-F	H	H
1-23	H	H	CH_2-(4-CO_2Me-1-Pyza)	2-F	4-F	H
1-24	Ac	H	CH_2-(4-CO_2Me-1-Pyza)	2-F	4-F	H
1-25	H	H	CH_2-(4-CO_2Et-1-Pyza)	2-F	H	H
1-26	Ac	H	CH_2-(4-CO_2Et-1-Pyza)	2-F	H	H
1-27	H	H	CH_2-(4-CO_2Et-1-Pyza)	2-F	4-F	H
1-28	Ac	H	CH_2-(4-CO_2Et-1-Pyza)	2-F	4-F	H
1-29	H	H	CH_2-(5-CO_2H-1-Pyza)	2-F	H	H
1-30	Ac	H	CH_2-(5-CO_2H-1-Pyza)	2-F	H	H
1-31	H	H	CH_2-(5-CO_2H-1-Pyza)	2-F	4-F	H
1-32	Ac	H	CH_2-(5-CO_2H-1-Pyza)	2-F	4-F	H
1-33	H	H	CH_2-(5-CO_2Me-1-Pyza)	2-F	H	H
1-34	Ac	H	CH_2-(5-CO_2Me-1-Pyza)	2-F	H	H
1-35	H	H	CH_2-(5-CO_2Me-1-Pyza)	2-F	4-F	H
1-36	Ac	H	CH_2-(5-CO_2Me-1-Pyza)	2-F	4-F	H
1-37	H	H	CH_2-(5-CO_2Et-1-Pyza)	2-F	H	H
1-38	Ac	H	CH_2-(5-CO_2Et-1-Pyza)	2-F	H	H
1-39	H	H	CH_2-(5-CO_2Et-1-Pyza)	2-F	4-F	H
1-40	Ac	H	CH_2-(5-CO_2Et-1-Pyza)	2-F	4-F	H
1-41	H	H	CH_2-(3-CH_2CO_2H-1-Pyza)	2-F	H	H
1-42	Ac	H	CH_2-(3-CH_2CO_2H-1-Pyza)	2-F	H	H
1-43	H	H	CH_2-(3-CH_2CO_2H-1-Pyza)	2-F	4-F	H
1-44	Ac	H	CH_2-(3-CH_2CO_2H-1-Pyza)	2-F	4-F	H
1-45	H	H	CH_2-(3-CH_2CO_2Me-1-Pyza)	2-F	H	H
1-46	Ac	H	CH_2-(3-CH_2CO_2Me-1-Pyza)	2-F	H	H
1-47	H	H	CH_2-(3-CH_2CO_2Me-1-Pyza)	2-F	4-F	H

1-48	Ac	H	CH_2-(3-CH_2CO_2Me-1-Pyza)	2-F	4-F	H
1-49	H	H	CH_2-(3-CH_2CO_2Et-1-Pyza)	2-F	H	H
1-50	Ac	H	CH_2-(3-CH_2CO_2Et-1-Pyza)	2-F	H	H
1-51	H	H	CH_2-(3-CH_2CO_2Et-1-Pyza)	2-F	4-F	H
1-52	Ac	H	CH_2-(3-CH_2CO_2Et-1-Pyza)	2-F	4-F	H
1-53	H	H	CH_2-(4-CH_2CO_2H-1-Pyza)	2-F	H	H
1-54	Ac	H	CH_2-(4-CH_2CO_2H-1-Pyza)	2-F	H	H
1-55	H	H	CH_2-(4-CH_2CO_2H-1-Pyza)	2-F	4-F	H
1-56	Ac	H	CH_2-(4-CH_2CO_2H-1-Pyza)	2-F	4-F	H
1-57	H	H	CH_2-(4-CH_2CO_2Me-1-Pyza)	2-F	H	H
1-58	Ac	H	CH_2-(4-CH_2CO_2Me-1-Pyza)	2-F	H	H
1-59	H	H	CH_2-(4-CH_2CO_2Me-1-Pyza)	2-F	4-F	H
1-60	Ac	H	CH_2-(4-CH_2CO_2Me-1-Pyza)	2-F	4-F	H
1-61	H	H	CH_2-(4-CH_2CO_2Et-1-Pyza)	2-F	H	H
1-62	Ac	H	CH_2-(4-CH_2CO_2Et-1-Pyza)	2-F	H	H
1-63	H	H	CH_2-(4-CH_2CO_2Et-1-Pyza)	2-F	4-F	H
1-64	Ac	H	CH_2-(4-CH_2CO_2Et-1-Pyza)	2-F	4-F	H
1-65	H	H	CH_2-(5-CH_2CO_2H-1-Pyza)	2-F	H	H
1-66	Ac	H	CH_2-(5-CH_2CO_2H-1-Pyza)	2-F	H	H
1-67	H	H	CH_2-(5-CH_2CO_2H-1-Pyza)	2-F	4-F	H
1-68	Ac	H	CH_2-(5-CH_2CO_2H-1-Pyza)	2-F	4-F	H
1-69	H	H	CH_2-(5-CH_2CO_2Me-1-Pyza)	2-F	H	H
1-70	Ac	H	CH_2-(5-CH_2CO_2Me-1-Pyza)	2-F	H	H
1-71	H	H	CH_2-(5-CH_2CO_2Me-1-Pyza)	2-F	4-F	H
1-72	Ac	H	CH_2-(5-CH_2CO_2Me-1-Pyza)	2-F	4-F	H
1-73	H	H	CH_2-(5-CH_2CO_2Et-1-Pyza)	2-F	H	H
1-74	Ac	H	CH_2-(5-CH_2CO_2Et-1-Pyza)	2-F	H	H
1-75	H	H	CH_2-(5-CH_2CO_2Et-1-Pyza)	2-F	4-F	H
1-76	Ac	H	CH_2-(5-CH_2CO_2Et-1-Pyza)	2-F	4-F	H
1-77	H	H	CH_2-(3-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
1-78	Ac	H	CH_2-(3-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H

1-79	H	H	CH_2-(3-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
1-80	Ac	H	CH_2-(3-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
1-81	H	H	CH_2-(3-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
1-82	Ac	H	CH_2-(3-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
1-83	H	H	CH_2-(4-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
1-84	Ac	H	CH_2-(4-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
1-85	H	H	CH_2-(4-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
1-86	Ac	H	CH_2-(4-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
1-87	H	H	CH_2-(4-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
1-88	Ac	H	CH_2-(4-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
1-89	H	H	CH_2-(5-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
1-90	Ac	H	CH_2-(5-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
1-91	H	H	CH_2-(5-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
1-92	Ac	H	CH_2-(5-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
1-93	H	H	CH_2-(5-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
1-94	Ac	H	CH_2-(5-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
1-95	H	H	CH_2-(3-$CH_2CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
1-96	Ac	H	CH_2-(3-$CH_2CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
1-97	H	H	CH_2-(3-$CH_2CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
1-98	Ac	H	CH_2-(3-$CH_2CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
1-99	H	H	CH_2-(3-$CH_2CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
1-100	Ac	H	CH_2-(3-$CH_2CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
1-101	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
1-102	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
1-103	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
1-104	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
1-105	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
1-106	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
1-107	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
1-108	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
1-109	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H

1-110	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
1-111	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
1-112	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
1-113	H	H	CH_2CH_2-1-Pyza	2-F	H	H
1-114	Ac	H	CH_2CH_2-1-Pyza	2-F	H	H
1-115	H	H	CH_2CH_2-(3-CO_2H-1-Pyza)	2-F	H	H
1-116	Ac	H	CH_2CH_2-(3-CO_2H-1-Pyza)	2-F	H	H
1-117	H	H	CH_2CH_2-(3-CO_2Me-1-Pyza)	2-F	H	H
1-118	Ac	H	CH_2CH_2-(3-CO_2Me-1-Pyza)	2-F	H	H
1-119	H	H	CH_2CH_2-(3-CO_2Et-1-Pyza)	2-F	H	H
1-120	Ac	H	CH_2CH_2-(3-CO_2Et-1-Pyza)	2-F	H	H
1-121	H	H	CH_2CH_2-(4-CO_2H-1-Pyza)	2-F	H	H
1-122	Ac	H	CH_2CH_2-(4-CO_2H-1-Pyza)	2-F	H	H
1-123	H	H	CH_2CH_2-(4-CO_2Me-1-Pyza)	2-F	H	H
1-124	Ac	H	CH_2CH_2-(4-CO_2Me-1-Pyza)	2-F	H	H
1-125	H	H	CH_2CH_2-(4-CO_2Et-1-Pyza)	2-F	H	H
1-126	Ac	H	CH_2CH_2-(4-CO_2Et-1-Pyza)	2-F	H	H
1-127	H	H	CH_2CH_2-(5-CO_2H-1-Pyza)	2-F	H	H
1-128	Ac	H	CH_2CH_2-(5-CO_2H-1-Pyza)	2-F	H	H
1-129	H	H	CH_2CH_2-(5-CO_2Me-1-Pyza)	2-F	H	H
1-130	Ac	H	CH_2CH_2-(5-CO_2Me-1-Pyza)	2-F	H	H
1-131	H	H	CH_2CH_2-(5-CO_2Et-1-Pyza)	2-F	H	H
1-132	Ac	H	CH_2CH_2-(5-CO_2Et-1-Pyza)	2-F	H	H
1-133	H	H	CH_2CH_2-(3-CH_2CO_2H-1-Pyza)	2-F	H	H
1-134	Ac	H	CH_2CH_2-(3-CH_2CO_2H-1-Pyza)	2-F	H	H
1-135	H	H	CH_2CH_2-(3-CH_2CO_2Me-1-Pyza)	2-F	H	H
1-136	Ac	H	CH_2CH_2-(3-CH_2CO_2Me-1-Pyza)	2-F	H	H
1-137	H	H	CH_2CH_2-(3-CH_2CO_2Et-1-Pyza)	2-F	H	H
1-138	Ac	H	CH_2CH_2-(3-CH_2CO_2Et-1-Pyza)	2-F	H	H
1-139	H	H	CH_2CH_2-(4-CH_2CO_2H-1-Pyza)	2-F	H	H
1-140	Ac	H	CH_2CH_2-(4-CH_2CO_2H-1-Pyza)	2-F	H	H

1-141	H	H	CH_2CH_2-(4-CH_2CO_2Me-1-Pyza)	2-F	H	H
1-142	Ac	H	CH_2CH_2-(4-CH_2CO_2Me-1-Pyza)	2-F	H	H
1-143	H	H	CH_2CH_2-(4-CH_2CO_2Et-1-Pyza)	2-F	H	H
1-144	Ac	H	CH_2CH_2-(4-CH_2CO_2Et-1-Pyza)	2-F	H	H
1-145	H	H	CH_2CH_2-(5-CH_2CO_2H-1-Pyza)	2-F	H	H
1-146	Ac	H	CH_2CH_2-(5-CH_2CO_2H-1-Pyza)	2-F	H	H
1-147	H	H	CH_2CH_2-(5-CH_2CO_2Me-1-Pyza)	2-F	H	H
1-148	Ac	H	CH_2CH_2-(5-CH_2CO_2Me-1-Pyza)	2-F	H	H
1-149	H	H	CH_2CH_2-(5-CH_2CO_2Et-1-Pyza)	2-F	H	H
1-150	Ac	H	CH_2CH_2-(5-CH_2CO_2Et-1-Pyza)	2-F	H	H
1-151	H	H	CH_2CH_2-(3-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
1-152	Ac	H	CH_2CH_2-(3-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
1-153	H	H	CH_2CH_2-(3-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
1-154	Ac	H	CH_2CH_2-(3-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
1-155	H	H	CH_2CH_2-(3-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
1-156	Ac	H	CH_2CH_2-(3-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
1-157	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
1-158	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
1-159	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
1-160	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
1-161	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
1-162	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
1-163	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
1-164	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
1-165	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
1-166	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
1-167	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2Et$-1-Pyza	2-F	H	H
1-168	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
1-169	H	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
1-170	Ac	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
1-171	H	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H

1-172	Ac	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
1-173	H	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
1-174	Ac	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
1-175	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
1-176	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
1-177	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
1-178	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
1-179	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
1-180	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
1-181	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
1-182	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
1-183	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
1-184	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
1-185	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
1-186	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
1-187	H	H	CH_2-3-Pyza	2-F	H	H
1-188	Ac	H	CH_2-3-Pyza	2-F	H	H
1-189	H	H	CH_2-3-Pyza	2-F	4-F	H
1-190	Ac	H	CH_2-3-Pyza	2-F	4-F	H
1-191	H	H	CH_2-(1-CO_2Me-3-Pyza)	2-F	H	H
1-192	Ac	H	CH_2-(1-CO_2Me-3-Pyza)	2-F	H	H
1-193	H	H	CH_2-(1-CO_2Et-3-Pyza)	2-F	H	H
1-194	Ac	H	CH_2-(1-CO_2Et-3-Pyza)	2-F	H	H
1-195	H	H	CH_2-(4-CO_2H-3-Pyza)	2-F	H	H
1-196	Ac	H	CH_2-(4-CO_2H-3-Pyza)	2-F	H	H
1-197	H	H	CH_2-(4-CO_2Me-3-Pyza)	2-F	H	H
1-198	Ac	H	CH_2-(4-CO_2Me-3-Pyza)	2-F	H	H
1-199	H	H	CH_2-(4-CO_2Et-3-Pyza)	2-F	H	H
1-200	Ac	H	CH_2-(4-CO_2Et-3-Pyza)	2-F	H	H
1-201	H	H	CH_2-(5-CO_2H-3-Pyza)	2-F	H	H
1-202	Ac	H	CH_2-(5-CO_2H-3-Pyza)	2-F	H	H

1-203	H	H	CH_2-(5-CO_2Me-3-Pyza)	2-F	H	H
1-204	Ac	H	CH_2-(5-CO_2Me-3-Pyza)	2-F	H	H
1-205	H	H	CH_2-(5-CO_2Et-3-Pyza)	2-F	H	H
1-206	Ac	H	CH_2-(5-CO_2Et-3-Pyza)	2-F	H	H
1-207	H	H	CH_2-(1-CH_2CO_2H-3-Pyza)	2-F	H	H
1-208	Ac	H	CH_2-(1-CH_2CO_2H-3-Pyza)	2-F	H	H
1-209	H	H	CH_2-(1-CH_2CO_2Me-3-Pyza)	2-F	H	H
1-210	Ac	H	CH_2-(1-CH_2CO_2Me-3-Pyza)	2-F	H	H
1-211	H	H	CH_2-(1-CH_2CO_2Et-3-Pyza)	2-F	H	H
1-212	Ac	H	CH_2-(1-CH_2CO_2Et-3-Pyza)	2-F	H	H
1-213	H	H	CH_2-(4-CH_2CO_2H-3-Pyza)	2-F	H	H
1-214	Ac	H	CH_2-(4-CH_2CO_2H-3-Pyza)	2-F	H	H
1-215	H	H	CH_2-(4-CH_2CO_2Me-3-Pyza)	2-F	H	H
1-216	Ac	H	CH_2-(4-CH_2CO_2Me-3-Pyza)	2-F	H	H
1-217	H	H	CH_2-(4-CH_2CO_2Et-3-Pyza)	2-F	H	H
1-218	Ac	H	CH_2-(4-CH_2CO_2Et-3-Pyza)	2-F	H	H
1-219	H	H	CH_2-(5-CH_2CO_2H-3-Pyza)	2-F	H	H
1-220	Ac	H	CH_2-(5-CH_2CO_2H-3-Pyza)	2-F	H	H
1-221	H	H	CH_2-(5-CH_2CO_2Me-3-Pyza)	2-F	H	H
1-222	Ac	H	CH_2-(5-CH_2CO_2Me-3-Pyza)	2-F	H	H
1-223	H	H	CH_2-(5-CH_2CO_2Et-3-Pyza)	2-F	H	H
1-224	Ac	H	CH_2-(5-CH_2CO_2Et-3-Pyza)	2-F	H	H
1-225	H	H	CH_2-(1-$CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
1-226	Ac	H	CH_2-(1-$CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
1-227	H	H	CH_2-(1-$CH_2CH_2CO_2$Me-3-Pyza)	2-F	H	H
1-228	Ac	H	CH_2-(1-$CH_2CH_2CO_2$Me-3-Pyza)	2-F	H	H
1-229	H	H	CH_2-(1-$CH_2CH_2CO_2$Et-3-Pyza)	2-F	H	H
1-230	Ac	H	CH_2-(1-$CH_2CH_2CO_2$Et-3-Pyza)	2-F	H	H
1-231	H	H	CH_2-(4-$CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
1-232	Ac	H	CH_2-(4-$CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
1-233	H	H	CH_2-(4-$CH_2CH_2CO_2$Me-3-Pyza)	2-F	H	H

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1-234	Ac	H	CH_2-(4-$CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
1-235	H	H	CH_2-(4-$CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
1-236	Ac	H	CH_2-(4-$CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
1-237	H	H	CH_2-(5-$CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
1-238	Ac	H	CH_2-(5-$CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
1-239	H	H	CH_2-(5-$CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
1-240	Ac	H	CH_2-(5-$CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
1-241	H	H	CH_2-(5-$CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
1-242	Ac	H	CH_2-(5-$CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
1-245	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
1-246	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
1-247	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
1-248	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
1-249	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
1-250	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
1-251	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
1-252	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
1-253	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
1-254	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
1-255	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
1-256	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
1-257	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
1-258	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
1-259	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
1-260	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
1-261	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
1-262	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
1-263	H	H	CH_2CH_2-3-Pyza	2-F	H	H
1-264	Ac	H	CH_2CH_2-3-Pyza	2-F	H	H
1-265	H	H	CH_2CH_2-3-Pyza	2-F	4-F	H
1-266	Ac	H	CH_2CH_2-3-Pyza	2-F	4-F	H

1-267	H	H	CH_2CH_2-(1-CO_2Me-3-Pyza)	2-F	H	H
1-268	Ac	H	CH_2CH_2-(1-CO_2Me-3-Pyza)	2-F	H	H
1-269	H	H	CH_2CH_2-(1-CO_2Et-3-Pyza)	2-F	H	H
1-270	Ac	H	CH_2CH_2-(1-CO_2Et-3-Pyza)	2-F	H	H
1-271	H	H	CH_2CH_2-(4-CO_2H-3-Pyza)	2-F	H	H
1-272	Ac	H	CH_2CH_2-(4-CO_2H-3-Pyza)	2-F	H	H
1-273	H	H	CH_2CH_2-(4-CO_2Me-3-Pyza)	2-F	H	H
1-274	Ac	H	CH_2CH_2-(4-CO_2Me-3-Pyza)	2-F	H	H
1-275	H	H	CH_2CH_2-(4-CO_2Et-3-Pyza)	2-F	H	H
1-276	Ac	H	CH_2CH_2-(4-CO_2Et-3-Pyza)	2-F	H	H
1-277	H	H	CH_2CH_2-(5-CO_2H-3-Pyza)	2-F	H	H
1-278	Ac	H	CH_2CH_2-(5-CO_2H-3-Pyza)	2-F	H	H
1-279	H	H	CH_2CH_2-(5-CO_2Me-3-Pyza)	2-F	H	H
1-280	Ac	H	CH_2CH_2-(5-CO_2Me-3-Pyza)	2-F	H	H
1-281	H	H	CH_2CH_2-(5-CO_2Et-3-Pyza)	2-F	H	H
1-282	Ac	H	CH_2CH_2-(5-CO_2Et-3-Pyza)	2-F	H	H
1-283	H	H	CH_2CH_2-(1-CH_2CO_2H-3-Pyza)	2-F	H	H
1-284	Ac	H	CH_2CH_2-(1-CH_2CO_2H-3-Pyza)	2-F	H	H
1-285	H	H	CH_2CH_2-(1-CH_2CO_2Me-3-Pyza)	2-F	H	H
1-286	Ac	H	CH_2CH_2-(1-CH_2CO_2Me-3-Pyza)	2-F	H	H
1-287	H	H	CH_2CH_2-(1-CH_2CO_2Et-3-Pyza)	2-F	H	H
1-288	Ac	H	CH_2CH_2-(1-CH_2CO_2Et-3-Pyza)	2-F	H	H
1-289	H	H	CH_2CH_2-(4-CH_2CO_2H-3-Pyza)	2-F	H	H
1-290	Ac	H	CH_2CH_2-(4-CH_2CO_2H-3-Pyza)	2-F	H	H
1-291	H	H	CH_2CH_2-(4-CH_2CO_2Me-3-Pyza)	2-F	H	H
1-292	Ac	H	CH_2CH_2-(4-CH_2CO_2Me-3-Pyza)	2-F	H	H
1-293	H	H	CH_2CH_2-(4-CH_2CO_2Et-3-Pyza)	2-F	H	H
1-294	Ac	H	CH_2CH_2-(4-CH_2CO_2Et-3-Pyza)	2-F	H	H
1-295	H	H	CH_2CH_2-(5-CH_2CO_2H-3-Pyza)	2-F	H	H
1-296	Ac	H	CH_2CH_2-(5-CH_2CO_2H-3-Pyza)	2-F	H	H
1-297	H	H	CH_2CH_2-(5-CH_2CO_2Me-3-Pyza)	2-F	H	H

1-298	Ac	H	CH_2CH_2-(5-CH_2CO_2Me-3-Pyza)	2-F	H	H
1-299	H	H	CH_2CH_2-(5-CH_2CO_2Et-3-Pyza)	2-F	H	H
1-300	Ac	H	CH_2CH_2-(5-CH_2CO_2Et-3-Pyza)	2-F	H	H
1-301	H	H	CH_2CH_2-(1-$CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
1-302	Ac	H	CH_2CH_2-(1-$CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
1-303	H	H	CH_2CH_2-(1-$CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
1-304	Ac	H	CH_2CH_2-(1-$CH_2CH_2CO_2Me$-3-Pyza	2-F	H	H
1-305	H	H	CH_2CH_2-(1-$CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
1-306	Ac	H	CH_2CH_2-(1-$CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
1-307	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
1-308	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
1-309	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
1-310	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-3-Pyza	2-F	H	H
1-311	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
1-312	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
1-313	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
1-314	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
1-315	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
1-316	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
1-317	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
1-318	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
1-319	H	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
1-320	Ac	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
1-321	H	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
1-322	Ac	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
1-323	H	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
1-324	Ac	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
1-325	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
1-326	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
1-327	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
1-328	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H

1-329	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
1-330	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
1-331	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
1-332	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
1-333	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
1-334	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
1-335	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
1-336	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
1-337	H	H	CH_2-4-Pyza	2-F	H	H
1-338	Ac	H	CH_2-4-Pyza	2-F	H	H
1-339	H	H	CH_2-4-Pyza	2-F	4-F	H
1-340	Ac	H	CH_2-4-Pyza	2-F	4-F	H
1-341	H	H	CH_2-(1-CO_2Me-4-Pyza)	2-F	H	H
1-342	Ac	H	CH_2-(1-CO_2Me-4-Pyza)	2-F	H	H
1-343	H	H	CH_2-(1-CO_2Et-4-Pyza)	2-F	H	H
1-344	Ac	H	CH_2-(1-CO_2Et-4-Pyza)	2-F	H	H
1-345	H	H	CH_2-(3-CO_2H-4-Pyza)	2-F	H	H
1-346	Ac	H	CH_2-(3-CO_2H-4-Pyza)	2-F	H	H
1-347	H	H	CH_2-(3-CO_2Me-4-Pyza)	2-F	H	H
1-348	Ac	H	CH_2-(3-CO_2Me-4-Pyza)	2-F	H	H
1-349	H	H	CH_2-(3-CO_2Et-4-Pyza)	2-F	H	H
1-350	Ac	H	CH_2-(3-CO_2Et-4-Pyza)	2-F	H	H
1-351	H	H	CH_2-(1-CH_2CO_2H-4-Pyza)	2-F	H	H
1-352	Ac	H	CH_2-(1-CH_2CO_2H-4-Pyza)	2-F	H	H
1-353	H	H	CH_2-(1-CH_2CO_2Me-4-Pyza)	2-F	H	H
1-354	Ac	H	CH_2-(1-CH_2CO_2Me-4-Pyza)	2-F	H	H
1-355	H	H	CH_2-(1-CH_2CO_2Et-4-Pyza)	2-F	H	H
1-356	Ac	H	CH_2-(1-CH_2CO_2Et-4-Pyza)	2-F	H	H
1-357	H	H	CH_2-(3-CH_2CO_2H-4-Pyza)	2-F	H	H
1-358	Ac	H	CH_2-(3-CH_2CO_2H-4-Pyza)	2-F	H	H
1-359	H	H	CH_2-(3-CH_2CO_2Me-4-Pyza)	2-F	H	H

1-360	Ac	H	CH_2-(3-CH_2CO_2Me-4-Pyza)	2-F	H	H
1-361	H	H	CH_2-(3-CH_2CO_2Et-4-Pyza)	2-F	H	H
1-362	Ac	H	CH_2-(3-CH_2CO_2Et-4-Pyza)	2-F	H	H
1-363	H	H	CH_2-(1-$CH_2CH_2CO_2H$-4-Pyza)	2-F	H	H
1-364	Ac	H	CH_2-(1-$CH_2CH_2CO_2H$-4-Pyza)	2-F	H	H
1-365	H	H	CH_2-(1-$CH_2CH_2CO_2Me$-4-Pyza)	2-F	H	H
1-366	Ac	H	CH_2-(1-$CH_2CH_2CO_2Me$-4-Pyza)	2-F	H	H
1-367	H	H	CH_2-(1-$CH_2CH_2CO_2Et$-4-Pyza)	2-F	H	H
1-368	Ac	H	CH_2-(1-$CH_2CH_2CO_2Et$-4-Pyza)	2-F	H	H
1-369	H	H	CH_2-(3-$CH_2CH_2CO_2H$-4-Pyza)	2-F	H	H
1-370	Ac	H	CH_2-(3-$CH_2CH_2CO_2H$-4-Pyza)	2-F	H	H
1-371	H	H	CH_2-(3-$CH_2CH_2CO_2Me$-4-Pyza)	2-F	H	H
1-372	Ac	H	CH_2-(3-$CH_2CH_2CO_2Me$-4-Pyza)	2-F	H	H
1-373	H	H	CH_2-(3-$CH_2CH_2CO_2Et$-4-Pyza)	2-F	H	H
1-374	Ac	H	CH_2-(3-$CH_2CH_2CO_2Et$-4-Pyza)	2-F	H	H
1-375	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2H$-4-Pyza)	2-F	H	H
1-376	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2H$-4-Pyza)	2-F	H	H
1-377	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2Me$-4-Pyza)	2-F	H	H
1-378	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2Me$-4-Pyza)	2-F	H	H
1-379	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2Et$-4-Pyza)	2-F	H	H
1-380	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2Et$-4-Pyza)	2-F	H	H
1-381	H	H	CH_2-(3-$CH_2CH_2CH_2CO_2H$-4-Pyza)	2-F	H	H
1-382	Ac	H	CH_2-(3-$CH_2CH_2CH_2CO_2H$-4-Pyza)	2-F	H	H
1-383	H	H	CH_2-(3-$CH_2CH_2CH_2CO_2Me$-4-Pyza)	2-F	H	H
1-384	Ac	H	CH_2-(3-$CH_2CH_2CH_2CO_2Me$-4-Pyza)	2-F	H	H
1-385	H	H	CH_2-(3-$CH_2CH_2CH_2CO_2Et$-4-Pyza)	2-F	H	H
1-386	Ac	H	CH_2-(3-$CH_2CH_2CH_2CO_2Et$-4-Pyza)	2-F	H	H
1-387	H	H	CH_2CH_2-4-Pyza	2-F	H	H
1-388	Ac	H	CH_2CH_2-4-Pyza	2-F	H	H
1-389	H	H	CH_2CH_2-4-Pyza	2-F	4-F	H
1-390	Ac	H	CH_2CH_2-4-Pyza	2-F	4-F	H

1-391	H	H	CH_2CH_2-(1-CO_2Me-4-Pyza)	2-F	H	H
1-392	Ac	H	CH_2CH_2-(1-CO_2Me-4-Pyza)	2-F	H	H
1-393	H	H	CH_2CH_2-(1-CO_2Et-4-Pyza)	2-F	H	H
1-394	Ac	H	CH_2CH_2-(1-CO_2Et-4-Pyza)	2-F	H	H
1-395	H	H	CH_2CH_2-(3-CO_2H-4-Pyza)	2-F	H	H
1-396	Ac	H	CH_2CH_2-(3-CO_2H-4-Pyza)	2-F	H	H
1-397	H	H	CH_2CH_2-(3-CO_2Me-4-Pyza)	2-F	H	H
1-398	Ac	H	CH_2CH_2-(3-CO_2Me-4-Pyza)	2-F	H	H
1-399	H	H	CH_2CH_2-(3-CO_2Et-4-Pyza)	2-F	H	H
1-400	Ac	H	CH_2CH_2-(3-CO_2Et-4-Pyza)	2-F	H	H
1-401	H	H	CH_2CH_2-(1-CH_2CO_2H-4-Pyza)	2-F	H	H
1-402	Ac	H	CH_2CH_2-(1-CH_2CO_2H-4-Pyza)	2-F	H	H
1-403	H	H	CH_2CH_2-(1-CH_2CO_2Me-4-Pyza)	2-F	H	H
1-404	Ac	H	CH_2CH_2-(1-CH_2CO_2Me-4-Pyza)	2-F	H	H
1-405	H	H	CH_2CH_2-(1-CH_2CO_2Et-4-Pyza)	2-F	H	H
1-406	Ac	H	CH_2CH_2-(1-CH_2CO_2Et-4-Pyza)	2-F	H	H
1-407	H	H	CH_2CH_2-(3-CH_2CO_2H-4-Pyza)	2-F	H	H
1-408	Ac	H	CH_2CH_2-(3-CH_2CO_2H-4-Pyza)	2-F	H	H
1-409	H	H	CH_2CH_2-(3-CH_2CO_2Me-4-Pyza)	2-F	H	H
1-410	Ac	H	CH_2CH_2-(3-CH_2CO_2Me-4-Pyza)	2-F	H	H
1-411	H	H	CH_2CH_2-(3-CH_2CO_2Et-4-Pyza)	2-F	H	H
1-412	Ac	H	CH_2CH_2-(3-CH_2CO_2Et-4-Pyza)	2-F	H	H
1-413	H	H	CH_2CH_2-(1-$CH_2CH_2CO_2H$-4-Pyza)	2-F	H	H
1-414	Ac	H	CH_2CH_2-(1-$CH_2CH_2CO_2H$-4-Pyza)	2-F	H	H
1-415	H	H	CH_2CH_2-(1-$CH_2CH_2CO_2Me$-4-Pyza)	2-F	H	H
1-416	Ac	H	CH_2CH_2-(1-$CH_2CH_2CO_2Me$-4-Pyza)	2-F	H	H
1-417	H	H	CH_2CH_2-(1-$CH_2CH_2CO_2Et$-4-Pyza)	2-F	H	H
1-418	Ac	H	CH_2CH_2-(1-$CH_2CH_2CO_2Et$-4-Pyza)	2-F	H	H
1-419	H	H	CH_2CH_2-(3-$CH_2CH_2CO_2H$-4-Pyza)	2-F	H	H
1-420	Ac	H	CH_2CH_2-(3-$CH_2CH_2CO_2H$-4-Pyza)	2-F	H	H
1-421	H	H	CH_2CH_2-(3-$CH_2CH_2CO_2Me$-4-Pyza)	2-F	H	H

1-422	Ac	H	CH_2CH_2-(3-$CH_2CH_2CO_2Me$-4-Pyza)	2-F	H	H
1-423	H	H	CH_2CH_2-(3-$CH_2CH_2CO_2Et$-4-Pyza)	2-F	H	H
1-424	Ac	H	CH_2CH_2-(3-$CH_2CH_2CO_2Et$-4-Pyza)	2-F	H	H
1-425	H	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2H$-4-Pyza)	2-F	H	H
1-426	Ac	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2H$-4-Pyza)	2-F	H	H
1-427	H	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Me$-4-Pyza)	2-F	H	H
1-428	Ac	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Me$-4-Pyza)	2-F	H	H
1-429	H	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Et$-4-Pyza)	2-F	H	H
1-430	Ac	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Et$-4-Pyza)	2-F	H	H
1-431	H	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2H$-4-Pyza)	2-F	H	H
1-432	Ac	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2H$-4-Pyza)	2-F	H	H
1-433	H	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2Me$-4-Pyza)	2-F	H	H
1-434	Ac	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2Me$-4-Pyza)	2-F	H	H
1-435	H	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2Et$-4-Pyza)	2-F	H	H
1-436	Ac	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2Et$-4-Pyza)	2-F	H	H
1-437	H	H	CH_2-(1-CO_2Me-5-Pyza)	2-F	4-F	H
1-438	Ac	H	CH_2-(1-CO_2Me-5-Pyza)	2-F	4-F	H
1-439	H	H	CH_2-(1-CO_2Me-5-Pyza)	2-F	H	H
1-440	Ac	H	CH_2-(1-CO_2Me-5-Pyza)	2-F	H	H
1-441	H	H	CH_2-(1-CO_2Et-5-Pyza)	2-F	H	H
1-442	Ac	H	CH_2-(1-CO_2Et-5-Pyza)	2-F	H	H
1-443	H	H	CH_2-(1-CH_2CO_2H-5-Pyza)	2-F	H	H
1-444	Ac	H	CH_2-(1-CH_2CO_2H-5-Pyza)	2-F	H	H
1-445	H	H	CH_2-(1-CH_2CO_2Me-5-Pyza)	2-F	H	H
1-446	Ac	H	CH_2-(1-CH_2CO_2Me-5-Pyza)	2-F	H	H
1-447	H	H	CH_2-(1-CH_2CO_2Et-5-Pyza)	2-F	H	H
1-448	Ac	H	CH_2-(1-CH_2CO_2Et-5-Pyza)	2-F	H	H
1-449	H	H	CH_2-(1-$CH_2CH_2CO_2H$-5-Pyza)	2-F	H	H
1-450	Ac	H	CH_2-(1-$CH_2CH_2CO_2H$-5-Pyza)	2-F	H	H
1-451	H	H	CH_2-(1-$CH_2CH_2CO_2Me$-5-Pyza)	2-F	H	H
1-452	Ac	H	CH_2-(1-$CH_2CH_2CO_2Me$-5-Pyza)	2-F	H	H

1-453	H	H	CH_2-(1-$CH_2CH_2CO_2Et$-5-Pyza)	2-F	H	H
1-454	Ac	H	CH_2-(1-$CH_2CH_2CO_2Et$-5-Pyza)	2-F	H	H
1-455	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2H$-5-Pyza)	2-F	H	H
1-456	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2H$-5-Pyza)	2-F	H	H
1-457	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2Me$-5-Pyza)	2-F	H	H
1-458	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2Me$-5-Pyza)	2-F	H	H
1-459	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2Et$-5-Pyza)	2-F	H	H
1-460	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2Et$-5-Pyza)	2-F	H	H
1-461	H	H	CH_2CH_2-(1-CO_2Me-5-Pyza)	2-F	4-F	H
1-462	Ac	H	CH_2CH_2-(1-CO_2Me-5-Pyza)	2-F	4-F	H
1-463	H	H	CH_2CH_2-(1-CO_2Me-5-Pyza)	2-F	H	H
1-464	Ac	H	CH_2CH_2-(1-CO_2Me-5-Pyza)	2-F	H	H
1-465	H	H	CH_2CH_2-(1-CO_2Et-5-Pyza)	2-F	H	H
1-466	Ac	H	CH_2CH_2-(1-CO_2Et-5-Pyza)	2-F	H	H
1-467	H	H	CH_2CH_2-(1-CH_2CO_2H-5-Pyza)	2-F	H	H
1-468	Ac	H	CH_2CH_2-(1-CH_2CO_2H-5-Pyza)	2-F	H	H
1-469	H	H	CH_2CH_2-(1-CH_2CO_2Me-5-Pyza)	2-F	H	H
1-470	Ac	H	CH_2CH_2-(1-CH_2CO_2Me-5-Pyza)	2-F	H	H
1-471	H	H	CH_2CH_2-(1-CH_2CO_2Et-5-Pyza)	2-F	H	H
1-472	Ac	H	CH_2CH_2-(1-CH_2CO_2Et-5-Pyza)	2-F	H	H
1-473	H	H	CH_2CH_2-(1-$CH_2CH_2CO_2H$-5-Pyza)	2-F	H	H
1-474	Ac	H	CH_2CH_2-(1-$CH_2CH_2CO_2H$-5-Pyza)	2-F	H	H
1-475	H	H	CH_2CH_2-(1-$CH_2CH_2CO_2Me$-5-Pyza)	2-F	H	H
1-476	Ac	H	CH_2CH_2-(1-$CH_2CH_2CO_2Me$-5-Pyza)	2-F	H	H
1-477	H	H	CH_2CH_2-(1-$CH_2CH_2CO_2Et$-5-Pyza)	2-F	H	H
1-478	Ac	H	CH_2CH_2-(1-$CH_2CH_2CO_2Et$-5-Pyza)	2-F	H	H
1-479	H	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2H$-5-Pyza)	2-F	H	H
1-480	Ac	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2H$-5-Pyza)	2-F	H	H
1-481	H	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Me$-5-Pyza)	2-F	H	H
1-482	Ac	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Me$-5-Pyza)	2-F	H	H
1-483	H	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Et$-5-Pyza)	2-F	H	H

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1-484	Ac	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Et$-5-Pyza)	2-F	H	H
1-485	H	H	CH_2-1-Triz	2-F	H	H
1-486	Ac	H	CH_2-1-Triz	2-F	H	H
1-487	H	H	CH_2-(4-CO_2H-1-Triz)	2-F	H	H
1-488	Ac	H	CH_2-(4-CO_2H-1-Triz)	2-F	H	H
1-489	H	H	CH_2-(4-CO_2Me-1-Triz)	2-F	H	H
1-490	Ac	H	CH_2-(4-CO_2Me-1-Triz)	2-F	H	H
1-491	H	H	CH_2-(4-CO_2Et-1-Triz)	2-F	H	H
1-492	Ac	H	CH_2-(4-CO_2Et-1-Triz)	2-F	H	H
1-493	H	H	CH_2-(5-CO_2H-1-Triz)	2-F	H	H
1-494	Ac	H	CH_2-(5-CO_2H-1-Triz)	2-F	H	H
1-495	H	H	CH_2-(5-CO_2Me-1-Triz)	2-F	H	H
1-496	Ac	H	CH_2-(5-CO_2Me-1-Triz)	2-F	H	H
1-497	H	H	CH_2-(5-CO_2Et-1-Triz)	2-F	H	H
1-498	Ac	H	CH_2-(5-CO_2Et-1-Triz)	2-F	H	H
1-499	H	H	CH_2-(4-CH_2CO_2H-1-Triz)	2-F	H	H
1-500	Ac	H	CH_2-(4-CH_2CO_2H-1-Triz)	2-F	H	H
1-501	H	H	CH_2-(4-CH_2CO_2Me-1-Triz)	2-F	H	H
1-502	Ac	H	CH_2-(4-CH_2CO_2Me-1-Triz)	2-F	H	H
1-503	H	H	CH_2-(4-CH_2CO_2Et-1-Triz)	2-F	H	H
1-504	Ac	H	CH_2-(4-CH_2CO_2Et-1-Triz)	2-F	H	H
1-505	H	H	CH_2-(5-CH_2CO_2H-1-Triz)	2-F	H	H
1-506	Ac	H	CH_2-(5-CH_2CO_2H-1-Triz)	2-F	H	H
1-507	H	H	CH_2-(5-CH_2CO_2Me-1-Triz)	2-F	H	H
1-508	Ac	H	CH_2-(5-CH_2CO_2Me-1-Triz)	2-F	H	H
1-509	H	H	CH_2-(5-CH_2CO_2Et-1-Triz)	2-F	H	H
1-510	Ac	H	CH_2-(5-CH_2CO_2Et-1-Triz)	2-F	H	H
1-511	H	H	CH_2-(4-$CH_2CH_2CO_2H$-1-Triz)	2-F	H	H
1-512	Ac	H	CH_2-(4-$CH_2CH_2CO_2H$-1-Triz)	2-F	H	H
1-513	H	H	CH_2-(4-$CH_2CH_2CO_2Me$-1-Triz)	2-F	H	H
1-514	Ac	H	CH_2-(4-$CH_2CH_2CO_2Me$-1-Triz)	2-F	H	H

1-515	H	H	CH_2-(4-$CH_2CH_2CO_2Et$-1-Triz)	2-F	H	H
1-516	Ac	H	CH_2-(4-$CH_2CH_2CO_2Et$-1-Triz)	2-F	H	H
1-517	H	H	CH_2-(5-$CH_2CH_2CO_2H$-1-Triz)	2-F	H	H
1-518	Ac	H	CH_2-(5-$CH_2CH_2CO_2H$-1-Triz)	2-F	H	H
1-519	H	H	CH_2-(5-$CH_2CH_2CO_2Me$-1-Triz)	2-F	H	H
1-520	Ac	H	CH_2-(5-$CH_2CH_2CO_2Me$-1-Triz)	2-F	H	H
1-521	H	H	CH_2-(5-$CH_2CH_2CO_2Et$-1-Triz)	2-F	H	H
1-522	Ac	H	CH_2-(5-$CH_2CH_2CO_2Et$-1-Triz)	2-F	H	H
1-523	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2H$-1-Triz)	2-F	H	H
1-524	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2H$-1-Triz)	2-F	H	H
1-525	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2Me$-1-Triz)	2-F	H	H
1-526	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2Me$-1-Triz)	2-F	H	H
1-527	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2Et$-1-Triz)	2-F	H	H
1-528	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2Et$-1-Triz)	2-F	H	H
1-529	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2H$-1-Triz)	2-F	H	H
1-530	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2H$-1-Triz)	2-F	H	H
1-531	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2Me$-1-Triz)	2-F	H	H
1-532	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2Me$-1-Triz)	2-F	H	H
1-533	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2Et$-1-Triz)	2-F	H	H
1-534	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2Et$-1-Triz)	2-F	H	H
1-535	H	H	CH_2CH_2-1-Triz	2-F	H	H
1-536	Ac	H	CH_2CH_2-1-Triz	2-F	H	H
1-537	H	H	CH_2CH_2-(4-CO_2H-1-Triz)	2-F	H	H
1-538	Ac	H	CH_2CH_2-(4-CO_2H-1-Triz)	2-F	H	H
1-539	H	H	CH_2CH_2-(4-CO_2Me-1-Triz)	2-F	H	H
1-540	Ac	H	CH_2CH_2-(4-CO_2Me-1-Triz)	2-F	H	H
1-541	H	H	CH_2CH_2-(4-CO_2Et-1-Triz)	2-F	H	H
1-542	Ac	H	CH_2CH_2-(4-CO_2Et-1-Triz)	2-F	H	H
1-543	H	H	CH_2CH_2-(5-CO_2H-1-Triz)	2-F	H	H
1-544	Ac	H	CH_2CH_2-(5-CO_2H-1-Triz)	2-F	H	H
1-545	H	H	CH_2CH_2-(5-CO_2Me-1-Triz)	2-F	H	H

1-546	Ac	H	CH_2CH_2-(5-CO_2Me-1-Triz)	2-F	H	H
1-547	H	H	CH_2CH_2-(5-CO_2Et-1-Triz)	2-F	H	H
1-548	Ac	H	CH_2CH_2-(5-CO_2Et-1-Triz)	2-F	H	H
1-549	H	H	CH_2CH_2-(4-CH_2CO_2H-1-Triz)	2-F	H	H
1-550	Ac	H	CH_2CH_2-(4-CH_2CO_2H-1-Triz)	2-F	H	H
1-551	H	H	CH_2CH_2-(4-CH_2CO_2Me-1-Triz)	2-F	H	H
1-552	Ac	H	CH_2CH_2-(4-CH_2CO_2Me-1-Triz)	2-F	H	H
1-553	H	H	CH_2CH_2-(4-CH_2CO_2Et-1-Triz)	2-F	H	H
1-554	Ac	H	CH_2CH_2-(4-CH_2CO_2Et-1-Triz)	2-F	H	H
1-555	H	H	CH_2CH_2-(5-CH_2CO_2H-1-Triz)	2-F	H	H
1-556	Ac	H	CH_2CH_2-(5-CH_2CO_2H-1-Triz)	2-F	H	H
1-557	H	H	CH_2CH_2-(5-CH_2CO_2Me-1-Triz)	2-F	H	H
1-558	Ac	H	CH_2CH_2-(5-CH_2CO_2Me-1-Triz)	2-F	H	H
1-559	H	H	CH_2CH_2-(5-CH_2CO_2Et-1-Triz)	2-F	H	H
1-560	Ac	H	CH_2CH_2-(5-CH_2CO_2Et-1-Triz)	2-F	H	H
1-561	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2$H-1-Triz)	2-F	H	H
1-562	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2$H-1-Triz)	2-F	H	H
1-563	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2$Me-1-Triz)	2-F	H	H
1-564	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2$Me-1-Triz)	2-F	H	H
1-565	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2$Et-1-Triz)	2-F	H	H
1-566	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2$Et-1-Triz)	2-F	H	H
1-567	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2$H-1-Triz)	2-F	H	H
1-568	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2$H-1-Triz)	2-F	H	H
1-569	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2$Me-1-Triz)	2-F	H	H
1-570	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2$Me-1-Triz)	2-F	H	H
1-571	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2$Et-1-Triz)	2-F	H	H
1-572	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2$Et-1-Triz)	2-F	H	H
1-573	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2$H-1-Triz)	2-F	H	H
1-574	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2$H-1-Triz)	2-F	H	H
1-575	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2$Me-1-Triz)	2-F	H	H
1-576	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2$Me-1-Triz)	2-F	H	H

1-577	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Et$-1-Triz)	2-F	H	H
1-578	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Et$-1-Triz)	2-F	H	H
1-579	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2H$-1-Triz)	2-F	H	H
1-580	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2H$-1-Triz)	2-F	H	H
1-581	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Me$-1-Triz)	2-F	H	H
1-582	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Me$-1-Triz)	2-F	H	H
1-583	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Et$-1-Triz)	2-F	H	H
1-584	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Et$-1-Triz)	2-F	H	H
1-585	H	H	CH_2-2-Triz	2-F	H	H
1-586	Ac	H	CH_2-2-Triz	2-F	H	H
1-587	H	H	CH_2-(4-CO_2H-2-Triz)	2-F	H	H
1-588	Ac	H	CH_2-(4-CO_2H-2-Triz)	2-F	H	H
1-589	H	H	CH_2-(4-CO_2Me-2-Triz)	2-F	H	H
1-590	Ac	H	CH_2-(4-CO_2Me-2-Triz)	2-F	H	H
1-591	H	H	CH_2-(4-CO_2Et-2-Triz)	2-F	H	H
1-592	Ac	H	CH_2-(4-CO_2Et-2-Triz)	2-F	H	H
1-593	H	H	CH_2-(4-CH_2CO_2H-2-Triz)	2-F	H	H
1-594	Ac	H	CH_2-(4-CH_2CO_2H-2-Triz)	2-F	H	H
1-595	H	H	CH_2-(4-CH_2CO_2Me-2-Triz)	2-F	H	H
1-596	Ac	H	CH_2-(4-CH_2CO_2Me-2-Triz)	2-F	H	H
1-597	H	H	CH_2-(4-CH_2CO_2Et-2-Triz)	2-F	H	H
1-598	Ac	H	CH_2-(4-CH_2CO_2Et-2-Triz)	2-F	H	H
1-599	H	H	CH_2-(4-$CH_2CH_2CO_2H$-2-Triz)	2-F	H	H
1-600	Ac	H	CH_2-(4-$CH_2CH_2CO_2H$-2-Triz)	2-F	H	H
1-601	H	H	CH_2-(4-$CH_2CH_2CO_2Me$-2-Triz)	2-F	H	H
1-602	Ac	H	CH_2-(4-$CH_2CH_2CO_2Me$-2-Triz)	2-F	H	H
1-603	H	H	CH_2-(4-$CH_2CH_2CO_2Et$-2-Triz)	2-F	H	H
1-604	Ac	H	CH_2-(4-$CH_2CH_2CO_2Et$-2-Triz)	2-F	H	H
1-605	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2H$-2-Triz)	2-F	H	H
1-606	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2H$-2-Triz)	2-F	H	H
1-607	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2Me$-2-Triz)	2-F	H	H

1-608	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2Me$-2-Triz)	2-F	H	H
1-609	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2Et$-2-Triz)	2-F	H	H
1-610	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2Et$-2-Triz)	2-F	H	H
1-611	H	H	CH_2CH_2-2-Triz	2-F	H	H
1-612	Ac	H	CH_2CH_2-2-Triz	2-F	H	H
1-613	H	H	CH_2CH_2-(4-CO_2H-2-Triz)	2-F	H	H
1-614	Ac	H	CH_2CH_2-(4-CO_2H-2-Triz)	2-F	H	H
1-615	H	H	CH_2CH_2-(4-CO_2Me-2-Triz)	2-F	H	H
1-616	Ac	H	CH_2CH_2-(4-CO_2Me-2-Triz)	2-F	H	H
1-617	H	H	CH_2CH_2-(4-CO_2Et-2-Triz)	2-F	H	H
1-618	Ac	H	CH_2CH_2-(4-CO_2Et-2-Triz)	2-F	H	H
1-619	H	H	CH_2CH_2-(4-CH_2CO_2H-2-Triz)	2-F	H	H
1-620	Ac	H	CH_2CH_2-(4-CH_2CO_2H-2-Triz)	2-F	H	H
1-621	H	H	CH_2CH_2-(4-CH_2CO_2Me-2-Triz)	2-F	H	H
1-622	Ac	H	CH_2CH_2-(4-CH_2CO_2Me-2-Triz)	2-F	H	H
1-623	H	H	CH_2CH_2-(4-CH_2CO_2Et-2-Triz)	2-F	H	H
1-624	Ac	H	CH_2CH_2-(4-CH_2CO_2Et-2-Triz)	2-F	H	H
1-625	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2H$-2-Triz)	2-F	H	H
1-626	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2H$-2-Triz)	2-F	H	H
1-627	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-2-Triz)	2-F	H	H
1-628	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-2-Triz)	2-F	H	H
1-629	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-2-Triz)	2-F	H	H
1-630	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-2-Triz)	2-F	H	H
1-631	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2H$-2-Triz)	2-F	H	H
1-632	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2H$-2-Triz)	2-F	H	H
1-633	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Me$-2-Triz)	2-F	H	H
1-634	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Me$-2-Triz)	2-F	H	H
1-635	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Et$-2-Triz)	2-F	H	H
1-636	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Et$-2-Triz)	2-F	H	H
1-637	H	H	CH_2-4-Triz	2-F	H	H
1-638	Ac	H	CH_2-4-Triz	2-F	H	H

1-639	H	H	CH_2-4-Triz	2-F	4-F	H
1-640	Ac	H	CH_2-4-Triz	2-F	4-F	H
1-641	H	H	CH_2-(1-CO_2Me-4-Triz)	2-F	H	H
1-642	Ac	H	CH_2-(1-CO_2Me-4-Triz)	2-F	H	H
1-643	H	H	CH_2-(1-CO_2Et-4-Triz)	2-F	H	H
1-644	Ac	H	CH_2-(1-CO_2Et-4-Triz)	2-F	H	H
1-645	H	H	CH_2-(5-CO_2H-4-Triz)	2-F	H	H
1-646	Ac	H	CH_2-(5-CO_2H-4-Triz)	2-F	H	H
1-647	H	H	CH_2-(5-CO_2Me-4-Triz)	2-F	H	H
1-648	Ac	H	CH_2-(5-CO_2Me-4-Triz)	2-F	H	H
1-649	H	H	CH_2-(5-CO_2Et-4-Triz)	2-F	H	H
1-650	Ac	H	CH_2-(5-CO_2Et-4-Triz)	2-F	H	H
1-651	H	H	CH_2-(1-CH_2CO_2H-4-Triz)	2-F	H	H
1-652	Ac	H	CH_2-(1-CH_2CO_2H-4-Triz)	2-F	H	H
1-653	H	H	CH_2-(1-CH_2CO_2Me-4-Triz)	2-F	H	H
1-654	Ac	H	CH_2-(1-CH_2CO_2Me-4-Triz)	2-F	H	H
1-655	H	H	CH_2-(1-CH_2CO_2Et-4-Triz)	2-F	H	H
1-656	Ac	H	CH_2-(1-CH_2CO_2Et-4-Triz)	2-F	H	H
1-657	H	H	CH_2-(5-CH_2CO_2H-4-Triz)	2-F	H	H
1-658	Ac	H	CH_2-(5-CH_2CO_2H-4-Triz)	2-F	H	H
1-659	H	H	CH_2-(5-CH_2CO_2Me-4-Triz)	2-F	H	H
1-660	Ac	H	CH_2-(5-CH_2CO_2Me-4-Triz)	2-F	H	H
1-661	H	H	CH_2-(5-CH_2CO_2Et-4-Triz)	2-F	H	H
1-662	Ac	H	CH_2-(5-CH_2CO_2Et-4-Triz)	2-F	H	H
1-663	H	H	CH_2-(1-$CH_2CH_2CO_2$H-4-Triz)	2-F	H	H
1-664	Ac	H	CH_2-(1-$CH_2CH_2CO_2$H-4-Triz)	2-F	H	H
1-665	H	H	CH_2-(1-$CH_2CH_2CO_2$Me-4-Triz)	2-F	H	H
1-666	Ac	H	CH_2-(1-$CH_2CH_2CO_2$Me-4-Triz)	2-F	H	H
1-667	H	H	CH_2-(1-$CH_2CH_2CO_2$Et-4-Triz)	2-F	H	H
1-668	Ac	H	CH_2-(1-$CH_2CH_2CO_2$Et-4-Triz)	2-F	H	H
1-669	H	H	CH_2-(5-$CH_2CH_2CO_2$H-4-Triz)	2-F	H	H

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1-670	Ac	H	CH_2-(5-$CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
1-671	H	H	CH_2-(5-$CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
1-672	Ac	H	CH_2-(5-$CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
1-673	H	H	CH_2-(5-$CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
1-674	Ac	H	CH_2-(5-$CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
1-675	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
1-676	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
1-677	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
1-678	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
1-679	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
1-680	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
1-681	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
1-682	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
1-683	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
1-684	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
1-685	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
1-686	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
1-687	H	H	CH_2CH_2-4-Triz	2-F	H	H
1-688	Ac	H	CH_2CH_2-4-Triz	2-F	H	H
1-689	H	H	CH_2CH_2-4-Triz	2-F	4-F	H
1-690	Ac	H	CH_2CH_2-4-Triz	2-F	4-F	H
1-691	H	H	CH_2CH_2-(1-CO_2Me-4-Triz)	2-F	H	H
1-692	Ac	H	CH_2CH_2-(1-CO_2Me-4-Triz)	2-F	H	H
1-693	H	H	CH_2CH_2-(1-CO_2Et-4-Triz)	2-F	H	H
1-694	Ac	H	CH_2CH_2-(1-CO_2Et-4-Triz)	2-F	H	H
1-695	H	H	CH_2CH_2-(5-CO_2H-4-Triz)	2-F	H	H
1-696	Ac	H	CH_2CH_2-(5-CO_2H-4-Triz)	2-F	H	H
1-697	H	H	CH_2CH_2-(5-CO_2Me-4-Triz)	2-F	H	H
1-698	Ac	H	CH_2CH_2-(5-CO_2Me-4-Triz)	2-F	H	H
1-699	H	H	CH_2CH_2-(5-CO_2Et-4-Triz)	2-F	H	H
1-700	Ac	H	CH_2CH_2-(5-CO_2Et-4-Triz)	2-F	H	H

1-701	H	H	CH_2CH_2-(1-CH_2CO_2H-4-Triz)	2-F	H	H
1-702	Ac	H	CH_2CH_2-(1-CH_2CO_2H-4-Triz)	2-F	H	H
1-703	H	H	CH_2CH_2-(1-CH_2CO_2Me-4-Triz)	2-F	H	H
1-704	Ac	H	CH_2CH_2-(1-CH_2CO_2Me-4-Triz)	2-F	H	H
1-705	H	H	CH_2CH_2-(1-CH_2CO_2Et-4-Triz)	2-F	H	H
1-706	Ac	H	CH_2CH_2-(1-CH_2CO_2Et-4-Triz)	2-F	H	H
1-707	H	H	CH_2CH_2-(5-CH_2CO_2H-4-Triz)	2-F	H	H
1-708	Ac	H	CH_2CH_2-(5-CH_2CO_2H-4-Triz)	2-F	H	H
1-709	H	H	CH_2CH_2-(5-CH_2CO_2Me-4-Triz)	2-F	H	H
1-710	Ac	H	CH_2CH_2-(5-CH_2CO_2Me-4-Triz)	2-F	H	H
1-711	H	H	CH_2CH_2-(5-CH_2CO_2Et-4-Triz)	2-F	H	H
1-712	Ac	H	CH_2CH_2-(5-CH_2CO_2Et-4-Triz)	2-F	H	H
1-713	H	H	CH_2CH_2-(1-$CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
1-714	Ac	H	CH_2CH_2-(1-$CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
1-715	H	H	CH_2CH_2-(1-$CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
1-716	Ac	H	CH_2CH_2-(1-$CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
1-717	H	H	CH_2CH_2-(1-$CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
1-718	Ac	H	CH_2CH_2-(1-$CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
1-719	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
1-720	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
1-721	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
1-722	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
1-723	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
1-724	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
1-725	H	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
1-726	Ac	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
1-727	H	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
1-728	Ac	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
1-729	H	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
1-730	Ac	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
1-731	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2H$-4-Triz)	2-F	H	H

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1-732	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
1-733	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
1-734	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
1-735	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
1-736	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
1-737	H	H	CH_2-(1-CO_2Me-5-Triz)	2-F	4-F	H
1-738	Ac	H	CH_2-(1-CO_2Me-5-Triz)	2-F	4-F	H
1-739	H	H	CH_2-(1-CO_2Me-5-Triz)	2-F	H	H
1-740	Ac	H	CH_2-(1-CO_2Me-5-Triz)	2-F	H	H
1-741	H	H	CH_2-(1-CO_2Et-5-Triz)	2-F	H	H
1-742	Ac	H	CH_2-(1-CO_2Et-5-Triz)	2-F	H	H
1-743	H	H	CH_2-(1-CH_2CO_2H-5-Triz)	2-F	H	H
1-744	Ac	H	CH_2-(1-CH_2CO_2H-5-Triz)	2-F	H	H
1-745	H	H	CH_2-(1-CH_2CO_2Me-5-Triz)	2-F	H	H
1-746	Ac	H	CH_2-(1-CH_2CO_2Me-5-Triz)	2-F	H	H
1-747	H	H	CH_2-(1-CH_2CO_2Et-5-Triz)	2-F	H	H
1-748	Ac	H	CH_2-(1-CH_2CO_2Et-5-Triz)	2-F	H	H
1-749	H	H	CH_2-(1-$CH_2CH_2CO_2H$-5-Triz)	2-F	H	H
1-750	Ac	H	CH_2-(1-$CH_2CH_2CO_2H$-5-Triz)	2-F	H	H
1-751	H	H	CH_2-(1-$CH_2CH_2CO_2Me$-5-Triz)	2-F	H	H
1-752	Ac	H	CH_2-(1-$CH_2CH_2CO_2Me$-5-Triz)	2-F	H	H
1-753	H	H	CH_2-(1-$CH_2CH_2CO_2Et$-5-Triz)	2-F	H	H
1-754	Ac	H	CH_2-(1-$CH_2CH_2CO_2Et$-5-Triz)	2-F	H	H
1-755	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2H$-5-Triz)	2-F	H	H
1-756	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2H$-5-Triz)	2-F	H	H
1-757	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2Me$-5-Triz)	2-F	H	H
1-758	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2Me$-5-Triz)	2-F	H	H
1-759	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2Et$-5-Triz)	2-F	H	H
1-760	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2Et$-5-Triz)	2-F	H	H
1-761	H	H	CH_2-1-Tez	2-F	H	H
1-762	Ac	H	CH_2-1-Tez	2-F	H	H

1-763	H	H	CH_2-(5-CO_2H-1-Tez)	2-F	H	H
1-764	Ac	H	CH_2-(5-CO_2H-1-Tez)	2-F	H	H
1-765	H	H	CH_2-(5-CO_2Me-1-Tez)	2-F	H	H
1-766	Ac	H	CH_2-(5-CO_2Me-1-Tez)	2-F	H	H
1-767	H	H	CH_2-(5-CO_2Et-1-Tez)	2-F	H	H
1-768	Ac	H	CH_2-(5-CO_2Et-1-Tez)	2-F	H	H
1-769	H	H	CH_2-(5-CH_2CO_2H-1-Tez)	2-F	H	H
1-770	Ac	H	CH_2-(5-CH_2CO_2H-1-Tez)	2-F	H	H
1-771	H	H	CH_2-(5-CH_2CO_2Me-1-Tez)	2-F	H	H
1-772	Ac	H	CH_2-(5-CH_2CO_2Me-1-Tez)	2-F	H	H
1-773	H	H	CH_2-(5-CH_2CO_2Et-1-Tez)	2-F	H	H
1-774	Ac	H	CH_2-(5-CH_2CO_2Et-1-Tez)	2-F	H	H
1-775	H	H	CH_2-(5-$CH_2CH_2CO_2H$-1-Tez)	2-F	H	H
1-776	Ac	H	CH_2-(5-$CH_2CH_2CO_2H$-1-Tez)	2-F	H	H
1-777	H	H	CH_2-(5-$CH_2CH_2CO_2Me$-1-Tez)	2-F	H	H
1-778	Ac	H	CH_2-(5-$CH_2CH_2CO_2Me$-1-Tez)	2-F	H	H
1-779	H	H	CH_2-(5-$CH_2CH_2CO_2Et$-1-Tez)	2-F	H	H
1-780	Ac	H	CH_2-(5-$CH_2CH_2CO_2Et$-1-Tez)	2-F	H	H
1-781	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2H$-1-Tez)	2-F	H	H
1-782	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2H$-1-Tez)	2-F	H	H
1-783	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2Me$-1-Tez)	2-F	H	H
1-784	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2Me$-1-Tez)	2-F	H	H
1-785	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2Et$-1-Tez)	2-F	H	H
1-786	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2Et$-1-Tez)	2-F	H	H
1-787	H	H	CH_2CH_2-1-Tez	2-F	H	H
1-788	Ac	H	CH_2CH_2-1-Tez	2-F	H	H
1-789	H	H	CH_2CH_2-(5-CO_2H-1-Tez)	2-F	H	H
1-790	Ac	H	CH_2CH_2-(5-CO_2H-1-Tez)	2-F	H	H
1-791	H	H	CH_2CH_2-(5-CO_2Me-1-Tez)	2-F	H	H
1-792	Ac	H	CH_2CH_2-(5-CO_2Me-1-Tez)	2-F	H	H
1-793	H	H	CH_2CH_2-(5-CO_2Et-1-Tez)	2-F	H	H

1-794	Ac	H	CH_2CH_2-(5-CO_2Et-1-Tez)	2-F	H	H
1-795	H	H	CH_2CH_2-(5-CH_2CO_2H-1-Tez)	2-F	H	H
1-796	Ac	H	CH_2CH_2-(5-CH_2CO_2H-1-Tez)	2-F	H	H
1-797	H	H	CH_2CH_2-(5-CH_2CO_2Me-1-Tez)	2-F	H	H
1-798	Ac	H	CH_2CH_2-(5-CH_2CO_2Me-1-Tez)	2-F	H	H
1-799	H	H	CH_2CH_2-(5-CH_2CO_2Et-1-Tez)	2-F	H	H
1-800	Ac	H	CH_2CH_2-(5-CH_2CO_2Et-1-Tez)	2-F	H	H
1-801	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2H$-1-Tez)	2-F	H	H
1-802	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2H$-1-Tez)	2-F	H	H
1-803	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2Me$-1-Tez)	2-F	H	H
1-804	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2Me$-1-Tez)	2-F	H	H
1-805	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2Et$-1-Tez)	2-F	H	H
1-806	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2Et$-1-Tez)	2-F	H	H
1-807	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2H$-1-Tez)	2-F	H	H
1-808	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2H$-1-Tez)	2-F	H	H
1-809	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Me$-1-Tez)	2-F	H	H
1-810	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Me$-1-Tez)	2-F	H	H
1-811	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Et$-1-Tez)	2-F	H	H
1-812	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Et$-1-Tez)	2-F	H	H
1-813	H	H	CH_2-2-Tez	2-F	H	H
1-814	Ac	H	CH_2-2-Tez	2-F	H	H
1-815	H	H	CH_2-(5-CO_2H-2-Tez)	2-F	H	H
1-816	Ac	H	CH_2-(5-CO_2H-2-Tez)	2-F	H	H
1-817	H	H	CH_2-(5-CO_2Me-2-Tez)	2-F	H	H
1-818	Ac	H	CH_2-(5-CO_2Me-2-Tez)	2-F	H	H
1-819	H	H	CH_2-(5-CO_2Et-2-Tez)	2-F	H	H
1-820	Ac	H	CH_2-(5-CO_2Et-2-Tez)	2-F	H	H
1-821	H	H	CH_2-(5-CH_2CO_2H-2-Tez)	2-F	H	H
1-822	Ac	H	CH_2-(5-CH_2CO_2H-2-Tez)	2-F	H	H
1-823	H	H	CH_2-(5-CH_2CO_2Me-2-Tez)	2-F	H	H
1-824	Ac	H	CH_2-(5-CH_2CO_2Me-2-Tez)	2-F	H	H

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1-825	H	H	CH_2-(5-CH_2CO_2Et-2-Tez)	2-F	H	H
1-826	Ac	H	CH_2-(5-CH_2CO_2Et-2-Tez)	2-F	H	H
1-827	H	H	CH_2-(5-$CH_2CH_2CO_2H$-2-Tez)	2-F	H	H
1-828	Ac	H	CH_2-(5-$CH_2CH_2CO_2H$-2-Tez)	2-F	H	H
1-829	H	H	CH_2-(5-$CH_2CH_2CO_2Me$-2-Tez)	2-F	H	H
1-830	Ac	H	CH_2-(5-$CH_2CH_2CO_2Me$-2-Tez)	2-F	H	H
1-831	H	H	CH_2-(5-$CH_2CH_2CO_2Et$-2-Tez)	2-F	H	H
1-832	Ac	H	CH_2-(5-$CH_2CH_2CO_2Et$-2-Tez)	2-F	H	H
1-833	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2H$-2-Tez)	2-F	H	H
1-834	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2H$-2-Tez)	2-F	H	H
1-835	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2Me$-2-Tez)	2-F	H	H
1-836	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2Me$-2-Tez)	2-F	H	H
1-837	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2Et$-2-Tez)	2-F	H	H
1-838	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2Et$-2-Tez)	2-F	H	H
1-839	H	H	CH_2CH_2-2-Tez	2-F	H	H
1-840	Ac	H	CH_2CH_2-2-Tez	2-F	H	H
1-841	H	H	CH_2CH_2-(5-CO_2H-2-Tez)	2-F	H	H
1-842	Ac	H	CH_2CH_2-(5-CO_2H-2-Tez)	2-F	H	H
1-843	H	H	CH_2CH_2-(5-CO_2Me-2-Tez)	2-F	H	H
1-844	Ac	H	CH_2CH_2-(5-CO_2Me-2-Tez)	2-F	H	H
1-845	H	H	CH_2CH_2-(5-CO_2Et-2-Tez)	2-F	H	H
1-846	Ac	H	CH_2CH_2-(5-CO_2Et-2-Tez)	2-F	H	H
1-847	H	H	CH_2CH_2-(5-CH_2CO_2H-2-Tez)	2-F	H	H
1-848	Ac	H	CH_2CH_2-(5-CH_2CO_2H-2-Tez)	2-F	H	H
1-849	H	H	CH_2CH_2-(5-CH_2CO_2Me-2-Tez)	2-F	H	H
1-850	Ac	H	CH_2CH_2-(5-CH_2CO_2Me-2-Tez)	2-F	H	H
1-851	H	H	CH_2CH_2-(5-CH_2CO_2Et-2-Tez)	2-F	H	H
1-852	Ac	H	CH_2CH_2-(5-CH_2CO_2Et-2-Tez)	2-F	H	H
1-853	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2H$-2-Tez)	2-F	H	H
1-854	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2H$-2-Tez)	2-F	H	H
1-855	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2Me$-2-Tez)	2-F	H	H

1-856	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2Me$-2-Tez)	2-F	H	H
1-857	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2Et$-2-Tez)	2-F	H	H
1-858	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2Et$-2-Tez)	2-F	H	H
1-859	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2H$-2-Tez)	2-F	H	H
1-860	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2H$-2-Tez)	2-F	H	H
1-861	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Me$-2-Tez)	2-F	H	H
1-862	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Me$-2-Tez)	2-F	H	H
1-863	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Et$-2-Tez)	2-F	H	H
1-864	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Et$-2-Tez)	2-F	H	H
1-865	H	H	CH_2-5-Tez	2-F	H	H
1-866	Ac	H	CH_2-5-Tez	2-F	H	H
1-867	H	H	CH_2-5-Tez	2-F	4-F	H
1-868	Ac	H	CH_2-5-Tez	2-F	4-F	H
1-869	H	H	CH_2-(1-CO_2Me-5-Tez)	2-F	H	H
1-870	Ac	H	CH_2-(1-CO_2Me-5-Tez)	2-F	H	H
1-871	H	H	CH_2-(1-CO_2Et-5-Tez)	2-F	H	H
1-872	Ac	H	CH_2-(1-CO_2Et-5-Tez)	2-F	H	H
1-873	H	H	CH_2-(2-CO_2Me-5-Tez)	2-F	4-F	H
1-874	Ac	H	CH_2-(2-CO_2Me-5-Tez)	2-F	4-F	H
1-875	H	H	CH_2-(2-CO_2Me-5-Tez)	2-F	H	H
1-876	Ac	H	CH_2-(2-CO_2Me-5-Tez)	2-F	H	H
1-877	H	H	CH_2-(2-CO_2Et-5-Tez)	2-F	H	H
1-878	Ac	H	CH_2-(2-CO_2Et-5-Tez)	2-F	H	H
1-879	H	H	CH_2-(1-CH_2CO_2H-5-Tez)	2-F	H	H
1-880	Ac	H	CH_2-(1-CH_2CO_2H-5-Tez)	2-F	H	H
1-881	H	H	CH_2-(1-CH_2CO_2Me-5-Tez)	2-F	H	H
1-882	Ac	H	CH_2-(1-CH_2CO_2Me-5-Tez)	2-F	H	H
1-883	H	H	CH_2-(1-CH_2CO_2Et-5-Tez)	2-F	H	H
1-884	Ac	H	CH_2-(1-CH_2CO_2Et-5-Tez)	2-F	H	H
1-885	H	H	CH_2-(2-CH_2CO_2H-5-Tez)	2-F	H	H
1-886	Ac	H	CH_2-(2-CH_2CO_2H-5-Tez)	2-F	H	H

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1-887	H	H	CH_2-(2-CH_2CO_2Me-5-Tez)	2-F	H	H
1-888	Ac	H	CH_2-(2-CH_2CO_2Me-5-Tez)	2-F	H	H
1-889	H	H	CH_2-(2-CH_2CO_2Et-5-Tez)	2-F	H	H
1-890	Ac	H	CH_2-(2-CH_2CO_2Et-5-Tez)	2-F	H	H
1-891	H	H	CH_2-(1-$CH_2CH_2CO_2H$-5-Tez)	2-F	H	H
1-892	Ac	H	CH_2-(1-$CH_2CH_2CO_2H$-5-Tez)	2-F	H	H
1-893	H	H	CH_2-(1-$CH_2CH_2CO_2Me$-5-Tez)	2-F	H	H
1-894	Ac	H	CH_2-(1-$CH_2CH_2CO_2Me$-5-Tez)	2-F	H	H
1-895	H	H	CH_2-(1-$CH_2CH_2CO_2Et$-5-Tez)	2-F	H	H
1-896	Ac	H	CH_2-(1-$CH_2CH_2CO_2Et$-5-Tez)	2-F	H	H
1-897	H	H	CH_2-(2-$CH_2CH_2CO_2H$-5-Tez)	2-F	H	H
1-898	Ac	H	CH_2-(2-$CH_2CH_2CO_2H$-5-Tez)	2-F	H	H
1-899	H	H	CH_2-(2-$CH_2CH_2CO_2Me$-5-Tez)	2-F	H	H
1-900	Ac	H	CH_2-(2-$CH_2CH_2CO_2Me$-5-Tez)	2-F	H	H
1-901	H	H	CH_2-(2-$CH_2CH_2CO_2Et$-5-Tez)	2-F	H	H
1-902	Ac	H	CH_2-(2-$CH_2CH_2CO_2Et$-5-Tez)	2-F	H	H
1-903	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2H$-5-Tez)	2-F	H	H
1-904	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2H$-5-Tez)	2-F	H	H
1-905	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2Me$-5-Tez)	2-F	H	H
1-906	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2Me$-5-Tez)	2-F	H	H
1-907	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2Et$-5-Tez)	2-F	H	H
1-908	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2Et$-5-Tez)	2-F	H	H
1-909	H	H	CH_2-(2-$CH_2CH_2CH_2CO_2H$-5-Tez)	2-F	H	H
1-910	Ac	H	CH_2-(2-$CH_2CH_2CH_2CO_2H$-5-Tez)	2-F	H	H
1-911	H	H	CH_2-(2-$CH_2CH_2CH_2CO_2Me$-5-Tez)	2-F	H	H
1-912	Ac	H	CH_2-(2-$CH_2CH_2CH_2CO_2Me$-5-Tez)	2-F	H	H
1-913	H	H	CH_2-(2-$CH_2CH_2CH_2CO_2Et$-5-Tez)	2-F	H	H
1-914	Ac	H	CH_2-(2-$CH_2CH_2CH_2CO_2Et$-5-Tez)	2-F	H	H
1-915	H	H	CH_2CH_2-5-Tez	2-F	H	H
1-916	Ac	H	CH_2CH_2-5-Tez	2-F	H	H
1-917	H	H	CH_2CH_2-5-Tez	2-F	4-F	H

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1-918	Ac	H	CH_2CH_2-5-Tez	2-F	4-F	H
1-919	H	H	CH_2CH_2-(1-CO_2Me-5-Tez)	2-F	H	H
1-920	Ac	H	CH_2CH_2-(1-CO_2Me-5-Tez)	2-F	H	H
1-921	H	H	CH_2CH_2-(1-CO_2Et-5-Tez)	2-F	H	H
1-922	Ac	H	CH_2CH_2-(1-CO_2Et-5-Tez)	2-F	H	H
1-923	H	H	CH_2CH_2-(2-CO_2Me-5-Tez)	2-F	4-F	H
1-924	Ac	H	CH_2CH_2-(2-CO_2Me-5-Tez)	2-F	4-F	H
1-925	H	H	CH_2CH_2-(2-CO_2Me-5-Tez)	2-F	H	H
1-926	Ac	H	CH_2CH_2-(2-CO_2Me-5-Tez)	2-F	H	H
1-927	H	H	CH_2CH_2-(2-CO_2Et-5-Tez)	2-F	H	H
1-928	Ac	H	CH_2CH_2-(2-CO_2Et-5-Tez)	2-F	H	H
1-929	H	H	CH_2CH_2-(1-CH_2CO_2H-5-Tez)	2-F	H	H
1-930	Ac	H	CH_2CH_2-(1-CH_2CO_2H-5-Tez)	2-F	H	H
1-931	H	H	CH_2CH_2-(1-CH_2CO_2Me-5-Tez)	2-F	H	H
1-932	Ac	H	CH_2CH_2-(1-CH_2CO_2Me-5-Tez)	2-F	H	H
1-933	H	H	CH_2CH_2-(1-CH_2CO_2Et-5-Tez)	2-F	H	H
1-934	Ac	H	CH_2CH_2-(1-CH_2CO_2Et-5-Tez)	2-F	H	H
1-935	H	H	CH_2CH_2-(2-CH_2CO_2H-5-Tez)	2-F	H	H
1-936	Ac	H	CH_2CH_2-(2-CH_2CO_2H-5-Tez)	2-F	H	H
1-937	H	H	CH_2CH_2-(2-CH_2CO_2Me-5-Tez)	2-F	H	H
1-938	Ac	H	CH_2CH_2-(2-CH_2CO_2Me-5-Tez)	2-F	H	H
1-939	H	H	CH_2CH_2-(2-CH_2CO_2Et-5-Tez)	2-F	H	H
1-940	Ac	H	CH_2CH_2-(2-CH_2CO_2Et-5-Tez)	2-F	H	H
1-941	H	H	CH_2CH_2-(1-$CH_2CH_2CO_2H$-5-Tez)	2-F	H	H
1-942	Ac	H	CH_2CH_2-(1-$CH_2CH_2CO_2H$-5-Tez)	2-F	H	H
1-943	H	H	CH_2CH_2-(1-$CH_2CH_2CO_2Me$-5-Tez)	2-F	H	H
1-944	Ac	H	CH_2CH_2-(1-$CH_2CH_2CO_2Me$-5-Tez)	2-F	H	H
1-945	H	H	CH_2CH_2-(1-$CH_2CH_2CO_2Et$-5-Tez)	2-F	H	H
1-946	Ac	H	CH_2CH_2-(1-$CH_2CH_2CO_2Et$-5-Tez)	2-F	H	H
1-947	H	H	CH_2CH_2-(2-$CH_2CH_2CO_2H$-5-Tez)	2-F	H	H
1-948	Ac	H	CH_2CH_2-(2-$CH_2CH_2CO_2H$-5-Tez)	2-F	H	H

1-949	H	H	CH_2CH_2-(2-$CH_2CH_2CO_2Me$-5-Tez)	2-F	H	H
1-950	Ac	H	CH_2CH_2-(2-$CH_2CH_2CO_2Me$-5-Tez)	2-F	H	H
1-951	H	H	CH_2CH_2-(2-$CH_2CH_2CO_2Et$-5-Tez)	2-F	H	H
1-952	Ac	H	CH_2CH_2-(2-$CH_2CH_2CO_2Et$-5-Tez)	2-F	H	H
1-953	H	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2H$-5-Tez)	2-F	H	H
1-954	Ac	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2H$-5-Tez)	2-F	H	H
1-955	H	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Me$-5-Tez)	2-F	H	H
1-956	Ac	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Me$-5-Tez)	2-F	H	H
1-957	H	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Et$-5-Tez)	2-F	H	H
1-958	Ac	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Et$-5-Tez)	2-F	H	H
1-959	H	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2H$-5-Tez)	2-F	H	H
1-960	Ac	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2H$-5-Tez)	2-F	H	H
1-961	H	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2Me$-5-Tez)	2-F	H	H
1-962	Ac	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2Me$-5-Tez)	2-F	H	H
1-963	H	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2Et$-5-Tez)	2-F	H	H
1-964	Ac	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2Et$-5-Tez)	2-F	H	H
1-965	H	Me	CH_2-1-Pyza	2-F	H	H
1-966	Ac	Me	CH_2-1-Pyza	2-F	H	H
1-967	H	Me	CH_2-(3-CO_2H-1-Pyza)	2-F	H	H
1-968	Ac	Me	CH_2-(3-CO_2H-1-Pyza)	2-F	H	H
1-969	H	Me	CH_2-(3-CO_2Me-1-Pyza)	2-F	H	H
1-970	Ac	Me	CH_2-(3-CO_2Me-1-Pyza)	2-F	H	H
1-971	H	Me	CH_2-(3-CO_2Et-1-Pyza)	2-F	H	H
1-972	Ac	Me	CH_2-(3-CO_2Et-1-Pyza)	2-F	H	H
1-973	H	Me	CH_2-(4-CO_2H-1-Pyza)	2-F	H	H
1-974	Ac	Me	CH_2-(4-CO_2H-1-Pyza)	2-F	H	H
1-975	H	Me	CH_2-(4-CO_2Me-1-Pyza)	2-F	H	H
1-976	Ac	Me	CH_2-(4-CO_2Me-1-Pyza)	2-F	H	H
1-977	H	Me	CH_2-(4-CO_2Et-1-Pyza)	2-F	H	H
1-978	Ac	Me	CH_2-(4-CO_2Et-1-Pyza)	2-F	H	H
1-979	H	Me	CH_2-(3-CH_2CO_2H-1-Pyza)	2-F	H	H

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1-980	Ac	Me	CH_2-(3-CH_2CO_2H-1-Pyza)	2-F	H	H
1-981	H	Me	CH_2-(3-CH_2CO_2Me-1-Pyza)	2-F	H	H
1-982	Ac	Me	CH_2-(3-CH_2CO_2Me-1-Pyza)	2-F	H	H
1-983	H	Me	CH_2-(3-CH_2CO_2Et-1-Pyza)	2-F	H	H
1-984	Ac	Me	CH_2-(3-CH_2CO_2Et-1-Pyza)	2-F	H	H
1-985	H	Me	CH_2-(4-CH_2CO_2H-1-Pyza)	2-F	H	H
1-986	Ac	Me	CH_2-(4-CH_2CO_2H-1-Pyza)	2-F	H	H
1-987	H	Me	CH_2-(4-CH_2CO_2Me-1-Pyza)	2-F	H	H
1-988	Ac	Me	CH_2-(4-CH_2CO_2Me-1-Pyza)	2-F	H	H
1-989	H	Me	CH_2-(4-CH_2CO_2Et-1-Pyza)	2-F	H	H
1-990	Ac	Me	CH_2-(4-CH_2CO_2Et-1-Pyza)	2-F	H	H
1-991	H	Me	CH_2-(3-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
1-992	Ac	Me	CH_2-(3-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
1-993	H	Me	CH_2-(3-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
1-994	Ac	Me	CH_2-(3-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
1-995	H	Me	CH_2-(3-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
1-996	Ac	Me	CH_2-(3-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
1-997	H	Me	CH_2-(4-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
1-998	Ac	Me	CH_2-(4-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
1-999	H	Me	CH_2-(4-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
1-1000	Ac	Me	CH_2-(4-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
1-1001	H	Me	CH_2-(4-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
1-1002	Ac	Me	CH_2-(4-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
1-1003	H	Me	CH_2CH_2-1-Pyza	2-F	H	H
1-1004	Ac	Me	CH_2CH_2-1-Pyza	2-F	H	H
1-1005	H	Me	CH_2CH_2-(3-CO_2H-1-Pyza)	2-F	H	H
1-1006	Ac	Me	CH_2CH_2-(3-CO_2H-1-Pyza)	2-F	H	H
1-1007	H	Me	CH_2CH_2-(3-CO_2Me-1-Pyza)	2-F	H	H
1-1008	Ac	Me	CH_2CH_2-(3-CO_2Me-1-Pyza)	2-F	H	H
1-1009	H	Me	CH_2CH_2-(3-CO_2Et-1-Pyza)	2-F	H	H
1-1010	Ac	Me	CH_2CH_2-(3-CO_2Et-1-Pyza)	2-F	H	H

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1-1011	H	Me	CH_2CH_2-(4-CO_2H-1-Pyza)	2-F	H	H
1-1012	Ac	Me	CH_2CH_2-(4-CO_2H-1-Pyza)	2-F	H	H
1-1013	H	Me	CH_2CH_2-(4-CO_2Me-1-Pyza)	2-F	H	H
1-1014	Ac	Me	CH_2CH_2-(4-CO_2Me-1-Pyza)	2-F	H	H
1-1015	H	Me	CH_2CH_2-(4-CO_2Et-1-Pyza)	2-F	H	H
1-1016	Ac	Me	CH_2CH_2-(4-CO_2Et-1-Pyza)	2-F	H	H
1-1017	H	Me	CH_2CH_2-(3-CH_2CO_2H-1-Pyza)	2-F	H	H
1-1018	Ac	Me	CH_2CH_2-(3-CH_2CO_2H-1-Pyza)	2-F	H	H
1-1019	H	Me	CH_2CH_2-(3-CH_2CO_2Me-1-Pyza)	2-F	H	H
1-1020	Ac	Me	CH_2CH_2-(3-CH_2CO_2Me-1-Pyza)	2-F	H	H
1-1021	H	Me	CH_2CH_2-(3-CH_2CO_2Et-1-Pyza)	2-F	H	H
1-1022	Ac	Me	CH_2CH_2-(3-CH_2CO_2Et-1-Pyza)	2-F	H	H
1-1023	H	Me	CH_2CH_2-(4-CH_2CO_2H-1-Pyza)	2-F	H	H
1-1024	Ac	Me	CH_2CH_2-(4-CH_2CO_2H-1-Pyza)	2-F	H	H
1-1025	H	Me	CH_2CH_2-(4-CH_2CO_2Me-1-Pyza)	2-F	H	H
1-1026	Ac	Me	CH_2CH_2-(4-CH_2CO_2Me-1-Pyza)	2-F	H	H
1-1027	H	Me	CH_2CH_2-(4-CH_2CO_2Et-1-Pyza)	2-F	H	H
1-1028	Ac	Me	CH_2CH_2-(4-CH_2CO_2Et-1-Pyza)	2-F	H	H
1-1029	H	Me	CH_2CH_2-(3-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
1-1030	Ac	Me	CH_2CH_2-(3-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
1-1031	H	Me	CH_2CH_2-(3-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
1-1032	Ac	Me	CH_2CH_2-(3-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
1-1033	H	Me	CH_2CH_2-(3-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
1-1034	Ac	Me	CH_2CH_2-(3-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
1-1035	H	Me	CH_2CH_2-(4-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
1-1036	Ac	Me	CH_2CH_2-(4-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
1-1037	H	Me	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
1-1038	Ac	Me	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
1-1039	H	Me	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
1-1040	Ac	Me	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
1-1041	H	H	CH_2-(2-CO_2Me-4-Triz)	2-F	H	H

1-1042	Ac	H	CH_2-(2-CO_2Me-4-Triz)	2-F	H	H
1-1043	H	H	CH_2-(2-CO_2Et-4-Triz)	2-F	H	H
1-1044	Ac	H	CH_2-(2-CO_2Et-4-Triz)	2-F	H	H
1-1045	H	H	CH_2-(2-CH_2CO_2H-4-Triz)	2-F	H	H
1-1046	Ac	H	CH_2-(2-CH_2CO_2H-4-Triz)	2-F	H	H
1-1047	H	H	CH_2-(2-CH_2CO_2Me-4-Triz)	2-F	H	H
1-1048	Ac	H	CH_2-(2-CH_2CO_2Me-4-Triz)	2-F	H	H
1-1049	H	H	CH_2-(2-CH_2CO_2Et-4-Triz)	2-F	H	H
1-1050	Ac	H	CH_2-(2-CH_2CO_2Et-4-Triz)	2-F	H	H
1-1051	H	H	CH_2-(2-$CH_2CH_2CO_2$H-4-Triz)	2-F	H	H
1-1052	Ac	H	CH_2-(2-$CH_2CH_2CO_2$H-4-Triz)	2-F	H	H
1-1053	H	H	CH_2-(2-$CH_2CH_2CO_2$Me-4-Triz)	2-F	H	H
1-1054	Ac	H	CH_2-(2-$CH_2CH_2CO_2$Me-4-Triz)	2-F	H	H
1-1055	H	H	CH_2-(2-$CH_2CH_2CO_2$Et-4-Triz)	2-F	H	H
1-1056	Ac	H	CH_2-(2-$CH_2CH_2CO_2$Et-4-Triz)	2-F	H	H
1-1057	H	H	CH_2-(2-$CH_2CH_2CH_2CO_2$H-4-Triz)	2-F	H	H
1-1058	Ac	H	CH_2-(2-$CH_2CH_2CH_2CO_2$H-4-Triz)	2-F	H	H
1-1059	H	H	CH_2-(2-$CH_2CH_2CH_2CO_2$Me-4-Triz)	2-F	H	H
1-1060	Ac	H	CH_2-(2-$CH_2CH_2CH_2CO_2$Me-4-Triz)	2-F	H	H
1-1061	H	H	CH_2-(2-$CH_2CH_2CH_2CO_2$Et-4-Triz)	2-F	H	H
1-1062	Ac	H	CH_2-(2-$CH_2CH_2CH_2CO_2$Et-4-Triz)	2-F	H	H
1-1063	H	H	CH_2CH_2-(2-CO_2Me-4-Triz)	2-F	H	H
1-1064	Ac	H	CH_2CH_2-(2-CO_2Me-4-Triz)	2-F	H	H
1-1065	H	H	CH_2CH_2-(2-CO_2Et-4-Triz)	2-F	H	H
1-1066	Ac	H	CH_2CH_2-(2-CO_2Et-4-Triz)	2-F	H	H
1-1067	H	H	CH_2CH_2-(2-CH_2CO_2H-4-Triz)	2-F	H	H
1-1068	Ac	H	CH_2CH_2-(2-CH_2CO_2H-4-Triz)	2-F	H	H
1-1069	H	H	CH_2CH_2-(2-CH_2CO_2Me-4-Triz)	2-F	H	H
1-1070	Ac	H	CH_2CH_2-(2-CH_2CO_2Me-4-Triz)	2-F	H	H
1-1071	H	H	CH_2CH_2-(2-CH_2CO_2Et-4-Triz)	2-F	H	H
1-1072	Ac	H	CH_2CH_2-(2-CH_2CO_2Et-4-Triz)	2-F	H	H

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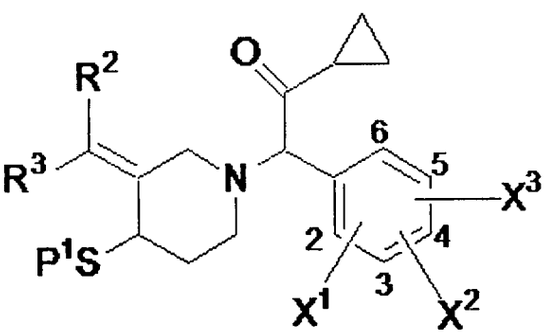
1-1073	H	H	CH_2CH_2-(2-$CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
1-1074	Ac	H	CH_2CH_2-(2-$CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
1-1075	H	H	CH_2CH_2-(2-$CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
1-1076	Ac	H	CH_2CH_2-(2-$CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
1-1077	H	H	CH_2CH_2-(2-$CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
1-1078	Ac	H	CH_2CH_2-(2-$CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
1-1079	H	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
1-1080	Ac	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
1-1081	H	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
1-1082	Ac	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
1-1083	H	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
1-1084	Ac	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H

(Tabla 2)



Comp. No.	P^1	R^2	R^3	X^1	X^2	X^3
2-1	H	H	CH_2-1-Pyza	2-F	H	H
2-2	Ac	H	CH_2-1-Pyza	2-F	H	H
2-3	H	H	CH_2-1-Pyza	2-F	4-F	H
2-4	Ac	H	CH_2-1-Pyza	2-F	4-F	H
2-5	H	H	CH_2-(3-CO_2H-1-Pyza)	2-F	H	H
2-6	Ac	H	CH_2-(3-CO_2H-1-Pyza)	2-F	H	H
2-7	H	H	CH_2-(3-CO_2H-1-Pyza)	2-F	4-F	H
2-8	Ac	H	CH_2-(3-CO_2H-1-Pyza)	2-F	4-F	H
2-9	H	H	CH_2-(3-CO_2Me-1-Pyza)	2-F	H	H

2-10	Ac	H	CH_2-(3-CO_2Me-1-Pyza)	2-F	H	H
2-11	H	H	CH_2-(3-CO_2Me-1-Pyza)	2-F	4-F	H
2-12	Ac	H	CH_2-(3-CO_2Me-1-Pyza)	2-F	4-F	H
2-13	H	H	CH_2-(3-CO_2Et-1-Pyza)	2-F	H	H
2-14	Ac	H	CH_2-(3-CO_2Et-1-Pyza)	2-F	H	H
2-15	H	H	CH_2-(3-CO_2Et-1-Pyza)	2-F	4-F	H
2-16	Ac	H	CH_2-(3-CO_2Et-1-Pyza)	2-F	4-F	H
2-17	H	H	CH_2-(4-CO_2H-1-Pyza)	2-F	H	H
2-18	Ac	H	CH_2-(4-CO_2H-1-Pyza)	2-F	H	H
2-19	H	H	CH_2-(4-CO_2H-1-Pyza)	2-F	4-F	H
2-20	Ac	H	CH_2-(4-CO_2H-1-Pyza)	2-F	4-F	H
2-21	H	H	CH_2-(4-CO_2Me-1-Pyza)	2-F	H	H
2-22	Ac	H	CH_2-(4-CO_2Me-1-Pyza)	2-F	H	H
2-23	H	H	CH_2-(4-CO_2Me-1-Pyza)	2-F	4-F	H
2-24	Ac	H	CH_2-(4-CO_2Me-1-Pyza)	2-F	4-F	H
2-25	H	H	CH_2-(4-CO_2Et-1-Pyza)	2-F	H	H
2-26	Ac	H	CH_2-(4-CO_2Et-1-Pyza)	2-F	H	H
2-27	H	H	CH_2-(4-CO_2Et-1-Pyza)	2-F	4-F	H
2-28	Ac	H	CH_2-(4-CO_2Et-1-Pyza)	2-F	4-F	H
2-29	H	H	CH_2-(5-CO_2H-1-Pyza)	2-F	H	H
2-30	Ac	H	CH_2-(5-CO_2H-1-Pyza)	2-F	H	H
2-31	H	H	CH_2-(5-CO_2H-1-Pyza)	2-F	4-F	H
2-32	Ac	H	CH_2-(5-CO_2H-1-Pyza)	2-F	4-F	H
2-33	H	H	CH_2-(5-CO_2Me-1-Pyza)	2-F	H	H
2-34	Ac	H	CH_2-(5-CO_2Me-1-Pyza)	2-F	H	H
2-35	H	H	CH_2-(5-CO_2Me-1-Pyza)	2-F	4-F	H
2-36	Ac	H	CH_2-(5-CO_2Me-1-Pyza)	2-F	4-F	H
2-37	H	H	CH_2-(5-CO_2Et-1-Pyza)	2-F	H	H
2-38	Ac	H	CH_2-(5-CO_2Et-1-Pyza)	2-F	H	H
2-39	H	H	CH_2-(5-CO_2Et-1-Pyza)	2-F	4-F	H
2-40	Ac	H	CH_2-(5-CO_2Et-1-Pyza)	2-F	4-F	H

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2-41	H	H	CH_2-(3-CH_2CO_2H-1-Pyza)	2-F	H	H
2-42	Ac	H	CH_2-(3-CH_2CO_2H-1-Pyza)	2-F	H	H
2-43	H	H	CH_2-(3-CH_2CO_2H-1-Pyza)	2-F	4-F	H
2-44	Ac	H	CH_2-(3-CH_2CO_2H-1-Pyza)	2-F	4-F	H
2-45	H	H	CH_2-(3-CH_2CO_2Me-1-Pyza)	2-F	H	H
2-46	Ac	H	CH_2-(3-CH_2CO_2Me-1-Pyza)	2-F	H	H
2-47	H	H	CH_2-(3-CH_2CO_2Me-1-Pyza)	2-F	4-F	H
2-48	Ac	H	CH_2-(3-CH_2CO_2Me-1-Pyza)	2-F	4-F	H
2-49	H	H	CH_2-(3-CH_2CO_2Et-1-Pyza)	2-F	H	H
2-50	Ac	H	CH_2-(3-CH_2CO_2Et-1-Pyza)	2-F	H	H
2-51	H	H	CH_2-(3-CH_2CO_2Et-1-Pyza)	2-F	4-F	H
2-52	Ac	H	CH_2-(3-CH_2CO_2Et-1-Pyza)	2-F	4-F	H
2-53	H	H	CH_2-(4-CH_2CO_2H-1-Pyza)	2-F	H	H
2-54	Ac	H	CH_2-(4-CH_2CO_2H-1-Pyza)	2-F	H	H
2-55	H	H	CH_2-(4-CH_2CO_2H-1-Pyza)	2-F	4-F	H
2-56	Ac	H	CH_2-(4-CH_2CO_2H-1-Pyza)	2-F	4-F	H
2-57	H	H	CH_2-(4-CH_2CO_2Me-1-Pyza)	2-F	H	H
2-58	Ac	H	CH_2-(4-CH_2CO_2Me-1-Pyza)	2-F	H	H
2-59	H	H	CH_2-(4-CH_2CO_2Me-1-Pyza)	2-F	4-F	H
2-60	Ac	H	CH_2-(4-CH_2CO_2Me-1-Pyza)	2-F	4-F	H
2-61	H	H	CH_2-(4-CH_2CO_2Et-1-Pyza)	2-F	H	H
2-62	Ac	H	CH_2-(4-CH_2CO_2Et-1-Pyza)	2-F	H	H
2-63	H	H	CH_2-(4-CH_2CO_2Et-1-Pyza)	2-F	4-F	H
2-64	Ac	H	CH_2-(4-CH_2CO_2Et-1-Pyza)	2-F	4-F	H
2-65	H	H	CH_2-(5-CH_2CO_2H-1-Pyza)	2-F	H	H
2-66	Ac	H	CH_2-(5-CH_2CO_2H-1-Pyza)	2-F	H	H
2-67	H	H	CH_2-(5-CH_2CO_2H-1-Pyza)	2-F	4-F	H
2-68	Ac	H	CH_2-(5-CH_2CO_2H-1-Pyza)	2-F	4-F	H
2-69	H	H	CH_2-(5-CH_2CO_2Me-1-Pyza)	2-F	H	H
2-70	Ac	H	CH_2-(5-CH_2CO_2Me-1-Pyza)	2-F	H	H
2-71	H	H	CH_2-(5-CH_2CO_2Me-1-Pyza)	2-F	4-F	H

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2-72	Ac	H	CH_2-(5-CH_2CO_2Me-1-Pyza)	2-F	4-F	H
2-73	H	H	CH_2-(5-CH_2CO_2Et-1-Pyza)	2-F	H	H
2-74	Ac	H	CH_2-(5-CH_2CO_2Et-1-Pyza)	2-F	H	H
2-75	H	H	CH_2-(5-CH_2CO_2Et-1-Pyza)	2-F	4-F	H
2-76	Ac	H	CH_2-(5-CH_2CO_2Et-1-Pyza)	2-F	4-F	H
2-77	H	H	CH_2-(3-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
2-78	Ac	H	CH_2-(3-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
2-79	H	H	CH_2-(3-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
2-80	Ac	H	CH_2-(3-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
2-81	H	H	CH_2-(3-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
2-82	Ac	H	CH_2-(3-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
2-83	H	H	CH_2-(4-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
2-84	Ac	H	CH_2-(4-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
2-85	H	H	CH_2-(4-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
2-86	Ac	H	CH_2-(4-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
2-87	H	H	CH_2-(4-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
2-88	Ac	H	CH_2-(4-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
2-89	H	H	CH_2-(5-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
2-90	Ac	H	CH_2-(5-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
2-91	H	H	CH_2-(5-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
2-92	Ac	H	CH_2-(5-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
2-93	H	H	CH_2-(5-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
2-94	Ac	H	CH_2-(5-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
2-95	H	H	CH_2-(3-$CH_2CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
2-96	Ac	H	CH_2-(3-$CH_2CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
2-97	H	H	CH_2-(3-$CH_2CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
2-98	Ac	H	CH_2-(3-$CH_2CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
2-99	H	H	CH_2-(3-$CH_2CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
2-100	Ac	H	CH_2-(3-$CH_2CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
2-101	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
2-102	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H

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2-103	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
2-104	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
2-105	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
2-106	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
2-107	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
2-108	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
2-109	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
2-110	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
2-111	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
2-112	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
2-113	H	H	CH_2CH_2-1-Pyza	2-F	H	H
2-114	Ac	H	CH_2CH_2-1-Pyza	2-F	H	H
2-115	H	H	CH_2CH_2-(3-CO_2H-1-Pyza)	2-F	H	H
2-116	Ac	H	CH_2CH_2-(3-CO_2H-1-Pyza)	2-F	H	H
2-117	H	H	CH_2CH_2-(3-CO_2Me-1-Pyza)	2-F	H	H
2-118	Ac	H	CH_2CH_2-(3-CO_2Me-1-Pyza)	2-F	H	H
2-119	H	H	CH_2CH_2-(3-CO_2Et-1-Pyza)	2-F	H	H
2-120	Ac	H	CH_2CH_2-(3-CO_2Et-1-Pyza)	2-F	H	H
2-121	H	H	CH_2CH_2-(4-CO_2H-1-Pyza)	2-F	H	H
2-122	Ac	H	CH_2CH_2-(4-CO_2H-1-Pyza)	2-F	H	H
2-123	H	H	CH_2CH_2-(4-CO_2Me-1-Pyza)	2-F	H	H
2-124	Ac	H	CH_2CH_2-(4-CO_2Me-1-Pyza)	2-F	H	H
2-125	H	H	CH_2CH_2-(4-CO_2Et-1-Pyza)	2-F	H	H
2-126	Ac	H	CH_2CH_2-(4-CO_2Et-1-Pyza)	2-F	H	H
2-127	H	H	CH_2CH_2-(5-CO_2H-1-Pyza)	2-F	H	H
2-128	Ac	H	CH_2CH_2-(5-CO_2H-1-Pyza)	2-F	H	H
2-129	H	H	CH_2CH_2-(5-CO_2Me-1-Pyza)	2-F	H	H
2-130	Ac	H	CH_2CH_2-(5-CO_2Me-1-Pyza)	2-F	H	H
2-131	H	H	CH_2CH_2-(5-CO_2Et-1-Pyza)	2-F	H	H
2-132	Ac	H	CH_2CH_2-(5-CO_2Et-1-Pyza)	2-F	H	H
2-133	H	H	CH_2CH_2-(3-CH_2CO_2H-1-Pyza)	2-F	H	H

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2-134	Ac	H	CH_2CH_2-(3-CH_2CO_2H-1-Pyza)	2-F	H	H
2-135	H	H	CH_2CH_2-(3-CH_2CO_2Me-1-Pyza)	2-F	H	H
2-136	Ac	H	CH_2CH_2-(3-CH_2CO_2Me-1-Pyza)	2-F	H	H
2-137	H	H	CH_2CH_2-(3-CH_2CO_2Et-1-Pyza)	2-F	H	H
2-138	Ac	H	CH_2CH_2-(3-CH_2CO_2Et-1-Pyza)	2-F	H	H
2-139	H	H	CH_2CH_2-(4-CH_2CO_2H-1-Pyza)	2-F	H	H
2-140	Ac	H	CH_2CH_2-(4-CH_2CO_2H-1-Pyza)	2-F	H	H
2-141	H	H	CH_2CH_2-(4-CH_2CO_2Me-1-Pyza)	2-F	H	H
2-142	Ac	H	CH_2CH_2-(4-CH_2CO_2Me-1-Pyza)	2-F	H	H
2-143	H	H	CH_2CH_2-(4-CH_2CO_2Et-1-Pyza)	2-F	H	H
2-144	Ac	H	CH_2CH_2-(4-CH_2CO_2Et-1-Pyza)	2-F	H	H
2-145	H	H	CH_2CH_2-(5-CH_2CO_2H-1-Pyza)	2-F	H	H
2-146	Ac	H	CH_2CH_2-(5-CH_2CO_2H-1-Pyza)	2-F	H	H
2-147	H	H	CH_2CH_2-(5-CH_2CO_2Me-1-Pyza)	2-F	H	H
2-148	Ac	H	CH_2CH_2-(5-CH_2CO_2Me-1-Pyza)	2-F	H	H
2-149	H	H	CH_2CH_2-(5-CH_2CO_2Et-1-Pyza)	2-F	H	H
2-150	Ac	H	CH_2CH_2-(5-CH_2CO_2Et-1-Pyza)	2-F	H	H
2-151	H	H	CH_2CH_2-(3-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
2-152	Ac	H	CH_2CH_2-(3-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
2-153	H	H	CH_2CH_2-(3-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
2-154	Ac	H	CH_2CH_2-(3-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
2-155	H	H	CH_2CH_2-(3-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
2-156	Ac	H	CH_2CH_2-(3-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
2-157	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
2-158	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
2-159	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
2-160	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
2-161	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
2-162	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
2-163	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
2-164	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H

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2-165	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
2-166	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
2-167	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
2-168	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
2-169	H	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
2-170	Ac	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
2-171	H	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
2-172	Ac	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
2-173	H	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
2-174	Ac	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
2-175	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
2-176	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
2-177	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
2-178	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
2-179	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
2-180	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
2-181	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
2-182	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
2-183	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
2-184	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
2-185	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
2-186	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
2-187	H	H	CH_2-3-Pyza	2-F	H	H
2-188	Ac	H	CH_2-3-Pyza	2-F	H	H
2-189	H	H	CH_2-3-Pyza	2-F	4-F	H
2-190	Ac	H	CH_2-3-Pyza	2-F	4-F	H
2-191	H	H	CH_2-(1-CO_2Me-3-Pyza)	2-F	H	H
2-192	Ac	H	CH_2-(1-CO_2Me-3-Pyza)	2-F	H	H
2-193	H	H	CH_2-(1-CO_2Et-3-Pyza)	2-F	H	H
2-194	Ac	H	CH_2-(1-CO_2Et-3-Pyza)	2-F	H	H
2-195	H	H	CH_2-(4-CO_2H-3-Pyza)	2-F	H	H

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2-196	Ac	H	CH_2-(4-CO_2H-3-Pyza)	2-F	H	H
2-197	H	H	CH_2-(4-CO_2Me-3-Pyza)	2-F	H	H
2-198	Ac	H	CH_2-(4-CO_2Me-3-Pyza)	2-F	H	H
2-199	H	H	CH_2-(4-CO_2Et-3-Pyza)	2-F	H	H
2-200	Ac	H	CH_2-(4-CO_2Et-3-Pyza)	2-F	H	H
2-201	H	H	CH_2-(5-CO_2H-3-Pyza)	2-F	H	H
2-202	Ac	H	CH_2-(5-CO_2H-3-Pyza)	2-F	H	H
2-203	H	H	CH_2-(5-CO_2Me-3-Pyza)	2-F	H	H
2-204	Ac	H	CH_2-(5-CO_2Me-3-Pyza)	2-F	H	H
2-205	H	H	CH_2-(5-CO_2Et-3-Pyza)	2-F	H	H
2-206	Ac	H	CH_2-(5-CO_2Et-3-Pyza)	2-F	H	H
2-207	H	H	CH_2-(1-CH_2CO_2H-3-Pyza)	2-F	H	H
2-208	Ac	H	CH_2-(1-CH_2CO_2H-3-Pyza)	2-F	H	H
2-209	H	H	CH_2-(1-CH_2CO_2Me-3-Pyza)	2-F	H	H
2-210	Ac	H	CH_2-(1-CH_2CO_2Me-3-Pyza)	2-F	H	H
2-211	H	H	CH_2-(1-CH_2CO_2Et-3-Pyza)	2-F	H	H
2-212	Ac	H	CH_2-(1-CH_2CO_2Et-3-Pyza)	2-F	H	H
2-213	H	H	CH_2-(4-CH_2CO_2H-3-Pyza)	2-F	H	H
2-214	Ac	H	CH_2-(4-CH_2CO_2H-3-Pyza)	2-F	H	H
2-215	H	H	CH_2-(4-CH_2CO_2Me-3-Pyza)	2-F	H	H
2-216	Ac	H	CH_2-(4-CH_2CO_2Me-3-Pyza)	2-F	H	H
2-217	H	H	CH_2-(4-CH_2CO_2Et-3-Pyza)	2-F	H	H
2-218	Ac	H	CH_2-(4-CH_2CO_2Et-3-Pyza)	2-F	H	H
2-219	H	H	CH_2-(5-CH_2CO_2H-3-Pyza)	2-F	H	H
2-220	Ac	H	CH_2-(5-CH_2CO_2H-3-Pyza)	2-F	H	H
2-221	H	H	CH_2-(5-CH_2CO_2Me-3-Pyza)	2-F	H	H
2-222	Ac	H	CH_2-(5-CH_2CO_2Me-3-Pyza)	2-F	H	H
2-223	H	H	CH_2-(5-CH_2CO_2Et-3-Pyza)	2-F	H	H
2-224	Ac	H	CH_2-(5-CH_2CO_2Et-3-Pyza)	2-F	H	H
2-225	H	H	CH_2-(1-$CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
2-226	Ac	H	CH_2-(1-$CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H

2-227	H	H	CH_2-(1-$CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
2-228	Ac	H	CH_2-(1-$CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
2-229	H	H	CH_2-(1-$CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
2-230	Ac	H	CH_2-(1-$CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
2-231	H	H	CH_2-(4-$CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
2-232	Ac	H	CH_2-(4-$CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
2-233	H	H	CH_2-(4-$CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
2-234	Ac	H	CH_2-(4-$CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
2-235	H	H	CH_2-(4-$CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
2-236	Ac	H	CH_2-(4-$CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
2-237	H	H	CH_2-(5-$CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
2-238	Ac	H	CH_2-(5-$CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
2-239	H	H	CH_2-(5-$CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
2-240	Ac	H	CH_2-(5-$CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
2-241	H	H	CH_2-(5-$CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
2-242	Ac	H	CH_2-(5-$CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
2-245	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
2-246	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
2-247	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
2-248	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
2-249	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
2-250	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
2-251	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
2-252	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
2-253	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
2-254	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
2-255	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
2-256	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
2-257	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
2-258	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
2-259	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H

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2-260	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
2-261	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
2-262	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
2-263	H	H	CH_2CH_2-3-Pyza	2-F	H	H
2-264	Ac	H	CH_2CH_2-3-Pyza	2-F	H	H
2-265	H	H	CH_2CH_2-3-Pyza	2-F	4-F	H
2-266	Ac	H	CH_2CH_2-3-Pyza	2-F	4-F	H
2-267	H	H	CH_2CH_2-(1-CO_2Me-3-Pyza)	2-F	H	H
2-268	Ac	H	CH_2CH_2-(1-CO_2Me-3-Pyza)	2-F	H	H
2-269	H	H	CH_2CH_2-(1-CO_2Et-3-Pyza)	2-F	H	H
2-270	Ac	H	CH_2CH_2-(1-CO_2Et-3-Pyza)	2-F	H	H
2-271	H	H	CH_2CH_2-(4-CO_2H-3-Pyza)	2-F	H	H
2-272	Ac	H	CH_2CH_2-(4-CO_2H-3-Pyza)	2-F	H	H
2-273	H	H	CH_2CH_2-(4-CO_2Me-3-Pyza)	2-F	H	H
2-274	Ac	H	CH_2CH_2-(4-CO_2Me-3-Pyza)	2-F	H	H
2-275	H	H	CH_2CH_2-(4-CO_2Et-3-Pyza)	2-F	H	H
2-276	Ac	H	CH_2CH_2-(4-CO_2Et-3-Pyza)	2-F	H	H
2-277	H	H	CH_2CH_2-(5-CO_2H-3-Pyza)	2-F	H	H
2-278	Ac	H	CH_2CH_2-(5-CO_2H-3-Pyza)	2-F	H	H
2-279	H	H	CH_2CH_2-(5-CO_2Me-3-Pyza)	2-F	H	H
2-280	Ac	H	CH_2CH_2-(5-CO_2Me-3-Pyza)	2-F	H	H
2-281	H	H	CH_2CH_2-(5-CO_2Et-3-Pyza)	2-F	H	H
2-282	Ac	H	CH_2CH_2-(5-CO_2Et-3-Pyza)	2-F	H	H
2-283	H	H	CH_2CH_2-(1-CH_2CO_2H-3-Pyza)	2-F	H	H
2-284	Ac	H	CH_2CH_2-(1-CH_2CO_2H-3-Pyza)	2-F	H	H
2-285	H	H	CH_2CH_2-(1-CH_2CO_2Me-3-Pyza)	2-F	H	H
2-286	Ac	H	CH_2CH_2-(1-CH_2CO_2Me-3-Pyza)	2-F	H	H
2-287	H	H	CH_2CH_2-(1-CH_2CO_2Et-3-Pyza)	2-F	H	H
2-288	Ac	H	CH_2CH_2-(1-CH_2CO_2Et-3-Pyza)	2-F	H	H
2-289	H	H	CH_2CH_2-(4-CH_2CO_2H-3-Pyza)	2-F	H	H
2-290	Ac	H	CH_2CH_2-(4-CH_2CO_2H-3-Pyza)	2-F	H	H

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2-291	H	H	CH_2CH_2-(4-CH_2CO_2Me-3-Pyza)	2-F	H	H
2-292	Ac	H	CH_2CH_2-(4-CH_2CO_2Me-3-Pyza)	2-F	H	H
2-293	H	H	CH_2CH_2-(4-CH_2CO_2Et-3-Pyza)	2-F	H	H
2-294	Ac	H	CH_2CH_2-(4-CH_2CO_2Et-3-Pyza)	2-F	H	H
2-295	H	H	CH_2CH_2-(5-CH_2CO_2H-3-Pyza)	2-F	H	H
2-296	Ac	H	CH_2CH_2-(5-CH_2CO_2H-3-Pyza)	2-F	H	H
2-297	H	H	CH_2CH_2-(5-CH_2CO_2Me-3-Pyza)	2-F	H	H
2-298	Ac	H	CH_2CH_2-(5-CH_2CO_2Me-3-Pyza)	2-F	H	H
2-299	H	H	CH_2CH_2-(5-CH_2CO_2Et-3-Pyza)	2-F	H	H
2-300	Ac	H	CH_2CH_2-(5-CH_2CO_2Et-3-Pyza)	2-F	H	H
2-301	H	H	CH_2CH_2-(1-$CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
2-302	Ac	H	CH_2CH_2-(1-$CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
2-303	H	H	CH_2CH_2-(1-$CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
2-304	Ac	H	CH_2CH_2-(1-$CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
2-305	H	H	CH_2CH_2-(1-$CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
2-306	Ac	H	CH_2CH_2-(1-$CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
2-307	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
2-308	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
2-309	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
2-310	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
2-311	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
2-312	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
2-313	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
2-314	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
2-315	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
2-316	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
2-317	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
2-318	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
2-319	H	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
2-320	Ac	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
2-321	H	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H

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2-322	Ac	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
2-323	H	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
2-324	Ac	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
2-325	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
2-326	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
2-327	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
2-328	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
2-329	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
2-330	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
2-331	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
2-332	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2H$-3-Pyza)	2-F	H	H
2-333	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
2-334	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Me$-3-Pyza)	2-F	H	H
2-335	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
2-336	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Et$-3-Pyza)	2-F	H	H
2-337	H	H	CH_2-4-Pyza	2-F	H	H
2-338	Ac	H	CH_2-4-Pyza	2-F	H	H
2-339	H	H	CH_2-4-Pyza	2-F	4-F	H
2-340	Ac	H	CH_2-4-Pyza	2-F	4-F	H
2-341	H	H	CH_2-(1-CO_2Me-4-Pyza)	2-F	H	H
2-342	Ac	H	CH_2-(1-CO_2Me-4-Pyza)	2-F	H	H
2-343	H	H	CH_2-(1-CO_2Et-4-Pyza)	2-F	H	H
2-344	Ac	H	CH_2-(1-CO_2Et-4-Pyza)	2-F	H	H
2-345	H	H	CH_2-(3-CO_2H-4-Pyza)	2-F	H	H
2-346	Ac	H	CH_2-(3-CO_2H-4-Pyza)	2-F	H	H
2-347	H	H	CH_2-(3-CO_2Me-4-Pyza)	2-F	H	H
2-348	Ac	H	CH_2-(3-CO_2Me-4-Pyza)	2-F	H	H
2-349	H	H	CH_2-(3-CO_2Et-4-Pyza)	2-F	H	H
2-350	Ac	H	CH_2-(3-CO_2Et-4-Pyza)	2-F	H	H
2-351	H	H	CH_2-(1-CH_2CO_2H-4-Pyza)	2-F	H	H
2-352	Ac	H	CH_2-(1-CH_2CO_2H-4-Pyza)	2-F	H	H

2-353	H	H	CH_2-(1-CH_2CO_2Me-4-Pyza)	2-F	H	H
2-354	Ac	H	CH_2-(1-CH_2CO_2Me-4-Pyza)	2-F	H	H
2-355	H	H	CH_2-(1-CH_2CO_2Et-4-Pyza)	2-F	H	H
2-356	Ac	H	CH_2-(1-CH_2CO_2Et-4-Pyza)	2-F	H	H
2-357	H	H	CH_2-(3-CH_2CO_2H-4-Pyza)	2-F	H	H
2-358	Ac	H	CH_2-(3-CH_2CO_2H-4-Pyza)	2-F	H	H
2-359	H	H	CH_2-(3-CH_2CO_2Me-4-Pyza)	2-F	H	H
2-360	Ac	H	CH_2-(3-CH_2CO_2Me-4-Pyza)	2-F	H	H
2-361	H	H	CH_2-(3-CH_2CO_2Et-4-Pyza)	2-F	H	H
2-362	Ac	H	CH_2-(3-CH_2CO_2Et-4-Pyza)	2-F	H	H
2-363	H	H	CH_2-(1-$CH_2CH_2CO_2H$-4-Pyza)	2-F	H	H
2-364	Ac	H	CH_2-(1-$CH_2CH_2CO_2H$-4-Pyza)	2-F	H	H
2-365	H	H	CH_2-(1-$CH_2CH_2CO_2Me$-4-Pyza)	2-F	H	H
2-366	Ac	H	CH_2-(1-$CH_2CH_2CO_2Me$-4-Pyza)	2-F	H	H
2-367	H	H	CH_2-(1-$CH_2CH_2CO_2Et$-4-Pyza)	2-F	H	H
2-368	Ac	H	CH_2-(1-$CH_2CH_2CO_2Et$-4-Pyza)	2-F	H	H
2-369	H	H	CH_2-(3-$CH_2CH_2CO_2H$-4-Pyza)	2-F	H	H
2-370	Ac	H	CH_2-(3-$CH_2CH_2CO_2H$-4-Pyza)	2-F	H	H
2-371	H	H	CH_2-(3-$CH_2CH_2CO_2Me$-4-Pyza)	2-F	H	H
2-372	Ac	H	CH_2-(3-$CH_2CH_2CO_2Me$-4-Pyza)	2-F	H	H
2-373	H	H	CH_2-(3-$CH_2CH_2CO_2Et$-4-Pyza)	2-F	H	H
2-374	Ac	H	CH_2-(3-$CH_2CH_2CO_2Et$-4-Pyza)	2-F	H	H
2-375	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2H$-4-Pyza)	2-F	H	H
2-376	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2H$-4-Pyza)	2-F	H	H
2-377	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2Me$-4-Pyza)	2-F	H	H
2-378	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2Me$-4-Pyza)	2-F	H	H
2-379	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2Et$-4-Pyza)	2-F	H	H
2-380	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2Et$-4-Pyza)	2-F	H	H
2-381	H	H	CH_2-(3-$CH_2CH_2CH_2CO_2H$-4-Pyza)	2-F	H	H
2-382	Ac	H	CH_2-(3-$CH_2CH_2CH_2CO_2H$-4-Pyza)	2-F	H	H
2-383	H	H	CH_2-(3-$CH_2CH_2CH_2CO_2Me$-4-Pyza)	2-F	H	H

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2-384	Ac	H	CH_2-(3-$CH_2CH_2CH_2CO_2Me$-4-Pyza)	2-F	H	H
2-385	H	H	CH_2-(3-$CH_2CH_2CH_2CO_2Et$-4-Pyza)	2-F	H	H
2-386	Ac	H	CH_2-(3-$CH_2CH_2CH_2CO_2Et$-4-Pyza)	2-F	H	H
2-387	H	H	CH_2CH_2-4-Pyza	2-F	H	H
2-388	Ac	H	CH_2CH_2-4-Pyza	2-F	H	H
2-389	H	H	CH_2CH_2-4-Pyza	2-F	4-F	H
2-390	Ac	H	CH_2CH_2-4-Pyza	2-F	4-F	H
2-391	H	H	CH_2CH_2-(1-CO_2Me-4-Pyza)	2-F	H	H
2-392	Ac	H	CH_2CH_2-(1-CO_2Me-4-Pyza)	2-F	H	H
2-393	H	H	CH_2CH_2-(1-CO_2Et-4-Pyza)	2-F	H	H
2-394	Ac	H	CH_2CH_2-(1-CO_2Et-4-Pyza)	2-F	H	H
2-395	H	H	CH_2CH_2-(3-CO_2H-4-Pyza)	2-F	H	H
2-396	Ac	H	CH_2CH_2-(3-CO_2H-4-Pyza)	2-F	H	H
2-397	H	H	CH_2CH_2-(3-CO_2Me-4-Pyza)	2-F	H	H
2-398	Ac	H	CH_2CH_2-(3-CO_2Me-4-Pyza)	2-F	H	H
2-399	H	H	CH_2CH_2-(3-CO_2Et-4-Pyza)	2-F	H	H
2-400	Ac	H	CH_2CH_2-(3-CO_2Et-4-Pyza)	2-F	H	H
2-401	H	H	CH_2CH_2-(1-CH_2CO_2H-4-Pyza)	2-F	H	H
2-402	Ac	H	CH_2CH_2-(1-CH_2CO_2H-4-Pyza)	2-F	H	H
2-403	H	H	CH_2CH_2-(1-CH_2CO_2Me-4-Pyza)	2-F	H	H
2-404	Ac	H	CH_2CH_2-(1-CH_2CO_2Me-4-Pyza)	2-F	H	H
2-405	H	H	CH_2CH_2-(1-CH_2CO_2Et-4-Pyza)	2-F	H	H
2-406	Ac	H	CH_2CH_2-(1-CH_2CO_2Et-4-Pyza)	2-F	H	H
2-407	H	H	CH_2CH_2-(3-CH_2CO_2H-4-Pyza)	2-F	H	H
2-408	Ac	H	CH_2CH_2-(3-CH_2CO_2H-4-Pyza)	2-F	H	H
2-409	H	H	CH_2CH_2-(3-CH_2CO_2Me-4-Pyza)	2-F	H	H
2-410	Ac	H	CH_2CH_2-(3-CH_2CO_2Me-4-Pyza)	2-F	H	H
2-411	H	H	CH_2CH_2-(3-CH_2CO_2Et-4-Pyza)	2-F	H	H
2-412	Ac	H	CH_2CH_2-(3-CH_2CO_2Et-4-Pyza)	2-F	H	H
2-413	H	H	CH_2CH_2-(1-$CH_2CH_2CO_2H$-4-Pyza)	2-F	H	H
2-414	Ac	H	CH_2CH_2-(1-$CH_2CH_2CO_2H$-4-Pyza)	2-F	H	H

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2-415	H	H	CH_2CH_2-(1-$CH_2CH_2CO_2Me$-4-Pyza)	2-F	H	H
2-416	Ac	H	CH_2CH_2-(1-$CH_2CH_2CO_2Me$-4-Pyza)	2-F	H	H
2-417	H	H	CH_2CH_2-(1-$CH_2CH_2CO_2Et$-4-Pyza)	2-F	H	H
2-418	Ac	H	CH_2CH_2-(1-$CH_2CH_2CO_2Et$-4-Pyza)	2-F	H	H
2-419	H	H	CH_2CH_2-(3-$CH_2CH_2CO_2H$-4-Pyza)	2-F	H	H
2-420	Ac	H	CH_2CH_2-(3-$CH_2CH_2CO_2H$-4-Pyza)	2-F	H	H
2-421	H	H	CH_2CH_2-(3-$CH_2CH_2CO_2Me$-4-Pyza)	2-F	H	H
2-422	Ac	H	CH_2CH_2-(3-$CH_2CH_2CO_2Me$-4-Pyza)	2-F	H	H
2-423	H	H	CH_2CH_2-(3-$CH_2CH_2CO_2Et$-4-Pyza)	2-F	H	H
2-424	Ac	H	CH_2CH_2-(3-$CH_2CH_2CO_2Et$-4-Pyza)	2-F	H	H
2-425	H	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2H$-4-Pyza)	2-F	H	H
2-426	Ac	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2H$-4-Pyza)	2-F	H	H
2-427	H	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Me$-4-Pyza)	2-F	H	H
2-428	Ac	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Me$-4-Pyza)	2-F	H	H
2-429	H	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Et$-4-Pyza)	2-F	H	H
2-430	Ac	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Et$-4-Pyza)	2-F	H	H
2-431	H	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2H$-4-Pyza)	2-F	H	H
2-432	Ac	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2H$-4-Pyza)	2-F	H	H
2-433	H	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2Me$-4-Pyza)	2-F	H	H
2-434	Ac	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2Me$-4-Pyza)	2-F	H	H
2-435	H	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2Et$-4-Pyza)	2-F	H	H
2-436	Ac	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2Et$-4-Pyza)	2-F	H	H
2-437	H	H	CH_2-(1-CO_2Me-5-Pyza)	2-F	4-F	H
2-438	Ac	H	CH_2-(1-CO_2Me-5-Pyza)	2-F	4-F	H
2-439	H	H	CH_2-(1-CO_2Me-5-Pyza)	2-F	H	H
2-440	Ac	H	CH_2-(1-CO_2Me-5-Pyza)	2-F	H	H
2-441	H	H	CH_2-(1-CO_2Et-5-Pyza)	2-F	H	H
2-442	Ac	H	CH_2-(1-CO_2Et-5-Pyza)	2-F	H	H
2-443	H	H	CH_2-(1-CH_2CO_2H-5-Pyza)	2-F	H	H
2-444	Ac	H	CH_2-(1-CH_2CO_2H-5-Pyza)	2-F	H	H
2-445	H	H	CH_2-(1-CH_2CO_2Me-5-Pyza)	2-F	H	H

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2-446	Ac	H	CH_2-(1-CH_2CO_2Me-5-Pyza)	2-F	H	H
2-447	H	H	CH_2-(1-CH_2CO_2Et-5-Pyza)	2-F	H	H
2-448	Ac	H	CH_2-(1-CH_2CO_2Et-5-Pyza)	2-F	H	H
2-449	H	H	CH_2-(1-$CH_2CH_2CO_2H$-5-Pyza)	2-F	H	H
2-450	Ac	H	CH_2-(1-$CH_2CH_2CO_2H$-5-Pyza)	2-F	H	H
2-451	H	H	CH_2-(1-$CH_2CH_2CO_2Me$-5-Pyza)	2-F	H	H
2-452	Ac	H	CH_2-(1-$CH_2CH_2CO_2Me$-5-Pyza)	2-F	H	H
2-453	H	H	CH_2-(1-$CH_2CH_2CO_2Et$-5-Pyza)	2-F	H	H
2-454	Ac	H	CH_2-(1-$CH_2CH_2CO_2Et$-5-Pyza)	2-F	H	H
2-455	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2H$-5-Pyza)	2-F	H	H
2-456	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2H$-5-Pyza)	2-F	H	H
2-457	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2Me$-5-Pyza)	2-F	H	H
2-458	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2Me$-5-Pyza)	2-F	H	H
2-459	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2Et$-5-Pyza)	2-F	H	H
2-460	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2Et$-5-Pyza)	2-F	H	H
2-461	H	H	CH_2CH_2-(1-CO_2Me-5-Pyza)	2-F	4-F	H
2-462	Ac	H	CH_2CH_2-(1-CO_2Me-5-Pyza)	2-F	4-F	H
2-463	H	H	CH_2CH_2-(1-CO_2Me-5-Pyza)	2-F	H	H
2-464	Ac	H	CH_2CH_2-(1-CO_2Me-5-Pyza)	2-F	H	H
2-465	H	H	CH_2CH_2-(1-CO_2Et-5-Pyza)	2-F	H	H
2-466	Ac	H	CH_2CH_2-(1-CO_2Et-5-Pyza)	2-F	H	H
2-467	H	H	CH_2CH_2-(1-CH_2CO_2H-5-Pyza)	2-F	H	H
2-468	Ac	H	CH_2CH_2-(1-CH_2CO_2H-5-Pyza)	2-F	H	H
2-469	H	H	CH_2CH_2-(1-CH_2CO_2Me-5-Pyza)	2-F	H	H
2-470	Ac	H	CH_2CH_2-(1-CH_2CO_2Me-5-Pyza)	2-F	H	H
2-471	H	H	CH_2CH_2-(1-CH_2CO_2Et-5-Pyza)	2-F	H	H
2-472	Ac	H	CH_2CH_2-(1-CH_2CO_2Et-5-Pyza)	2-F	H	H
2-473	H	H	CH_2CH_2-(1-$CH_2CH_2CO_2H$-5-Pyza)	2-F	H	H
2-474	Ac	H	CH_2CH_2-(1-$CH_2CH_2CO_2H$-5-Pyza)	2-F	H	H
2-475	H	H	CH_2CH_2-(1-$CH_2CH_2CO_2Me$-5-Pyza)	2-F	H	H
2-476	Ac	H	CH_2CH_2-(1-$CH_2CH_2CO_2Me$-5-Pyza)	2-F	H	H

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2-477	H	H	CH_2CH_2-(1-$CH_2CH_2CO_2Et$-5-Pyza)	2-F	H	H
2-478	Ac	H	CH_2CH_2-(1-$CH_2CH_2CO_2Et$-5-Pyza)	2-F	H	H
2-479	H	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2H$-5-Pyza)	2-F	H	H
2-480	Ac	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2H$-5-Pyza)	2-F	H	H
2-481	H	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Me$-5-Pyza)	2-F	H	H
2-482	Ac	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Me$-5-Pyza)	2-F	H	H
2-483	H	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Et$-5-Pyza)	2-F	H	H
2-484	Ac	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Et$-5-Pyza)	2-F	H	H
2-485	H	H	CH_2-1-Triz	2-F	H	H
2-486	Ac	H	CH_2-1-Triz	2-F	H	H
2-487	H	H	CH_2-(4-CO_2H-1-Triz)	2-F	H	H
2-488	Ac	H	CH_2-(4-CO_2H-1-Triz)	2-F	H	H
2-489	H	H	CH_2-(4-CO_2Me-1-Triz)	2-F	H	H
2-490	Ac	H	CH_2-(4-CO_2Me-1-Triz)	2-F	H	H
2-491	H	H	CH_2-(4-CO_2Et-1-Triz)	2-F	H	H
2-492	Ac	H	CH_2-(4-CO_2Et-1-Triz)	2-F	H	H
2-493	H	H	CH_2-(5-CO_2H-1-Triz)	2-F	H	H
2-494	Ac	H	CH_2-(5-CO_2H-1-Triz)	2-F	H	H
2-495	H	H	CH_2-(5-CO_2Me-1-Triz)	2-F	H	H
2-496	Ac	H	CH_2-(5-CO_2Me-1-Triz)	2-F	H	H
2-497	H	H	CH_2-(5-CO_2Et-1-Triz)	2-F	H	H
2-498	Ac	H	CH_2-(5-CO_2Et-1-Triz)	2-F	H	H
2-499	H	H	CH_2-(4-CH_2CO_2H-1-Triz)	2-F	H	H
2-500	Ac	H	CH_2-(4-CH_2CO_2H-1-Triz)	2-F	H	H
2-501	H	H	CH_2-(4-CH_2CO_2Me-1-Triz)	2-F	H	H
2-502	Ac	H	CH_2-(4-CH_2CO_2Me-1-Triz)	2-F	H	H
2-503	H	H	CH_2-(4-CH_2CO_2Et-1-Triz)	2-F	H	H
2-504	Ac	H	CH_2-(4-CH_2CO_2Et-1-Triz)	2-F	H	H
2-505	H	H	CH_2-(5-CH_2CO_2H-1-Triz)	2-F	H	H
2-506	Ac	H	CH_2-(5-CH_2CO_2H-1-Triz)	2-F	H	H
2-507	H	H	CH_2-(5-CH_2CO_2Me-1-Triz)	2-F	H	H

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2-508	Ac	H	CH_2-(5-CH_2CO_2Me-1-Triz)	2-F	H	H
2-509	H	H	CH_2-(5-CH_2CO_2Et-1-Triz)	2-F	H	H
2-510	Ac	H	CH_2-(5-CH_2CO_2Et-1-Triz)	2-F	H	H
2-511	H	H	CH_2-(4-$CH_2CH_2CO_2H$-1-Triz)	2-F	H	H
2-512	Ac	H	CH_2-(4-$CH_2CH_2CO_2H$-1-Triz)	2-F	H	H
2-513	H	H	CH_2-(4-$CH_2CH_2CO_2Me$-1-Triz)	2-F	H	H
2-514	Ac	H	CH_2-(4-$CH_2CH_2CO_2Me$-1-Triz)	2-F	H	H
2-515	H	H	CH_2-(4-$CH_2CH_2CO_2Et$-1-Triz)	2-F	H	H
2-516	Ac	H	CH_2-(4-$CH_2CH_2CO_2Et$-1-Triz)	2-F	H	H
2-517	H	H	CH_2-(5-$CH_2CH_2CO_2H$-1-Triz)	2-F	H	H
2-518	Ac	H	CH_2-(5-$CH_2CH_2CO_2H$-1-Triz)	2-F	H	H
2-519	H	H	CH_2-(5-$CH_2CH_2CO_2Me$-1-Triz)	2-F	H	H
2-520	Ac	H	CH_2-(5-$CH_2CH_2CO_2Me$-1-Triz)	2-F	H	H
2-521	H	H	CH_2-(5-$CH_2CH_2CO_2Et$-1-Triz)	2-F	H	H
2-522	Ac	H	CH_2-(5-$CH_2CH_2CO_2Et$-1-Triz)	2-F	H	H
2-523	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2H$-1-Triz)	2-F	H	H
2-524	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2H$-1-Triz)	2-F	H	H
2-525	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2Me$-1-Triz)	2-F	H	H
2-526	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2Me$-1-Triz)	2-F	H	H
2-527	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2Et$-1-Triz)	2-F	H	H
2-528	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2Et$-1-Triz)	2-F	H	H
2-529	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2H$-1-Triz)	2-F	H	H
2-530	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2H$-1-Triz)	2-F	H	H
2-531	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2Me$-1-Triz)	2-F	H	H
2-532	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2Me$-1-Triz)	2-F	H	H
2-533	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2Et$-1-Triz)	2-F	H	H
2-534	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2Et$-1-Triz)	2-F	H	H
2-535	H	H	CH_2CH_2-1-Triz	2-F	H	H
2-536	Ac	H	CH_2CH_2-1-Triz	2-F	H	H
2-537	H	H	CH_2CH_2-(4-CO_2H-1-Triz)	2-F	H	H
2-538	Ac	H	CH_2CH_2-(4-CO_2H-1-Triz)	2-F	H	H

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2-539	H	H	CH_2CH_2-(4-CO_2Me-1-Triz)	2-F	H	H
2-540	Ac	H	CH_2CH_2-(4-CO_2Me-1-Triz)	2-F	H	H
2-541	H	H	CH_2CH_2-(4-CO_2Et-1-Triz)	2-F	H	H
2-542	Ac	H	CH_2CH_2-(4-CO_2Et-1-Triz)	2-F	H	H
2-543	H	H	CH_2CH_2-(5-CO_2H-1-Triz)	2-F	H	H
2-544	Ac	H	CH_2CH_2-(5-CO_2H-1-Triz)	2-F	H	H
2-545	H	H	CH_2CH_2-(5-CO_2Me-1-Triz)	2-F	H	H
2-546	Ac	H	CH_2CH_2-(5-CO_2Me-1-Triz)	2-F	H	H
2-547	H	H	CH_2CH_2-(5-CO_2Et-1-Triz)	2-F	H	H
2-548	Ac	H	CH_2CH_2-(5-CO_2Et-1-Triz)	2-F	H	H
2-549	H	H	CH_2CH_2-(4-CH_2CO_2H-1-Triz)	2-F	H	H
2-550	Ac	H	CH_2CH_2-(4-CH_2CO_2H-1-Triz)	2-F	H	H
2-551	H	H	CH_2CH_2-(4-CH_2CO_2Me-1-Triz)	2-F	H	H
2-552	Ac	H	CH_2CH_2-(4-CH_2CO_2Me-1-Triz)	2-F	H	H
2-553	H	H	CH_2CH_2-(4-CH_2CO_2Et-1-Triz)	2-F	H	H
2-554	Ac	H	CH_2CH_2-(4-CH_2CO_2Et-1-Triz)	2-F	H	H
2-555	H	H	CH_2CH_2-(5-CH_2CO_2H-1-Triz)	2-F	H	H
2-556	Ac	H	CH_2CH_2-(5-CH_2CO_2H-1-Triz)	2-F	H	H
2-557	H	H	CH_2CH_2-(5-CH_2CO_2Me-1-Triz)	2-F	H	H
2-558	Ac	H	CH_2CH_2-(5-CH_2CO_2Me-1-Triz)	2-F	H	H
2-559	H	H	CH_2CH_2-(5-CH_2CO_2Et-1-Triz)	2-F	H	H
2-560	Ac	H	CH_2CH_2-(5-CH_2CO_2Et-1-Triz)	2-F	H	H
2-561	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2H$-1-Triz)	2-F	H	H
2-562	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2H$-1-Triz)	2-F	H	H
2-563	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-1-Triz)	2-F	H	H
2-564	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-1-Triz)	2-F	H	H
2-565	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-1-Triz)	2-F	H	H
2-566	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-1-Triz)	2-F	H	H
2-567	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2H$-1-Triz)	2-F	H	H
2-568	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2H$-1-Triz)	2-F	H	H
2-569	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2Me$-1-Triz)	2-F	H	H

2-570	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2Me$-1-Triz)	2-F	H	H
2-571	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2Et$-1-Triz)	2-F	H	H
2-572	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2Et$-1-Triz)	2-F	H	H
2-573	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2H$-1-Triz)	2-F	H	H
2-574	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2H$-1-Triz)	2-F	H	H
2-575	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Me$-1-Triz)	2-F	H	H
2-576	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Me$-1-Triz)	2-F	H	H
2-577	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Et$-1-Triz)	2-F	H	H
2-578	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Et$-1-Triz)	2-F	H	H
2-579	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2H$-1-Triz)	2-F	H	H
2-580	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2H$-1-Triz)	2-F	H	H
2-581	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Me$-1-Triz)	2-F	H	H
2-582	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Me$-1-Triz)	2-F	H	H
2-583	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Et$-1-Triz)	2-F	H	H
2-584	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Et$-1-Triz)	2-F	H	H
2-585	H	H	CH_2-2-Triz	2-F	H	H
2-586	Ac	H	CH_2-2-Triz	2-F	H	H
2-587	H	H	CH_2-(4-CO_2H-2-Triz)	2-F	H	H
2-588	Ac	H	CH_2-(4-CO_2H-2-Triz)	2-F	H	H
2-589	H	H	CH_2-(4-CO_2Me-2-Triz)	2-F	H	H
2-590	Ac	H	CH_2-(4-CO_2Me-2-Triz)	2-F	H	H
2-591	H	H	CH_2-(4-CO_2Et-2-Triz)	2-F	H	H
2-592	Ac	H	CH_2-(4-CO_2Et-2-Triz)	2-F	H	H
2-593	H	H	CH_2-(4-CH_2CO_2H-2-Triz)	2-F	H	H
2-594	Ac	H	CH_2-(4-CH_2CO_2H-2-Triz)	2-F	H	H
2-595	H	H	CH_2-(4-CH_2CO_2Me-2-Triz)	2-F	H	H
2-596	Ac	H	CH_2-(4-CH_2CO_2Me-2-Triz)	2-F	H	H
2-597	H	H	CH_2-(4-CH_2CO_2Et-2-Triz)	2-F	H	H
2-598	Ac	H	CH_2-(4-CH_2CO_2Et-2-Triz)	2-F	H	H
2-599	H	H	CH_2-(4-$CH_2CH_2CO_2H$-2-Triz)	2-F	H	H
2-600	Ac	H	CH_2-(4-$CH_2CH_2CO_2H$-2-Triz)	2-F	H	H

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2-601	H	H	CH_2-(4-$CH_2CH_2CO_2Me$-2-Triz)	2-F	H	H
2-602	Ac	H	CH_2-(4-$CH_2CH_2CO_2Me$-2-Triz)	2-F	H	H
2-603	H	H	CH_2-(4-$CH_2CH_2CO_2Et$-2-Triz)	2-F	H	H
2-604	Ac	H	CH_2-(4-$CH_2CH_2CO_2Et$-2-Triz)	2-F	H	H
2-605	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2H$-2-Triz)	2-F	H	H
2-606	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2H$-2-Triz)	2-F	H	H
2-607	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2Me$-2-Triz)	2-F	H	H
2-608	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2Me$-2-Triz)	2-F	H	H
2-609	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2Et$-2-Triz)	2-F	H	H
2-610	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2Et$-2-Triz)	2-F	H	H
2-611	H	H	CH_2CH_2-2-Triz	2-F	H	H
2-612	Ac	H	CH_2CH_2-2-Triz	2-F	H	H
2-613	H	H	CH_2CH_2-(4-CO_2H-2-Triz)	2-F	H	H
2-614	Ac	H	CH_2CH_2-(4-CO_2H-2-Triz)	2-F	H	H
2-615	H	H	CH_2CH_2-(4-CO_2Me-2-Triz)	2-F	H	H
2-616	Ac	H	CH_2CH_2-(4-CO_2Me-2-Triz)	2-F	H	H
2-617	H	H	CH_2CH_2-(4-CO_2Et-2-Triz)	2-F	H	H
2-618	Ac	H	CH_2CH_2-(4-CO_2Et-2-Triz)	2-F	H	H
2-619	H	H	CH_2CH_2-(4-CH_2CO_2H-2-Triz)	2-F	H	H
2-620	Ac	H	CH_2CH_2-(4-CH_2CO_2H-2-Triz)	2-F	H	H
2-621	H	H	CH_2CH_2-(4-CH_2CO_2Me-2-Triz)	2-F	H	H
2-622	Ac	H	CH_2CH_2-(4-CH_2CO_2Me-2-Triz)	2-F	H	H
2-623	H	H	CH_2CH_2-(4-CH_2CO_2Et-2-Triz)	2-F	H	H
2-624	Ac	H	CH_2CH_2-(4-CH_2CO_2Et-2-Triz)	2-F	H	H
2-625	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2H$-2-Triz)	2-F	H	H
2-626	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2H$-2-Triz)	2-F	H	H
2-627	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-2-Triz)	2-F	H	H
2-628	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-2-Triz)	2-F	H	H
2-629	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-2-Triz)	2-F	H	H
2-630	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-2-Triz)	2-F	H	H
2-631	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2H$-2-Triz)	2-F	H	H

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2-632	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2H$-2-Triz)	2-F	H	H
2-633	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Me$-2-Triz)	2-F	H	H
2-634	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Me$-2-Triz)	2-F	H	H
2-635	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Et$-2-Triz)	2-F	H	H
2-636	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Et$-2-Triz)	2-F	H	H
2-637	H	H	CH_2-4-Triz	2-F	H	H
2-638	Ac	H	CH_2-4-Triz	2-F	H	H
2-639	H	H	CH_2-4-Triz	2-F	4-F	H
2-640	Ac	H	CH_2-4-Triz	2-F	4-F	H
2-641	H	H	CH_2-(1-CO_2Me-4-Triz)	2-F	H	H
2-642	Ac	H	CH_2-(1-CO_2Me-4-Triz)	2-F	H	H
2-643	H	H	CH_2-(1-CO_2Et-4-Triz)	2-F	H	H
2-644	Ac	H	CH_2-(1-CO_2Et-4-Triz)	2-F	H	H
2-645	H	H	CH_2-(5-CO_2H-4-Triz)	2-F	H	H
2-646	Ac	H	CH_2-(5-CO_2H-4-Triz)	2-F	H	H
2-647	H	H	CH_2-(5-CO_2Me-4-Triz)	2-F	H	H
2-648	Ac	H	CH_2-(5-CO_2Me-4-Triz)	2-F	H	H
2-649	H	H	CH_2-(5-CO_2Et-4-Triz)	2-F	H	H
2-650	Ac	H	CH_2-(5-CO_2Et-4-Triz)	2-F	H	H
2-651	H	H	CH_2-(1-CH_2CO_2H-4-Triz)	2-F	H	H
2-652	Ac	H	CH_2-(1-CH_2CO_2H-4-Triz)	2-F	H	H
2-653	H	H	CH_2-(1-CH_2CO_2Me-4-Triz)	2-F	H	H
2-654	Ac	H	CH_2-(1-CH_2CO_2Me-4-Triz)	2-F	H	H
2-655	H	H	CH_2-(1-CH_2CO_2Et-4-Triz)	2-F	H	H
2-656	Ac	H	CH_2-(1-CH_2CO_2Et-4-Triz)	2-F	H	H
2-657	H	H	CH_2-(5-CH_2CO_2H-4-Triz)	2-F	H	H
2-658	Ac	H	CH_2-(5-CH_2CO_2H-4-Triz)	2-F	H	H
2-659	H	H	CH_2-(5-CH_2CO_2Me-4-Triz)	2-F	H	H
2-660	Ac	H	CH_2-(5-CH_2CO_2Me-4-Triz)	2-F	H	H
2-661	H	H	CH_2-(5-CH_2CO_2Et-4-Triz)	2-F	H	H
2-662	Ac	H	CH_2-(5-CH_2CO_2Et-4-Triz)	2-F	H	H
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]
[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]	[illegible]

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2-663	H	H	CH_2-(1-$CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
2-664	Ac	H	CH_2-(1-$CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
2-665	H	H	CH_2-(1-$CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
2-666	Ac	H	CH_2-(1-$CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
2-667	H	H	CH_2-(1-$CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
2-668	Ac	H	CH_2-(1-$CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
2-669	H	H	CH_2-(5-$CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
2-670	Ac	H	CH_2-(5-$CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
2-671	H	H	CH_2-(5-$CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
2-672	Ac	H	CH_2-(5-$CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
2-673	H	H	CH_2-(5-$CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
2-674	Ac	H	CH_2-(5-$CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
2-675	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
2-676	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
2-677	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
2-678	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
2-679	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
2-680	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
2-681	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
2-682	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
2-683	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
2-684	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
2-685	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
2-686	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
2-687	H	H	CH_2CH_2-4-Triz	2-F	H	H
2-688	Ac	H	CH_2CH_2-4-Triz	2-F	H	H
2-689	H	H	CH_2CH_2-4-Triz	2-F	4-F	H
2-690	Ac	H	CH_2CH_2-4-Triz	2-F	4-F	H
2-691	H	H	CH_2CH_2-(1-CO_2Me-4-Triz)	2-F	H	H
2-692	Ac	H	CH_2CH_2-(1-CO_2Me-4-Triz)	2-F	H	H
2-693	H	H	CH_2CH_2-(1-CO_2Et-4-Triz)	2-F	H	H

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2-694	Ac	H	CH_2CH_2-(1-CO_2Et-4-Triz)	2-F	H	H
2-695	H	H	CH_2CH_2-(5-CO_2H-4-Triz)	2-F	H	H
2-696	Ac	H	CH_2CH_2-(5-CO_2H-4-Triz)	2-F	H	H
2-697	H	H	CH_2CH_2-(5-CO_2Me-4-Triz)	2-F	H	H
2-698	Ac	H	CH_2CH_2-(5-CO_2Me-4-Triz)	2-F	H	H
2-699	H	H	CH_2CH_2-(5-CO_2Et-4-Triz)	2-F	H	H
2-700	Ac	H	CH_2CH_2-(5-CO_2Et-4-Triz)	2-F	H	H
2-701	H	H	CH_2CH_2-(1-CH_2CO_2H-4-Triz)	2-F	H	H
2-702	Ac	H	CH_2CH_2-(1-CH_2CO_2H-4-Triz)	2-F	H	H
2-703	H	H	CH_2CH_2-(1-CH_2CO_2Me-4-Triz)	2-F	H	H
2-704	Ac	H	CH_2CH_2-(1-CH_2CO_2Me-4-Triz)	2-F	H	H
2-705	H	H	CH_2CH_2-(1-CH_2CO_2Et-4-Triz)	2-F	H	H
2-706	Ac	H	CH_2CH_2-(1-CH_2CO_2Et-4-Triz)	2-F	H	H
2-707	H	H	CH_2CH_2-(5-CH_2CO_2H-4-Triz)	2-F	H	H
2-708	Ac	H	CH_2CH_2-(5-CH_2CO_2H-4-Triz)	2-F	H	H
2-709	H	H	CH_2CH_2-(5-CH_2CO_2Me-4-Triz)	2-F	H	H
2-710	Ac	H	CH_2CH_2-(5-CH_2CO_2Me-4-Triz)	2-F	H	H
2-711	H	H	CH_2CH_2-(5-CH_2CO_2Et-4-Triz)	2-F	H	H
2-712	Ac	H	CH_2CH_2-(5-CH_2CO_2Et-4-Triz)	2-F	H	H
2-713	H	H	CH_2CH_2-(1-$CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
2-714	Ac	H	CH_2CH_2-(1-$CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
2-715	H	H	CH_2CH_2-(1-$CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
2-716	Ac	H	CH_2CH_2-(1-$CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
2-717	H	H	CH_2CH_2-(1-$CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
2-718	Ac	H	CH_2CH_2-(1-$CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
2-719	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
2-720	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
2-721	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
2-722	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
2-723	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
2-724	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H

2-725	H	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
2-726	Ac	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
2-727	H	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
2-728	Ac	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
2-729	H	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
2-730	Ac	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
2-731	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
2-732	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
2-733	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
2-734	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
2-735	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
2-736	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
2-737	H	H	CH_2-(1-CO_2Me-5-Triz)	2-F	4-F	H
2-738	Ac	H	CH_2-(1-CO_2Me-5-Triz)	2-F	4-F	H
2-739	H	H	CH_2-(1-CO_2Me-5-Triz)	2-F	H	H
2-740	Ac	H	CH_2-(1-CO_2Me-5-Triz)	2-F	H	H
2-741	H	H	CH_2-(1-CO_2Et-5-Triz)	2-F	H	H
2-742	Ac	H	CH_2-(1-CO_2Et-5-Triz)	2-F	H	H
2-743	H	H	CH_2-(1-CH_2CO_2H-5-Triz)	2-F	H	H
2-744	Ac	H	CH_2-(1-CH_2CO_2H-5-Triz)	2-F	H	H
2-745	H	H	CH_2-(1-CH_2CO_2Me-5-Triz)	2-F	H	H
2-746	Ac	H	CH_2-(1-CH_2CO_2Me-5-Triz)	2-F	H	H
2-747	H	H	CH_2-(1-CH_2CO_2Et-5-Triz)	2-F	H	H
2-748	Ac	H	CH_2-(1-CH_2CO_2Et-5-Triz)	2-F	H	H
2-749	H	H	CH_2-(1-$CH_2CH_2CO_2H$-5-Triz)	2-F	H	H
2-750	Ac	H	CH_2-(1-$CH_2CH_2CO_2H$-5-Triz)	2-F	H	H
2-751	H	H	CH_2-(1-$CH_2CH_2CO_2Me$-5-Triz)	2-F	H	H
2-752	Ac	H	CH_2-(1-$CH_2CH_2CO_2Me$-5-Triz)	2-F	H	H
2-753	H	H	CH_2-(1-$CH_2CH_2CO_2Et$-5-Triz)	2-F	H	H
2-754	Ac	H	CH_2-(1-$CH_2CH_2CO_2Et$-5-Triz)	2-F	H	H
2-755	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2H$-5-Triz)	2-F	H	H

2-756	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2H$-5-Triz)	2-F	H	H
2-757	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2Me$-5-Triz)	2-F	H	H
2-758	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2Me$-5-Triz)	2-F	H	H
2-759	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2Et$-5-Triz)	2-F	H	H
2-760	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2Et$-5-Triz)	2-F	H	H
2-761	H	H	CH_2-1-Tez	2-F	H	H
2-762	Ac	H	CH_2-1-Tez	2-F	H	H
2-763	H	H	CH_2-(5-CO_2H-1-Tez)	2-F	H	H
2-764	Ac	H	CH_2-(5-CO_2H-1-Tez)	2-F	H	H
2-765	H	H	CH_2-(5-CO_2Me-1-Tez)	2-F	H	H
2-766	Ac	H	CH_2-(5-CO_2Me-1-Tez)	2-F	H	H
2-767	H	H	CH_2-(5-CO_2Et-1-Tez)	2-F	H	H
2-768	Ac	H	CH_2-(5-CO_2Et-1-Tez)	2-F	H	H
2-769	H	H	CH_2-(5-CH_2CO_2H-1-Tez)	2-F	H	H
2-770	Ac	H	CH_2-(5-CH_2CO_2H-1-Tez)	2-F	H	H
2-771	H	H	CH_2-(5-CH_2CO_2Me-1-Tez)	2-F	H	H
2-772	Ac	H	CH_2-(5-CH_2CO_2Me-1-Tez)	2-F	H	H
2-773	H	H	CH_2-(5-CH_2CO_2Et-1-Tez)	2-F	H	H
2-774	Ac	H	CH_2-(5-CH_2CO_2Et-1-Tez)	2-F	H	H
2-775	H	H	CH_2-(5-$CH_2CH_2CO_2H$-1-Tez)	2-F	H	H
2-776	Ac	H	CH_2-(5-$CH_2CH_2CO_2H$-1-Tez)	2-F	H	H
2-777	H	H	CH_2-(5-$CH_2CH_2CO_2Me$-1-Tez)	2-F	H	H
2-778	Ac	H	CH_2-(5-$CH_2CH_2CO_2Me$-1-Tez)	2-F	H	H
2-779	H	H	CH_2-(5-$CH_2CH_2CO_2Et$-1-Tez)	2-F	H	H
2-780	Ac	H	CH_2-(5-$CH_2CH_2CO_2Et$-1-Tez)	2-F	H	H
2-781	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2H$-1-Tez)	2-F	H	H
2-782	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2H$-1-Tez)	2-F	H	H
2-783	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2Me$-1-Tez)	2-F	H	H
2-784	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2Me$-1-Tez)	2-F	H	H
2-785	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2Et$-1-Tez)	2-F	H	H
2-786	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2Et$-1-Tez)	2-F	H	H

2-787	H	H	CH_2CH_2-1-Tez	2-F	H	H
2-788	Ac	H	CH_2CH_2-1-Tez	2-F	H	H
2-789	H	H	CH_2CH_2-(5-CO_2H-1-Tez)	2-F	H	H
2-790	Ac	H	CH_2CH_2-(5-CO_2H-1-Tez)	2-F	H	H
2-791	H	H	CH_2CH_2-(5-CO_2Me-1-Tez)	2-F	H	H
2-792	Ac	H	CH_2CH_2-(5-CO_2Me-1-Tez)	2-F	H	H
2-793	H	H	CH_2CH_2-(5-CO_2Et-1-Tez)	2-F	H	H
2-794	Ac	H	CH_2CH_2-(5-CO_2Et-1-Tez)	2-F	H	H
2-795	H	H	CH_2CH_2-(5-CH_2CO_2H-1-Tez)	2-F	H	H
2-796	Ac	H	CH_2CH_2-(5-CH_2CO_2H-1-Tez)	2-F	H	H
2-797	H	H	CH_2CH_2-(5-CH_2CO_2Me-1-Tez)	2-F	H	H
2-798	Ac	H	CH_2CH_2-(5-CH_2CO_2Me-1-Tez)	2-F	H	H
2-799	H	H	CH_2CH_2-(5-CH_2CO_2Et-1-Tez)	2-F	H	H
2-800	Ac	H	CH_2CH_2-(5-CH_2CO_2Et-1-Tez)	2-F	H	H
2-801	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2H$-1-Tez)	2-F	H	H
2-802	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2H$-1-Tez)	2-F	H	H
2-803	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2Me$-1-Tez)	2-F	H	H
2-804	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2Me$-1-Tez)	2-F	H	H
2-805	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2Et$-1-Tez)	2-F	H	H
2-806	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2Et$-1-Tez)	2-F	H	H
2-807	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2H$-1-Tez)	2-F	H	H
2-808	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2H$-1-Tez)	2-F	H	H
2-809	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Me$-1-Tez)	2-F	H	H
2-810	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Me$-1-Tez)	2-F	H	H
2-811	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Et$-1-Tez)	2-F	H	H
2-812	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Et$-1-Tez)	2-F	H	H
2-813	H	H	CH_2-2-Tez	2-F	H	H
2-814	Ac	H	CH_2-2-Tez	2-F	H	H
2-815	H	H	CH_2-(5-CO_2H-2-Tez)	2-F	H	H
2-816	Ac	H	CH_2-(5-CO_2H-2-Tez)	2-F	H	H
2-817	H	H	CH_2-(5-CO_2Me-2-Tez)	2-F	H	H

2-818	Ac	H	CH_2-(5-CO_2Me-2-Tez)	2-F	H	H
2-819	H	H	CH_2-(5-CO_2Et-2-Tez)	2-F	H	H
2-820	Ac	H	CH_2-(5-CO_2Et-2-Tez)	2-F	H	H
2-821	H	H	CH_2-(5-CH_2CO_2H-2-Tez)	2-F	H	H
2-822	Ac	H	CH_2-(5-CH_2CO_2H-2-Tez)	2-F	H	H
2-823	H	H	CH_2-(5-CH_2CO_2Me-2-Tez)	2-F	H	H
2-824	Ac	H	CH_2-(5-CH_2CO_2Me-2-Tez)	2-F	H	H
2-825	H	H	CH_2-(5-CH_2CO_2Et-2-Tez)	2-F	H	H
2-826	Ac	H	CH_2-(5-CH_2CO_2Et-2-Tez)	2-F	H	H
2-827	H	H	CH_2-(5-$CH_2CH_2CO_2H$-2-Tez)	2-F	H	H
2-828	Ac	H	CH_2-(5-$CH_2CH_2CO_2H$-2-Tez)	2-F	H	H
2-829	H	H	CH_2-(5-$CH_2CH_2CO_2Me$-2-Tez)	2-F	H	H
2-830	Ac	H	CH_2-(5-$CH_2CH_2CO_2Me$-2-Tez)	2-F	H	H
2-831	H	H	CH_2-(5-$CH_2CH_2CO_2Et$-2-Tez)	2-F	H	H
2-832	Ac	H	CH_2-(5-$CH_2CH_2CO_2Et$-2-Tez)	2-F	H	H
2-833	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2H$-2-Tez)	2-F	H	H
2-834	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2H$-2-Tez)	2-F	H	H
2-835	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2Me$-2-Tez)	2-F	H	H
2-836	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2Me$-2-Tez)	2-F	H	H
2-837	H	H	CH_2-(5-$CH_2CH_2CH_2CO_2Et$-2-Tez)	2-F	H	H
2-838	Ac	H	CH_2-(5-$CH_2CH_2CH_2CO_2Et$-2-Tez)	2-F	H	H
2-839	H	H	CH_2CH_2-2-Tez	2-F	H	H
2-840	Ac	H	CH_2CH_2-2-Tez	2-F	H	H
2-841	H	H	CH_2CH_2-(5-CO_2H-2-Tez)	2-F	H	H
2-842	Ac	H	CH_2CH_2-(5-CO_2H-2-Tez)	2-F	H	H
2-843	H	H	CH_2CH_2-(5-CO_2Me-2-Tez)	2-F	H	H
2-844	Ac	H	CH_2CH_2-(5-CO_2Me-2-Tez)	2-F	H	H
2-845	H	H	CH_2CH_2-(5-CO_2Et-2-Tez)	2-F	H	H
2-846	Ac	H	CH_2CH_2-(5-CO_2Et-2-Tez)	2-F	H	H
2-847	H	H	CH_2CH_2-(5-CH_2CO_2H-2-Tez)	2-F	H	H
2-848	Ac	H	CH_2CH_2-(5-CH_2CO_2H-2-Tez)	2-F	H	H

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2-849	H	H	CH_2CH_2-(5-CH_2CO_2Me-2-Tez)	2-F	H	H
2-850	Ac	H	CH_2CH_2-(5-CH_2CO_2Me-2-Tez)	2-F	H	H
2-851	H	H	CH_2CH_2-(5-CH_2CO_2Et-2-Tez)	2-F	H	H
2-852	Ac	H	CH_2CH_2-(5-CH_2CO_2Et-2-Tez)	2-F	H	H
2-853	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2H$-2-Tez)	2-F	H	H
2-854	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2H$-2-Tez)	2-F	H	H
2-855	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2Me$-2-Tez)	2-F	H	H
2-856	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2Me$-2-Tez)	2-F	H	H
2-857	H	H	CH_2CH_2-(5-$CH_2CH_2CO_2Et$-2-Tez)	2-F	H	H
2-858	Ac	H	CH_2CH_2-(5-$CH_2CH_2CO_2Et$-2-Tez)	2-F	H	H
2-859	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2H$-2-Tez)	2-F	H	H
2-860	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2H$-2-Tez)	2-F	H	H
2-861	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Me$-2-Tez)	2-F	H	H
2-862	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Me$-2-Tez)	2-F	H	H
2-863	H	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Et$-2-Tez)	2-F	H	H
2-864	Ac	H	CH_2CH_2-(5-$CH_2CH_2CH_2CO_2Et$-2-Tez)	2-F	H	H
2-865	H	H	CH_2-5-Tez	2-F	H	H
2-866	Ac	H	CH_2-5-Tez	2-F	H	H
2-867	H	H	CH_2-5-Tez	2-F	4-F	H
2-868	Ac	H	CH_2-5-Tez	2-F	4-F	H
2-869	H	H	CH_2-(1-CO_2Me-5-Tez)	2-F	H	H
2-870	Ac	H	CH_2-(1-CO_2Me-5-Tez)	2-F	H	H
2-871	H	H	CH_2-(1-CO_2Et-5-Tez)	2-F	H	H
2-872	Ac	H	CH_2-(1-CO_2Et-5-Tez)	2-F	H	H
2-873	H	H	CH_2-(2-CO_2Me-5-Tez)	2-F	4-F	H
2-874	Ac	H	CH_2-(2-CO_2Me-5-Tez)	2-F	4-F	H
2-875	H	H	CH_2-(2-CO_2Me-5-Tez)	2-F	H	H
2-876	Ac	H	CH_2-(2-CO_2Me-5-Tez)	2-F	H	H
2-877	H	H	CH_2-(2-CO_2Et-5-Tez)	2-F	H	H
2-878	Ac	H	CH_2-(2-CO_2Et-5-Tez)	2-F	H	H
2-879	H	H	CH_2-(1-CH_2CO_2H-5-Tez)	2-F	H	H

2-880	Ac	H	CH_2-(1-CH_2CO_2H-5-Tez)	2-F	H	H
2-881	H	H	CH_2-(1-CH_2CO_2Me-5-Tez)	2-F	H	H
2-882	Ac	H	CH_2-(1-CH_2CO_2Me-5-Tez)	2-F	H	H
2-883	H	H	CH_2-(1-CH_2CO_2Et-5-Tez)	2-F	H	H
2-884	Ac	H	CH_2-(1-CH_2CO_2Et-5-Tez)	2-F	H	H
2-885	H	H	CH_2-(2-CH_2CO_2H-5-Tez)	2-F	H	H
2-886	Ac	H	CH_2-(2-CH_2CO_2H-5-Tez)	2-F	H	H
2-887	H	H	CH_2-(2-CH_2CO_2Me-5-Tez)	2-F	H	H
2-888	Ac	H	CH_2-(2-CH_2CO_2Me-5-Tez)	2-F	H	H
2-889	H	H	CH_2-(2-CH_2CO_2Et-5-Tez)	2-F	H	H
2-890	Ac	H	CH_2-(2-CH_2CO_2Et-5-Tez)	2-F	H	H
2-891	H	H	CH_2-(1-$CH_2CH_2CO_2H$-5-Tez)	2-F	H	H
2-892	Ac	H	CH_2-(1-$CH_2CH_2CO_2H$-5-Tez)	2-F	H	H
2-893	H	H	CH_2-(1-$CH_2CH_2CO_2Me$-5-Tez)	2-F	H	H
2-894	Ac	H	CH_2-(1-$CH_2CH_2CO_2Me$-5-Tez)	2-F	H	H
2-895	H	H	CH_2-(1-$CH_2CH_2CO_2Et$-5-Tez)	2-F	H	H
2-896	Ac	H	CH_2-(1-$CH_2CH_2CO_2Et$-5-Tez)	2-F	H	H
2-897	H	H	CH_2-(2-$CH_2CH_2CO_2H$-5-Tez)	2-F	H	H
2-898	Ac	H	CH_2-(2-$CH_2CH_2CO_2H$-5-Tez)	2-F	H	H
2-899	H	H	CH_2-(2-$CH_2CH_2CO_2Me$-5-Tez)	2-F	H	H
2-900	Ac	H	CH_2-(2-$CH_2CH_2CO_2Me$-5-Tez)	2-F	H	H
2-901	H	H	CH_2-(2-$CH_2CH_2CO_2Et$-5-Tez)	2-F	H	H
2-902	Ac	H	CH_2-(2-$CH_2CH_2CO_2Et$-5-Tez)	2-F	H	H
2-903	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2H$-5-Tez)	2-F	H	H
2-904	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2H$-5-Tez)	2-F	H	H
2-905	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2Me$-5-Tez)	2-F	H	H
2-906	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2Me$-5-Tez)	2-F	H	H
2-907	H	H	CH_2-(1-$CH_2CH_2CH_2CO_2Et$-5-Tez)	2-F	H	H
2-908	Ac	H	CH_2-(1-$CH_2CH_2CH_2CO_2Et$-5-Tez)	2-F	H	H
2-909	H	H	CH_2-(2-$CH_2CH_2CH_2CO_2H$-5-Tez)	2-F	H	H
2-910	Ac	H	CH_2-(2-$CH_2CH_2CH_2CO_2H$-5-Tez)	2-F	H	H

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2-911	H	H	CH_2-(2-$CH_2CH_2CH_2CO_2Me$-5-Tez)	2-F	H	H
2-912	Ac	H	CH_2-(2-$CH_2CH_2CH_2CO_2Me$-5-Tez)	2-F	H	H
2-913	H	H	CH_2-(2-$CH_2CH_2CH_2CO_2Et$-5-Tez)	2-F	H	H
2-914	Ac	H	CH_2-(2-$CH_2CH_2CH_2CO_2Et$-5-Tez)	2-F	H	H
2-915	H	H	CH_2CH_2-5-Tez	2-F	H	H
2-916	Ac	H	CH_2CH_2-5-Tez	2-F	H	H
2-917	H	H	CH_2CH_2-5-Tez	2-F	4-F	H
2-918	Ac	H	CH_2CH_2-5-Tez	2-F	4-F	H
2-919	H	H	CH_2CH_2-(1-CO_2Me-5-Tez)	2-F	H	H
2-920	Ac	H	CH_2CH_2-(1-CO_2Me-5-Tez)	2-F	H	H
2-921	H	H	CH_2CH_2-(1-CO_2Et-5-Tez)	2-F	H	H
2-922	Ac	H	CH_2CH_2-(1-CO_2Et-5-Tez)	2-F	H	H
2-923	H	H	CH_2CH_2-(2-CO_2Me-5-Tez)	2-F	H	H
2-924	Ac	H	CH_2CH_2-(2-CO_2Me-5-Tez)	2-F	H	H
2-925	H	H	CH_2CH_2-(2-CO_2Me-5-Tez)	2-F	H	H
2-926	Ac	H	CH_2CH_2-(2-CO_2Me-5-Tez)	2-F	H	H
2-927	H	H	CH_2CH_2-(2-CO_2Et-5-Tez)	2-F	H	H
2-928	Ac	H	CH_2CH_2-(2-CO_2Et-5-Tez)	2-F	H	H
2-929	H	H	CH_2CH_2-(1-CH_2CO_2H-5-Tez)	2-F	H	H
2-930	Ac	H	CH_2CH_2-(1-CH_2CO_2H-5-Tez)	2-F	H	H
2-931	H	H	CH_2CH_2-(1-CH_2CO_2Me-5-Tez)	2-F	H	H
2-932	Ac	H	CH_2CH_2-(1-CH_2CO_2Me-5-Tez)	2-F	H	H
2-933	H	H	CH_2CH_2-(1-CH_2CO_2Et-5-Tez)	2-F	H	H
2-934	Ac	H	CH_2CH_2-(1-CH_2CO_2Et-5-Tez)	2-F	H	H
2-935	H	H	CH_2CH_2-(2-CH_2CO_2H-5-Tez)	2-F	H	H
2-936	Ac	H	CH_2CH_2-(2-CH_2CO_2H-5-Tez)	2-F	H	H
2-937	H	H	CH_2CH_2-(2-CH_2CO_2Me-5-Tez)	2-F	H	H
2-938	Ac	H	CH_2CH_2-(2-CH_2CO_2Me-5-Tez)	2-F	H	H
2-939	H	H	CH_2CH_2-(2-CH_2CO_2Et-5-Tez)	2-F	H	H
2-940	Ac	H	CH_2CH_2-(2-CH_2CO_2Et-5-Tez)	2-F	H	H
2-941	H	H	CH_2CH_2-(1-$CH_2CH_2CO_2H$-5-Tez)	2-F	H	H

2-942	Ac	H	CH_2CH_2-(1-$CH_2CH_2CO_2H$-5-Tez)	2-F	H	H
2-943	H	H	CH_2CH_2-(1-$CH_2CH_2CO_2Me$-5-Tez)	2-F	H	H
2-944	Ac	H	CH_2CH_2-(1-$CH_2CH_2CO_2Me$-5-Tez)	2-F	H	H
2-945	H	H	CH_2CH_2-(1-$CH_2CH_2CO_2Et$-5-Tez)	2-F	H	H
2-946	Ac	H	CH_2CH_2-(1-$CH_2CH_2CO_2Et$-5-Tez)	2-F	H	H
2-947	H	H	CH_2CH_2-(2-$CH_2CH_2CO_2H$-5-Tez)	2-F	H	H
2-948	Ac	H	CH_2CH_2-(2-$CH_2CH_2CO_2H$-5-Tez)	2-F	H	H
2-949	H	H	CH_2CH_2-(2-$CH_2CH_2CO_2Me$-5-Tez)	2-F	H	H
2-950	Ac	H	CH_2CH_2-(2-$CH_2CH_2CO_2Me$-5-Tez)	2-F	H	H
2-951	H	H	CH_2CH_2-(2-$CH_2CH_2CO_2Et$-5-Tez)	2-F	H	H
2-952	Ac	H	CH_2CH_2-(2-$CH_2CH_2CO_2Et$-5-Tez)	2-F	H	H
2-953	H	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2H$-5-Tez)	2-F	H	H
2-954	Ac	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2H$-5-Tez)	2-F	H	H
2-955	H	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Me$-5-Tez)	2-F	H	H
2-956	Ac	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Me$-5-Tez)	2-F	H	H
2-957	H	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Et$-5-Tez)	2-F	H	H
2-958	Ac	H	CH_2CH_2-(1-$CH_2CH_2CH_2CO_2Et$-5-Tez)	2-F	H	H
2-959	H	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2H$-5-Tez)	2-F	H	H
2-960	Ac	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2H$-5-Tez)	2-F	H	H
2-961	H	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2Me$-5-Tez)	2-F	H	H
2-962	Ac	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2Me$-5-Tez)	2-F	H	H
2-963	H	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2Et$-5-Tez)	2-F	H	H
2-964	Ac	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2Et$-5-Tez)	2-F	H	H
2-965	H	Me	CH_2-1-Pyza	2-F	H	H
2-966	Ac	Me	CH_2-1-Pyza	2-F	H	H
2-967	H	Me	CH_2-(3-CO_2H-1-Pyza)	2-F	H	H
2-968	Ac	Me	CH_2-(3-CO_2H-1-Pyza)	2-F	H	H
2-969	H	Me	CH_2-(3-CO_2Me-1-Pyza)	2-F	H	H
2-970	Ac	Me	CH_2-(3-CO_2Me-1-Pyza)	2-F	H	H
2-971	H	Me	CH_2-(3-CO_2Et-1-Pyza)	2-F	H	H
2-972	Ac	Me	CH_2-(3-CO_2Et-1-Pyza)	2-F	H	H

2-973	H	Me	CH_2-(4-CO_2H-1-Pyza)	2-F	H	H
2-974	Ac	Me	CH_2-(4-CO_2H-1-Pyza)	2-F	H	H
2-975	H	Me	CH_2-(4-CO_2Me-1-Pyza)	2-F	H	H
2-976	Ac	Me	CH_2-(4-CO_2Me-1-Pyza)	2-F	H	H
2-977	H	Me	CH_2-(4-CO_2Et-1-Pyza)	2-F	H	H
2-978	Ac	Me	CH_2-(4-CO_2Et-1-Pyza)	2-F	H	H
2-979	H	Me	CH_2-(3-CH_2CO_2H-1-Pyza)	2-F	H	H
2-980	Ac	Me	CH_2-(3-CH_2CO_2H-1-Pyza)	2-F	H	H
2-981	H	Me	CH_2-(3-CH_2CO_2Me-1-Pyza)	2-F	H	H
2-982	Ac	Me	CH_2-(3-CH_2CO_2Me-1-Pyza)	2-F	H	H
2-983	H	Me	CH_2-(3-CH_2CO_2Et-1-Pyza)	2-F	H	H
2-984	Ac	Me	CH_2-(3-CH_2CO_2Et-1-Pyza)	2-F	H	H
2-985	H	Me	CH_2-(4-CH_2CO_2H-1-Pyza)	2-F	H	H
2-986	Ac	Me	CH_2-(4-CH_2CO_2H-1-Pyza)	2-F	H	H
2-987	H	Me	CH_2-(4-CH_2CO_2Me-1-Pyza)	2-F	H	H
2-988	Ac	Me	CH_2-(4-CH_2CO_2Me-1-Pyza)	2-F	H	H
2-989	H	Me	CH_2-(4-CH_2CO_2Et-1-Pyza)	2-F	H	H
2-990	Ac	Me	CH_2-(4-CH_2CO_2Et-1-Pyza)	2-F	H	H
2-991	H	Me	CH_2-(3-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
2-992	Ac	Me	CH_2-(3-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
2-993	H	Me	CH_2-(3-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
2-994	Ac	Me	CH_2-(3-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
2-995	H	Me	CH_2-(3-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
2-996	Ac	Me	CH_2-(3-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
2-997	H	Me	CH_2-(4-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
2-998	Ac	Me	CH_2-(4-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
2-999	H	Me	CH_2-(4-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
2-1000	Ac	Me	CH_2-(4-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
2-1001	H	Me	CH_2-(4-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
2-1002	Ac	Me	CH_2-(4-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
2-1003	H	Me	CH_2CH_2-1-Pyza	2-F	H	H

2-1004	Ac	Me	CH_2CH_2-1-Pyza	2-F	H	H
2-1005	H	Me	CH_2CH_2-(3-CO_2H-1-Pyza)	2-F	H	H
2-1006	Ac	Me	CH_2CH_2-(3-CO_2H-1-Pyza)	2-F	H	H
2-1007	H	Me	CH_2CH_2-(3-CO_2Me-1-Pyza)	2-F	H	H
2-1008	Ac	Me	CH_2CH_2-(3-CO_2Me-1-Pyza)	2-F	H	H
2-1009	H	Me	CH_2CH_2-(3-CO_2Et-1-Pyza)	2-F	H	H
2-1010	Ac	Me	CH_2CH_2-(3-CO_2Et-1-Pyza)	2-F	H	H
2-1011	H	Me	CH_2CH_2-(4-CO_2H-1-Pyza)	2-F	H	H
2-1012	Ac	Me	CH_2CH_2-(4-CO_2H-1-Pyza)	2-F	H	H
2-1013	H	Me	CH_2CH_2-(4-CO_2Me-1-Pyza)	2-F	H	H
2-1014	Ac	Me	CH_2CH_2-(4-CO_2Me-1-Pyza)	2-F	H	H
2-1015	H	Me	CH_2CH_2-(4-CO_2Et-1-Pyza)	2-F	H	H
2-1016	Ac	Me	CH_2CH_2-(4-CO_2Et-1-Pyza)	2-F	H	H
2-1017	H	Me	CH_2CH_2-(3-CH_2CO_2H-1-Pyza)	2-F	H	H
2-1018	Ac	Me	CH_2CH_2-(3-CH_2CO_2H-1-Pyza)	2-F	H	H
2-1019	H	Me	CH_2CH_2-(3-CH_2CO_2Me-1-Pyza)	2-F	H	H
2-1020	Ac	Me	CH_2CH_2-(3-CH_2CO_2Me-1-Pyza)	2-F	H	H
2-1021	H	Me	CH_2CH_2-(3-CH_2CO_2Et-1-Pyza)	2-F	H	H
2-1022	Ac	Me	CH_2CH_2-(3-CH_2CO_2Et-1-Pyza)	2-F	H	H
2-1023	H	Me	CH_2CH_2-(4-CH_2CO_2H-1-Pyza)	2-F	H	H
2-1024	Ac	Me	CH_2CH_2-(4-CH_2CO_2H-1-Pyza)	2-F	H	H
2-1025	H	Me	CH_2CH_2-(4-CH_2CO_2Me-1-Pyza)	2-F	H	H
2-1026	Ac	Me	CH_2CH_2-(4-CH_2CO_2Me-1-Pyza)	2-F	H	H
2-1027	H	Me	CH_2CH_2-(4-CH_2CO_2Et-1-Pyza)	2-F	H	H
2-1028	Ac	Me	CH_2CH_2-(4-CH_2CO_2Et-1-Pyza)	2-F	H	H
2-1029	H	Me	CH_2CH_2-(3-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
2-1030	Ac	Me	CH_2CH_2-(3-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
2-1031	H	Me	CH_2CH_2-(3-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
2-1032	Ac	Me	CH_2CH_2-(3-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
2-1033	H	Me	CH_2CH_2-(3-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
2-1034	Ac	Me	CH_2CH_2-(3-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H

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2-1035	H	Me	CH_2CH_2-(4-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
2-1036	Ac	Me	CH_2CH_2-(4-$CH_2CH_2CO_2H$-1-Pyza)	2-F	H	H
2-1037	H	Me	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
2-1038	Ac	Me	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-1-Pyza)	2-F	H	H
2-1039	H	Me	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
2-1040	Ac	Me	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-1-Pyza)	2-F	H	H
2-1041	H	H	CH_2-(2-CO_2Me-4-Triz)	2-F	H	H
2-1042	Ac	H	CH_2-(2-CO_2Me-4-Triz)	2-F	H	H
2-1043	H	H	CH_2-(2-CO_2Et-4-Triz)	2-F	H	H
2-1044	Ac	H	CH_2-(2-CO_2Et-4-Triz)	2-F	H	H
2-1045	H	H	CH_2-(2-CH_2CO_2H-4-Triz)	2-F	H	H
2-1046	Ac	H	CH_2-(2-CH_2CO_2H-4-Triz)	2-F	H	H
2-1047	H	H	CH_2-(2-CH_2CO_2Me-4-Triz)	2-F	H	H
2-1048	Ac	H	CH_2-(2-CH_2CO_2Me-4-Triz)	2-F	H	H
2-1049	H	H	CH_2-(2-CH_2CO_2Et-4-Triz)	2-F	H	H
2-1050	Ac	H	CH_2-(2-CH_2CO_2Et-4-Triz)	2-F	H	H
2-1051	H	H	CH_2-(2-$CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
2-1052	Ac	H	CH_2-(2-$CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
2-1053	H	H	CH_2-(2-$CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
2-1054	Ac	H	CH_2-(2-$CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
2-1055	H	H	CH_2-(2-$CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
2-1056	Ac	H	CH_2-(2-$CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
2-1057	H	H	CH_2-(2-$CH_2CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
2-1058	Ac	H	CH_2-(2-$CH_2CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
2-1059	H	H	CH_2-(2-$CH_2CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
2-1060	Ac	H	CH_2-(2-$CH_2CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
2-1061	H	H	CH_2-(2-$CH_2CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
2-1062	Ac	H	CH_2-(2-$CH_2CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
2-1063	H	H	CH_2CH_2-(2-CO_2Me-4-Triz)	2-F	H	H
2-1064	Ac	H	CH_2CH_2-(2-CO_2Me-4-Triz)	2-F	H	H
2-1065	H	H	CH_2CH_2-(2-CO_2Et-4-Triz)	2-F	H	H

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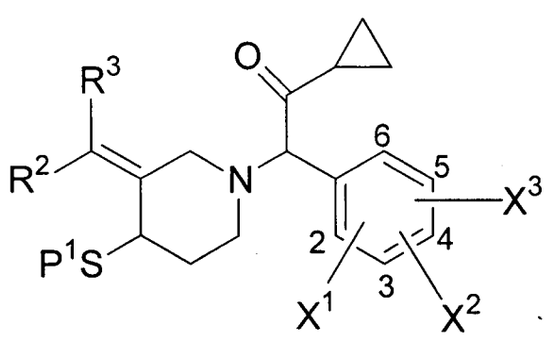
2-1066	Ac	H	CH_2CH_2-(2-CO_2Et-4-Triz)	2-F	H	H
2-1067	H	H	CH_2CH_2-(2-CH_2CO_2H-4-Triz)	2-F	H	H
2-1068	Ac	H	CH_2CH_2-(2-CH_2CO_2H-4-Triz)	2-F	H	H
2-1069	H	H	CH_2CH_2-(2-CH_2CO_2Me-4-Triz)	2-F	H	H
2-1070	Ac	H	CH_2CH_2-(2-CH_2CO_2Me-4-Triz)	2-F	H	H
2-1071	H	H	CH_2CH_2-(2-CH_2CO_2Et-4-Triz)	2-F	H	H
2-1072	Ac	H	CH_2CH_2-(2-CH_2CO_2Et-4-Triz)	2-F	H	H
2-1073	H	H	CH_2CH_2-(2-$CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
2-1074	Ac	H	CH_2CH_2-(2-$CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
2-1075	H	H	CH_2CH_2-(2-$CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
2-1076	Ac	H	CH_2CH_2-(2-$CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
2-1077	H	H	CH_2CH_2-(2-$CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
2-1078	Ac	H	CH_2CH_2-(2-$CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
2-1079	H	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
2-1080	Ac	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2H$-4-Triz)	2-F	H	H
2-1081	H	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
2-1082	Ac	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2Me$-4-Triz)	2-F	H	H
2-1083	H	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H
2-1084	Ac	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2Et$-4-Triz)	2-F	H	H

(Tabla 3)



Comp. No.	P^1	R^2	R^3	X^1	X^2	X^3

3-1	H	H	CH_2OH	2-F	H	H
3-2	Ac	H	CH_2OH	2-F	H	H
3-3	H	H	CH_2CH_2OH	2-F	H	H
3-4	Ac	H	CH_2CH_2OH	2-F	H	H
3-5	H	H	CH_2OMe	2-F	H	H
3-6	Ac	H	CH_2OMe	2-F	H	H
3-7	H	H	CH_2CH_2OMe	2-F	H	H
3-8	Ac	H	CH_2CH_2OMe	2-F	H	H
3-9	H	H	CH_2OEt	2-F	H	H
3-10	Ac	H	CH_2OEt	2-F	H	H
3-11	H	H	CH_2CH_2OEt	2-F	H	H
3-12	Ac	H	CH_2CH_2OEt	2-F	H	H
3-13	H	H	CH_2CO_2H	2-F	H	H
3-14	Ac	H	CH_2CO_2H	2-F	H	H
3-15	H	H	CH_2CO_2Me	2-F	H	H
3-16	Ac	H	CH_2CO_2Me	2-F	H	H
3-17	H	H	CH_2CO_2Et	2-F	H	H
3-18	Ac	H	CH_2CO_2Et	2-F	H	H
3-19	H	H	4-Pip	2-F	H	H
3-20	Ac	H	4-Pip	2-F	H	H
3-21	H	H	4-Pip	2-F	4-F	H
3-22	Ac	H	4-Pip	2-F	4-F	H
3-23	H	H	1-CO_2Me-4-Pip	2-F	H	H
3-24	Ac	H	1-CO_2Me-4-Pip	2-F	H	H
3-25	H	H	1-CO_2Et-4-Pip	2-F	H	H
3-26	Ac	H	1-CO_2Et-4-Pip	2-F	H	H
3-27	H	H	1-CH_2CO_2H-4-Pip	2-F	H	H
3-28	Ac	H	1-CH_2CO_2H-4-Pip	2-F	H	H
3-29	H	H	1-CH_2CO_2Me-4-Pip	2-F	H	H
3-30	Ac	H	1-CH_2CO_2Me-4-Pip	2-F	H	H
3-31	H	H	1-CH_2CO_2Et-4-Pip	2-F	H	H

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3-32	Ac	H	1-CH_2CO_2Et-4-Pip	2-F	H	H
3-33	H	H	1-$CH_2CH_2CO_2H$-4-Pip	2-F	H	H
3-34	Ac	H	1-$CH_2CH_2CO_2H$-4-Pip	2-F	H	H
3-35	H	H	1-$CH_2CH_2CO_2Me$-4-Pip	2-F	H	H
3-36	Ac	H	1-$CH_2CH_2CO_2Me$-4-Pip	2-F	H	H
3-37	H	H	1-$CH_2CH_2CO_2Et$-4-Pip	2-F	H	H
3-38	Ac	H	1-$CH_2CH_2CO_2Et$-4-Pip	2-F	H	H
3-39	Ac	H	1-$CH_2CH_2CO_2Et$-4-Pip	2-F	4-F	H
3-40	H	H	1-$CH_2CH_2CH_2CO_2H$-4-Pip	2-F	H	H
3-41	Ac	H	1-$CH_2CH_2CH_2CO_2H$-4-Pip	2-F	H	H
3-42	H	H	1-$CH_2CH_2CH_2CO_2Me$-4-Pip	2-F	H	H
3-43	Ac	H	1-$CH_2CH_2CH_2CO_2Me$-4-Pip	2-F	H	H
3-44	H	H	1-$CH_2CH_2CH_2CO_2Et$-4-Pip	2-F	H	H
3-45	Ac	H	1-$CH_2CH_2CH_2CO_2Et$-4-Pip	2-F	H	H
3-46	H	H	CH_2CN	2-F	H	H
3-47	Ac	H	CH_2CN	2-F	H	H
3-48	H	H	CH_2CH_2CN	2-F	H	H
3-49	Ac	H	CH_2CH_2CN	2-F	H	H
3-50	H	H	$CH_2N(Me)CH_2CO_2H$	2-F	H	H
3-51	Ac	H	$CH_2N(Me)CH_2CO_2H$	2-F	H	H
3-52	H	H	$CH_2N(Me)CH_2CO_2Me$	2-F	H	H
3-53	Ac	H	$CH_2N(Me)CH_2CO_2Me$	2-F	H	H
3-54	H	H	$CH_2N(Me)CH_2CO_2Et$	2-F	H	H
3-55	Ac	H	$CH_2N(Me)CH_2CO_2Et$	2-F	H	H
3-56	H	H	$CH_2N(Me)CH_2CH_2CO_2H$	2-F	H	H
3-57	Ac	H	$CH_2N(Me)CH_2CH_2CO_2H$	2-F	H	H
3-58	H	H	$CH_2N(Me)CH_2CH_2CO_2Me$	2-F	H	H
3-59	Ac	H	$CH_2N(Me)CH_2CH_2CO_2Me$	2-F	H	H
3-60	H	H	$CH_2N(Me)CH_2CH_2CO_2Et$	2-F	H	H
3-61	Ac	H	$CH_2N(Me)CH_2CH_2CO_2Et$	2-F	H	H
3-62	H	H	$CH_2N(Me)CH_2CH_2CH_2CO_2H$	2-F	H	H

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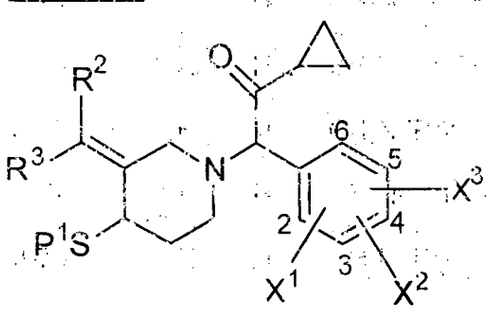
3-63	Ac	H	$CH_2N(Me)CH_2CH_2CH_2CO_2H$	2-F	H	H
3-64	H	H	$CH_2N(Me)CH_2CH_2CH_2CO_2Me$	2-F	H	H
3-65	Ac	H	$CH_2N(Me)CH_2CH_2CH_2CO_2Me$	2-F	H	H
3-66	H	H	$CH_2N(Me)CH_2CH_2CH_2CO_2Et$	2-F	H	H
3-67	Ac	H	$CH_2N(Me)CH_2CH_2CH_2CO_2Et$	2-F	H	H
3-68	H	H	$CH_2N(Et)CH_2CO_2H$	2-F	H	H
3-69	Ac	H	$CH_2N(Et)CH_2CO_2H$	2-F	H	H
3-70	H	H	$CH_2N(Et)CH_2CO_2Me$	2-F	H	H
3-71	Ac	H	$CH_2N(Et)CH_2CO_2Me$	2-F	H	H
3-72	H	H	$CH_2N(Et)CH_2CO_2Et$	2-F	H	H
3-73	Ac	H	$CH_2N(Et)CH_2CO_2Et$	2-F	H	H
3-74	H	H	$CH_2N(iPr)CH_2CO_2H$	2-F	H	H
3-75	Ac	H	$CH_2N(iPr)CH_2CO_2H$	2-F	H	H
3-76	H	H	$CH_2N(iPr)CH_2CO_2Me$	2-F	H	H
3-77	Ac	H	$CH_2N(iPr)CH_2CO_2Me$	2-F	H	H
3-78	H	H	$CH_2N(iPr)CH_2CO_2Et$	2-F	H	H
3-79	Ac	H	$CH_2N(iPr)CH_2CO_2Et$	2-F	H	H

(Tabla 4)



Comp. No.	P^1	R^2	R^3	X^1	X^2	X^3
4-1	H	H	CH_2OH	2-F	H	H
4-2	Ac	H	CH_2OH	2-F	H	H

4-3	H	H	CH_2CH_2OH	2-F	H	H
4-4	Ac	H	CH_2CH_2OH	2-F	H	H
4-5	H	H	CH_2OMe	2-F	H	H
4-6	Ac	H	CH_2OMe	2-F	H	H
4-7	H	H	CH_2CH_2OMe	2-F	H	H
4-8	Ac	H	CH_2CH_2OMe	2-F	H	H
4-9	H	H	CH_2OEt	2-F	H	H
4-10	Ac	H	CH_2OEt	2-F	H	H
4-11	H	H	CH_2CH_2OEt	2-F	H	H
4-12	Ac	H	CH_2CH_2OEt	2-F	H	H
4-13	H	H	CH_2CO_2H	2-F	H	H
4-14	Ac	H	CH_2CO_2H	2-F	H	H
4-15	H	H	CH_2CO_2Me	2-F	H	H
4-16	Ac	H	CH_2CO_2Me	2-F	H	H
4-17	H	H	CH_2CO_2Et	2-F	H	H
4-18	Ac	H	CH_2CO_2Et	2-F	H	H
4-19	H	H	4-Pip	2-F	H	H
4-20	Ac	H	4-Pip	2-F	H	H
4-21	H	H	4-Pip	2-F	4-F	H
4-22	Ac	H	4-Pip	2-F	4-F	H
4-23	H	H	1-CO_2Me-4-Pip	2-F	H	H
4-24	Ac	H	1-CO_2Me-4-Pip	2-F	H	H
4-25	H	H	1-CO_2Et-4-Pip	2-F	H	H
4-26	Ac	H	1-CO_2Et-4-Pip	2-F	H	H
4-27	H	H	1-CH_2CO_2H-4-Pip	2-F	H	H
4-28	Ac	H	1-CH_2CO_2H-4-Pip	2-F	H	H
4-29	H	H	1-CH_2CO_2Me-4-Pip	2-F	H	H
4-30	Ac	H	1-CH_2CO_2Me-4-Pip	2-F	H	H
4-31	H	H	1-CH_2CO_2Et-4-Pip	2-F	H	H
4-32	Ac	H	1-CH_2CO_2Et-4-Pip	2-F	H	H
4-33	H	H	1-$CH_2CH_2CO_2H$-4-Pip	2-F	H	H

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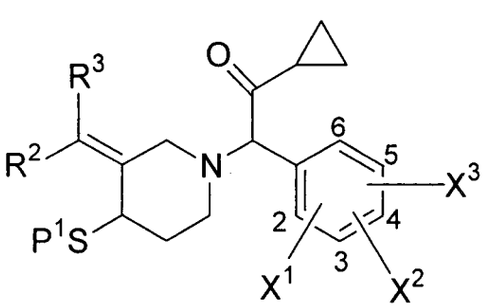
4-34	Ac	H	1-$CH_2CH_2CO_2H$-4-Pip	2-F	H	H
4-35	H	H	1-$CH_2CH_2CO_2Me$-4-Pip	2-F	H	H
4-36	Ac	H	1-$CH_2CH_2CO_2Me$-4-Pip	2-F	H	H
4-37	H	H	1-$CH_2CH_2CO_2Et$-4-Pip	2-F	H	H
4-38	Ac	H	1-$CH_2CH_2CO_2Et$-4-Pip	2-F	H	H
4-39	Ac	H	1-$CH_2CH_2CO_2Et$-4-Pip	2-F	4-F	H
4-40	H	H	1-$CH_2CH_2CH_2CO_2H$-4-Pip	2-F	H	H
4-41	Ac	H	1-$CH_2CH_2CH_2CO_2H$-4-Pip	2-F	H	H
4-42	H	H	1-$CH_2CH_2CH_2CO_2Me$-4-Pip	2-F	H	H
4-43	Ac	H	1-$CH_2CH_2CH_2CO_2Me$-4-Pip	2-F	H	H
4-44	H	H	1-$CH_2CH_2CH_2CO_2Et$-4-Pip	2-F	H	H
4-45	Ac	H	1-$CH_2CH_2CH_2CO_2Et$-4-Pip	2-F	H	H
4-46	H	H	CH_2CN	2-F	H	H
4-47	Ac	H	CH_2CN	2-F	H	H
4-48	H	H	CH_2CH_2CN	2-F	H	H
4-49	Ac	H	CH_2CH_2CN	2-F	H	H
4-50	H	H	$CH_2N(Me)CH_2CO_2H$	2-F	H	H
4-51	Ac	H	$CH_2N(Me)CH_2CO_2H$	2-F	H	H
4-52	H	H	$CH_2N(Me)CH_2CO_2Me$	2-F	H	H
4-53	Ac	H	$CH_2N(Me)CH_2CO_2Me$	2-F	H	H
4-54	H	H	$CH_2N(Me)CH_2CO_2Et$	2-F	H	H
4-55	Ac	H	$CH_2N(Me)CH_2CO_2Et$	2-F	H	H
4-56	H	H	$CH_2N(Me)CH_2CH_2CO_2H$	2-F	H	H
4-57	Ac	H	$CH_2N(Me)CH_2CH_2CO_2H$	2-F	H	H
4-58	H	H	$CH_2N(Me)CH_2CH_2CO_2Me$	2-F	H	H
4-59	Ac	H	$CH_2N(Me)CH_2CH_2CO_2Me$	2-F	H	H
4-60	H	H	$CH_2N(Me)CH_2CH_2CO_2Et$	2-F	H	H
4-61	Ac	H	$CH_2N(Me)CH_2CH_2CO_2Et$	2-F	H	H
4-62	H	H	$CH_2N(Me)CH_2CH_2CH_2CO_2H$	2-F	H	H
4-63	Ac	H	$CH_2N(Me)CH_2CH_2CH_2CO_2H$	2-F	H	H
4-64	H	H	$CH_2N(Me)CH_2CH_2CH_2CO_2Me$	2-F	H	H

4-65	Ac	H	$CH_2N(Me)CH_2CH_2CH_2CO_2Me$	2-F	H	H
4-66	H	H	$CH_2N(Me)CH_2CH_2CH_2CO_2Et$	2-F	H	H
4-67	Ac	H	$CH_2N(Me)CH_2CH_2CH_2CO_2Et$	2-F	H	H
4-68	H	H	$CH_2N(Et)CH_2CO_2H$	2-F	H	H
4-69	Ac	H	$CH_2N(Et)CH_2CO_2H$	2-F	H	H
4-70	H	H	$CH_2N(Et)CH_2CO_2Me$	2-F	H	H
4-71	Ac	H	$CH_2N(Et)CH_2CO_2Me$	2-F	H	H
4-72	H	H	$CH_2N(Et)CH_2CO_2Et$	2-F	H	H
4-73	Ac	H	$CH_2N(Et)CH_2CO_2Et$	2-F	H	H
4-74	H	H	$CH_2N(iPr)CH_2CO_2H$	2-F	H	H
4-75	Ac	H	$CH_2N(iPr)CH_2CO_2H$	2-F	H	H
4-76	H	H	$CH_2N(iPr)CH_2CO_2Me$	2-F	H	H
4-77	Ac	H	$CH_2N(iPr)CH_2CO_2Me$	2-F	H	H
4-78	H	H	$CH_2N(iPr)CH_2CO_2Et$	2-F	H	H
4-79	Ac	H	$CH_2N(iPr)CH_2CO_2Et$	2-F	H	H

(Tabla 5)



Comp. No.	P^1	R^2	R^3	X^1	X^2	X^3
5-1	H	H	CH_2-1-Pip	2-F	H	H
5-2	Ac	H	CH_2-1-Pip	2-F	H	H
5-3	H	H	CH_2-(4-CO_2H-1-Pip)	2-F	H	H
5-4	Ac	H	CH_2-(4-CO_2H-1-Pip)	2-F	H	H
5-5	H	H	CH_2-(4-CO_2Me-1-Pip)	2-F	H	H

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5-6	Ac	H	CH_2-(4-CO_2Me-1-Pip)	2-F	H	H
5-7	H	H	CH_2-(4-CO_2Et-1-Pip)	2-F	H	H
5-8	Ac	H	CH_2-(4-CO_2Et-1-Pip)	2-F	H	H
5-9	H	H	CH_2-(4-CH_2CO_2H-1-Pip)	2-F	H	H
5-10	Ac	H	CH_2-(4-CH_2CO_2H-1-Pip)	2-F	H	H
5-11	H	H	CH_2-(4-CH_2CO_2Me-1-Pip)	2-F	H	H
5-12	Ac	H	CH_2-(4-CH_2CO_2Me-1-Pip)	2-F	H	H
5-13	H	H	CH_2-(4-CH_2CO_2Et-1-Pip)	2-F	H	H
5-14	Ac	H	CH_2-(4-CH_2CO_2Et-1-Pip)	2-F	H	H
5-15	H	H	CH_2-(4-$CH_2CH_2CO_2H$-1-Pip)	2-F	H	H
5-16	Ac	H	CH_2-(4-$CH_2CH_2CO_2H$-1-Pip)	2-F	H	H
5-17	H	H	CH_2-(4-$CH_2CH_2CO_2$Me-1-Pip)	2-F	H	H
5-18	Ac	H	CH_2-(4-$CH_2CH_2CO_2$Me-1-Pip)	2-F	H	H
5-19	H	H	CH_2-(4-$CH_2CH_2CO_2$Et-1-Pip)	2-F	H	H
5-20	Ac	H	CH_2-(4-$CH_2CH_2CO_2$Et-1-Pip)	2-F	H	H
5-21	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2H$-1-Pip)	2-F	H	H
5-22	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2H$-1-Pip)	2-F	H	H
5-23	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2$Me-1-Pip)	2-F	H	H
5-24	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2$Me-1-Pip)	2-F	H	H
5-25	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2$Et-1-Pip)	2-F	H	H
5-26	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2$Et-1-Pip)	2-F	H	H
5-27	H	H	CH_2-Mor	2-F	H	H
5-28	Ac	H	CH_2-Mor	2-F	H	H
5-29	H	H	CH_2-Thim	2-F	H	H
5-30	Ac	H	CH_2-Thim	2-F	H	H
5-31	H	H	CH_2-1-Piz	2-F	H	H
5-32	Ac	H	CH_2-1-Piz	2-F	H	H
5-33	H	H	CH_2-(4-Ac-1-Piz)	2-F	H	H
5-34	Ac	H	CH_2-(4-Ac-1-Piz)	2-F	H	H
5-35	H	H	CH_2-(4-Ac-1-Piz)	2-F	4-F	H
5-36	Ac	H	CH_2-(4-Ac-1-Piz)	2-F	4-F	H

5-37	H	H	CH_2-(4-CO_2Me-1-Piz)	2-F	H	H
5-38	Ac	H	CH_2-(4-CO_2Me-1-Piz)	2-F	H	H
5-39	H	H	CH_2-(4-CO_2Et-1-Piz)	2-F	H	H
5-40	Ac	H	CH_2-(4-CO_2Et-1-Piz)	2-F	H	H
5-41	H	H	CH_2-(4-CH_2CO_2H-1-Piz)	2-F	H	H
5-42	Ac	H	CH_2-(4-CH_2CO_2H-1-Piz)	2-F	H	H
5-43	H	H	CH_2-(4-CH_2CO_2Me-1-Piz)	2-F	H	H
5-44	Ac	H	CH_2-(4-CH_2CO_2Me-1-Piz)	2-F	H	H
5-45	H	H	CH_2-(4-CH_2CO_2Et-1-Piz)	2-F	H	H
5-46	Ac	H	CH_2-(4-CH_2CO_2Et-1-Piz)	2-F	H	H
5-47	H	H	CH_2-(4-$CH_2CH_2CO_2$H-1-Piz)	2-F	H	H
5-48	Ac	H	CH_2-(4-$CH_2CH_2CO_2$H-1-Piz)	2-F	H	H
5-49	H	H	CH_2-(4-$CH_2CH_2CO_2$Me-1-Piz)	2-F	H	H
5-50	Ac	H	CH_2-(4-$CH_2CH_2CO_2$Me-1-Piz)	2-F	H	H
5-51	H	H	CH_2-(4-$CH_2CH_2CO_2$Et-1-Piz)	2-F	H	H
5-52	Ac	H	CH_2-(4-$CH_2CH_2CO_2$Et-1-Piz)	2-F	H	H
5-53	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2$H-1-Piz)	2-F	H	H
5-54	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2$H-1-Piz)	2-F	H	H
5-55	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2$Me-1-Piz)	2-F	H	H
5-56	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2$Me-1-Piz)	2-F	H	H
5-57	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2$Et-1-Piz)	2-F	H	H
5-58	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2$Et-1-Piz)	2-F	H	H
5-59	H	H	CH_2-(2-oxo-1-Piz)	2-F	H	H
5-60	Ac	H	CH_2-(2-oxo-1-Piz)	2-F	H	H
5-61	H	H	CH_2-(4-Ac-2-oxo-1-Piz)	2-F	H	H
5-62	Ac	H	CH_2-(4-Ac-2-oxo-1-Piz)	2-F	H	H
5-63	H	H	CH_2-(4-Ac-2-oxo-1-Piz)	2-F	4-F	H
5-64	Ac	H	CH_2-(4-Ac-2-oxo-1-Piz)	2-F	4-F	H
5-65	H	H	CH_2-(4-CO_2Me-2-oxo-1-Piz)	2-F	H	H
5-66	Ac	H	CH_2-(4-CO_2Me-2-oxo-1-Piz)	2-F	H	H
5-67	H	H	CH_2-(4-CO_2Et-2-oxo-1-Piz)	2-F	H	H

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5-68	Ac	H	CH_2-(4-CO_2Et-2-oxo-1-Piz)	2-F	H	H
5-69	H	H	CH_2-(4-CH_2CO_2H-2-oxo-1-Piz)	2-F	H	H
5-70	Ac	H	CH_2-(4-CH_2CO_2H-2-oxo-1-Piz)	2-F	H	H
5-71	H	H	CH_2-(4-CH_2CO_2Me-2-oxo-1-Piz)	2-F	H	H
5-72	Ac	H	CH_2-(4-CH_2CO_2Me-2-oxo-1-Piz)	2-F	H	H
5-73	H	H	CH_2-(4-CH_2CO_2Et-2-oxo-1-Piz)	2-F	H	H
5-74	Ac	H	CH_2-(4-CH_2CO_2Et-2-oxo-1-Piz)	2-F	H	H
5-75	H	H	CH_2-(4-$CH_2CH_2CO_2H$-2-oxo-1-Piz)	2-F	H	H
5-76	Ac	H	CH_2-(4-$CH_2CH_2CO_2H$-2-oxo-1-Piz)	2-F	H	H
5-77	H	H	CH_2-(4-$CH_2CH_2CO_2Me$-2-oxo-1-Piz)	2-F	H	H
5-78	Ac	H	CH_2-(4-$CH_2CH_2CO_2Me$-2-oxo-1-Piz)	2-F	H	H
5-79	H	H	CH_2-(4-$CH_2CH_2CO_2Et$-2-oxo-1-Piz)	2-F	H	H
5-80	Ac	H	CH_2-(4-$CH_2CH_2CO_2Et$-2-oxo-1-Piz)	2-F	H	H
5-81	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2H$-2-oxo-1-Piz)	2-F	H	H
5-82	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2H$-2-oxo-1-Piz)	2-F	H	H
5-83	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2Me$-2-oxo-1-Piz)	2-F	H	H
5-84	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2Me$-2-oxo-1-Piz)	2-F	H	H
5-85	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2Et$-2-oxo-1-Piz)	2-F	H	H
5-86	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2Et$-2-oxo-1-Piz)	2-F	H	H
5-87	H	H	CH_2-(3-oxo-1-Piz)	2-F	H	H
5-88	Ac	H	CH_2-(3-oxo-1-Piz)	2-F	H	H
5-89	H	H	CH_2-(4-Ac-3-oxo-1-Piz)	2-F	H	H
5-90	Ac	H	CH_2-(4-Ac-3-oxo-1-Piz)	2-F	H	H
5-91	H	H	CH_2-(4-Ac-3-oxo-1-Piz)	2-F	4-F	H
5-92	Ac	H	CH_2-(4-Ac-3-oxo-1-Piz)	2-F	4-F	H
5-93	H	H	CH_2-(4-CO_2Me-3-oxo-1-Piz)	2-F	H	H
5-94	Ac	H	CH_2-(4-CO_2Me-3-oxo-1-Piz)	2-F	H	H
5-95	H	H	CH_2-(4-CO_2Et-3-oxo-1-Piz)	2-F	H	H
5-96	Ac	H	CH_2-(4-CO_2Et-3-oxo-1-Piz)	2-F	H	H
5-97	H	H	CH_2-(4-CH_2CO_2H-3-oxo-1-Piz)	2-F	H	H
5-98	Ac	H	CH_2-(4-CH_2CO_2H-3-oxo-1-Piz)	2-F	H	H

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5-99	H	H	CH_2-(4-CH_2CO_2Me-3-oxo-1-Piz)	2-F	H	H
5-100	Ac	H	CH_2-(4-CH_2CO_2Me-3-oxo-1-Piz)	2-F	H	H
5-101	H	H	CH_2-(4-CH_2CO_2Et-3-oxo-1-Piz)	2-F	H	H
5-102	Ac	H	CH_2-(4-CH_2CO_2Et-3-oxo-1-Piz)	2-F	H	H
5-103	H	H	CH_2-(4-$CH_2CH_2CO_2H$-3-oxo-1-Piz)	2-F	H	H
5-104	Ac	H	CH_2-(4-$CH_2CH_2CO_2H$-3-oxo-1-Piz)	2-F	H	H
5-105	H	H	CH_2-(4-$CH_2CH_2CO_2Me$-3-oxo-1-Piz)	2-F	H	H
5-106	Ac	H	CH_2-(4-$CH_2CH_2CO_2Me$-3-oxo-1-Piz)	2-F	H	H
5-107	H	H	CH_2-(4-$CH_2CH_2CO_2Et$-3-oxo-1-Piz)	2-F	H	H
5-108	Ac	H	CH_2-(4-$CH_2CH_2CO_2Et$-3-oxo-1-Piz)	2-F	H	H
5-109	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2H$-3-oxo-1-Piz)	2-F	H	H
5-110	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2H$-3-oxo-1-Piz)	2-F	H	H
5-111	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2Me$-3-oxo-1-Piz)	2-F	H	H
5-112	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2Me$-3-oxo-1-Piz)	2-F	H	H
5-113	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2Et$-3-oxo-1-Piz)	2-F	H	H
5-114	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2Et$-3-oxo-1-Piz)	2-F	H	H
5-115	H	H	CH_2-(2,5-dioxo-1-Piz)	2-F	H	H
5-116	Ac	H	CH_2-(2,5-dioxo-1-Piz)	2-F	H	H
5-117	H	H	CH_2-(4-Ac-2,5-dioxo-1-Piz)	2-F	H	H
5-118	Ac	H	CH_2-(4-Ac-2,5-dioxo-1-Piz)	2-F	H	H
5-119	H	H	CH_2-(4-Ac-2,5-dioxo-1-Piz)	2-F	4-F	H
5-120	Ac	H	CH_2-(4-Ac-2,5-dioxo-1-Piz)	2-F	4-F	H
5-121	H	H	CH_2-(4-CO_2Me-2,5-dioxo-1-Piz)	2-F	H	H
5-122	Ac	H	CH_2-(4-CO_2Me-2,5-dioxo-1-Piz)	2-F	H	H
5-123	H	H	CH_2-(4-CO_2Et-2,5-dioxo-1-Piz)	2-F	H	H
5-124	Ac	H	CH_2-(4-CO_2Et-2,5-dioxo-1-Piz)	2-F	H	H
5-125	H	H	CH_2-(4-CH_2CO_2H-2,5-dioxo-1-Piz)	2-F	H	H
5-126	Ac	H	CH_2-(4-CH_2CO_2H-2,5-dioxo-1-Piz)	2-F	H	H
5-127	H	H	CH_2-(4-CH_2CO_2Me-2,5-dioxo-1-Piz)	2-F	H	H
5-128	Ac	H	CH_2-(4-CH_2CO_2Me-2,5-dioxo-1-Piz)	2-F	H	H
5-129	H	H	CH_2-(4-CH_2CO_2Et-2,5-dioxo-1-Piz)	2-F	H	H

5-130	Ac	H	CH_2-(4-CH_2CO_2Et-2,5-dioxo-1-Piz)	2-F	H	H
5-131	H	H	CH_2-(4-$CH_2CH_2CO_2H$-2,5-dioxo-1-Piz)	2-F	H	H
5-132	Ac	H	CH_2-(4-$CH_2CH_2CO_2H$-2,5-dioxo-1-Piz)	2-F	H	H
5-133	H	H	CH_2-(4-$CH_2CH_2CO_2Me$-2,5-dioxo-1-Piz)	2-F	H	H
5-134	Ac	H	CH_2-(4-$CH_2CH_2CO_2Me$-2,5-dioxo-1-Piz)	2-F	H	H
5-135	H	H	CH_2-(4-$CH_2CH_2CO_2Et$-2,5-dioxo-1-Piz)	2-F	H	H
5-136	Ac	H	CH_2-(4-$CH_2CH_2CO_2Et$-2,5-dioxo-1-Piz)	2-F	H	H
5-137	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2H$-2,5-dioxo-1-Piz)	2-F	H	H
5-138	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2H$-2,5-dioxo-1-Piz)	2-F	H	H
5-139	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2Me$-2,5-dioxo-1-Piz)	2-F	H	H
5-140	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2Me$-2,5-dioxo-1-Piz)	2-F	H	H
5-141	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2Et$-2,5-dioxo-1-Piz)	2-F	H	H
5-142	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2Et$-2,5-dioxo-1-Piz)	2-F	H	H
5-143	H	H	CH_2-1-Pyrd	2-F	H	H
5-144	Ac	H	CH_2-1-Pyrd	2-F	H	H
5-145	H	H	CH_2-(2-CO_2H-1-Pyrd)	2-F	H	H
5-146	Ac	H	CH_2-(2-CO_2H-1-Pyrd)	2-F	H	H
5-147	H	H	CH_2-(2-CO_2Me-1-Pyrd)	2-F	H	H
5-148	Ac	H	CH_2-(2-CO_2Me-1-Pyrd)	2-F	H	H
5-149	H	H	CH_2-(2-CO_2Et-1-Pyrd)	2-F	H	H
5-150	Ac	H	CH_2-(2-CO_2Et-1-Pyrd)	2-F	H	H
5-151	H	H	CH_2-(2-CH_2CO_2H-1-Pyrd)	2-F	H	H
5-152	Ac	H	CH_2-(2-CH_2CO_2H-1-Pyrd)	2-F	H	H
5-153	H	H	CH_2-(2-CH_2CO_2Me-1-Pyrd)	2-F	H	H
5-154	Ac	H	CH_2-(2-CH_2CO_2Me-1-Pyrd)	2-F	H	H
5-155	H	H	CH_2-(2-CH_2CO_2Et-1-Pyrd)	2-F	H	H
5-156	Ac	H	CH_2-(2-CH_2CO_2Et-1-Pyrd)	2-F	H	H
5-157	H	H	CH_2-(2-$CH_2CH_2CO_2H$-1-Pyrd)	2-F	H	H
5-158	Ac	H	CH_2-(2-$CH_2CH_2CO_2H$-1-Pyrd)	2-F	H	H
5-159	H	H	CH_2-(2-$CH_2CH_2CO_2Me$-1-Pyrd)	2-F	H	H
5-160	Ac	H	CH_2-(2-$CH_2CH_2CO_2Me$-1-Pyrd)	2-F	H	H

5-161	H	H	CH_2-(2-$CH_2CH_2CO_2Et$-1-Pyrd)	2-F	H	H
5-162	Ac	H	CH_2-(2-$CH_2CH_2CO_2Et$-1-Pyrd)	2-F	H	H
5-163	H	H	CH_2-(2-$CH_2CH_2CH_2CO_2H$-1-Pyrd)	2-F	H	H
5-164	Ac	H	CH_2-(2-$CH_2CH_2CH_2CO_2H$-1-Pyrd)	2-F	H	H
5-165	H	H	CH_2-(2-$CH_2CH_2CH_2CO_2Me$-1-Pyrd)	2-F	H	H
5-166	Ac	H	CH_2-(2-$CH_2CH_2CH_2CO_2Me$-1-Pyrd)	2-F	H	H
5-167	H	H	CH_2-(2-$CH_2CH_2CH_2CO_2Et$-1-Pyrd)	2-F	H	H
5-168	Ac	H	CH_2-(2-$CH_2CH_2CH_2CO_2Et$-1-Pyrd)	2-F	H	H
5-169	H	H	CH_2CH_2-1-Pip	2-F	H	H
5-170	Ac	H	CH_2CH_2-1-Pip	2-F	H	H
5-171	H	H	CH_2CH_2-(4-CO_2H-1-Pip)	2-F	H	H
5-172	Ac	H	CH_2CH_2-(4-CO_2H-1-Pip)	2-F	H	H
5-173	H	H	CH_2CH_2-(4-CO_2Me-1-Pip)	2-F	H	H
5-174	Ac	H	CH_2CH_2-(4-CO_2Me-1-Pip)	2-F	H	H
5-175	H	H	CH_2CH_2-(4-CO_2Et-1-Pip)	2-F	H	H
5-176	Ac	H	CH_2CH_2-(4-CO_2Et-1-Pip)	2-F	H	H
5-177	H	H	CH_2CH_2-(4-CH_2CO_2H-1-Pip)	2-F	H	H
5-178	Ac	H	CH_2CH_2-(4-CH_2CO_2H-1-Pip)	2-F	H	H
5-179	H	H	CH_2CH_2-(4-CH_2CO_2Me-1-Pip)	2-F	H	H
5-180	Ac	H	CH_2CH_2-(4-CH_2CO_2Me-1-Pip)	2-F	H	H
5-181	H	H	CH_2CH_2-(4-CH_2CO_2Et-1-Pip)	2-F	H	H
5-182	Ac	H	CH_2CH_2-(4-CH_2CO_2Et-1-Pip)	2-F	H	H
5-183	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2H$-1-Pip)	2-F	H	H
5-184	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2H$-1-Pip)	2-F	H	H
5-185	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-1-Pip)	2-F	H	H
5-186	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-1-Pip)	2-F	H	H
5-187	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-1-Pip)	2-F	H	H
5-188	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-1-Pip)	2-F	H	H
5-189	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2H$-1-Pip)	2-F	H	H
5-190	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2H$-1-Pip)	2-F	H	H
5-191	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Me$-1-Pip)	2-F	H	H

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5-192	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Me$-1-Pip)	2-F	H	H
5-193	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Et$-1-Pip)	2-F	H	H
5-194	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Et$-1-Pip)	2-F	H	H
5-195	H	H	CH_2CH_2-Mor	2-F	H	H
5-196	Ac	H	CH_2CH_2-Mor	2-F	H	H
5-197	H	H	CH_2CH_2-Thim	2-F	H	H
5-198	Ac	H	CH_2CH_2-Thim	2-F	H	H
5-199	H	H	CH_2CH_2-1-Piz	2-F	H	H
5-200	Ac	H	CH_2CH_2-1-Piz	2-F	H	H
5-201	H	H	CH_2CH_2-(4-Ac-1-Piz)	2-F	H	H
5-202	Ac	H	CH_2CH_2-(4-Ac-1-Piz)	2-F	H	H
5-203	H	H	CH_2CH_2-(4-Ac-1-Piz)	2-F	4-F	H
5-204	Ac	H	CH_2CH_2-(4-Ac-1-Piz)	2-F	4-F	H
5-205	H	H	CH_2CH_2-(4-CO_2Me-1-Piz)	2-F	H	H
5-206	Ac	H	CH_2CH_2-(4-CO_2Me-1-Piz)	2-F	H	H
5-207	H	H	CH_2CH_2-(4-CO_2Et-1-Piz)	2-F	H	H
5-208	Ac	H	CH_2CH_2-(4-CO_2Et-1-Piz)	2-F	H	H
5-209	H	H	CH_2CH_2-(4-CH_2CO_2H-1-Piz)	2-F	H	H
5-210	Ac	H	CH_2CH_2-(4-CH_2CO_2H-1-Piz)	2-F	H	H
5-211	H	H	CH_2CH_2-(4-CH_2CO_2Me-1-Piz)	2-F	H	H
5-212	Ac	H	CH_2CH_2-(4-CH_2CO_2Me-1-Piz)	2-F	H	H
5-213	H	H	CH_2CH_2-(4-CH_2CO_2Et-1-Piz)	2-F	H	H
5-214	Ac	H	CH_2CH_2-(4-CH_2CO_2Et-1-Piz)	2-F	H	H
5-215	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2H$-1-Piz)	2-F	H	H
5-216	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2H$-1-Piz)	2-F	H	H
5-217	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-1-Piz)	2-F	H	H
5-218	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-1-Piz)	2-F	H	H
5-219	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-1-Piz)	2-F	H	H
5-220	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-1-Piz)	2-F	H	H
5-221	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2H$-1-Piz)	2-F	H	H
5-222	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2H$-1-Piz)	2-F	H	H

5-223	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Me$-1-Piz)	2-F	H	H
5-224	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Me$-1-Piz)	2-F	H	H
5-225	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Et$-1-Piz)	2-F	H	H
5-226	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Et$-1-Piz)	2-F	H	H
5-227	H	H	CH_2CH_2-(2-oxo-1-Piz)	2-F	H	H
5-228	Ac	H	CH_2CH_2-(2-oxo-1-Piz)	2-F	H	H
5-229	H	H	CH_2CH_2-(4-Ac-2-oxo-1-Piz)	2-F	H	H
5-230	Ac	H	CH_2CH_2-(4-Ac-2-oxo-1-Piz)	2-F	H	H
5-231	H	H	CH_2CH_2-(4-Ac-2-oxo-1-Piz)	2-F	4-F	H
5-232	Ac	H	CH_2CH_2-(4-Ac-2-oxo-1-Piz)	2-F	4-F	H
5-233	H	H	CH_2CH_2-(4-CO_2Me-2-oxo-1-Piz)	2-F	H	H
5-234	Ac	H	CH_2CH_2-(4-CO_2Me-2-oxo-1-Piz)	2-F	H	H
5-235	H	H	CH_2CH_2-(4-CO_2Et-2-oxo-1-Piz)	2-F	H	H
5-236	Ac	H	CH_2CH_2-(4-CO_2Et-2-oxo-1-Piz)	2-F	H	H
5-237	H	H	CH_2CH_2-(4-CH_2CO_2H-2-oxo-1-Piz)	2-F	H	H
5-238	Ac	H	CH_2CH_2-(4-CH_2CO_2H-2-oxo-1-Piz)	2-F	H	H
5-239	H	H	CH_2CH_2-(4-CH_2CO_2Me-2-oxo-1-Piz)	2-F	H	H
5-240	Ac	H	CH_2CH_2-(4-CH_2CO_2Me-2-oxo-1-Piz)	2-F	H	H
5-241	H	H	CH_2CH_2-(4-CH_2CO_2Et-2-oxo-1-Piz)	2-F	H	H
5-242	Ac	H	CH_2CH_2-(4-CH_2CO_2Et-2-oxo-1-Piz)	2-F	H	H
5-243	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2H$-2-oxo-1-Piz)	2-F	H	H
5-244	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2H$-2-oxo-1-Piz)	2-F	H	H
5-245	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-2-oxo-1-Piz)	2-F	H	H
5-246	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-2-oxo-1-Piz)	2-F	H	H
5-247	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-2-oxo-1-Piz)	2-F	H	H
5-248	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-2-oxo-1-Piz)	2-F	H	H
5-249	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2H$-2-oxo-1-Piz)	2-F	H	H
5-250	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2H$-2-oxo-1-Piz)	2-F	H	H
5-251	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Me$-2-oxo-1-Piz)	2-F	H	H
5-252	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Me$-2-oxo-1-Piz)	2-F	H	H
5-253	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Et$-2-oxo-1-Piz)	2-F	H	H

5-254	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Et$-2-oxo-1-Piz)	2-F	H	H
5-255	H	H	CH_2CH_2-(3-oxo-1-Piz)	2-F	H	H
5-256	Ac	H	CH_2CH_2-(3-oxo-1-Piz)	2-F	H	H
5-257	H	H	CH_2CH_2-(4-Ac-3-oxo-1-Piz)	2-F	H	H
5-258	Ac	H	CH_2CH_2-(4-Ac-3-oxo-1-Piz)	2-F	H	H
5-259	H	H	CH_2CH_2-(4-Ac-3-oxo-1-Piz)	2-F	4-F	H
5-260	Ac	H	CH_2CH_2-(4-Ac-3-oxo-1-Piz)	2-F	4-F	H
5-261	H	H	CH_2CH_2-(4-CO_2Me-3-oxo-1-Piz)	2-F	H	H
5-262	Ac	H	CH_2CH_2-(4-CO_2Me-3-oxo-1-Piz)	2-F	H	H
5-263	H	H	CH_2CH_2-(4-CO_2Et-3-oxo-1-Piz)	2-F	H	H
5-264	Ac	H	CH_2CH_2-(4-CO_2Et-3-oxo-1-Piz)	2-F	H	H
5-265	H	H	CH_2CH_2-(4-CH_2CO_2H-3-oxo-1-Piz)	2-F	H	H
5-266	Ac	H	CH_2CH_2-(4-CH_2CO_2H-3-oxo-1-Piz)	2-F	H	H
5-267	H	H	CH_2CH_2-(4-CH_2CO_2Me-3-oxo-1-Piz)	2-F	H	H
5-268	Ac	H	CH_2CH_2-(4-CH_2CO_2Me-3-oxo-1-Piz)	2-F	H	H
5-269	H	H	CH_2CH_2-(4-CH_2CO_2Et-3-oxo-1-Piz)	2-F	H	H
5-270	Ac	H	CH_2CH_2-(4-CH_2CO_2Et-3-oxo-1-Piz)	2-F	H	H
5-271	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2H$-3-oxo-1-Piz)	2-F	H	H
5-272	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2H$-3-oxo-1-Piz)	2-F	H	H
5-273	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-3-oxo-1-Piz)	2-F	H	H
5-274	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-3-oxo-1-Piz)	2-F	H	H
5-275	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-3-oxo-1-Piz)	2-F	H	H
5-276	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-3-oxo-1-Piz)	2-F	H	H
5-277	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2H$-3-oxo-1-Piz)	2-F	H	H
5-278	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2H$-3-oxo-1-Piz)	2-F	H	H
5-279	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Me$-3-oxo-1-Piz)	2-F	H	H
5-280	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Me$-3-oxo-1-Piz)	2-F	H	H
5-281	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Et$-3-oxo-1-Piz)	2-F	H	H
5-282	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Et$-3-oxo-1-Piz)	2-F	H	H
5-283	H	H	CH_2CH_2-(2,5-dioxo-1-Piz)	2-F	H	H
5-284	Ac	H	CH_2CH_2-(2,5-dioxo-1-Piz)	2-F	H	H

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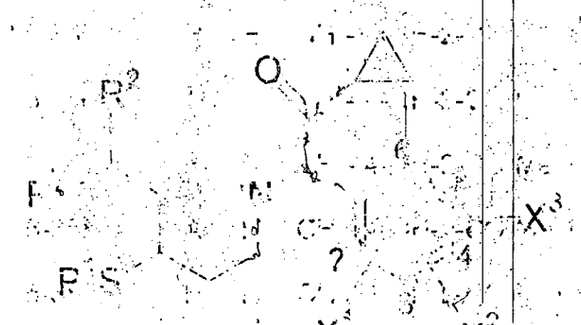
5-285	H	H	CH_2CH_2-(4-Ac-2,5-dioxo-1-Piz)	2-F	H	H
5-286	Ac	H	CH_2CH_2-(4-Ac-2,5-dioxo-1-Piz)	2-F	H	H
5-287	H	H	CH_2CH_2-(4-Ac-2,5-dioxo-1-Piz)	2-F	4-F	H
5-288	Ac	H	CH_2CH_2-(4-Ac-2,5-dioxo-1-Piz)	2-F	4-F	H
5-289	H	H	CH_2CH_2-(4-CO_2Me-2,5-dioxo-1-Piz)	2-F	H	H
5-290	Ac	H	CH_2CH_2-(4-CO_2Me-2,5-dioxo-1-Piz)	2-F	H	H
5-291	H	H	CH_2CH_2-(4-CO_2Et-2,5-dioxo-1-Piz)	2-F	H	H
5-292	Ac	H	CH_2CH_2-(4-CO_2Et-2,5-dioxo-1-Piz)	2-F	H	H
5-293	H	H	CH_2CH_2-(4-CH_2CO_2H-2,5-dioxo-1-Piz)	2-F	H	H
5-294	Ac	H	CH_2CH_2-(4-CH_2CO_2H-2,5-dioxo-1-Piz)	2-F	H	H
5-295	H	H	CH_2CH_2-(4-CH_2CO_2Me-2,5-dioxo-1-Piz)	2-F	H	H
5-296	Ac	H	CH_2CH_2-(4-CH_2CO_2Me-2,5-dioxo-1-Piz)	2-F	H	H
5-297	H	H	CH_2CH_2-(4-CH_2CO_2Et-2,5-dioxo-1-Piz)	2-F	H	H
5-298	Ac	H	CH_2CH_2-(4-CH_2CO_2Et-2,5-dioxo-1-Piz)	2-F	H	H
5-299	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2H$-2,5-dioxo-1-Piz)	2-F	H	H
5-300	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2H$-2,5-dioxo-1-Piz)	2-F	H	H
5-301	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-2,5-dioxo-1-Piz)	2-F	H	H
5-302	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-2,5-dioxo-1-Piz)	2-F	H	H
5-303	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-2,5-dioxo-1-Piz)	2-F	H	H
5-304	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-2,5-dioxo-1-Piz)	2-F	H	H
5-305	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2H$-2,5-dioxo-1-Piz)	2-F	H	H
5-306	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2H$-2,5-dioxo-1-Piz)	2-F	H	H
5-307	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Me$-2,5-dioxo-1-Piz)	2-F	H	H
5-308	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Me$-2,5-dioxo-1-Piz)	2-F	H	H
5-309	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Et$-2,5-dioxo-1-Piz)	2-F	H	H
5-310	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Et$-2,5-dioxo-1-Piz)	2-F	H	H
5-311	H	H	CH_2CH_2-1-Pyrd	2-F	H	H
5-312	Ac	H	CH_2CH_2-1-Pyrd	2-F	H	H
5-313	H	H	CH_2CH_2-(2-CO_2H-1-Pyrd)	2-F	H	H
5-314	Ac	H	CH_2CH_2-(2-CO_2H-1-Pyrd)	2-F	H	H
5-315	H	H	CH_2CH_2-(2-CO_2Me-1-Pyrd)	2-F	H	H

5-316	Ac	H	CH_2CH_2-(2-CO_2Me-1-Pyrd)	2-F	H	H
5-317	H	H	CH_2CH_2-(2-CO_2Et-1-Pyrd)	2-F	H	H
5-318	Ac	H	CH_2CH_2-(2-CO_2Et-1-Pyrd)	2-F	H	H
5-319	H	H	CH_2CH_2-(2-CH_2CO_2H-1-Pyrd)	2-F	H	H
5-320	Ac	H	CH_2CH_2-(2-CH_2CO_2H-1-Pyrd)	2-F	H	H
5-321	H	H	CH_2CH_2-(2-CH_2CO_2Me-1-Pyrd)	2-F	H	H
5-322	Ac	H	CH_2CH_2-(2-CH_2CO_2Me-1-Pyrd)	2-F	H	H
5-323	H	H	CH_2CH_2-(2-CH_2CO_2Et-1-Pyrd)	2-F	H	H
5-324	Ac	H	CH_2CH_2-(2-CH_2CO_2Et-1-Pyrd)	2-F	H	H
5-325	H	H	CH_2CH_2-(2-$CH_2CH_2CO_2$H-1-Pyrd)	2-F	H	H
5-326	Ac	H	CH_2CH_2-(2-$CH_2CH_2CO_2$H-1-Pyrd)	2-F	H	H
5-327	H	H	CH_2CH_2-(2-$CH_2CH_2CO_2$Me-1-Pyrd)	2-F	H	H
5-328	Ac	H	CH_2CH_2-(2-$CH_2CH_2CO_2$Me-1-Pyrd)	2-F	H	H
5-329	H	H	CH_2CH_2-(2-$CH_2CH_2CO_2$Et-1-Pyrd)	2-F	H	H
5-330	Ac	H	CH_2CH_2-(2-$CH_2CH_2CO_2$Et-1-Pyrd)	2-F	H	H
5-331	H	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2$H-1-Pyrd)	2-F	H	H
5-332	Ac	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2$H-1-Pyrd)	2-F	H	H
5-333	H	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2$Me-1-Pyrd)	2-F	H	H
5-334	Ac	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2$Me-1-Pyrd)	2-F	H	H
5-335	H	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2$Et-1-Pyrd)	2-F	H	H
5-336	Ac	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2$Et-1-Pyrd)	2-F	H	H
5-337	H	H	CH_2-(3-CO_2H-1-Pip)	2-F	H	H
5-338	Ac	H	CH_2-(3-CO_2H-1-Pip)	2-F	H	H
5-339	H	H	CH_2-(3-CO_2Me-1-Pip)	2-F	H	H
5-340	Ac	H	CH_2-(3-CO_2Me-1-Pip)	2-F	H	H
5-341	H	H	CH_2-(3-CO_2Et-1-Pip)	2-F	H	H
5-342	Ac	H	CH_2-(3-CO_2Et-1-Pip)	2-F	H	H
5-343	H	H	CH_2-(3-CH_2CO_2H-1-Pip)	2-F	H	H
5-344	Ac	H	CH_2-(3-CH_2CO_2H-1-Pip)	2-F	H	H
5-345	H	H	CH_2-(3-CH_2CO_2Me-1-Pip)	2-F	H	H
5-346	Ac	H	CH_2-(3-CH_2CO_2Me-1-Pip)	2-F	H	H

5-347	H	H	CH_2-(3-CH_2CO_2Et-1-Pip)	2-F	H	H
5-348	Ac	H	CH_2-(3-CH_2CO_2Et-1-Pip)	2-F	H	H
5-349	H	H	CH_2-(3-$CH_2CH_2CO_2H$-1-Pip)	2-F	H	H
5-350	Ac	H	CH_2-(3-$CH_2CH_2CO_2H$-1-Pip)	2-F	H	H
5-351	H	H	CH_2-(3-$CH_2CH_2CO_2Me$-1-Pip)	2-F	H	H
5-352	Ac	H	CH_2-(3-$CH_2CH_2CO_2Me$-1-Pip)	2-F	H	H
5-353	H	H	CH_2-(3-$CH_2CH_2CO_2Et$-1-Pip)	2-F	H	H
5-354	Ac	H	CH_2-(3-$CH_2CH_2CO_2Et$-1-Pip)	2-F	H	H
5-355	H	H	CH_2-(3-$CH_2CH_2CH_2CO_2H$-1-Pip)	2-F	H	H
5-356	Ac	H	CH_2-(3-$CH_2CH_2CH_2CO_2H$-1-Pip)	2-F	H	H
5-357	H	H	CH_2-(3-$CH_2CH_2CH_2CO_2Me$-1-Pip)	2-F	H	H
5-358	Ac	H	CH_2-(3-$CH_2CH_2CH_2CO_2Me$-1-Pip)	2-F	H	H
5-359	H	H	CH_2-(3-$CH_2CH_2CH_2CO_2Et$-1-Pip)	2-F	H	H
5-360	Ac	H	CH_2-(3-$CH_2CH_2CH_2CO_2Et$-1-Pip)	2-F	H	H
5-361	H	H	CH_2CH_2-(3-CO_2H-1-Pip)	2-F	H	H
5-362	Ac	H	CH_2CH_2-(3-CO_2H-1-Pip)	2-F	H	H
5-363	H	H	CH_2CH_2-(3-CO_2Me-1-Pip)	2-F	H	H
5-364	Ac	H	CH_2CH_2-(3-CO_2Me-1-Pip)	2-F	H	H
5-365	H	H	CH_2CH_2-(3-CO_2Et-1-Pip)	2-F	H	H
5-366	Ac	H	CH_2CH_2-(3-CO_2Et-1-Pip)	2-F	H	H
5-367	H	H	CH_2CH_2-(3-CH_2CO_2H-1-Pip)	2-F	H	H
5-368	Ac	H	CH_2CH_2-(3-CH_2CO_2H-1-Pip)	2-F	H	H
5-369	H	H	CH_2CH_2-(3-CH_2CO_2Me-1-Pip)	2-F	H	H
5-370	Ac	H	CH_2CH_2-(3-CH_2CO_2Me-1-Pip)	2-F	H	H
5-371	H	H	CH_2CH_2-(3-CH_2CO_2Et-1-Pip)	2-F	H	H
5-372	Ac	H	CH_2CH_2-(3-CH_2CO_2Et-1-Pip)	2-F	H	H
5-373	H	H	CH_2CH_2-(3-$CH_2CH_2CO_2H$-1-Pip)	2-F	H	H
5-374	Ac	H	CH_2CH_2-(3-$CH_2CH_2CO_2H$-1-Pip)	2-F	H	H
5-375	H	H	CH_2CH_2-(3-$CH_2CH_2CO_2Me$-1-Pip)	2-F	H	H
5-376	Ac	H	CH_2CH_2-(3-$CH_2CH_2CO_2Me$-1-Pip)	2-F	H	H
5-377	H	H	CH_2CH_2-(3-$CH_2CH_2CO_2Et$-1-Pip)	2-F	H	H

5-378	Ac	H	CH_2CH_2-(3-$CH_2CH_2CO_2Et$-1-Pip)	2-F	H	H
5-379	H	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2H$-1-Pip)	2-F	H	H
5-380	Ac	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2H$-1-Pip)	2-F	H	H
5-381	H	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2Me$-1-Pip)	2-F	H	H
5-382	Ac	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2Me$-1-Pip)	2-F	H	H
5-383	H	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2Et$-1-Pip)	2-F	H	H
5-384	Ac	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2Et$-1-Pip)	2-F	H	H
5-385	H	H	CH_2-(4-$CH_2CH_2CO_2H$-1-Pyrd)	2-F	H	H
5-386	Ac	H	CH_2-(4-$CH_2CH_2CO_2H$-1-Pyrd)	2-F	H	H
5-387	H	H	CH_2-(4-$CH_2CH_2CO_2Me$-1-Pyrd)	2-F	H	H
5-388	Ac	H	CH_2-(4-$CH_2CH_2CO_2Me$-1-Pyrd)	2-F	H	H
5-389	H	H	CH_2-(4-$CH_2CH_2CO_2Et$-1-Pyrd)	2-F	H	H
5-390	Ac	H	CH_2-(4-$CH_2CH_2CO_2Et$-1-Pyrd)	2-F	H	H

(Table 6)



Comp					X	X
6-1	H	H	CH_2-1-Pip	2-F	H	H
6-2	Ac	H	CH_2-1-Pip	2-F	H	H
6-3	H	H	CH_2-(4-CO_2H-1-Pip)	2-F	H	H
6-4	Ac	H	CH_2-(4-CO_2H-1-Pip)	2-F	H	H
6-5	H	H	CH_2-(4-CO_2Me-1-Pip)	2-F	H	H
6-6	Ac	H	CH_2-(4-CO_2Me-1-Pip)	2-F	H	H
6-7	Ac	H	CH_2-(4-CO_2Et-1-Pip)	2-F	H	H

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6-8	Ac	H	CH_2-(4-CO_2Et-1-Pip)	2-F	H	H
6-9	H	H	CH_2-(4-CH_2CO_2H-1-Pip)	2-F	H	H
6-10	Ac	H	CH_2-(4-CH_2CO_2H-1-Pip)	2-F	H	H
6-11	H	H	CH_2-(4-CH_2CO_2Me-1-Pip)	2-F	H	H
6-12	Ac	H	CH_2-(4-CH_2CO_2Me-1-Pip)	2-F	H	H
6-13	H	H	CH_2-(4-CH_2CO_2Et-1-Pip)	2-F	H	H
6-14	Ac	H	CH_2-(4-CH_2CO_2Et-1-Pip)	2-F	H	H
6-15	H	H	CH_2-(4-$CH_2CH_2CO_2H$-1-Pip)	2-F	H	H
6-16	Ac	H	CH_2-(4-$CH_2CH_2CO_2H$-1-Pip)	2-F	H	H
6-17	H	H	CH_2-(4-$CH_2CH_2CO_2Me$-1-Pip)	2-F	H	H
6-18	Ac	H	CH_2-(4-$CH_2CH_2CO_2Me$-1-Pip)	2-F	H	H
6-19	H	H	CH_2-(4-$CH_2CH_2CO_2Et$-1-Pip)	2-F	H	H
6-20	Ac	H	CH_2-(4-$CH_2CH_2CO_2Et$-1-Pip)	2-F	H	H
6-21	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2H$-1-Pip)	2-F	H	H
6-22	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2H$-1-Pip)	2-F	H	H
6-23	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2Me$-1-Pip)	2-F	H	H
6-24	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2Me$-1-Pip)	2-F	H	H
6-25	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2Et$-1-Pip)	2-F	H	H
6-26	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2Et$-1-Pip)	2-F	H	H
6-27	H	H	CH_2-Mor	2-F	H	H
6-28	Ac	H	CH_2-Mor	2-F	H	H
6-29	H	H	CH_2-Thim	2-F	H	H
6-30	Ac	H	CH_2-Thim	2-F	H	H
6-31	H	H	CH_2-1-Piz	2-F	H	H
6-32	Ac	H	CH_2-1-Piz	2-F	H	H
6-33	H	H	CH_2-(4-Ac-1-Piz)	2-F	H	H
6-34	Ac	H	CH_2-(4-Ac-1-Piz)	2-F	H	H
6-35	H	H	CH_2-(4-Ac-1-Piz)	2-F	4-F	H
6-36	Ac	H	CH_2-(4-Ac-1-Piz)	2-F	4-F	H
6-37	H	H	CH_2-(4-CO_2Me-1-Piz)	2-F	H	H
6-38	Ac	H	CH_2-(4-CO_2Me-1-Piz)	2-F	H	H

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6-39	H	H	CH_2-(4-CO_2Et-1-Piz)	2-F	H	H
6-40	Ac	H	CH_2-(4-CO_2Et-1-Piz)	2-F	H	H
6-41	H	H	CH_2-(4-CH_2CO_2H-1-Piz)	2-F	H	H
6-42	Ac	H	CH_2-(4-CH_2CO_2H-1-Piz)	2-F	H	H
6-43	H	H	CH_2-(4-CH_2CO_2Me-1-Piz)	2-F	H	H
6-44	Ac	H	CH_2-(4-CH_2CO_2Me-1-Piz)	2-F	H	H
6-45	H	H	CH_2-(4-CH_2CO_2Et-1-Piz)	2-F	H	H
6-46	Ac	H	CH_2-(4-CH_2CO_2Et-1-Piz)	2-F	H	H
6-47	H	H	CH_2-(4-$CH_2CH_2CO_2H$-1-Piz)	2-F	H	H
6-48	Ac	H	CH_2-(4-$CH_2CH_2CO_2H$-1-Piz)	2-F	H	H
6-49	H	H	CH_2-(4-$CH_2CH_2CO_2Me$-1-Piz)	2-F	H	H
6-50	Ac	H	CH_2-(4-$CH_2CH_2CO_2Me$-1-Piz)	2-F	H	H
6-51	H	H	CH_2-(4-$CH_2CH_2CO_2Et$-1-Piz)	2-F	H	H
6-52	Ac	H	CH_2-(4-$CH_2CH_2CO_2Et$-1-Piz)	2-F	H	H
6-53	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2H$-1-Piz)	2-F	H	H
6-54	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2H$-1-Piz)	2-F	H	H
6-55	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2Me$-1-Piz)	2-F	H	H
6-56	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2Me$-1-Piz)	2-F	H	H
6-57	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2Et$-1-Piz)	2-F	H	H
6-58	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2Et$-1-Piz)	2-F	H	H
6-59	H	H	CH_2-(2-oxo-1-Piz)	2-F	H	H
6-60	Ac	H	CH_2-(2-oxo-1-Piz)	2-F	H	H
6-61	H	H	CH_2-(4-Ac-2-oxo-1-Piz)	2-F	H	H
6-62	Ac	H	CH_2-(4-Ac-2-oxo-1-Piz)	2-F	H	H
6-63	H	H	CH_2-(4-Ac-2-oxo-1-Piz)	2-F	4-F	H
6-64	Ac	H	CH_2-(4-Ac-2-oxo-1-Piz)	2-F	4-F	H
6-65	H	H	CH_2-(4-CO_2Me-2-oxo-1-Piz)	2-F	H	H
6-66	Ac	H	CH_2-(4-CO_2Me-2-oxo-1-Piz)	2-F	H	H
6-67	H	H	CH_2-(4-CO_2Et-2-oxo-1-Piz)	2-F	H	H
6-68	Ac	H	CH_2-(4-CO_2Et-2-oxo-1-Piz)	2-F	H	H
6-69	H	H	CH_2-(4-CH_2CO_2H-2-oxo-1-Piz)	2-F	H	H

6-70	Ac	H	CH_2-(4-CH_2CO_2H-2-oxo-1-Piz)	2-F	H	H
6-71	H	H	CH_2-(4-CH_2CO_2Me-2-oxo-1-Piz)	2-F	H	H
6-72	Ac	H	CH_2-(4-CH_2CO_2Me-2-oxo-1-Piz)	2-F	H	H
6-73	H	H	CH_2-(4-CH_2CO_2Et-2-oxo-1-Piz)	2-F	H	H
6-74	Ac	H	CH_2-(4-CH_2CO_2Et-2-oxo-1-Piz)	2-F	H	H
6-75	H	H	CH_2-(4-$CH_2CH_2CO_2H$-2-oxo-1-Piz)	2-F	H	H
6-76	Ac	H	CH_2-(4-$CH_2CH_2CO_2H$-2-oxo-1-Piz)	2-F	H	H
6-77	H	H	CH_2-(4-$CH_2CH_2CO_2Me$-2-oxo-1-Piz)	2-F	H	H
6-78	Ac	H	CH_2-(4-$CH_2CH_2CO_2Me$-2-oxo-1-Piz)	2-F	H	H
6-79	H	H	CH_2-(4-$CH_2CH_2CO_2Et$-2-oxo-1-Piz)	2-F	H	H
6-80	Ac	H	CH_2-(4-$CH_2CH_2CO_2Et$-2-oxo-1-Piz)	2-F	H	H
6-81	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2H$-2-oxo-1-Piz)	2-F	H	H
6-82	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2H$-2-oxo-1-Piz)	2-F	H	H
6-83	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2Me$-2-oxo-1-Piz)	2-F	H	H
6-84	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2Me$-2-oxo-1-Piz)	2-F	H	H
6-85	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2Et$-2-oxo-1-Piz)	2-F	H	H
6-86	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2Et$-2-oxo-1-Piz)	2-F	H	H
6-87	H	H	CH_2-(3-oxo-1-Piz)	2-F	H	H
6-88	Ac	H	CH_2-(3-oxo-1-Piz)	2-F	H	H
6-89	H	H	CH_2-(4-Ac-3-oxo-1-Piz)	2-F	H	H
6-90	Ac	H	CH_2-(4-Ac-3-oxo-1-Piz)	2-F	H	H
6-91	H	H	CH_2-(4-Ac-3-oxo-1-Piz)	2-F	4-F	H
6-92	Ac	H	CH_2-(4-Ac-3-oxo-1-Piz)	2-F	4-F	H
6-93	H	H	CH_2-(4-CO_2Me-3-oxo-1-Piz)	2-F	H	H
6-94	Ac	H	CH_2-(4-CO_2Me-3-oxo-1-Piz)	2-F	H	H
6-95	H	H	CH_2-(4-CO_2Et-3-oxo-1-Piz)	2-F	H	H
6-96	Ac	H	CH_2-(4-CO_2Et-3-oxo-1-Piz)	2-F	H	H
6-97	H	H	CH_2-(4-CH_2CO_2H-3-oxo-1-Piz)	2-F	H	H
6-98	Ac	H	CH_2-(4-CH_2CO_2H-3-oxo-1-Piz)	2-F	H	H
6-99	H	H	CH_2-(4-CH_2CO_2Me-3-oxo-1-Piz)	2-F	H	H
6-100	Ac	H	CH_2-(4-CH_2CO_2Me-3-oxo-1-Piz)	2-F	H	H

6-101	H	H	CH_2-(4-CH_2CO_2Et-3-oxo-1-Piz)	2-F	H	H
6-102	Ac	H	CH_2-(4-CH_2CO_2Et-3-oxo-1-Piz)	2-F	H	H
6-103	H	H	CH_2-(4-$CH_2CH_2CO_2H$-3-oxo-1-Piz)	2-F	H	H
6-104	Ac	H	CH_2-(4-$CH_2CH_2CO_2H$-3-oxo-1-Piz)	2-F	H	H
6-105	H	H	CH_2-(4-$CH_2CH_2CO_2Me$-3-oxo-1-Piz)	2-F	H	H
6-106	Ac	H	CH_2-(4-$CH_2CH_2CO_2Me$-3-oxo-1-Piz)	2-F	H	H
6-107	H	H	CH_2-(4-$CH_2CH_2CO_2Et$-3-oxo-1-Piz)	2-F	H	H
6-108	Ac	H	CH_2-(4-$CH_2CH_2CO_2Et$-3-oxo-1-Piz)	2-F	H	H
6-109	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2H$-3-oxo-1-Piz)	2-F	H	H
6-110	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2H$-3-oxo-1-Piz)	2-F	H	H
6-111	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2Me$-3-oxo-1-Piz)	2-F	H	H
6-112	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2Me$-3-oxo-1-Piz)	2-F	H	H
6-113	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2Et$-3-oxo-1-Piz)	2-F	H	H
6-114	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2Et$-3-oxo-1-Piz)	2-F	H	H
6-115	H	H	CH_2-(2,5-dioxo-1-Piz)	2-F	H	H
6-116	Ac	H	CH_2-(2,5-dioxo-1-Piz)	2-F	H	H
6-117	H	H	CH_2-(4-Ac-2,5-dioxo-1-Piz)	2-F	H	H
6-118	Ac	H	CH_2-(4-Ac-2,5-dioxo-1-Piz)	2-F	H	H
6-119	H	H	CH_2-(4-Ac-2,5-dioxo-1-Piz)	2-F	4-F	H
6-120	Ac	H	CH_2-(4-Ac-2,5-dioxo-1-Piz)	2-F	4-F	H
6-121	H	H	CH_2-(4-CO_2Me-2,5-dioxo-1-Piz)	2-F	H	H
6-122	Ac	H	CH_2-(4-CO_2Me-2,5-dioxo-1-Piz)	2-F	H	H
6-123	H	H	CH_2-(4-CO_2Et-2,5-dioxo-1-Piz)	2-F	H	H
6-124	Ac	H	CH_2-(4-CO_2Et-2,5-dioxo-1-Piz)	2-F	H	H
6-125	H	H	CH_2-(4-CH_2CO_2H-2,5-dioxo-1-Piz)	2-F	H	H
6-126	Ac	H	CH_2-(4-CH_2CO_2H-2,5-dioxo-1-Piz)	2-F	H	H
6-127	H	H	CH_2-(4-CH_2CO_2Me-2,5-dioxo-1-Piz)	2-F	H	H
6-128	Ac	H	CH_2-(4-CH_2CO_2Me-2,5-dioxo-1-Piz	2-F	H	H
6-130	Ac	H	CH_2-(4-CH_2CO_2Et-2,5-dioxo-1-Piz)	2-F	H	H
6-131	H	H	CH_2-(4-$CH_2CH_2CO_2H$-2,5-dioxo-1-Piz)	2-F	H	H
6-132	Ac	H	CH_2-(4-$CH_2CH_2CO_2H$-2,5-dioxo-1-Piz)	2-F	H	H

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6-133	H	H	CH_2-(4-$CH_2CH_2CO_2Me$-2,5-dioxo-1-Piz)	2-F	H	H
6-134	Ac	H	CH_2-(4-$CH_2CH_2CO_2Me$-2,5-dioxo-1-Piz)	2-F	H	H
6-135	H	H	CH_2-(4-$CH_2CH_2CO_2Et$-2,5-dioxo-1-Piz)	2-F	H	H
6-136	Ac	H	CH_2-(4-$CH_2CH_2CO_2Et$-2,5-dioxo-1-Piz)	2-F	H	H
6-137	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2H$-2,5-dioxo-1-Piz)	2-F	H	H
6-138	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2H$-2,5-dioxo-1-Piz)	2-F	H	H
6-139	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2Me$-2,5-dioxo-1-Piz)	2-F	H	H
5-140	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2Me$-2,5-dioxo-1-Piz)	2-F	H	H
6-141	H	H	CH_2-(4-$CH_2CH_2CH_2CO_2Et$-2,5-dioxo-1-Piz)	2-F	H	H
6-142	Ac	H	CH_2-(4-$CH_2CH_2CH_2CO_2Et$-2,5-dioxo-1-Piz)	2-F	H	H
6-143	H	H	CH_2-1-Pyrd	2-F	H	H
6-144	Ac	H	CH_2-1-Pyrd	2-F	H	H
6-145	H	H	CH_2-(2-CO_2H-1-Pyrd)	2-F	H	H
6-146	Ac	H	CH_2-(2-CO_2H-1-Pyrd)	2-F	H	H
6-147	H	H	CH_2-(2-CO_2Me-1-Pyrd)	2-F	H	H
6-148	Ac	H	CH_2-(2-CO_2Me-1-Pyrd)	2-F	H	H
6-149	H	H	CH_2-(2-CO_2Et-1-Pyrd)	2-F	H	H
6-150	Ac	H	CH_2-(2-CO_2Et-1-Pyrd)	2-F	H	H
6-151	H	H	CH_2-(2-CH_2CO_2H-1-Pyrd)	2-F	H	H
6-152	Ac	H	CH_2-(2-CH_2CO_2H-1-Pyrd)	2-F	H	H
6-153	H	H	CH_2-(2-CH_2CO_2Me-1-Pyrd)	2-F	H	H
6-154	Ac	H	CH_2-(2-CH_2CO_2Me-1-Pyrd)	2-F	H	H
6-155	H	H	CH_2-(2-CH_2CO_2Et-1-Pyrd)	2-F	H	H
6-156	Ac	H	CH_2-(2-CH_2CO_2Et-1-Pyrd)	2-F	H	H
6-157	H	H	CH_2-(2-$CH_2CH_2CO_2H$-1-Pyrd)	2-F	H	H
6-158	Ac	H	CH_2-(2-$CH_2CH_2CO_2H$-1-Pyrd)	2-F	H	H
6-159	H	H	CH_2-(2-$CH_2CH_2CO_2Me$-1-Pyrd)	2-F	H	H
6-160	Ac	H	CH_2-(2-$CH_2CH_2CO_2Me$-1-Pyrd)	2-F	H	H
6-161	H	H	CH_2-(2-$CH_2CH_2CO_2Et$-1-Pyrd)	2-F	H	H
6-162	Ac	H	CH_2-(2-$CH_2CH_2CO_2Et$-1-Pyrd)	2-F	H	H
6-163	H	H	CH_2-(2-$CH_2CH_2CH_2CO_2H$-1-Pyrd)	2-F	H	H

6-164	Ac	H	CH_2-(2-$CH_2CH_2CH_2CO_2H$-1-Pyrd)	2-F	H	H
6-165	H	H	CH_2-(2-$CH_2CH_2CH_2CO_2Me$-1-Pyrd)	2-F	H	H
6-166	Ac	H	CH_2-(2-$CH_2CH_2CH_2CO_2Me$-1-Pyrd)	2-F	H	H
6-167	H	H	CH_2-(2-$CH_2CH_2CH_2CO_2Et$-1-Pyrd)	2-F	H	H
6-168	Ac	H	CH_2-(2-$CH_2CH_2CH_2CO_2Et$-1-Pyrd)	2-F	H	H
6-169	H	H	CH_2CH_2-1-Pip	2-F	H	H
6-170	Ac	H	CH_2CH_2-1-Pip	2-F	H	H
6-171	H	H	CH_2CH_2-(4-CO_2H-1-Pip)	2-F	H	H
6-172	Ac	H	CH_2CH_2-(4-CO_2H-1-Pip)	2-F	H	H
6-173	H	H	CH_2CH_2-(4-CO_2Me-1-Pip)	2-F	H	H
6-174	Ac	H	CH_2CH_2-(4-CO_2Me-1-Pip)	2-F	H	H
6-175	H	H	CH_2CH_2-(4-CO_2Et-1-Pip)	2-F	H	H
6-176	Ac	H	CH_2CH_2-(4-CO_2Et-1-Pip)	2-F	H	H
6-177	H	H	CH_2CH_2-(4-CH_2CO_2H-1-Pip)	2-F	H	H
6-178	Ac	H	CH_2CH_2-(4-CH_2CO_2H-1-Pip)	2-F	H	H
6-179	H	H	CH_2CH_2-(4-CH_2CO_2Me-1-Pip)	2-F	H	H
6-180	Ac	H	CH_2CH_2-(4-CH_2CO_2Me-1-Pip)	2-F	H	H
6-181	H	H	CH_2CH_2-(4-CH_2CO_2Et-1-Pip)	2-F	H	H
6-182	Ac	H	CH_2CH_2-(4-CH_2CO_2Et-1-Pip)	2-F	H	H
6-183	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2H$-1-Pip)	2-F	H	H
6-184	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2H$-1-Pip)	2-F	H	H
6-185	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-1-Pip)	2-F	H	H
6-186	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-1-Pip)	2-F	H	H
6-187	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-1-Pip)	2-F	H	H
6-188	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-1-Pip)	2-F	H	H
6-189	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2H$-1-Pip)	2-F	H	H
6-190	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2H$-1-Pip)	2-F	H	H
6-191	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Me$-1-Pip)	2-F	H	H
6-192	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Me$-1-Pip)	2-F	H	H
6-193	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Et$-1-Pip)	2-F	H	H
6-194	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Et$-1-Pip)	2-F	H	H

6-195	H	H	CH_2CH_2-Mor	2-F	H	H
6-196	Ac	H	CH_2CH_2-Mor	2-F	H	H
6-197	H	H	CH_2CH_2-Thim	2-F	H	H
6-198	Ac	H	CH_2CH_2-Thim	2-F	H	H
6-199	H	H	CH_2CH_2-1-Piz	2-F	H	H
6-200	Ac	H	CH_2CH_2-1-Piz	2-F	H	H
6-201	H	H	CH_2CH_2-(4-Ac-1-Piz)	2-F	H	H
6-202	Ac	H	CH_2CH_2-(4-Ac-1-Piz)	2-F	H	H
6-203	H	H	CH_2CH_2-(4-Ac-1-Piz)	2-F	4-F	H
6-204	Ac	H	CH_2CH_2-(4-Ac-1-Piz)	2-F	4-F	H
6-205	H	H	CH_2CH_2-(4-CO_2Me-1-Piz)	2-F	H	H
6-206	Ac	H	CH_2CH_2-(4-CO_2Me-1-Piz)	2-F	H	H
6-207	H	H	CH_2CH_2-(4-CO_2Et-1-Piz)	2-F	H	H
6-208	Ac	H	CH_2CH_2-(4-CO_2Et-1-Piz)	2-F	H	H
6-209	H	H	CH_2CH_2-(4-CH_2CO_2H-1-Piz)	2-F	H	H
6-210	Ac	H	CH_2CH_2-(4-CH_2CO_2H-1-Piz)	2-F	H	H
6-211	H	H	CH_2CH_2-(4-CH_2CO_2Me-1-Piz)	2-F	H	H
6-212	Ac	H	CH_2CH_2-(4-CH_2CO_2Me-1-Piz)	2-F	H	H
6-213	H	H	CH_2CH_2-(4-CH_2CO_2Et-1-Piz)	2-F	H	H
6-214	Ac	H	CH_2CH_2-(4-CH_2CO_2Et-1-Piz)	2-F	H	H
6-215	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2H$-1-Piz)	2-F	H	H
6-216	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2H$-1-Piz)	2-F	H	H
6-217	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-1-Piz)	2-F	H	H
6-218	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-1-Piz)	2-F	H	H
6-219	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-1-Piz)	2-F	H	H
6-220	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-1-Piz)	2-F	H	H
6-221	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2H$-1-Piz)	2-F	H	H
6-222	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2H$-1-Piz)	2-F	H	H
6-223	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Me$-1-Piz)	2-F	H	H
6-224	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Me$-1-Piz)	2-F	H	H
6-225	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Et$-1-Piz)	2-F	H	H

6-226	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Et$-1-Piz)	2-F	H	H
6-227	H	H	CH_2CH_2-(2-oxo-1-Piz)	2-F	H	H
6-228	Ac	H	CH_2CH_2-(2-oxo-1-Piz)	2-F	H	H
6-229	H	H	CH_2CH_2-(4-Ac-2-oxo-1-Piz)	2-F	H	H
6-230	Ac	H	CH_2CH_2-(4-Ac-2-oxo-1-Piz)	2-F	H	H
6-231	H	H	CH_2CH_2-(4-Ac-2-oxo-1-Piz)	2-F	4-F	H
6-232	Ac	H	CH_2CH_2-(4-Ac-2-oxo-1-Piz)	2-F	4-F	H
6-233	H	H	CH_2CH_2-(4-CO_2Me-2-oxo-1-Piz)	2-F	H	H
6-234	Ac	H	CH_2CH_2-(4-CO_2Me-2-oxo-1-Piz)	2-F	H	H
6-235	H	H	CH_2CH_2-(4-CO_2Et-2-oxo-1-Piz)	2-F	H	H
6-236	Ac	H	CH_2CH_2-(4-CO_2Et-2-oxo-1-Piz)	2-F	H	H
6-237	H	H	CH_2CH_2-(4-CH_2CO_2H-2-oxo-1-Piz)	2-F	H	H
6-238	Ac	H	CH_2CH_2-(4-CH_2CO_2H-2-oxo-1-Piz)	2-F	H	H
6-239	H	H	CH_2CH_2-(4-CH_2CO_2Me-2-oxo-1-Piz)	2-F	H	H
6-240	Ac	H	CH_2CH_2-(4-CH_2CO_2Me-2-oxo-1-Piz)	2-F	H	H
6-241	H	H	CH_2CH_2-(4-CH_2CO_2Et-2-oxo-1-Piz)	2-F	H	H
6-242	Ac	H	CH_2CH_2-(4-CH_2CO_2Et-2-oxo-1-Piz)	2-F	H	H
6-243	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2H$-2-oxo-1-Piz)	2-F	H	H
6-244	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2H$-2-oxo-1-Piz)	2-F	H	H
6-245	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-2-oxo-1-Piz)	2-F	H	H
6-246	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-2-oxo-1-Piz)	2-F	H	H
6-247	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-2-oxo-1-Piz)	2-F	H	H
6-248	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-2-oxo-1-Piz)	2-F	H	H
6-249	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2H$-2-oxo-1-Piz)	2-F	H	H
6-250	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2H$-2-oxo-1-Piz)	2-F	H	H
6-251	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Me$-2-oxo-1-Piz)	2-F	H	H
6-252	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Me$-2-oxo-1-Piz)	2-F	H	H
6-253	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Et$-2-oxo-1-Piz)	2-F	H	H
6-254	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Et$-2-oxo-1-Piz)	2-F	H	H
6-255	H	H	CH_2CH_2-(3-oxo-1-Piz)	2-F	H	H
6-256	Ac	H	CH_2CH_2-(3-oxo-1-Piz)	2-F	H	H

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6-257	H	H	CH_2CH_2-(4-Ac-3-oxo-1-Piz)	2-F	H	H
6-258	Ac	H	CH_2CH_2-(4-Ac-3-oxo-1-Piz)	2-F	H	H
6-259	H	H	CH_2CH_2-(4-Ac-3-oxo-1-Piz)	2-F	4-F	H
6-260	Ac	H	CH_2CH_2-(4-Ac-3-oxo-1-Piz)	2-F	4-F	H
6-261	H	H	CH_2CH_2-(4-CO_2Me-3-oxo-1-Piz)	2-F	H	H
6-262	Ac	H	CH_2CH_2-(4-CO_2Me-3-oxo-1-Piz)	2-F	H	H
6-263	H	H	CH_2CH_2-(4-CO_2Et-3-oxo-1-Piz)	2-F	H	H
6-264	Ac	H	CH_2CH_2-(4-CO_2Et-3-oxo-1-Piz)	2-F	H	H
6-265	H	H	CH_2CH_2-(4-CH_2CO_2H-3-oxo-1-Piz)	2-F	H	H
6-266	Ac	H	CH_2CH_2-(4-CH_2CO_2H-3-oxo-1-Piz)	2-F	H	H
6-267	H	H	CH_2CH_2-(4-CH_2CO_2Me-3-oxo-1-Piz)	2-F	H	H
6-268	Ac	H	CH_2CH_2-(4-CH_2CO_2Me-3-oxo-1-Piz)	2-F	H	H
6-269	H	H	CH_2CH_2-(4-CH_2CO_2Et-3-oxo-1-Piz)	2-F	H	H
6-270	Ac	H	CH_2CH_2-(4-CH_2CO_2Et-3-oxo-1-Piz)	2-F	H	H
6-271	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2H$-3-oxo-1-Piz)	2-F	H	H
6-272	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2H$-3-oxo-1-Piz)	2-F	H	H
6-273	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-3-oxo-1-Piz)	2-F	H	H
6-274	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2Me$-3-oxo-1-Piz)	2-F	H	H
6-275	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-3-oxo-1-Piz)	2-F	H	H
6-276	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2Et$-3-oxo-1-Piz)	2-F	H	H
6-277	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2H$-3-oxo-1-Piz)	2-F	H	H
6-278	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2H$-3-oxo-1-Piz)	2-F	H	H
6-279	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Me$-3-oxo-1-Piz)	2-F	H	H
6-280	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Me$-3-oxo-1-Piz)	2-F	H	H
6-281	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Et$-3-oxo-1-Piz)	2-F	H	H
6-282	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2Et$-3-oxo-1-Piz)	2-F	H	H
6-283	H	H	CH_2CH_2-(2,5-dioxo-1-Piz)	2-F	H	H
6-284	Ac	H	CH_2CH_2-(2,5-dioxo-1-Piz)	2-F	H	H
6-285	H	H	CH_2CH_2-(4-Ac-2,5-dioxo-1-Piz)	2-F	H	H
6-286	Ac	H	CH_2CH_2-(4-Ac-2,5-dioxo-1-Piz)	2-F	H	H
6-287	H	H	CH_2CH_2-(4-Ac-2,5-dioxo-1-Piz)	2-F	4-F	H

6-288	Ac	H	CH_2CH_2-(4-Ac-2,5-dioxo-1-Piz)	2-F	4-F	H
6-289	H	H	CH_2CH_2-(4-CO_2Me-2,5-dioxo-1-Piz)	2-F	H	H
6-290	Ac	H	CH_2CH_2-(4-CO_2Me-2,5-dioxo-1-Piz)	2-F	H	H
6-291	H	H	CH_2CH_2-(4-CO_2Et-2,5-dioxo-1-Piz)	2-F	H	H
6-292	Ac	H	CH_2CH_2-(4-CO_2Et-2,5-dioxo-1-Piz)	2-F	H	H
6-293	H	H	CH_2CH_2-(4-CH_2CO_2H-2,5-dioxo-1-Piz)	2-F	H	H
6-294	Ac	H	CH_2CH_2-(4-CH_2CO_2H-2,5-dioxo-1-Piz)	2-F	H	H
6-295	H	H	CH_2CH_2-(4-CH_2CO_2Me-2,5-dioxo-1-Piz)	2-F	H	H
6-296	Ac	H	CH_2CH_2-(4-CH_2CO_2Me-2,5-dioxo-1-Piz)	2-F	H	H
6-297	H	H	CH_2CH_2-(4-CH_2CO_2Et-2,5-dioxo-1-Piz)	2-F	H	H
6-298	Ac	H	CH_2CH_2-(4-CH_2CO_2Et-2,5-dioxo-1-Piz)	2-F	H	H
6-299	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2H$-2,5-dioxo-1-Piz)	2-F	H	H
6-300	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2H$-2,5-dioxo-1-Piz)	2-F	H	H
6-301	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2$Me-2,5-dioxo-1-Piz)	2-F	H	H
6-302	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2$Me-2,5-dioxo-1-Piz)	2-F	H	H
6-303	H	H	CH_2CH_2-(4-$CH_2CH_2CO_2$Et-2,5-dioxo-1-Piz)	2-F	H	H
6-304	Ac	H	CH_2CH_2-(4-$CH_2CH_2CO_2$Et-2,5-dioxo-1-Piz)	2-F	H	H
6-305	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2H$-2,5-dioxo-1-Piz)	2-F	H	H
6-306	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2H$-2,5-dioxo-1-Piz)	2-F	H	H
6-307	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2$Me-2,5-dioxo-1-Piz)	2-F	H	H
6-308	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2$Me-2,5-dioxo-1-Piz)	2-F	H	H
6-309	H	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2$Et-2,5-dioxo-1-Piz)	2-F	H	H
6-310	Ac	H	CH_2CH_2-(4-$CH_2CH_2CH_2CO_2$Et-2,5-dioxo-1-Piz)	2-F	H	H
6-311	H	H	CH_2CH_2-1-Pyrd	2-F	H	H
6-312	Ac	H	CH_2CH_2-1-Pyrd	2-F	H	H
6-313	H	H	CH_2CH_2-(2-CO_2H-1-Pyrd)	2-F	H	H
6-314	Ac	H	CH_2CH_2-(2-CO_2H-1-Pyrd)	2-F	H	H
6-315	H	H	CH_2CH_2-(2-CO_2Me-1-Pyrd)	2-F	H	H
6-316	Ac	H	CH_2CH_2-(2-CO_2Me-1-Pyrd)	2-F	H	H
6-317	H	H	CH_2CH_2-(2-CO_2Et-1-Pyrd)	2-F	H	H
6-318	Ac	H	CH_2CH_2-(2-CO_2Et-1-Pyrd)	2-F	H	H

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6-319	H	H	CH_2CH_2-(2-CH_2CO_2H-1-Pyrd)	2-F	H	H
6-320	Ac	H	CH_2CH_2-(2-CH_2CO_2H-1-Pyrd)	2-F	H	H
6-321	H	H	CH_2CH_2-(2-CH_2CO_2Me-1-Pyrd)	2-F	H	H
6-322	Ac	H	CH_2CH_2-(2-CH_2CO_2Me-1-Pyrd)	2-F	H	H
6-323	H	H	CH_2CH_2-(2-CH_2CO_2Et-1-Pyrd)	2-F	H	H
6-324	Ac	H	CH_2CH_2-(2-CH_2CO_2Et-1-Pyrd)	2-F	H	H
6-325	H	H	CH_2CH_2-(2-$CH_2CH_2CO_2H$-1-Pyrd)	2-F	H	H
6-326	Ac	H	CH_2CH_2-(2-$CH_2CH_2CO_2H$-1-Pyrd)	2-F	H	H
6-327	H	H	CH_2CH_2-(2-$CH_2CH_2CO_2Me$-1-Pyrd)	2-F	H	H
6-328	Ac	H	CH_2CH_2-(2-$CH_2CH_2CO_2Me$-1-Pyrd)	2-F	H	H
6-329	H	H	CH_2CH_2-(2-$CH_2CH_2CO_2Et$-1-Pyrd)	2-F	H	H
6-330	Ac	H	CH_2CH_2-(2-$CH_2CH_2CO_2Et$-1-Pyrd)	2-F	H	H
6-331	H	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2H$-1-Pyrd)	2-F	H	H
6-332	Ac	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2H$-1-Pyrd)	2-F	H	H
6-333	H	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2Me$-1-Pyrd)	2-F	H	H
6-334	Ac	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2Me$-1-Pyrd)	2-F	H	H
6-335	H	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2Et$-1-Pyrd)	2-F	H	H
6-336	Ac	H	CH_2CH_2-(2-$CH_2CH_2CH_2CO_2Et$-1-Pyrd)	2-F	H	H
6-337	H	H	CH_2-(3-CO_2H-1-Pip)	2-F	H	H
6-338	Ac	H	CH_2-(3-CO_2H-1-Pip)	2-F	H	H
6-339	H	H	CH_2-(3-CO_2Me-1-Pip)	2-F	H	H
6-340	Ac	H	CH_2-(3-CO_2Me-1-Pip)	2-F	H	H
6-341	H	H	CH_2-(3-CO_2Et-1-Pip)	2-F	H	H
6-342	Ac	H	CH_2-(3-CO_2Et-1-Pip)	2-F	H	H
6-343	H	H	CH_2-(3-CH_2CO_2H-1-Pip)	2-F	H	H
6-344	Ac	H	CH_2-(3-CH_2CO_2H-1-Pip)	2-F	H	H
6-345	H	H	CH_2-(3-CH_2CO_2Me-1-Pip)	2-F	H	H
6-346	Ac	H	CH_2-(3-CH_2CO_2Me-1-Pip)	2-F	H	H
6-347	H	H	CH_2-(3-CH_2CO_2Et-1-Pip)	2-F	H	H
6-348	Ac	H	CH_2-(3-CH_2CO_2Et-1-Pip)	2-F	H	H
6-349	H	H	CH_2-(3-$CH_2CH_2CO_2H$-1-Pip)	2-F	H	H

6-350	Ac	H	CH_2-(3-$CH_2CH_2CO_2H$-1-Pip)	2-F	H	H
6-351	H	H	CH_2-(3-$CH_2CH_2CO_2Me$-1-Pip)	2-F	H	H
6-352	Ac	H	CH_2-(3-$CH_2CH_2CO_2Me$-1-Pip)	2-F	H	H
6-353	H	H	CH_2-(3-$CH_2CH_2CO_2Et$-1-Pip)	2-F	H	H
6-354	Ac	H	CH_2-(3-$CH_2CH_2CO_2Et$-1-Pip)	2-F	H	H
6-355	H	H	CH_2-(3-$CH_2CH_2CH_2CO_2H$-1-Pip)	2-F	H	H
6-356	Ac	H	CH_2-(3-$CH_2CH_2CH_2CO_2H$-1-Pip)	2-F	H	H
6-357	H	H	CH_2-(3-$CH_2CH_2CH_2CO_2Me$-1-Pip)	2-F	H	H
6-358	Ac	H	CH_2-(3-$CH_2CH_2CH_2CO_2Me$-1-Pip)	2-F	H	H
6-359	H	H	CH_2-(3-$CH_2CH_2CH_2CO_2Et$-1-Pip)	2-F	H	H
6-360	Ac	H	CH_2-(3-$CH_2CH_2CH_2CO_2Et$-1-Pip)	2-F	H	H
6-361	H	H	CH_2CH_2-(3-CO_2H-1-Pip)	2-F	H	H
6-362	Ac	H	CH_2CH_2-(3-CO_2H-1-Pip)	2-F	H	H
6-363	H	H	CH_2CH_2-(3-CO_2Me-1-Pip)	2-F	H	H
6-364	Ac	H	CH_2CH_2-(3-CO_2Me-1-Pip)	2-F	H	H
6-365	H	H	CH_2CH_2-(3-CO_2Et-1-Pip)	2-F	H	H
6-366	Ac	H	CH_2CH_2-(3-CO_2Et-1-Pip)	2-F	H	H
6-367	H	H	CH_2CH_2-(3-CH_2CO_2H-1-Pip)	2-F	H	H
6-368	Ac	H	CH_2CH_2-(3-CH_2CO_2H-1-Pip)	2-F	H	H
6-369	H	H	CH_2CH_2-(3-CH_2CO_2Me-1-Pip)	2-F	H	H
6-370	Ac	H	CH_2CH_2-(3-CH_2CO_2Me-1-Pip)	2-F	H	H
6-371	H	H	CH_2CH_2-(3-CH_2CO_2Et-1-Pip)	2-F	H	H
6-372	Ac	H	CH_2CH_2-(3-CH_2CO_2Et-1-Pip)	2-F	H	H
6-373	H	H	CH_2CH_2-(3-$CH_2CH_2CO_2H$-1-Pip)	2-F	H	H
6-374	Ac	H	CH_2CH_2-(3-$CH_2CH_2CO_2H$-1-Pip)	2-F	H	H
6-375	H	H	CH_2CH_2-(3-$CH_2CH_2CO_2Me$-1-Pip)	2-F	H	H
6-376	Ac	H	CH_2CH_2-(3-$CH_2CH_2CO_2Me$-1-Pip)	2-F	H	H
6-377	H	H	CH_2CH_2-(3-$CH_2CH_2CO_2Et$-1-Pip)	2-F	H	H
6-378	Ac	H	CH_2CH_2-(3-$CH_2CH_2CO_2Et$-1-Pip)	2-F	H	H
6-379	H	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2H$-1-Pip)	2-F	H	H
6-380	Ac	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2H$-1-Pip)	2-F	H	H

6-381	H	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2Me$-1-Pip)	2-F	H	H
6-382	Ac	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2Me$-1-Pip)	2-F	H	H
6-383	H	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2Et$-1-Pip)	2-F	H	H
6-384	Ac	H	CH_2CH_2-(3-$CH_2CH_2CH_2CO_2Et$-1-Pip)	2-F	H	H
6-385	H	H	CH_2-(4-OH-2-CO_2H-1-Pyrd)	2-F	H	H
6-386	Ac	H	CH_2-(4-OH-2-CO_2H-1-Pyrd)	2-F	H	H
6-387	H	H	CH_2-(4-OH-2-CO_2Me-1-Pyrd)	2-F	H	H
6-388	Ac	H	CH_2-(4-OH-2-CO_2Me-1-Pyrd)	2-F	H	H
6-389	H	H	CH_2-(4-OH-2-CO_2Et-1-Pyrd)	2-F	H	H
6-390	Ac	H	CH_2-(4-OH-2-CO_2Et-1-Pyrd)	2-F	H	H

Los números de los compuestos, de los compuestos de ejemplo obtenidos sustituyendo un grupo ciclopropilo de los compuestos de ejemplo números 1-1 hasta 1-1084, 2-1 hasta 2-1084, 3-1 hasta 3-79, 4-1 hasta 4-79, 5-1 hasta 5-390 y 6-1 hasta 6-390 en las tablas 1 hasta 6 con un grupo metoxi, son respectivamente 7-1 hasta 7-1084, 8-1 hasta 8-1084, 9-1 hasta 9-79, 10-1 hasta 10-79, 11-1 hasta 11-390 y 12-1 hasta 12-390. Por ejemplo, un compuesto obtenido sustituyendo un grupo ciclopropilo del compuesto de ejemplo No. 5-103 en la Tabla 7 con un grupo metoxi, es un compuesto de ejemplo No. 11-103.

Entre los compuestos anteriores, los compuestos preferidos son los compuestos de ejemplo números 1-1, 1-2, 1-5, 1-6, 1-9, 1-10, 1-13, 1-14, 1-17, 1-18, 1-21, 1-22, 1-25, 1-26, 1-29, 1-30, 1-33, 1-34, 1-37, 1-38, 1-41, 1-42, 1-45, 1-46, 1-49, 1-50, 1-53, 1-54, 1-57, 1-58, 1-61, 1-62, 1-87, 1-88, 1-115, 1-116, 1-121, 1-122, 1-127, 1-128, 1-133, 1-134, 1-139, 1-140, 1-187, 1-188, 1-207, 1-208, 1-209, 1-210, 1-211, 1-212, 1-337, 1-338, 1-351, 1-352, 1-353, 1-354, 1-355, 1-356, 1-443, 1-444, 1-445, 1-446, 1-447, 1-448, 1-485, 1-486, 1-487, 1-488, 1-489, 1-490, 1-491, 1-492, 1-493, 1-494, 1-495, 1-496, 1-497, 1-498, 1-499, 1-500, 1-501, 1-502, 1-503, 1-504, 1-537, 1-538,

1-549, 1-550, 1-585, 1-586, 1-587, 1-588, 1-589, 1-590, 1-591, 1-592, 1-593, 1-594, 1-595, 1-596, 1-597, 1-598, 1-613, 1-614, 1-619, 1-620, 1-637, 1-638, 1-651, 1-652, 1-653, 1-654, 1-655, 1-656, 1-663, 1-664, 1-665, 1-666, 1-667, 1-668, 1-743, 1-744, 1-745, 1-746, 1-747, 1-748, 1-749, 1-750, 1-751, 1-752, 1-753, 1-754, 1-761, 1-762, 1-763, 1-764, 1-765, 1-766, 1-767, 1-768, 1-789, 1-790, 1-813, 1-814, 1-815, 1-816, 1-817, 1-818, 1-819, 1-820, 1-841, 1-842, 1-865, 1-866, 1-879, 1-880, 1-881, 1-882, 1-883, 1-884, 1-885, 1-886, 1-887, 1-888, 1-889, 1-890, 1-965, 1-966, 1-967, 1-968, 1-969, 1-970, 1-971, 1-972, 1-973, 1-974, 1-975, 1-976, 1-977, 1-978, 1-979, 1-980, 1-981, 1-982, 1-983, 1-984, 1-985, 1-986, 1-987, 1-988, 1-989, 1-990, 1-1005, 1-1006, 1-1011, 1-1012, 1-1017, 1-1018, 1-1023, 1-1024, 1-1045, 1-1046, 1-1047, 1-1048, 1-1049, 1-1050, 2-1, 2-2, 2-5, 2-6, 2-9, 2-10, 2-13, 2-14, 2-17, 2-18, 2-21, 2-22, 2-25, 2-26, 2-29, 2-30, 2-33, 2-34, 2-37, 2-38, 2-41, 2-42, 2-45, 2-46, 2-49, 2-50, 2-53, 2-54, 2-57, 2-58, 2-61, 2-62, 2-87, 2-88, 2-115, 2-116, 2-121, 2-122, 2-127, 2-128, 2-133, 2-134, 2-139, 2-140, 2-187, 2-188, 2-207, 2-208, 2-209, 2-210, 2-211, 2-212, 2-337, 2-338, 2-351, 2-352, 2-353, 2-354, 2-355, 2-356, 2-443, 2-444, 2-445, 2-446, 2-447, 2-448, 2-485, 2-486, 2-487, 2-488, 2-489, 2-490, 2-491, 2-492, 2-493, 2-494, 2-495, 2-496, 2-497, 2-498, 2-499, 2-500, 2-501, 2-502, 2-503, 2-504, 2-537, 2-538, 2-549, 2-550, 2-585, 2-586, 2-587, 2-588, 2-589, 2-590, 2-591, 2-592, 2-593, 2-594, 2-595, 2-596, 2-597, 2-598, 2-613, 2-614, 2-619, 2-620, 2-637, 2-638, 2-651, 2-652, 2-653, 2-654, 2-655, 2-656, 2-663, 2-664, 2-665, 2-666, 2-667, 2-668, 2-743, 2-744, 2-745, 2-746, 2-747, 2-748, 2-749, 2-750, 2-751, 2-752, 2-753, 2-754, 2-761, 2-762, 2-763, 2-764, 2-765, 2-766, 2-767, 2-768, 2-789, 2-790, 2-813, 2-814, 2-815, 2-816, 2-817, 2-818, 2-819, 2-820, 2-841, 2-842, 2-865, 2-866, 2-879, 2-880, 2-881, 2-882, 2-883, 2-884, 2-885, 2-886, 2-887, 2-888, 2-889, 2-890, 2-965, 2-966, 2-967, 2-968, 2-969, 2-970, 2-971, 2-972, 2-973, 2-974, 2-975, 2-976, 2-

977, 2-978, 2-979, 2-980, 2-981, 2-982, 2-983, 2-984, 2-985, 2-986, 2-987, 2-988, 2-989, 2-990, 2-1005, 2-1006, 2-1011, 2-1012, 2-1017, 2-1018, 2-1023, 2-1024, 2-1045, 2-1046, 2-1047, 2-1048, 2-1049, 2-1050, 3-1, 3-2, 3-5, 3-6, 3-13, 3-14, 3-15, 3-16, 3-17, 3-18, 3-27, 3-28, 3-29, 3-30, 3-31, 3-32, 3-33, 3-34, 3-35, 3-36, 3-37, 3-38, 3-39, 3-46, 3-47, 3-50, 3-51, 3-52, 3-53, 3-54, 3-55, 3-56, 3-57, 3-58, 3-59, 3-60, 3-61, 3-62, 3-63, 3-64, 3-65, 3-66, 3-67, 3-68, 3-69, 3-70, 3-71, 3-72, 3-73, 3-74, 3-75, 3-76, 3-77, 3-78, 3-79, 4-1, 4-2, 4-5, 4-6, 4-13, 4-14, 4-15, 4-16, 4-17, 4-18, 4-27, 4-28, 4-29, 4-30, 4-31, 4-32, 4-33, 4-34, 4-35, 4-36, 4-37, 4-38, 4-39, 4-46, 4-47, 4-50, 4-51, 4-52, 4-53, 4-54, 4-55, 4-56, 4-57, 4-58, 4-59, 4-60, 4-61, 4-62, 4-63, 4-64, 4-65, 4-66, 4-67, 4-68, 4-69, 4-70, 4-71, 4-72, 4-73, 4-74, 4-75, 4-76, 4-77, 4-78, 4-79, 5-1, 5-2, 5-3, 5-4, 5-5, 5-6, 5-7, 5-8, 5-9, 5-10, 5-11, 5-12, 5-13, 5-14, 5-27, 5-28, 5-29, 5-30, 5-31, 5-32, 5-33, 5-34, 5-41, 5-42, 5-43, 5-44, 5-45, 5-46, 5-59, 5-60, 5-61, 5-62, 5-69, 5-70, 5-71, 5-72, 5-73, 5-74, 5-75, 5-76, 5-77, 5-78, 5-79, 5-80, 5-81, 5-82, 5-85, 5-86, 5-87, 5-88, 5-89, 5-90, 5-93, 5-94, 5-95, 5-96, 5-97, 5-98, 5-99, 5-100, 5-101, 5-102, 5-103, 5-104, 5-105, 5-106, 5-107, 5-108, 5-115, 5-116, 5-117, 5-118, 5-125, 5-126, 5-127, 5-128, 5-129, 5-130, 5-131, 5-132, 5-133, 5-134, 5-135, 5-136, 5-143, 5-144, 5-145, 5-146, 5-147, 5-148, 5-149, 5-150, 5-151, 5-152, 5-153, 5-154, 5-155, 5-156, 5-171, 5-172, 5-177, 5-178, 5-209, 5-210, 5-237, 5-238, 5-265, 5-266, 5-293, 5-294, 5-313, 5-314, 5-319, 5-320, 5-337, 5-338, 5-339, 5-340, 5-341, 5-342, 5-343, 5-344, 5-345, 5-346, 5-347, 5-348, 5-361, 5-362, 5-367, 5-368, 5-385, 5-386, 5-387, 5-388, 6-1, 6-2, 6-3, 6-4, 6-5, 6-6, 6-7, 6-8, 6-9, 6-10, 6-11, 6-12, 6-13, 6-14, 6-27, 6-28, 6-29, 6-30, 6-31, 6-32, 6-33, 6-34, 6-41, 6-42, 6-43, 6-44, 6-45, 6-46, 6-59, 6-60, 6-61, 6-62, 6-69, 6-70, 6-71, 6-72, 6-73, 6-74, 6-75, 6-76, 6-77, 6-78, 6-79, 6-80, 6-81, 6-82, 6-85, 6-86, 6-87, 6-88, 6-89, 6-90, 6-93, 6-94, 6-95, 6-96, 6-97, 6-98, 6-99, 6-100, 6-101, 6-102, 6-103, 6-104, 6-105, 6-106, 6-107, 6-108, 6-115, 6-116, 6-117,

6-118, 6-125, 6-126, 6-127, 6-128, 6-129, 6-130, 6-131, 6-132, 6-133, 6-134, 6-135, 6-136, 6-143, 6-144, 6-145, 6-146, 6-147, 6-148, 6-149, 6-150, 6-151, 6-152, 6-153, 6-154, 6-155, 6-156, 6-171, 6-172, 6-177, 6-178, 6-209, 6-210, 6-237, 6-238, 6-265, 6-266, 6-293, 6-294, 6-313, 6-314, 6-319, 6-320, 6-337, 6-338, 6-339, 6-340, 6-341, 6-342, 6-343, 6-344, 6-345, 6-346, 6-347, 6-348, 6-361, 6-362, 6-367, 6-368, 6-385, 6-386, 6-387 y 6-388,

Los compuestos más preferidos son los compuestos de ejemplo números 1-1, 1-2, 1-5, 1-6, 1-17, 1-18, 1-21, 1-22, 1-25, 1-26, 1-53, 1-54, 1-207, 1-208, 1-351, 1-352, 1-443, 1-444, 1-485, 1-486, 1-487, 1-488, 1-489, 1-490, 1-491, 1-492, 1-493, 1-494, 1-587, 1-588, 1-589, 1-590, 1-591, 1-592, 1-651, 1-652, 1-743, 1-744, 1-763, 1-764, 1-815, 1-816, 1-967, 1-968, 1-973, 1-974, 1-975, 1-976, 1-977, 1-978, 2-1, 2-2, 2-5, 2-6, 2-17, 2-18, 2-21, 2-22, 2-25, 2-26, 2-53, 2-54, 2-207, 2-208, 2-351, 2-352, 2-443, 2-444, 2-485, 2-486, 2-487, 2-488, 2-489, 2-490, 2-491, 2-492, 2-493, 2-494, 2-587, 2-588, 2-589, 2-590, 2-591, 2-592, 2-651, 2-652, 2-743, 2-744, 2-763, 2-764, 2-815, 2-816, 2-967, 2-968, 2-973, 2-974, 2-975, 2-976, 2-977, 2-978, 3-1, 3-2, 3-13, 3-14, 3-15, 3-16, 3-17, 3-18, 3-27, 3-28, 3-29, 3-30, 3-31, 3-32, 3-50, 3-51, 3-54, 3-55, 3-62, 3-63, 3-66, 3-67, 4-1, 4-2, 4-13, 4-14, 4-15, 4-16, 4-17, 4-18, 4-27, 4-28, 4-29, 4-30, 4-31, 4-32, 4-50, 4-51, 4-54, 4-55, 4-62, 4-63, 4-66, 4-67, 5-3, 5-4, 5-5, 5-6, 5-7, 5-8, 5-9, 5-10, 5-11, 5-12, 5-13, 5-14, 5-27, 5-28, 5-29, 5-30, 5-33, 5-34, 5-69, 5-70, 5-71, 5-72, 5-73, 5-74, 5-75, 5-76, 5-77, 5-78, 5-79, 5-80, 5-81, 5-82, 5-85, 5-86, 5-87, 5-88, 5-89, 5-90, 5-93, 5-94, 5-95, 5-96, 5-97, 5-98, 5-99, 5-100, 5-101, 5-102, 5-103, 5-104, 5-105, 5-106, 5-107, 5-108, 5-145, 5-146, 5-147, 5-148, 5-149, 5-150, 5-151, 5-152, 5-153, 5-154, 5-155, 5-156, 5-337, 5-338, 5-339, 5-340, 5-341, 5-342, 5-343, 5-344, 5-345, 5-346, 5-347, 5-348, 5-387, 5-388, 6-3, 6-4, 6-5, 6-6, 6-7, 6-8, 6-9, 6-10, 6-11, 6-12, 6-13, 6-14, 6-27, 6-28, 6-29, 6-30, 6-33, 6-34, 6-69, 6-70, 6-71, 6-72, 6-73, 6-74, 6-75,

6-76, 6-77, 6-78, 6-79, 6-80, 6-81, 6-82, 6-85, 6-86, 6-87, 6-88, 6-89, 6-90, 6-93, 6-94, 6-95, 6-96, 6-97, 6-98, 6-99, 6-100, 6-101, 6-102, 6-103, 6-104, 6-105, 6-106, 6-107, 6-108, 6-145, 6-146, 6-147, 6-148, 6-149, 6-150, 6-151, 6-152, 6-153, 6-154, 6-155, 6-156, 6-337, 6-338, 6-339, 6-340, 6-341, 6-342, 6-343, 6-344, 6-345, 6-346, 6-347, 6-348, 6-387 y 6-388,

Los compuestos todavía más preferidos son los compuestos de ejemplo números 1-17, 1-18, 1-53, 1-54, 1-487, 1-488, 1-489, 1-490, 1-491, 1-492, 1-587, 1-588, 1-589, 1-590, 1-591, 1-592, 1-973, 1-974, 2-17, 2-18, 2-53, 2-54, 2-487, 2-488, 2-489, 2-490, 2-491, 2-492, 2-587, 2-588, 2-589, 2-590, 2-591, 2-592, 2-973, 2-974, 3-1, 3-2, 3-13, 3-14, 3-31, 3-32, 3-50, 3-51, 3-54, 3-55, 3-62, 3-63, 3-66, 3-67, 4-1, 4-2, 4-13, 4-14, 4-31, 4-32, 4-50, 4-51, 4-54, 4-55, 4-62, 4-63, 4-66, 4-67, 5-3, 5-4, 5-5, 5-6, 5-7, 5-8, 5-75, 5-76, 5-77, 5-78, 5-79, 5-80, 5-81, 5-82, 5-89, 5-90, 5-93, 5-94, 5-95, 5-96, 5-97, 5-98, 5-99, 5-100, 5-101, 5-102, 5-103, 5-104, 5-105, 5-106, 5-107, 5-108, 5-145, 5-146, 5-147, 5-148, 5-149, 5-150, 5-151, 5-152, 5-153, 5-154, 5-155, 5-156, 5-337, 5-338, 5-339, 5-340, 5-341, 5-342, 5-387, 5-388, 6-3, 6-4, 6-5, 6-6, 6-7, 6-8, 6-75, 6-76, 6-77, 6-78, 6-79, 6-80, 6-81, 6-82, 6-89, 6-90, 6-93, 6-94, 6-95, 6-96, 6-97, 6-98, 6-99, 6-100, 6-101, 6-102, 6-103, 6-104, 6-105, 6-106, 6-107, 6-108, 6-145, 6-146, 6-147, 6-148, 6-149, 6-150, 6-151, 6-152, 6-153, 6-154, 6-155, 6-156, 6-337, 6-338, 6-339, 6-340, 6-341, 6-342, 6-387 y 6-388, y

los compuestos particularmente preferidos son

Compuesto del Ejemplo No. 1-17:

(E)-3-[2-(4-carboxi-1H-pirazol-1-il)etiliden]-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-sulfanilpiperidina,

Compuesto del Ejemplo No. 1-53:

(E)-3-{2-[4-(carboximetil)-1H-pirazol-1-il]etiliden}-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-sulfanilpiperidina,

Compuesto del Ejemplo No. 1-487:

(E)-3-[2-(4-carboxi-1H-1,2,3-triazol-1-il)etiliden]-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-sulfanilpiperidina,

Compuesto del Ejemplo No. 1-587:

(E)-3-[2-(4-carboxi-2H-1,2,3-triazol-2-il)etiliden]-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-sulfanilpiperidina

Compuesto del Ejemplo No. 1-973:

(E)-3-{[2-(4-carboxi-1H-pirazol-1-il)-1-metil]etiliden}-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-sulfanilpiperidina,

Compuesto del Ejemplo No. 3-1:

(E)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-hidroxietiliden)-4-sulfanilpiperidina,

Compuesto del Ejemplo No. 3-13:

(E)-3-(2-carboxietiliden)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-sulfanilpiperidina,

Compuesto del Ejemplo No. 3-31:

(E)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{[1-(etoxicarbonilmetil)piperidin-4-il]metiliden}-4-sulfanilpiperidina,

Compuesto del Ejemplo No. 3-50:

(E)-3-{2-[N-(carboximetil)-N-metilamino]etiliden}-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-sulfanilpiperidina,

Compuesto del Ejemplo No. 3-54:

(E)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[N-(etoxicarbonilmetil)-N-metilamino]etiliden}-4-sulfanilpiperidina,

Compuesto del Ejemplo No. 3-62:

(E)-3-(2-{N-[3-(carboxi)propil]-N-metilamino}etiliden)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-sulfanilpiperidina,

Compuesto del Ejemplo No. 3-66:

(E)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-{N-[3-(etoxicarbonil)propil]-N-metilamino}etiliden)-4-sulfanilpiperidina,

Compuesto del Ejemplo No. 5-3:

(E)-3-{2-[4-(carboxipiperidin)-1-il]etiliden}-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-sulfanilpiperidina,

Compuesto del Ejemplo No. 5-7:

(E)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[4-(etoxicarbonil)piperidin-1-il]etiliden}-4-sulfanilpiperidina,

Compuesto del Ejemplo No. 5-75:

(E)-3-(2-{4-[2-(carboxietil)]-2-oxopiperazin-1-il}etiliden)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-sulfanilpiperidina,

Compuesto del Ejemplo No. 5-79:

(E)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-{4-[2-(etoxicarbonil)etil]-2-oxopiperazin-1-il}etiliden)-4-sulfanilpiperidina,

Compuesto del Ejemplo No. 5-81:

(E)-3-(2-{4-[3-(carboxipropil)]-2-oxopiperazin-1-il}etiliden)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-sulfanilpiperidina,

Compuesto del Ejemplo No. 5-97:

(E)-3-{2-[4-(carboximetil)-3-oxopiperazin-1-il]etiliden}-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-sulfanilpiperidina,

Compuesto del Ejemplo No. 5-101:

(E)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[4-(etoxicarbonilmetil)-3-oxopiperazin-1-il]etiliden}-4-sulfanilpiperidina,

Compuesto del Ejemplo No. 5-103:

(E)-3-(2-{4-[2-(carboxietil)]-3-oxopiperazin-1-il}etiliden)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-sulfanilpiperidina,

Compuesto del Ejemplo No. 5-105:

(E)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-{4-[2-(metoxicarbonil)etil]-3-oxopiperazin-1-il}etiliden)-4-sulfanilpiperidina,

Compuesto del Ejemplo No. 5-107:

(E)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-{4-[2-(etoxicarbonil)etil]-3-oxopiperazin-1-il}etiliden)-4-sulfanilpiperidina,

Compuesto del Ejemplo No. 5-147:

(E)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[(2S)-

(metoxicarbonil)pirrolidin-1-il]etiliden}-4-sulfanilpiperidina,

Compuesto del Ejemplo No. 5-151:

(E)-3-{2-[(2S)-(carboximetil)pirrolidin-1-il]etiliden}-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-sulfanilpiperidina,

Compuesto del Ejemplo No. 5-153:

(E)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[(2S)-(metoxicarbonilmetil)pirrolidin-1-il]etiliden}-4-sulfanilpiperidina,

Compuesto del Ejemplo No. 5-337:

(E)-3-{2-[3-(carboxipiperidin)-1-il]etiliden}-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-sulfanilpiperidina,

Compuesto del Ejemplo No. 5-387:

(E)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[(2S,4R)-4-hidroxi-2-(metoxicarbonil)pirrolidin-1-il]etiliden}-4-sulfanilpiperidina, y

Sus derivados S-acetilo (Compuestos No.: 1-18, 1-54, 1-488, 1-588, 1-974, 3-2, 3-14, 3-32, 3-51, 3-55, 3-63, 3-67, 5-4, 5-8, 5-76, 5-80, 5-82, 5-98, 5-102, 5-104, 5-106, 5-108, 5-148, 5-152, 5-154, 5-338 y 5-388) o isómeros geométricos de ellos (isómeros (Z), Compuestos No.: 2-17, 2-18, 2-53, 2-54, 2-487, 2-488, 2-587, 2-588, 2-973, 2-974, 4-1, 4-2, 4-13, 4-14, 4-31, 4-32, 4-50, 4-51, 4-54, 4-55, 4-62, 4-63, 4-66, 4-67, 6-3, 6-4, 6-7, 6-8, 6-75, 6-76, 6-79, 6-80, 6-81, 6-82, 6-97, 6-98, 6-101, 6-102, 6-103, 6-104, 6-105, 6-106, 6-107, 6-108, 6-147, 6-148, 6-151, 6-152, 6-153, 6-154, 6-337, 6-338, 6-387 y 6-388).

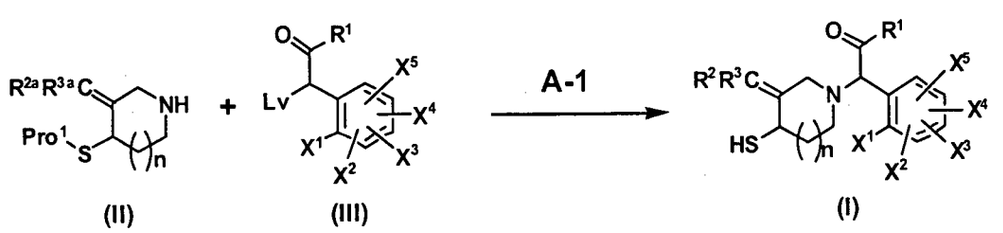
Efecto de la invención

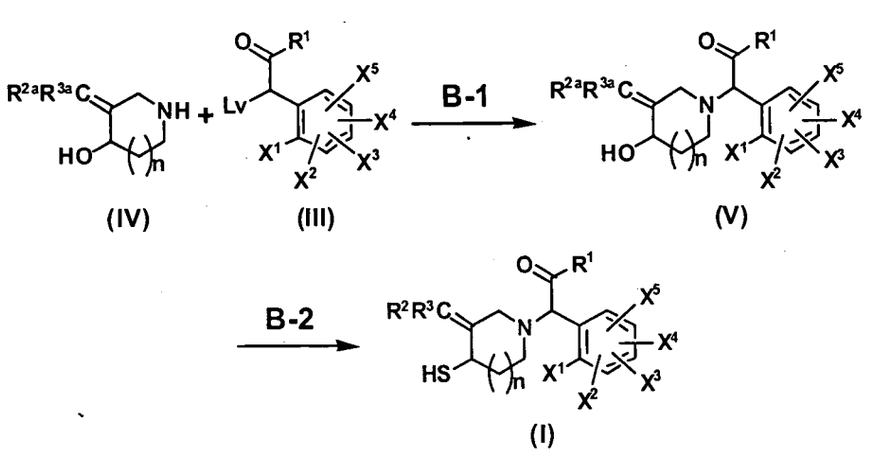
Los compuestos de la presente invención son estables químicamente y ejercen excelentes actividades anticoagulantes de plaquetas y acción inhibidora contra la formación de trombosis. Además, los compuestos de la presente invención ejercen dichas acciones con tiempos de espera cortos para el inicio y muestran bajo grado de toxicidad. Así, los compuestos de la presente invención pueden ser útiles para establecer medidas profilácticas, previr

recurrencia y establecer medidas terapéuticas (particularmente estas últimas) contra enfermedades inducidas por activación de plaquetas, tales como formación de trombosis y coagulación de plaquetas y respuestas de liberación de plaquetas, por ejemplo en intervención coronaria percutánea (PCI), angioplastia, endarterectomía, restenosis después de colocación de endoprótesis; síndrome coronario agudo, angina estable o inestable, infarto al miocardio, fibrilación atrial, ataque isquémico cerebral, infarto cerebral, y ateroesclerosis y enfermedades inducidas por formación de trombosis o formación de émbolos que están asociadas con diabetes mellitus, enfermedad arterial periférica, trombocitopenia inducida por heparina (HIT), púrpura trombocitopénica trombótica (TTP), síndrome de anticuerpo antifosfolípido, trombosis venosa, e icoremia.

Mejor forma de llevar a cabo la invención

El compuesto (I) en la presente invención puede ser obtenido mediante el Proceso A o el Proceso B descritos más adelante.





En lo anterior, desde R^1 hasta R^3 y X^1 hasta X^5 tienen los mismos significados definidos anteriormente; R^{2a} y R^{3a} representan R^2 y R^3 descritos anteriormente o un grupo mediante el cual un grupo

amino o un grupo hidroxilo en R^2 y R^3 puede ser protegido, si es necesario, mediante un grupo protector para un grupo amino o un grupo hidroxilo; Pro^1 representa un grupo protector para un grupo sulfanilo; y Lv representa un grupo suprimible.

El grupo protector para un grupo sulfanilo como Pro^1 puede ser el mismo grupo que el que se describe como el grupo protector para un grupo sulfanilo del "profármaco" anterior, y preferiblemente es un grupo acetilo.

El grupo protector para un grupo amino de R^{2a} y R^{3a} no está restringido particularmente siempre que usualmente pueda proteger a un grupo amino en reacciones químicas, y específicamente indica un grupo protector que puede ser segmentado mediante un proceso químico tal como hidrogenólisis, hidrólisis, electrólisis y fotólisis. Este grupo protector puede ser, por ejemplo, el "grupo acilo alifático" anterior; el "grupo acilo aromático" anterior; el "grupo alcoxicarbonilo" anterior; el "grupo aralquiloxicarbonilo" anterior; el "grupo sililo" anterior; el "grupo aralquilo" anterior; un "grupo metileno sustituido" que puede formar una base Schiff tal como un grupo N,N-dimetilaminometileno, bencilideno, 4-metoxibencilideno, 4-nitrobencilideno, salicilideno, 5-clorosalicilideno, difenilmetileno o (5-cloro-2-hidroxifenil)fenilmetileno; un "grupo sulfonilo aromático" que consiste en: un grupo arilsulfonilo tal como un grupo bencenosulfonilo, y un grupo arilsulfonilo sustituido con alquilo inferior o con grupo(s) alcoxi inferior tal como un grupo p-toluenosulfonilo, pentametilbencenosulfonilo, p-metoxibencenosulfonilo, 2,4,6-trimetoxibencenosulfonilo o 3-metoxi-4-t-butilbencenosulfonilo; y un "un grupo sulfonilo alifático", incluyendo un grupo alquilsulfonilo tal como un grupo metanosulfonilo o t-butilsulfonilo, y un grupo alquilsulfonilo sustituido con átomo(s) de halógeno, grupo(s) sililo, o grupo(s) arilo tal como un grupo trifluorometilsulfonilo, trisililetanosulfonilo o bencilsulfonilo.

El grupo protector para un grupo hidroxilo de R^{2a} y R^{3a} no está restringido particularmente siempre que usualmente pueda proteger a un grupo hidroxilo en reacciones químicas, y específicamente indica un grupo protector que puede ser segmentado mediante un proceso químico tal como hidrogenólisis, hidrólisis, electrólisis y fotólisis. Este grupo protector puede ser, por ejemplo, el "grupo acilo alifático" anterior; el "grupo acilo aromático" anterior; el "grupo carboniloxialquilo" anterior; el "grupo residual de una sal de un semi éster de ácido succínico" anterior; el "grupo residual de una sal de un semi éster de ácido fosfórico" anterior; el "grupo residual que forma un éster de aminoácido"; un grupo carbamoilo; un grupo carbamoilo sustituido con 1 o 2 grupos alquilo inferior; el "grupo carboniloxialquiloxicarbonilo" anterior; o el "grupo sililo" anterior, y preferiblemente es un grupo que forma un éster aceptable farmacológicamente tal como un "grupo acilo alifático", un "grupo acilo aromático" o un "grupo sililo", más preferiblemente un "grupo alcanoilo de 1 a 6 átomos de carbono" tal como un grupo acetilo, propionilo, butirilo, isobutirilo, pentanoilo, o pivaloilo, o un "grupo sililo" tal como a t-butildimetilsililo o t-butildifenilsililo, y en particular preferiblemente un grupo acetilo, un grupo t-butildimetilsililo o un grupo t-butildifenilsililo.

El grupo suprimible de Lv no está restringido particularmente siempre que este grupo sea un grupo funcional que puede lograr una reacción de desplazamiento reaccionando con un sustituyente nucleofílico, y puede ser, por ejemplo, el "átomo de halógeno" anterior; un "grupo alquilsulfoniloxi inferior" tal como un grupo metanosulfoniloxi o etanosulfoniloxi un "grupo alquilsulfoniloxi inferior halogenado" tal como un grupo trifluorometanosulfoniloxi; o un "grupo sulfoniloxi aromático" incluyendo un grupo arilsulfoniloxi tal como a grupo bencenosulfoniloxi, un grupo arilsulfoniloxi alquilado inferior tal como un grupo p-toluenosulfoniloxi, un grupo

arilsulfoniloxi halogenado tal como un grupo p-clorobencenosulfoniloxi y un grupo arilsulfoniloxi nitrado tal como un grupo p-nitrobencenosulfoniloxi.

Cada paso del Proceso A y del Proceso B se describe aquí en detalle en lo sucesivo.

(Proceso A)

El Proceso A es un paso para la preparación del compuesto (I) realizando una reacción de desplazamiento nucleofílico en la presencia de una base usando el compuesto (II), que se obtiene mediante el Proceso C y un compuesto (III) que es bien conocido o se prepara fácilmente a partir del compuestos conocidos (A-1). Además, si es necesario, también es posible llevar a cabo varias reacciones, tales como desprotección de un grupo protector de un grupo sulfanilo (A-2), introducción de un sustituyente en un grupo sulfanilo (A-3), hidrólisis de un grupo éster (A-4), conversión de un grupo carboxi en un grupo amida (A-5), conversión de un grupo carboxi en un grupo éster (A-6), desprotección de un grupo protector para un grupo amino (A-7), conversión de un grupo carboxi en un grupo hidroxiamino (A-8) y conversión de un grupo R^3 incluyendo un grupo hidroxilo en un grupo R^3 (A-9). Los pasos desde A-2 hasta A-9 pueden ser realizados antes o después del paso A-1, y el orden de estos pasos puede ser seleccionado fácilmente de acuerdo con las circunstancias por una persona con habilidades ordinarias en la técnica.

(A-1)

El solvente empleado puede ser, por ejemplo, un hidrocarburo aromático tal como benceno, tolueno o xileno; un hidrocarburo halogenado tal como diclorometano, cloroformo, tetracloruro de carbono, dicloroetano, clorobenceno o diclorobenceno; un éter tal como éter dietílico, éter diisopropílico, tetrahidrofurano, dioxano, dimetoxietano o éter dimetílico de di(etilen glicol); una cetona tal

como acetona, metil etil cetona, metil isobutil cetona, isoforona o ciclohexanona; un nitrilo, tal como acetonitrilo o isobutironitrilo; una amida, tal como formamida, N,N-dimetilformamida, N,N-dimetilacetamida, N-metil-2-pirrolidinona o triamida hexametilfosfórica; o un sulfóxido, tal como sulfóxido de dimetilo o sulfolano, y preferiblemente es un hidrocarburo halogenado, un nitrilo o una amida, y más preferiblemente N,N-dimetilformamida, N,N-dimetilacetamida, acetonitrilo o diclorometano.

La base empleada puede ser, por ejemplo, una base inorgánica, incluyendo un carbonato de metal alcalino tal como carbonato de sodio, carbonato de potasio o carbonato de litio; un carbonato hidrogenado de metal alcalino tal como carbonato hidrogenado de sodio, carbonato hidrogenado de potasio o carbonato hidrogenado de litio; un hidruro de metal alcalino tal como hidruro de litio, hidruro de sodio o hidruro de potasio; un hidróxido de metal alcalino tal como hidróxido de sodio, hidróxido de potasio o hidróxido de litio; y un fluoruro de metal alcalino tal como fluoruro de sodio o fluoruro de potasio; un alcóxido de metal alcalino tal como metóxido de sodio, etóxido de sodio, metóxido de potasio, etóxido de potasio, t-butóxido de potasio o metóxido de litio; un mercaptano de metal alcalino tal como mercaptano de sodio o etilmercaptano de sodio; o una base orgánica tal como N-metilmorfolina, trietilamina, tripropilamina, tributilamina, diisopropiletilamina, diciclohexilamina, N-metilpiperidina, piridina, 4-pirrolidinopiridina, picolina, 4-(N,N-dimetilamino)piridina, 2,6-di(t-butil)-4-metilpiridina, quinolina, N,N-dimetilanilina, N,N-dietilanilina, 1,5-diazabiciclo[4.3.0]non-5-eno (DBN), 1,4-diazabiciclo[2.2.2]octano (DABCO) o 1,8-diazabiciclo[5.4.0]undec-7-eno (DBU), y preferiblemente es un carbonato de metal alcalino o una base orgánica, y más preferiblemente carbonato de potasio o trietilamina.

La temperatura de la reacción varía dependiendo del material

inicial y del reactivo, y está entre -50°C y 100°C, y preferiblemente entre 0°C y 50°C.

El tiempo de la reacción varía dependiendo de la temperatura de la reacción, el material inicial, el reactivo y el tipo de solvente empleado, y generalmente es desde 30 minutos hasta 48 horas, y preferiblemente desde 1 hora hasta 24 horas.

Después de terminada la reacción, se puede obtener el compuesto deseado de esta reacción, por ejemplo, mediante concentración de la mezcla de la reacción, adición a la mezcla de un solvente orgánico inmiscible con agua tal como acetato de etilo, lavando la mezcla con agua, separación de la capa orgánica que contiene el compuesto deseado, secando la capa orgánica sobre sulfato de magnesio anhidro o similar, y luego evaporación del solvente orgánico para dar el producto deseado.

El producto obtenido, si es necesario, es purificado adicionalmente mediante tratamientos convencionales, por ejemplo, mediante recristalización, reprecipitación, cromatografía de columna en gel de sílice o similares.

(A-2)

Este paso es un paso para la desprotección de un grupo protector para un grupo sulfanilo, y se puede lograr fácilmente de acuerdo con procedimientos que son bien conocidos por una persona hábil en la técnica (por ejemplo, el procedimiento descrito en Protective Groups in Organic Synthesis, Tercera edición, T. W. Green, et al., John Wiley & Sons, Inc. (1999)), y preferiblemente se lleva a cabo mediante un método para desprotección en la presencia de un ácido (A-2a) o un método para desprotección en la presencia de una base (A-2b).

(A-2a)

El solvente empleado puede ser, por ejemplo, un hidrocarburo aromático tal como benceno, tolueno o xileno; un hidrocarburo

halogenado tal como diclorometano, cloroformo, tetracloruro de carbono, dicloroetano, clorobenceno o diclorobenceno; un éster tal como formato de etilo, acetato de etilo, acetato de propilo, acetato de butilo o carbonato de dietilo; un éter tal como éter dietílico, éter diisopropílico, tetrahidrofurano, dioxano, dimetoxietano o éter dimetílico de di(etilen glicol); un alcohol tal como metanol, etanol, n-propanol, isopropanol, n-butanol, isobutanol, t-butanol, alcohol isoamílico, dietilen glicol, glicerol, octanol, ciclohexanol o 2-metoxietanol; una amida tal como formamida, N,N-dimetilformamida, N,N-dimetilacetamida, N-metil-2-pirrolidinona o triamida hexametilfosfórica; un sulfóxido tal como sulfóxido de dimetilo o sulfolano; o una mezcla de los solventes anteriores, y preferiblemente es un alcohol o un solvente mezcla de un hidrocarburo halogenado y un alcohol, y más preferiblemente metanol, etanol o un solvente mezcla de diclorometano y metanol o etanol.

El ácido empleado no está restringido particularmente siempre que pueda ser usado en reacciones generales, y puede ser preferiblemente un ácido inorgánico tal como ácido clorhídrico, cloruro de hidrógeno, ácido bromhídrico, ácido sulfúrico, ácido perclórico o ácido fosfórico; o un ácido orgánico tal como ácido acético, ácido fórmico, ácido oxálico, ácido metanosulfónico, ácido p-toluenosulfónico, ácido alcanforsulfónico, ácido trifluoroacético o ácido trifluorometanosulfónico, y preferiblemente es un ácido inorgánico, y más preferiblemente cloruro de hidrógeno o ácido clorhídrico.

La temperatura de la reacción varía dependiendo del material inicial y del reactivo, y está entre -50°C y 100°C, y preferiblemente entre 0°C y 50°C.

El tiempo de la reacción varía dependiendo de la temperatura de la reacción, el material inicial, el reactivo y el tipo de solvente

empleado, y generalmente es desde 30 minutos hasta 48 horas, y preferiblemente desde 1 hora hasta 24 horas.

Después de terminada la reacción, se puede obtener el compuesto deseado de esta reacción, por ejemplo, mediante concentración de la mezcla de la reacción; adición a la mezcla de un solvente orgánico inmiscible con agua tal como acetato de etilo, lavando la mezcla con agua, separación de la capa orgánica que contiene el compuesto deseado, secando la capa orgánica sobre sulfato de magnesio anhidro o similar, y luego evaporación del solvente orgánico para dar el producto deseado.

El producto obtenido, si es necesario, es purificado adicionalmente mediante tratamientos convencionales, por ejemplo, mediante recristalización, reprecipitación, cromatografía de columna en gel de sílice o similares.

(A-2b)

El solvente empleado puede ser, por ejemplo, un hidrocarburo aromático tal como benceno, tolueno o xileno; un hidrocarburo halogenado tal como diclorometano, cloroformo, tetracloruro de carbono, dicloroetano, clorobenceno o diclorobenceno; un éter tal como éter dietílico, éter diisopropílico, tetrahidrofurano, dioxano, dimetoxietano o éter dimetílico de di(etilen glicol); un alcohol tal como metanol, etanol, n-propanol, isopropanol, n-butanol, isobutanol, t-butanol, alcohol isoamílico, dietilen glicol, glicerol, octanol, ciclohexanol o 2-metoxietanol; una amida tal como formamida, N,N-dimetilformamida, N,N-dimetilacetamida, N-metil-2-pirrolidinona o triamida hexametilfosfórica; un sulfóxido tal como sulfóxido de dimetilo o sulfolano; agua; o una mezcla de los solventes anteriores, y preferiblemente es un alcohol o un solvente mezclado de un alcohol y agua, y más preferiblemente metanol, etanol, metanol que contiene agua o etanol que contiene agua.

La base empleada puede ser, por ejemplo, una base

inorgánica, incluyendo un carbonato de metal alcalino tal como carbonato de sodio, carbonato de potasio o carbonato de litio; un carbonato hidrogenado de metal alcalino tal como carbonato hidrogenado de sodio, carbonato hidrogenado de potasio o carbonato hidrogenado de litio; un hidruro de metal alcalino tal como hidruro de litio, hidruro de sodio o hidruro de potasio; un hidróxido de metal alcalino tal como hidróxido de sodio, hidróxido de potasio o hidróxido de litio; y un fluoruro de metal alcalino tal como fluoruro de sodio o fluoruro de potasio; un alcóxido de metal alcalino tal como metóxido de sodio, etóxido de sodio, metóxido de potasio, etóxido de potasio, t-butóxido de potasio o metóxido de litio; un mercaptano de metal alcalino tal como mercaptano de sodio o etilmercaptano de sodio; o una base orgánica tal como N-metilmorfolina, trietilamina, tripropilamina, tributilamina, diisopropiletilamina, diciclohexilamina, N-metilpiperidina, piridina, 4-pirrolidinopiridina, picolina, 4-(N,N-dimetilamino)piridina, 2,6-di(t-butil)-4-metilpiridina, quinolina, N,N-dimetilanilina, N,N-dietilanilina, 1,5-diazabiciclo[4.3.0]non-5-eno (DBN), 1,4-diazabiciclo[2.2.2]octano (DABCO) o 1,8-diazabiciclo[5.4.0]undec-7-eno (DBU), y preferiblemente es un carbonato de metal alcalino o un hidróxido de metal alcalino, y más preferiblemente carbonato de potasio o hidróxido de sodio.

La temperatura de la reacción varía dependiendo del material inicial y del reactivo, y está entre -50°C y 100°C, y preferiblemente entre -20°C y 50°C.

El tiempo de la reacción varía dependiendo de la temperatura de la reacción, el material inicial, el reactivo y el tipo de solvente empleado, y generalmente es desde 1 minuto hasta 24 horas, y preferiblemente desde 5 minutos hasta 5 horas.

Después de terminada la reacción, se puede obtener el compuesto deseado de esta reacción, por ejemplo, mediante concentración de la mezcla de la reacción, adición a la mezcla de un

solvente orgánico inmiscible con agua tal como acetato de etilo, lavando la mezcla con agua, separación de la capa orgánica que contiene el compuesto deseado, secando la capa orgánica sobre sulfato de magnesio anhidro o similar, y luego evaporación del solvente orgánico para dar el producto deseado.

El producto obtenido, si es necesario, es purificado adicionalmente mediante tratamientos convencionales, por ejemplo, mediante recristalización, reprecipitación, cromatografía de columna en gel de sílice o similares.

(A-3)

Este paso es un paso para introducir un sustituyente en un grupo sulfanilo en la presencia de una base o similares. Cuando un cloruro ácido, un anhídrido ácido, un haluro de sulfanilo o un éster activo se emplea como reactivo, este paso se lleva a cabo en la presencia de una base (A-3a), cuando se emplea un ácido carboxílico, este paso se lleva a cabo en la presencia de un agente de condensación (A-3b), y cuando se emplea un tiol, este paso se lleva a cabo en la presencia de yodo o una base (A-3c).

(A-3a)

El solvente empleado puede ser, por ejemplo, un hidrocarburo aromático tal como benceno, tolueno o xileno; un hidrocarburo halogenado tal como diclorometano, cloroformo, tetracloruro de carbono, dicloroetano, clorobenceno o diclorobenceno; un éster tal como formato de etilo, acetato de etilo, acetato de propilo, acetato de butilo o carbonato de dietilo; un éter tal como éter dietílico, éter diisopropílico, tetrahidrofurano, dioxano, dimetoxietano o éter dimetílico de di(etilen glicol); una cetona tal como acetona, metil etil cetona, metil isobutil cetona, isoforona o ciclohexanona; una amida tal como formamida, N,N-dimetilformamida, N,N-dimetilacetamida, N-metil-2-pirrolidinona o triamida hexametilfosfórica; o un sulfóxido tal como sulfóxido de dimetilo o sulfolano, y preferiblemente es un

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hidrocarburo halogenado, una cetona o una amida, y más preferiblemente N,N-dimetilformamida, N,N-dimetilacetamida, diclorometano o acetona.

La base empleada puede ser, por ejemplo, una base inorgánica, incluyendo un carbonato de metal alcalino tal como carbonato de sodio, carbonato de potasio o carbonato de litio; un carbonato hidrogenado de metal alcalino tal como carbonato hidrogenado de sodio, carbonato hidrogenado de potasio o carbonato hidrogenado de litio; un hidruro de metal alcalino tal como hidruro de litio, hidruro de sodio o hidruro de potasio; un hidróxido de metal alcalino tal como hidróxido de sodio, hidróxido de potasio o hidróxido de litio; y un fluoruro de metal alcalino tal como fluoruro de sodio o fluoruro de potasio; un alcóxido de metal alcalino tal como metóxido de sodio, etóxido de sodio, metóxido de potasio, etóxido de potasio, t-butóxido de potasio o metóxido de litio; un mercaptano de metal alcalino tal como mercaptano de sodio o etilmercaptano de sodio; o una base orgánica tal como N-metilmorfolina, trietilamina, tripropilamina, tributilamina, diisopropiletilamina, diciclohexilamina, N-metilpiperidina, piridina, 4-pirrolidinopiridina, picolina, 4-(N,N-dimetilamino)piridina, 2,6-di(t-butil)-4-metilpiridina, quinolina, N,N-dimetilanilina, N,N-dietilanilina, 1,5-diazabiciclo[4.3.0]non-5-eno (DBN), 1,4-diazabiciclo[2.2.2]octano (DABCO) o 1,8-diazabiciclo[5.4.0]undec-7-eno (DBU), y preferiblemente es un carbonato de metal alcalino, un hidruro de metal alcalino o una base orgánica, y más preferiblemente hidruro de sodio, carbonato de potasio o trietilamina.

La temperatura de la reacción varía dependiendo del material inicial y del reactivo, y está entre -30°C y 100°C, y preferiblemente entre -10°C y 50°C.

El tiempo de la reacción varía dependiendo de la temperatura de la reacción, el material inicial, el reactivo y el tipo de solvente

empleado, y generalmente es desde 5 minutos hasta 24 horas, y preferiblemente desde 15 minutos hasta 10 horas.

Después de terminada la reacción, se puede obtener el compuesto deseado de esta reacción, por ejemplo, mediante concentración de la mezcla de la reacción, adición a la mezcla de un solvente orgánico inmiscible con agua tal como acetato de etilo, lavando la mezcla con agua, separación de la capa orgánica que contiene el compuesto deseado, secando la capa orgánica sobre sulfato de magnesio anhidro o similar, y luego evaporación del solvente orgánico para dar el producto deseado.

El producto obtenido, si es necesario, es purificado adicionalmente mediante tratamientos convencionales, por ejemplo, mediante recristalización, reprecipitación, cromatografía de columna en gel de sílice o similares.

(A-3b)

El solvente empleado puede ser, por ejemplo, un hidrocarburo aromático tal como benceno, tolueno o xileno; un hidrocarburo halogenado tal como diclorometano, cloroformo, tetracloruro de carbono, dicloroetano, clorobenceno o diclorobenceno; un éster tal como formato de etilo, acetato de etilo, acetato de propilo, acetato de butilo o carbonato de dietilo; un éter tal como éter dietílico, éter diisopropílico, tetrahidrofurano, dioxano, dimetoxietano o éter dimetílico de di(etilen glicol); una cetona tal como acetona, metil etil cetona, metil isobutil cetona, isoforona o ciclohexanona; una amida tal como formamida, N,N-dimetilformamida, N,N-dimetilacetamida, N-metil-2-pirrolidinona o triamida hexametilfosfórica; o un sulfóxido tal como sulfóxido de dimetilo o sulfolano, y preferiblemente es un hidrocarburo halogenado o una amida, y más preferiblemente N,N-dimetilformamida, N,N-dimetilacetamida o diclorometano.

El "agente de condensación" empleado puede ser,

(i) una combinación de un éster fosfatado tal como cianuro de

dietilfosforilo, azida de difenilfosforilo o dietil cianofosfonato y una base que se muestra a continuación;

(ii) una carbodiimida, tal como 1,3-diciclohexilcarbodiimida (DCC), 1,3-diisopropilcarbodiimida o 1-(3-dimetilaminopropil)-3-etilcarbodiimida (WSC); una combinación de dicha carbodiimida y una base que se muestra a continuación; una combinación de dicha carbodiimida y una N-hidroxiimida tal como N-hidroxisuccinimida, 1-hidroxibenzotriazol o N-hidroxi-5-norborneno-2,3-dicarboxiimida; y una combinación de dicha carbodiimida, dicha N-hidroxiimida y una base que se muestra a continuación;

(iii) una combinación de un disulfuro tal como 2,2'-dipiridilo disulfuro o 2,2'-dibenzotiazolilo disulfuro y una fosfina tal como trifenilfosfina o tributilfosfina;

(iv) un carbonato tal como carbonato de N,N'-disuccinimidilo, pirocarbonato de dietilo (DEPC), carbonato de di-2-piridilo o ditiocarbonato de S,S'-bis(1-fenil-1H-tetrazol-5-ilo);

(v) un cloruro fosfínico tal como cloruro N,N'-bis(2-oxo-3-oxazolidinil)fosfínico;

(vi) un oxalato tal como oxalato de N,N'-disuccinimidilo, oxalato de N,N'-diftalimida, oxalato de N,N'-bis(5-norborneno-2,3-dicarboxiimidilo), oxalato de 1,1'-bis(benzotriazolilo), oxalato de 1,1'-bis(6-clorobenzotriazolilo) u oxalato de 1,1'-bis(6-trifluorometilbenzotriazolilo);

(vii) una combinación de dicha fosfina y azodicarboxilato o una azodicarboxiamida tal como azodicarboxilato de dietilo o 1,1'-(azodicarbonil)dipiperidina;

(viii) un N-alquilo inferior-5-arilisoxazolio-3'-sulfonato tal como N-etil-5-fenilisoxazolio-3'-sulfonato;

(ix) una di-heteroaril diselenida tal como di-2-piridil diselenida;

(x) una arilsulfonil triazolida tal como p-nitrobencenosulfonil triazolida;

(xi) un haluro de 2-halo-1-alquilpiridinio inferior tal como yoduro de 2-cloro-1-metilpiridinio;

(xii) un imidazol tal como 1,1'-oxalildiimidazol o N,N'-carbonildiimidazol (CDI);

(xiii) un fluoroborato de 3-alquilo inferior-2-halógeno-benzotiazolio tal como fluoroborato de 3-etil-2-cloro-benzotiazolio;

(xiv) una 3-alquilo inferior-benzotiazol-2-selona tal como 3-metil-benzotiazol-2-selona;

(xv) un fosfato tal como diclorofosfato de fenilo o éster de polifosfato;

(xvi) un isocianato de halogenosulfonilo tal como isocianato de clorosulfonilo;

(xvii) un halogenosilano tal como cloruro de trimetilsililo o cloruro de trietilsililo;

(xviii) una combinación de un haluro de alcanosulfonilo inferior tal como cloruro de metanosulfonilo y una base que se muestra más adelante;

(xix) un Cloruro de N,N,N',N'-tetra-alquilo inferior halogenoformamidio tal como cloruro de N,N,N',N'-tetrametilcloroformamido; o

(xx) una combinación de una sal piridinio (Reactivo Mukaiyama) tal como cloruro de 1-metil-2-cloropiridinio o cloruro de 1-etil-2-bromopiridinio y una base que se muestra a continuación,

y preferiblemente es una carbodiimida, y más preferiblemente 1-(3-dimetilaminopropil)-3-etilcarbodiimida o 1,3-diciclohexilcarbodiimida.

La base empleada puede ser, por ejemplo, una base orgánica tal como pirrolidina, piperidina, morfoleno, N-metilmorfolina, trietilamina, tributilamina, diisopropiletilamina, diciclohexilamina, N-metilpiperidina, piridina, 4-pirrolidinopiridina, picolina, 4-(N,N-dimetilamino)piridina, 2,6-di(t-butil)-4-metilpiridina, quinolina, N,N-

dimetilanilina o N,N-dietilanilina.

La temperatura de la reacción varía dependiendo del material inicial y del reactivo, y está entre -30°C y 100°C, y preferiblemente entre -10°C y 50°C.

El tiempo de la reacción varía dependiendo de la temperatura de la reacción, el material inicial, el reactivo y el tipo de solvente empleado, y generalmente es desde 5 minutos hasta 24 horas, y preferiblemente desde 30 minutos hasta 10 horas.

Después de terminada la reacción, se puede obtener el compuesto deseado de esta reacción, por ejemplo, mediante concentración de la mezcla de la reacción; adición a la mezcla de un solvente orgánico inmiscible con agua tal como acetato de etilo, lavando la mezcla con agua, separación de la capa orgánica que contiene el compuesto deseado, secando la capa orgánica sobre sulfato de magnesio anhidro o similar, y luego evaporación del solvente orgánico para dar el producto deseado.

El compuesto obtenido, si es necesario, es purificado adicionalmente mediante tratamientos convencionales, por ejemplo, mediante recristalización, reprecipitación, cromatografía de columna en gel de sílice o similares.

(A-3c)

El solvente empleado puede ser, por ejemplo, un hidrocarburo aromático tal como benceno, tolueno o xileno; un hidrocarburo halogenado tal como diclorometano, cloroformo, tetracloruro de carbono, dicloroetano, clorobenceno o diclorobenceno; un éster tal como formato de etilo, acetato de etilo, acetato de propilo, acetato de butilo o carbonato de dietilo; un éter tal como éter dietílico, éter diisopropílico, tetrahidrofurano, dioxano, dimetoxietano o éter dimetílico de di(etilen glicol); una cetona tal como acetona, metil etil cetona, metil isobutil cetona, isoforona o ciclohexanona; una amida tal como formamida, N,N-dimetilformamida, N,N-dimetilacetamida, N-

metil-2-pirrolidinona o triamida hexametilfosfórica; o un sulfóxido tal como sulfóxido de dimetilo o sulfolano, y preferiblemente es un éter, y más preferiblemente tetrahidrofurano.

La temperatura de la reacción varía dependiendo del material inicial y del reactivo, y está entre -30°C y 100°C, y preferiblemente entre -10°C y 50°C.

El tiempo de la reacción varía dependiendo de la temperatura de la reacción, el material inicial, el reactivo y el tipo de solvente empleado, y generalmente es desde 1 minuto hasta 5 horas, y preferiblemente desde 5 minutos hasta 1 hora.

Después de terminada la reacción, se puede obtener el compuesto deseado de esta reacción, por ejemplo, mediante concentración de la mezcla de la reacción; adición a la mezcla de un solvente orgánico inmiscible con agua tal como acetato de etilo, lavando la mezcla con agua, separación de la capa orgánica que contiene el compuesto deseado, secando la capa orgánica sobre sulfato de magnesio anhidro o similar, y luego evaporación del solvente orgánico para dar el producto deseado.

El producto obtenido, si es necesario, es purificado adicionalmente mediante tratamientos convencionales, por ejemplo, mediante recristalización, reprecipitación, cromatografía de columna en gel de sílice o similares.

(A-4)

Este paso se logra mediante hidrólisis de un grupo éster (A-4).

Este paso se lleva a cabo de una forma similar a la indicada aquí anteriormente (A-2).

(A-5)

Este paso se logra convirtiendo un grupo carboxi obtenido en el paso A-4 en un éster activo, seguido por hacer reaccionar dicho éster activo con un compuesto amino deseado.

El solvente empleado puede ser, por ejemplo, un hidrocarburo

aromático tal como benceno, tolueno o xileno; un hidrocarburo halogenado tal como diclorometano, cloroformo, tetracloruro de carbono, dicloroetano, clorobenceno o diclorobenceno; un éster tal como formato de etilo, acetato de etilo, acetato de propilo, acetato de butilo o carbonato de dietilo; un éter tal como éter dietílico, éter diisopropílico, tetrahidrofurano, dioxano, dimetoxietano o éter dimetílico de di(etilen glicol); una cetona tal como acetona, metil etil cetona, metil isobutil cetona, isoforona o ciclohexanona; una amida tal como formamida, N,N-dimetilformamida, N,N-dimetilacetamida, N-metil-2-pirrolidinona o triamida hexametilfosfórica; o un sulfóxido tal como sulfóxido de dimetilo o sulfolano, y preferiblemente es un hidrocarburo halogenado o una amida, y más preferiblemente N,N-dimetilformamida, N,N-dimetilacetamida o diclorometano.

El reactivo empleado no está restringido particularmente siempre que se utilice para formación de un éster activo, y, por ejemplo, puede ser cloroformato de isobutilo.

La base empleada puede ser, por ejemplo, una base inorgánica, incluyendo un carbonato de metal alcalino tal como carbonato de sodio, carbonato de potasio o carbonato de litio; un carbonato hidrogenado de metal alcalino tal como carbonato hidrogenado de sodio, carbonato hidrogenado de potasio o carbonato hidrogenado de litio; un hidruro de metal alcalino tal como hidruro de litio, hidruro de sodio o hidruro de potasio; un hidróxido de metal alcalino tal como hidróxido de sodio, hidróxido de potasio o hidróxido de litio; y un fluoruro de metal alcalino tal como fluoruro de sodio o fluoruro de potasio; un alcóxido de metal alcalino tal como metóxido de sodio, etóxido de sodio, metóxido de potasio, etóxido de potasio, t-butóxido de potasio o metóxido de litio; un mercaptano de metal alcalino tal como mercaptano de sodio o etilmercaptano de sodio; o una base orgánica tal como N-metilmorfolina, trietilamina, tripropilamina, tributilamina, diisopropiletilamina, diciclohexilamina,

N-metilpiperidina, piridina, 4-pirrolidinopiridina, picolina, 4-(N,N-dimetilamino)piridina, 2,6-di(t-butil)-4-metilpiridina, quinolina, N,N-dimetilanilina, N,N-dietilanilina, 1,5-diazabiciclo[4.3.0]non-5-eno (DBN), 1,4-diazabiciclo[2.2.2]octano (DABCO) o 1,8-diazabiciclo[5.4.0]undec-7-eno (DBU), y preferiblemente es un carbonato de metal alcalino o una base orgánica, y más preferiblemente carbonato de potasio o trietilamina.

La temperatura de la reacción varía dependiendo del material inicial y del reactivo, y está entre -30°C y 100°C, y preferiblemente entre -10°C y 50°C.

El tiempo de la reacción varía dependiendo de la temperatura de la reacción, el material inicial, el reactivo y el tipo de solvente empleado, y generalmente es desde 10 minutos hasta 24 horas, y preferiblemente desde 30 minutos hasta 10 horas.

Después de terminada la reacción, se puede obtener el compuesto deseado de esta reacción, por ejemplo, mediante concentración de la mezcla de la reacción, adición a la mezcla de un solvente orgánico inmiscible con agua tal como acetato de etilo, lavando la mezcla con agua, separación de la capa orgánica que contiene el compuesto deseado; secando la capa orgánica sobre sulfato de magnesio anhidro o similar; y luego evaporación del solvente orgánico para dar el producto deseado.

El producto obtenido, si es necesario, es purificado adicionalmente mediante tratamientos convencionales, por ejemplo, mediante recristalización, reprecipitación, cromatografía de columna en gel de sílice o similares.

(A-6)

Este paso se lleva a cabo realizando una reacción de condensación - deshidratación entre un ácido carboxílico obtenido en el paso A-4 y un alcohol (A-6a) o realizando una reacción de intercambio de éster usando un éster en la presencia de un ácido o

una base directamente sin realizar el proceso del paso A-4 (A-6b).

(A-6a)

El solvente empleado puede ser, por ejemplo, un hidrocarburo aromático tal como benceno, tolueno o xileno; un hidrocarburo halogenado tal como diclorometano, cloroformo, tetracloruro de carbono, dicloroetano, clorobenceno o diclorobenceno; un éter tal como éter dietílico, éter diisopropílico, tetrahidrofurano, dioxano, dimetoxietano o éter dimetílico de di(etilen glicol); un alcohol tal como metanol, etanol, n-propanol, isopropanol, n-butanol, isobutanol, t-butanol, alcohol isoamílico, dietilen glicol, glicerol, octanol, ciclohexanol o 2-metoxietanol; una amida tal como formamida, N,N-dimetilformamida, N,N-dimetilacetamida, N-metil-2-pirrolidinona o hexametilfosforotriamida; un sulfóxido tal como sulfóxido de dimetilo o sulfolano; o un solvente mezclado de un alcohol y el solvente anterior. Sin embargo, cuando un alcohol se emplea como solvente en la reacción anterior, no es necesaria la adición del alcohol como reactivo.

El ácido empleado puede ser, por ejemplo, un ácido inorgánico tal como ácido clorhídrico, cloruro de hidrógeno, ácido bromhídrico, ácido sulfúrico, ácido perclórico o ácido fosfórico; o un ácido sulfónico tal como ácido metanosulfónico, ácido p-toluenosulfónico o ácido alcanforsulfónico, y preferiblemente es un ácido inorgánico, y más preferiblemente cloruro de hidrógeno.

La temperatura de la reacción varía dependiendo del material inicial y del reactivo, está entre -30°C y 100°C, y preferiblemente entre -10°C y 50°C.

El tiempo de la reacción varía dependiendo de la temperatura de la reacción, el material inicial, el reactivo y el tipo de solvente empleado, y generalmente es desde 10 minutos hasta 24 horas, y preferiblemente desde 30 minutos hasta 10 horas.

Después de terminada la reacción, se puede obtener el

compuesto deseado de esta reacción, por ejemplo, mediante concentración de la mezcla de la reacción, adición a la mezcla de un solvente orgánico inmiscible con agua tal como acetato de etilo, lavando la mezcla con agua, separación de la capa orgánica que contiene el compuesto deseado; secando la capa orgánica sobre sulfato de magnesio anhidro o similar; y luego evaporación del solvente orgánico para dar el producto deseado.

El producto obtenido, si es necesario, es purificado adicionalmente mediante tratamientos convencionales, por ejemplo, mediante recristalización, reprecipitación, cromatografía de columna en gel de sílice o similares.

Este paso se lleva a cabo de una forma similar a la indicada aquí anteriormente en (A-3b).

(A-6b)

En este paso, se emplea como solvente un alcohol correspondiente al grupo alcoxi deseado. Cuando se emplea un ácido, este ácido empleado puede ser, por ejemplo, un ácido inorgánico tal como ácido clorhídrico, cloruro de hidrógeno, ácido bromhídrico, ácido sulfúrico, ácido perclórico o ácido fosfórico; o un ácido sulfónico tal como ácido metanosulfónico, ácido p-toluenosulfónico o ácido alcanforsulfónico, y preferiblemente es un ácido inorgánico, y más preferiblemente cloruro de hidrógeno.

Cuando se emplea una base, esta base empleada puede ser, por ejemplo, una base inorgánica, incluyendo un carbonato de metal alcalino tal como carbonato de sodio, carbonato de potasio o carbonato de litio; un carbonato hidrogenado de metal alcalino tal como carbonato hidrogenado de sodio, carbonato hidrogenado de potasio o carbonato hidrogenado de litio; un hidruro de metal alcalino tal como hidruro de litio, hidruro de sodio o hidruro de potasio; un hidróxido de metal alcalino tal como hidróxido de sodio, hidróxido de potasio o hidróxido de litio; o un fluoruro de metal alcalino tal como

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fluoruro de sodio o fluoruro de potasio, y preferiblemente es un carbonato de metal alcalino, y más preferiblemente carbonato de potasio.

La temperatura de la reacción varía dependiendo del material inicial y del reactivo, y está entre -30°C y 100°C, y preferiblemente entre -10°C y 50°C.

El tiempo de la reacción varía dependiendo de la temperatura de la reacción, el material inicial, el reactivo y el tipo de solvente empleado, y generalmente es desde 10 minutos hasta 24 horas, y preferiblemente desde 30 minutos hasta 10 horas.

Después de terminada la reacción, se puede obtener el compuesto deseado de esta reacción, por ejemplo, mediante concentración de la mezcla de la reacción, adición a la mezcla de un solvente orgánico inmiscible con agua tal como acetato de etilo, lavando la mezcla con agua, separación de la capa orgánica que contiene el compuesto deseado, secando la capa orgánica sobre sulfato de magnesio anhidro o similar, y luego evaporación del solvente orgánico para dar el producto deseado.

El compuesto obtenido, si es necesario, es purificado adicionalmente mediante tratamientos convencionales, por ejemplo, mediante recristalización, reprecipitación, cromatografía de columna en gel de sílice o similares.

(A-7)

Este paso se lleva a cabo de una forma similar a la indicada aquí anteriormente en el paso A-2. Cuando se emplea un ácido, se emplea ácido trifluoroacético o cloruro de hidrógeno como un reactivo particularmente preferido.

Cuando se obtiene el compuesto deseado como su isómero geométrico, el compuesto deseado puede ser obtenido realizando la reacción de fotoisomerización que se muestra a continuación.

El solvente empleado puede ser, por ejemplo, un éster tal como

formato de etilo, acetato de etilo, acetato de propilo, acetato de butilo o carbonato de dietilo; un éter tal como éter dietílico, éter diisopropílico, tetrahidrofurano, dioxano, dimetoxietano o éter dimetílico de di(etilen glicol); un alcohol tal como metanol, etanol, n-propanol, isopropanol, n-butanol, isobutanol, t-butanol, alcohol isoamílico, dietilen glicol, glicerol, octanol, ciclohexanol o metilo cellosolve; un nitrilo tal como acetonitrilo o isobutironitrilo; una amida tal como formamida, N,N-dimetilformamida, N,N-dimetilacetamida, N-metil-2-pirrolidona, N-metilpirrolidinona o hexametilfosforotriamida; un sulfóxido tal como sulfóxido de dimetilo o sulfolano; agua; o una mezcla de estos solventes, y preferiblemente es agua, un alcohol, un nitrilo o una mezcla de estos solventes.

La fuente de luz empleada es una lámpara de mercurio de baja presión (que tiene desde 20 W hasta 100 W, preferiblemente 32 W).

El sensibilizador empleado puede ser, por ejemplo, benzofenona, fluorenona o antraquinona.

Esta reacción también se puede llevar a cabo mediante la adición de un compuesto orgánico de azufre tal como disulfuro de dimetilo, disulfuro de dietilo o disulfuro de difenilo con el fin de acelerar la reacción.

La temperatura de la reacción varía dependiendo del material inicial y del reactivo, y está entre -20°C y 100°C, y preferiblemente entre 0°C y 50°C.

El tiempo de la reacción varía dependiendo de la temperatura de la reacción, el material inicial, el reactivo y el tipo de solvente empleado, y generalmente es desde 5 minutos hasta 8 horas, y preferiblemente desde 10 minutos hasta 3 horas.

Después de terminada la reacción, se puede obtener el compuesto deseado de esta reacción, por ejemplo, mediante concentración de la mezcla de la reacción, adición a la mezcla de un

solvente orgánico inmiscible con agua tal como acetato de etilo, lavando la mezcla con agua, separación de la capa orgánica que contiene el compuesto deseado, secando la capa orgánica sobre sulfato de magnesio anhidro o similar, y luego evaporación del solvente orgánico para dar el producto deseado.

El producto obtenido, si es necesario, es purificado adicionalmente mediante tratamientos convencionales, por ejemplo, mediante recristalización, reprecipitación, cromatografía de columna en gel de sílice o similares.

(A-8)

Este paso es un paso para la conversión de un grupo carboxi en un grupo hidroxilamino, y se puede llevar a cabo fácilmente de acuerdo con procedimientos que son bien conocidos por una persona con habilidades ordinarias en la técnica (por ejemplo, los métodos descritos en A. Sekar Reddy, M. Suresh Kumar y G. Rabindra Reddy: Tetrahedron Letters, (2000), 41, 6285-6288).

(A-9)

Este paso se puede llevar a cabo de acuerdo con una reacción Mitsunobu usando una amina en un solvente inerte o mediante conversión de un grupo hidroxilo en un grupo suprimible realizando luego una reacción de desplazamiento usando una amina, y llevada a cabo de manera similar a la que se indica aquí más adelante (C-2e).

(Proceso B)

El proceso B está constituido por los pasos que comprenden la preparación del compuesto (V) realizando una reacción de desplazamiento nucleofílica en la presencia de una base usando un compuesto (III) que es bien conocido o se prepara fácilmente a partir del compuestos conocidos y los compuestos (IV) obtenidos mediante el proceso C descrito más adelante (B-1) y la preparación del compuesto (I) mediante conversión de un grupo hidroxilo del compuesto (V) (B-2). Además, si es necesario, en el proceso B,

también se puede llevar a cabo la desprotección del grupo protector para un grupo sulfanilo (B-3), la introducción de un sustituyente en un grupo sulfanilo (B-4), la hidrólisis de un grupo éster (B-5), la conversión de un grupo carboxi en un grupo amida (B-6), la conversión de un grupo carboxi en un grupo éster (B-7), la desprotección de un grupo protector para un grupo amino (B-8) y la conversión de un grupo carboxi en un grupo hidroxiamino (B-9). Los pasos desde B-3 hasta B-9 se pueden realizar antes o después de los pasos B-1 y B-2, y el orden de estos pasos puede ser seleccionado de acuerdo con circunstancias por una persona con habilidades ordinarias en la técnica.

(B-1)

El solvente empleado puede ser, por ejemplo, un hidrocarburo aromático tal como benceno, tolueno o xileno; un hidrocarburo halogenado tal como diclorometano, cloroformo, tetracloruro de carbono, dicloroetano, clorobenceno o diclorobenceno; un éster tal como formato de etilo, acetato de etilo, acetato de propilo, acetato de butilo o carbonato de dietilo; un éter tal como éter dietílico, éter diisopropílico, tetrahidrofurano, dioxano, dimetoxietano o éter dimetílico de di(etilen glicol); una cetona tal como acetona, metil etil cetona, metil isobutil cetona, isoforona o ciclohexanona; una amida tal como formamida, N,N-dimetilformamida, N,N-dimetilacetamida, N-metil-2-pirrolidinona o triamida hexametilfosfórica; o un sulfóxido tal como sulfóxido de dimetilo o sulfolano, y preferiblemente es un hidrocarburo halogenado o una amida, y más preferiblemente N,N-dimetilformamida, N,N-dimetilacetamida o diclorometano.

La base empleada puede ser, por ejemplo, una base inorgánica, incluyendo un carbonato de metal alcalino tal como carbonato de sodio, carbonato de potasio o carbonato de litio; un carbonato hidrogenado de metal alcalino tal como carbonato hidrogenado de sodio, carbonato hidrogenado de potasio o carbonato

hidrogenado de litio; un hidruro de metal alcalino tal como hidruro de litio, hidruro de sodio o hidruro de potasio; un hidróxido de metal alcalino tal como hidróxido de sodio, hidróxido de potasio o hidróxido de litio; y un fluoruro de metal alcalino tal como fluoruro de sodio o fluoruro de potasio; un alcóxido de metal alcalino tal como metóxido de sodio, etóxido de sodio, metóxido de potasio, etóxido de potasio, t-butóxido de potasio o metóxido de litio; un mercaptano de metal alcalino tal como mercaptano de sodio o etilmercaptano de sodio; o una base orgánica tal como N-metilmorfolina, trietilamina, tripropilamina, tributilamina, diisopropiletilamina, diciclohexilamina, N-metilpiperidina, piridina, 4-pirrolidinopiridina, picolina, 4-(N,N-dimetilamino)piridina, 2,6-di-(t-butil)-4-metilpiridina, quinolina, N,N-dimetilanilina, N,N-dietilanilina, 1,5-diazabiciclo[4.3.0]non-5-eno (DBN), 1,4-diazabiciclo[2.2.2]octano (DABCO) o 1,8-diazabiciclo[5.4.0]undec-7-eno (DBU), y preferiblemente es un carbonato de metal alcalino o una base orgánica, y más preferiblemente carbonato de potasio o trietilamina.

La temperatura de la reacción varía dependiendo del material inicial y del reactivo, y está entre -30°C y 100°C, y preferiblemente entre -10°C y 50°C.

El tiempo de la reacción varía dependiendo de la temperatura de la reacción, el material inicial, el reactivo y el tipo de solvente empleado, y generalmente es desde 10 minutos hasta 48 horas, y preferiblemente desde 30 minutos hasta 24 horas.

Después de terminada la reacción, se puede obtener el compuesto deseado de esta reacción, por ejemplo, mediante concentración de la mezcla de la reacción, adición a la mezcla de un solvente orgánico inmiscible con agua tal como acetato de etilo, lavando la mezcla con agua, separación de la capa orgánica que contiene el compuesto deseado, secado de la capa orgánica sobre sulfato de magnesio anhidro o similares, y luego evaporación del

solvente orgánico para dar el producto deseado.

El producto obtenido, si es necesario, es purificado adicionalmente mediante tratamientos convencionales, por ejemplo, mediante recristalización, reprecipitación, cromatografía de columna en gel de sílice o similares.

(B-2)

Este paso se lleva a cabo mediante la reacción Mitsunobu en un solvente inerte (B-2a), mediante una reacción en la presencia de un reactivo amida-acetal (B-2b), convirtiendo un grupo hidroxilo en un grupo suprimible y realizando una reacción de sustitución usando Pro^1-SM (M representa un metal alcalino, preferiblemente potasio) (B-2c) o convirtiendo un grupo hidroxilo en un grupo suprimible y realizando una reacción de sustitución usando Pro^1-SM en la presencia de un catalizador de paladio y una fosfina (B-2d).

(B-2a)

El solvente empleado puede ser, por ejemplo, un hidrocarburo aromático tal como benceno, tolueno o xileno; un hidrocarburo halogenado tal como diclorometano, cloroformo, tetracloruro de carbono, dicloroetano, clorobenceno o diclorobenceno; o un éter tal como éter dietílico, éter diisopropílico, tetrahidrofurano, dioxano, dimetoxietano o éter dimetílico de di(etilen glicol), y preferiblemente es un hidrocarburo halogenado o un éter, y más preferiblemente diclorometano o tetrahidrofurano.

El reactivo empleado en la reacción Mitsunobu no está restringido particularmente siempre que se pueda usar en general para la reacción Mitsunobu, y, por ejemplo, preferiblemente es una combinación de un compuesto azo, incluyendo un di-alquilo inferior-azodicarboxilato tal como azodicarboxilato de dietilo o azodicarboxilato de diisopropilo o un azodicarbonilo heterociclilo tal como 1,1'-(azodicarbonil)dipiperidina, y una fosfina, incluyendo una triarilfosfina tal como trifenilfosfina o una tri-alquilo inferior-fosfina

tal como tri-n-butilfosfina, y más preferiblemente una combinación de un di-alquilo inferior-azodicarboxilato y una triarilfosfina, y mucho más preferiblemente una combinación de azodicarboxilato de dietilo o azodicarboxilato de diisopropilo y trifenilfosfina.

La temperatura de la reacción varía dependiendo del material inicial y del reactivo, y está entre -50°C y 100°C, y preferiblemente entre -10°C y 60°C.

El tiempo de la reacción varía dependiendo de la temperatura de la reacción, el material inicial, el reactivo y el tipo de solvente empleado, y generalmente es desde 10 minutos hasta 48 horas, y preferiblemente desde 30 minutos hasta 24 horas.

Después de terminada la reacción, se puede obtener el compuesto deseado de esta reacción, por ejemplo, mediante concentración de la mezcla de la reacción, adición a la mezcla de un solvente orgánico inmiscible con agua tal como acetato de etilo, lavando la mezcla con agua, separación de la capa orgánica que contiene el compuesto deseado, secado de la capa orgánica sobre sulfato de magnesio anhidro o similares, y luego evaporación del solvente orgánico para dar el producto deseado.

El producto obtenido, si es necesario, es purificado adicionalmente mediante tratamientos convencionales, por ejemplo, mediante recristalización, reprecipitación, cromatografía de columna en gel de sílice o similares.

(B-2b)

El solvente empleado puede ser, por ejemplo, un hidrocarburo aromático tal como benceno, tolueno o xileno; un hidrocarburo halogenado tal como diclorometano, cloroformo, tetracloruro de carbono, dicloroetano, clorobenceno o diclorobenceno; un éter tal como éter dietílico, éter diisopropílico, tetrahidrofurano, dioxano, dimetoxietano o éter dimetílico de di(etilen glicol); o una amida tal como formamida, N,N-dimetilformamida, N,N-dimetilacetamida, N-

metil-2-pirrolidinona o triamida hexametilfosfórica, y preferiblemente es un hidrocarburo aromático, y más preferiblemente tolueno.

El reactivo acetal amida empleado puede ser, por ejemplo, un grupo de la fórmula general $(CH_3)_2NCH(OR')_2$ (en donde R' representa un grupo alquilo de 1 a 6 átomos de carbono o un grupo aralquilo de 7 a 15 átomos de carbono), y preferiblemente es dineopentil acetal de N,N-dimetilformamida.

La temperatura de la reacción varía dependiendo del material inicial y del reactivo, y está entre -50°C y 150°C, y preferiblemente entre -10°C y 120°C.

El tiempo de la reacción varía dependiendo de la temperatura de la reacción, el material inicial, el reactivo y el tipo de solvente empleado, y generalmente es desde 1 minuto hasta 24 horas, y preferiblemente desde 5 minutos hasta 5 horas.

Después de terminada la reacción, se puede obtener el compuesto deseado de esta reacción, por ejemplo, mediante concentración de la mezcla de la reacción, adición a la mezcla de un solvente orgánico inmiscible con agua tal como acetato de etilo, lavando la mezcla con agua, separación de la capa orgánica que contiene el compuesto deseado, secado de la capa orgánica sobre sulfato de magnesio anhidro o similares, y luego evaporación del solvente orgánico para dar el producto deseado.

El producto obtenido, si es necesario, es purificado adicionalmente mediante tratamientos convencionales, por ejemplo, mediante recristalización, reprecipitación, cromatografía de columna en gel de sílice o similares.

(B-2c)

El solvente empleado para la reacción de conversión de un grupo hidroxilo en un grupo suprimible puede ser, por ejemplo, un hidrocarburo halogenado tal como diclorometano, cloroformo, tetracloruro de carbono, dicloroetano, clorobenceno o

diclorobenceno; o un éter tal como éter dietílico, éter diisopropílico, tetrahidrofurano, dioxano, dimetoxietano o éter dimetílico de di(etilen glicol), y preferiblemente es un hidrocarburo halogenado, y más preferiblemente diclorometano.

La base empleada puede ser, por ejemplo, una base orgánica tal como pirrolidina, piperidina, morfolina, N-metilmorfolina, trietilamina, tripropilamina, tributilamina, diisopropiletilamina, diciclohexilamina, N-metilpiperidina, piridina, 4-pirrolidinopiridina, picolina, 4-(N,N-dimetilamino)piridina, 2,6-di(t-butil)-4-metilpiridina, quinolina, N,N-dimetilanilina, N,N-dietilanilina, 1,5-diazabiciclo[4.3.0]non-5-eno (DBN), 1,4-diazabiciclo[2.2.2]octano (DABCO) o 1,8-diazabiciclo[5.4.0]undec-7-eno (DBU), y preferiblemente es 1,8-diazabiciclo[5.4.0]undec-7-eno (DBU).

El reactivo empleado no está restringido particularmente siempre que forme un grupo suprimible reaccionando con un grupo hidroxilo, y la conversión en el grupo suprimible se logra mediante adición de un agente de halogenación, un agente de sulfonilación o un agente de acilación. El agente de halogenación empleado puede ser un tetrahaluro de carbono tal como tetrabromuro de carbono o tetracloruro de carbono, y en estos casos, se usa una fosfina como reactivo. Esta fosfina puede ser, por ejemplo, una trialquilfosfina de 1 a 6 átomos de carbono tal como trimetilfosfina, trietilfosfina, tripropilfosfina, tributilfosfina, tripentilfosfina o trihexilfosfina; una triarilfosfina de 6 a 10 átomos de carbono tal como trifenilfosfina, triindenilfosfina o trinaftilfosfina; o una triarilfosfina de 6 a 10 átomos de carbono las cuales pueden tener Grupo(s) alquilo de 1 a 4 átomos de carbono como sustituyente(s), tales como tolildifenilfosfina, tritolilfosfina, trimesitilfosfina, tributilfenilfosfina o tri-6-etil-2-naftilfosfina, y preferiblemente es una trialquilfosfina de 1 a 6 átomos de carbono (particularmente trimetilfosfina, trietilfosfina, tripropilfosfina o tributilfosfina) o una triarilfosfina de 6 a 10 átomos

de carbono (particularmente trifenilfosfina, triindenilfosfina o trinaftilfosfina), y más preferiblemente una triarilfosfina de 6 a 10 átomos de carbono (particularmente trifenilfosfina). El agente de sulfonilación empleado puede ser, por ejemplo, un haluro de sulfonilo tal como cloruro de metanosulfonilo, cloruro de etanosulfonilo o cloruro de tosilo, y preferiblemente es cloruro de metanosulfonilo. El agente de acilación empleado puede ser, por ejemplo, cloruro de acetilo, anhídrido acético, anhídrido trifluoroacético o similares.

La temperatura de la reacción varía dependiendo del material inicial y del reactivo, y está entre -50°C y 100°C, y preferiblemente entre -20°C y 80°C.

El tiempo de la reacción varía dependiendo de la temperatura de la reacción, el material inicial, el reactivo y el tipo de solvente empleado, y generalmente es desde 30 minutos hasta 24 horas, y preferiblemente desde 1 hora hasta 10 horas.

El solvente empleado en la reacción de sustitución de Pro^1-SM puede ser, por ejemplo, un hidrocarburo aromático tal como benceno, tolueno o xileno; un hidrocarburo halogenado tal como diclorometano, cloroformo, tetracloruro de carbono, dicloroetano, clorobenceno o diclorobenceno; un éster tal como formato de etilo, acetato de etilo, acetato de propilo, acetato de butilo o carbonato de dietilo; un éter tal como éter dietílico, éter diisopropílico, tetrahidrofurano, dioxano, dimetoxietano o éter dimetílico de di(etilen glicol); una cetona tal como acetona, metil etil cetona, metil isobutil cetona, isoforona o ciclohexanona; un compuesto nitro tal como nitroetano o nitrobenceno; un nitrilo tal como acetonitrilo o isobutironitrilo; una amida tal como formamida, N,N-dimetilformamida, N,N-dimetilacetamida, N-metil-2-pirrolidinona o triamida hexametilfosfórica; o un sulfóxido tal como sulfóxido de dimetilo o sulfolano, y preferiblemente es un hidrocarburo halogenado, una amida o un sulfóxido, y más preferiblemente N,N-

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dimetilformamida, N,N-dimetilacetamida, diclorometano o sulfóxido de dimetilo.

La base empleada puede ser, por ejemplo, una base inorgánica que contiene un carbonato de metal alcalino tal como carbonato de sodio, carbonato de potasio o carbonato de litio; un carbonato hidrogenado de metal alcalino tal como carbonato hidrogenado de sodio, carbonato hidrogenado de potasio o carbonato hidrogenado de litio; un hidruro de metal alcalino tal como hidruro de litio, hidruro de sodio o hidruro de potasio; un hidróxido de metal alcalino tal como hidróxido de sodio, hidróxido de potasio o hidróxido de litio; y un fluoruro de metal alcalino tal como fluoruro de sodio o fluoruro de potasio; un alcóxido de metal alcalino tal como metóxido de sodio, etóxido de sodio, metóxido de potasio, etóxido de potasio, t-butóxido de potasio o metóxido de litio; un mercaptano de metal alcalino tal como mercaptano de sodio o etilmercaptano de sodio; o una base orgánica tal como N-metilmorfolina, trietilamina, tripropilamina, tributilamina, diisopropiletilamina, diciclohexilamina, N-metilpiperidina, piridina, 4-pirrolidinopiridina, picolina, 4-(N,N-dimetilamino)piridina, 2,6-di-(t-butil)-4-metilpiridina, quinolina, N,N-dimetilanilina, N,N-dietilanilina, 1,5-diazabiciclo[4.3.0]non-5-eno (DBN), 1,4-diazabiciclo[2.2.2]octano (DABCO) o 1,8-diazabiciclo[5.4.0]undec-7-eno (DBU), y preferiblemente es un carbonato de metal alcalino o una base orgánica, y más preferiblemente carbonato de potasio o trietilamina.

La temperatura de la reacción varía dependiendo del material inicial y del reactivo, y está entre -50°C y 100°C, y preferiblemente entre -20°C y 80°C.

El tiempo de la reacción varía dependiendo de la temperatura de la reacción, el material inicial, el reactivo y el tipo de solvente empleado, y generalmente es desde 30 minutos hasta 24 horas, y preferiblemente desde 1 hora hasta 10 horas.

Después de terminada la reacción, se puede obtener el compuesto deseado de esta reacción, por ejemplo, mediante concentración de la mezcla de la reacción, adición a la mezcla de un solvente orgánico inmiscible con agua tal como acetato de etilo, lavando la mezcla con agua, separación de la capa orgánica que contiene el compuesto deseado, secado de la capa orgánica sobre sulfato de magnesio anhidro o similares, y luego evaporación del solvente orgánico para dar el producto deseado.

El producto obtenido, si es necesario, es purificado adicionalmente mediante tratamientos convencionales, por ejemplo, mediante recristalización, reprecipitación, cromatografía de columna en gel de sílice o similares.

(B-2d)

La reacción para convertir un grupo hidroxilo en un grupo suprimible se puede llevar a cabo de una forma similar a (B-2c).

El solvente de la reacción de sustitución subsiguiente empleada puede ser, por ejemplo, un hidrocarburo alifático tal como hexano, ciclohexano, heptano, ligroina, o éter de petróleo; un hidrocarburo aromático tal como benceno, tolueno, o xileno; un hidrocarburo halogenado tal como diclorometano, cloroformo, tetracloruro de carbono, dicloroetano, clorobenceno, o diclorobenceno; un éter tal como éter dietílico, éter diisopropílico, tetrahidrofurano, dioxano, dimetoxietano, o éter dimetílico de di(etilen glicol); un nitrilo tal como acetonitrilo o isobutironitrilo; o una mezcla de agua y los solventes mencionados anteriormente, y preferiblemente es una mezcla de agua y dioxano.

El catalizador de paladio empleado puede ser, por ejemplo, cloruro de paladio, acetato de paladio, aducto de tris(dibencilidenacetona)dipaladio-cloroformo, tris(dibencilidenacetona)dipaladio, bis(dibencilidenacetona)paladio, dímero de cloruro de π-alil paladio, tetracis(trifenilfosfina)paladio,

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dicloruro de 1,1'-bis(difenilfosfino)ferroceno paladio, cloruro de bis(trifenilfosfina)paladio, acetato de bis(trifenilfosfina)paladio, dicloro(1,5-ciclooctadieno)paladio, diclorobis(acetonitrilo)paladio, dicloruro de bis(triciclohexilfosfina)paladio, bis(triciclohexilfosfina)paladio, o dicloruro de bis(tri-O-tolilfosfina)paladio, y preferiblemente es cloruro de paladio, acetato de paladio, aducto de tris(dibencilidenacetona)dipaladio-cloroformo o tris(dibencilidenacetona)dipaladio.

La fosfina empleada puede ser, por ejemplo, una trialquilfosfina de 1 a 6 átomos de carbono tal como trimetilfosfina, trietilfosfina, tripropilfosfina, tributilfosfina, tripentilfosfina o trihexilfosfina; una triarilfosfina de 6 a 10 átomos de carbono tal como trifenilfosfina, triindenilfosfina o trinaftilfosfina; una triarilfosfina de 6 a 10 átomos de carbono que puede estar sustituida con un grupo alquilo de 1 a 4 átomos de carbono tal como tolildifenilfosfina, tritolilfosfina, trimesitilfosfina, tributilfenilfosfina o tri-6-etil-2-naftilfosfina; un a bis(difenilfosfino)alcano de 1 a 6 átomos de carbono tal como bis(difenilfosfino)metano, 1,2-bis(difenilfosfino)etano, 1,3-bis(difenilfosfino)propano, 1,4-bis(difenilfosfino)butano, 1,5-bis(difenilfosfino)pentano o 1,6-bis(difenilfosfino)hexano; o bis(difenilfosfino)acetileno, 1,2-bis(difenilfosfino)benceno, (R)-(+)-2,2'-bis(difenilfosfino)-1,1'-binaftilo, 2,2'-bis(difenilfosfino)-1,1'-binaftilo, (S)-(-)-2,2'-bis(difenilfosfino)-1,1'-binaftilo, 1,1'-bis(difenilfosfino)ferroceno, 1,1-bis(difenilfosfino)etileno o 4,5-bis(difenilfosfino)-9,9-dimetilxanteno, y preferiblemente es 1,1'-bis(difenilfosfino)ferroceno, (R)-(+)-2,2'-bis(difenilfosfino)-1,1'-binaftilo, 2,2'-bis(difenilfosfino)-1,1'-binaftilo o (S)-(-)-2,2'-bis(difenilfosfino)-1,1'-binaftilo.

La temperatura de la reacción varía dependiendo del material inicial y del reactivo, y está entre 0°C y 150°C, y preferiblemente entre 50°C y 120°C.

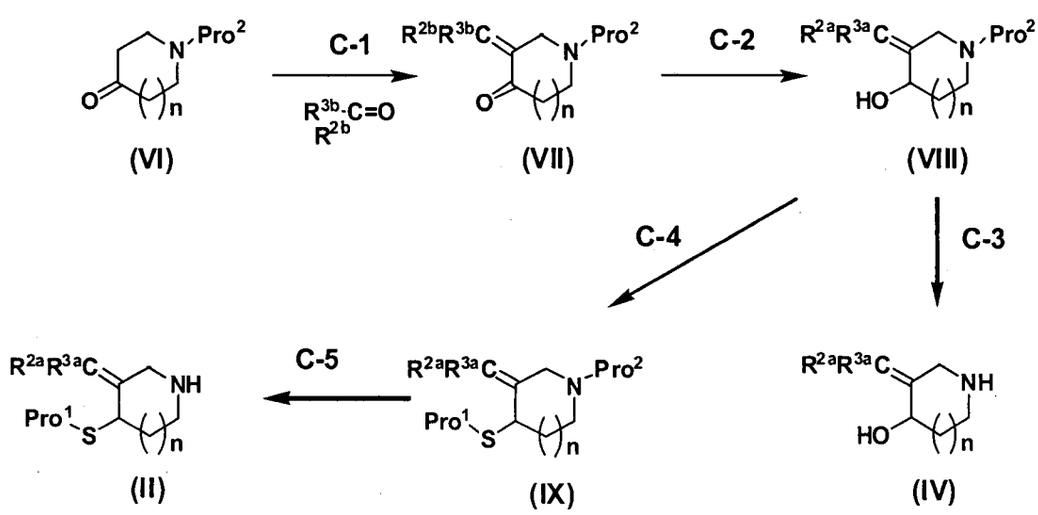
El tiempo de la reacción varía dependiendo de la temperatura de la reacción, el material inicial, el reactivo y el tipo de solvente empleado, y generalmente es desde 1 hora hasta 24 horas, y preferiblemente desde 6 horas hasta 20 horas.

Después de terminada la reacción, se puede obtener el compuesto deseado de esta reacción, por ejemplo, mediante concentración de la mezcla de la reacción, adición a la mezcla de un solvente orgánico inmiscible con agua tal como acetato de etilo, lavando la mezcla con agua, separación de la capa orgánica que contiene el compuesto deseado, secado de la capa orgánica sobre sulfato de magnesio anhidro o similares, y luego evaporación del solvente orgánico para dar el producto deseado.

El producto obtenido, si es necesario, es purificado adicionalmente mediante tratamientos convencionales, por ejemplo, mediante recristalización, reprecipitación, cromatografía de columna en gel de sílice o similares.

Desde (B-3) hasta (B-9)

Cada uno de estos pasos se lleva a cabo de una forma similar a la indicada en (A-2) hasta (A-8) aquí en lo anterior, respectivamente.



(Proceso C)

En lo anterior, Pro^1, R^{2a}, R^{3a} y, n tienen los mismos significados que los indicados aquí en lo anterior; R^{2b} y R^{3b} representan los mismos grupos que los indicados para R^{2a} y R^{3a} descritos aquí en lo anterior; y Pro^2 representa un grupo protector para un grupo amino.

El grupo protector para un grupo amino mostrado como Pro^2 es el mismo que el indicado para R^{2a} y R^{3a}.

El proceso C se describe aquí en detalle más adelante.

(C-1)

Este paso es un paso para la preparación del compuesto (VII) haciendo reaccionar el compuesto (VI) que es bien conocido o se prepara fácilmente a partir de compuestos conocidos con un compuesto que tiene la fórmula R^{2b}-C(=O)-R^{3b} que es bien conocido o que puede ser preparado fácilmente a partir de compuestos conocidos, y se lleva a cabo mediante una ruta por medio de la enaminación (C-1a) o por la reacción cruzada con aldol (C-1b).

(C-1a)

La base empleada puede ser, por ejemplo, una base orgánica tal como pirrolidina, piperidina, morfolina, N-metilmorfolina, trietilamina, tripropilamina, tributilamina, diisopropiletilamina, diciclohexilamina, N-metilpiperidina, piridina, 4-pirrolidinopiridina, picolina, 4-(N,N-dimetilamino)piridina, 2,6-di-(t-butil)-4-metilpiridina, quinolina, N,N-dimetilanilina, N,N-dietilanilina, 1,5-diazabiciclo[4.3.0]non-5-eno (DBN), 1,4-diazabiciclo[2.2.2]octano (DABCO) o 1,8-diazabiciclo[5.4.0]undec-7-eno (DBU), y preferiblemente es pirrolidina, piperidina o morfolina.

El solvente empleado puede ser, por ejemplo, un hidrocarburo aromático tal como benceno, tolueno o xileno; un hidrocarburo halogenado tal como diclorometano, cloroformo, tetracloruro de carbono, dicloroetano, clorobenceno o diclorobenceno; un alcohol tal como metanol, etanol, n-propanol, isopropanol, n-butanol, isobutanol,

t-butanol, alcohol isoamílico, dietilen glicol, glicerol, octanol, ciclohexanol o 2-metoxietanol; o un éter tal como éter dietílico, éter diisopropílico, tetrahidrofurano, dioxano, dimetoxietano o éter dimetílico de di(etilen glicol); y preferiblemente es benceno, tolueno o etanol.

La temperatura de la reacción varía dependiendo del material inicial y del reactivo, y está entre 0°C y 200°C, y preferiblemente entre 50°C y 150°C.

El tiempo de la reacción varía dependiendo de la temperatura de la reacción, el material inicial, el reactivo y el tipo de solvente empleado, y generalmente es desde 30 minutos hasta 24 horas, y preferiblemente desde 1 hora hasta 10 horas.

Después de terminada la reacción, se puede obtener el compuesto deseado de esta reacción, por ejemplo, mediante concentración de la mezcla de la reacción, adición a la mezcla de un solvente orgánico inmiscible con agua tal como acetato de etilo, lavando la mezcla con agua, separación de la capa orgánica que contiene el compuesto deseado, secado de la capa orgánica sobre sulfato de magnesio anhidro o similares, y luego evaporación del solvente orgánico para dar el producto deseado.

El producto obtenido, si es necesario, es purificado adicionalmente mediante tratamientos convencionales, por ejemplo, mediante recristalización, reprecipitación, cromatografía de columna en gel de sílice o similares.

Cuando el compuesto que tiene un grupo hidroxilo que es un producto intermedio de la reacción permanece y la reacción no se completa, el producto deseado puede ser obtenido realizando además una reacción de deshidratación en la presencia de una base.

El solvente empleado puede ser, por ejemplo, un hidrocarburo halogenado tal como diclorometano, cloroformo, tetracloruro de carbono, dicloroetano, clorobenceno o diclorobenceno; o un éter tal

como éter dietílico, éter diisopropílico, tetrahidrofurano, dioxano, dimetoxietano o éter dimetílico de di(etilen glicol), y preferiblemente es un hidrocarburo halogenado, y más preferiblemente diclorometano.

La base empleada puede ser una base orgánica tal como pirrolidina, piperidina, morfolina, N-metilmorfolina, trietilamina, tripropilamina, tributilamina, diisopropiletilamina, diciclohexilamina, N-metilpiperidina, piridina, 4-pirrolidinopiridina, picolina, 4-(N,N-dimetilamino)piridina, 2,6-di-(t-butil)-4-metilpiridina, quinolina, N,N-dimetilanilina, N,N-dietilanilina, 1,5-diazabiciclo[4.3.0]non-5-eno (DBN), 1,4-diazabiciclo[2.2.2]octano (DABCO) o 1,8-diazabiciclo[5.4.0]undec-7-eno (DBU), y preferiblemente es 1,8-diazabiciclo[5.4.0]undec-7-eno (DBU).

El reactivo empleado no está restringido particularmente siempre que forme un grupo suprimible reaccionando con un grupo hidroxilo, y la conversión en el grupo suprimible se logra mediante adición de un agente de halogenación, agente de sulfonilación o agente de acilación. El agente de halogenación empleado puede ser, por ejemplo, un tetrahaluro de carbono tal como tetrabromuro de carbono o tetracloruro de carbono, y en estos casos, se usa una fosfina como reactivo. Esta fosfina puede ser, por ejemplo, una trialquilfosfina de 1 a 6 átomos de carbono tal como trimetilfosfina, trietilfosfina, tripropilfosfina, tributilfosfina, tripentilfosfina o trihexilfosfina; una triarilfosfina de 6 a 10 átomos de carbono tal como trifenilfosfina, triindenilfosfina o trinaftilfosfina; o triarilfosfina de 6 a 10 átomos de carbono la cual puede tener grupo(s) alquilo de 1 a 4 átomos de carbono como sustituyente(s), tales como tolildifenilfosfina, tritolilfosfina, trimesitilfosfina, tributilfenilfosfina o tri-6-etil-2-naftilfosfina, y preferiblemente es una trialquilfosfina de 1 a 6 átomos de carbono (particularmente trimetilfosfina, trietilfosfina, tripropilfosfina o tributilfosfina) o una triarilfosfina de 6 a 10 átomos

de carbono (particularmente trifenilfosfina, triindenilfosfina o trinaftilfosfina), y más preferiblemente una triarilfosfina de 6 a 10 átomos de carbono (particularmente trifenilfosfina). El agente de sulfonilación empleado puede ser, por ejemplo, un haluro de sulfonilo tal como cloruro de metanosulfonilo, cloruro de etanosulfonilo o cloruro de tosilo, y preferiblemente es cloruro de metanosulfonilo. El agente de acilación empleado puede ser, por ejemplo, cloruro de acetilo, anhídrido acético, anhídrido trifluoroacético o similares.

La temperatura de la reacción varía dependiendo del material inicial y del reactivo, y está entre -50°C y 100°C, y preferiblemente entre -20°C y 80°C.

El tiempo de la reacción varía dependiendo de la temperatura de la reacción, el material inicial, el reactivo y el tipo de solvente empleado, y generalmente es desde 30 minutos hasta 24 horas, y preferiblemente desde 1 hora hasta 10 horas.

Después de terminada la reacción, se puede obtener el compuesto deseado de esta reacción, por ejemplo, mediante concentración de la mezcla de la reacción, adición a la mezcla de un solvente orgánico inmiscible con agua tal como acetato de etilo, lavando la mezcla con agua, separación de la capa orgánica que contiene el compuesto deseado, secado de la capa orgánica sobre sulfato de magnesio anhidro o similares, y luego evaporación del solvente orgánico para dar el producto deseado.

El producto obtenido, si es necesario, es purificado adicionalmente mediante tratamientos convencionales, por ejemplo, mediante recristalización, reprecipitación, cromatografía de columna en gel de sílice o similares.

(C-1b)

La base empleada puede ser, por ejemplo, una base orgánica tal como pirrolidina, piperidina, morfolina, N-metilmorfolina, trietilamina, tripropilamina, tributilamina, diisopropiletilamina,

diciclohexilamina, N-metilpiperidina, piridina, 4-pirrolidinopiridina, picolina, 4-(N,N-dimetilamino)piridina, 2,6-di-(t-butil)-4-metilpiridina, quinolina, N,N-dimetilanilina, N,N-dietilanilina, 1,5-diazabiciclo[4.3.0]non-5-eno (DBN), 1,4-diazabiciclo[2.2.2]octano (DABCO) o 1,8-diazabiciclo[5.4.0]undec-7-eno (DBU); o una base organometálica tal como butillitio, diisopropilamida de litio, bis(trimetilsilil)amida de litio, bis(trimetilsilil)amida de sodio o bis(trimetilsilil)amida de potasio, y preferiblemente es diisopropilamida de litio, bis(trimetilsilil)amida de litio, bis(trimetilsilil)amida de sodio o bis(trimetilsilil)amida de potasio.

El solvente empleado puede ser, por ejemplo, un hidrocarburo aromático tal como benceno, tolueno o xileno; un hidrocarburo halogenado tal como diclorometano, cloroformo, tetracloruro de carbono, dicloroetano, clorobenceno o diclorobenceno; un alcohol tal como metanol, etanol, n-propanol, isopropanol, n-butanol, isobutanol, t-butanol, alcohol isoamílico, dietilen glicol, glicerol, octanol, ciclohexanol o 2-metoxietanol; o un éter tal como éter dietílico, éter diisopropílico, tetrahidrofurano, dioxano, dimetoxietano o éter dimetílico de di(etilen glicol), y preferiblemente es tetrahidrofurano.

La temperatura de la reacción varía dependiendo del material inicial y del reactivo, y está entre -100°C y 20°C, y preferiblemente entre -78°C y 0°C.

El tiempo de la reacción varía dependiendo de la temperatura de la reacción, el material inicial, el reactivo y el tipo de solvente empleado, y generalmente es desde 30 minutos hasta 24 horas, y preferiblemente desde 1 hora hasta 5 horas.

Después de terminada la reacción, se puede obtener el compuesto deseado de esta reacción, por ejemplo, mediante concentración de la mezcla de la reacción, mediante adición a la mezcla de un solvente orgánico inmiscible con agua tal como acetato de etilo, lavando la mezcla con agua, mediante separación de la

capa orgánica que contiene el compuesto deseado, mediante secado de la capa orgánica sobre sulfato de magnesio anhidro o similares, y luego evaporación del solvente orgánico para dar el producto deseado.

El producto obtenido, si es necesario, es purificado adicionalmente mediante tratamientos convencionales, por ejemplo, mediante recristalización, reprecipitación, cromatografía de columna en gel de sílice o similares.

Cuando el compuesto que tiene un grupo hidroxilo que es un producto intermedio de la reacción permanece, se puede llevar a cabo una reacción de deshidratación de una forma similar a la indicada en (C-1a).

(C-2)

Este paso es un paso para la reacción de reducción mediante conversión de un grupo carbonilo del compuesto (VII) obtenido en (C-1) en un grupo hidroxilo (C-2a). Además, cuando R^{2b} es un átomo de hidrógeno, R^{2a} no es un átomo de hidrógeno y R^{3b} es un grupo alcoxicarbonilo, se puede llevar a cabo una reacción para introducir un grupo R^{2a} (C-2b). Además, cuando el grupo R^{3b} contiene un grupo éster, si es necesario, se puede llevar a cabo una reacción para introducir un grupo protector apropiado para el grupo hidroxilo (C-2c), una reacción de reducción para convertir el grupo éster en un grupo hidroximetilo (C-2d), una reacción para convertir el grupo R^{3b} que contiene el grupo hidroxilo en un grupo R^{3a} (C-2e) y una reacción para eliminar el grupo protector para el grupo hidroxilo (C-2f). Los pasos desde C-2c hasta C-2f se pueden realizar antes o después de los pasos C-2a y C-2b, y es fácil para una persona con habilidades en la técnica determinar un orden apropiado de estos pasos.

(C-2a)

El solvente empleado puede ser, por ejemplo, un hidrocarburo

aromático tal como benceno, tolueno o xileno; un hidrocarburo halogenado tal como diclorometano, cloroformo, tetracloruro de carbono, dicloroetano, clorobenceno o diclorobenceno; un éter tal como éter dietílico, éter diisopropílico, tetrahidrofurano, dioxano, dimetoxietano o éter dimetílico de di(etilen glicol); un alcohol tal como metanol, etanol, n-propanol, isopropanol, n-butanol, isobutanol, t-butanol, alcohol isoamílico, dietilen glicol, glicerol, octanol, ciclohexanol o 2-metoxietanol; o una mezcla de un alcohol y un hidrocarburo halogenado, y preferiblemente es un alcohol, una mezcla de un alcohol y un hidrocarburo halogenado, o un éter, y más preferiblemente metanol, etanol, tetrahidrofurano o una mezcla de dichos alcohol y diclorometano.

El reactivo empleado no está restringido particularmente siempre que pueda ser usado para una reacción de reducción de un grupo carbonilo en un grupo hidroxilo, y puede ser, por ejemplo, un reactivo de hidruro de aluminio o compuesto de boro tal como borohidruro de sodio o diborano, y preferiblemente es borohidruro de sodio.

La temperatura de la reacción varía dependiendo del material inicial y del reactivo, y está entre -78°C y 100°C, y preferiblemente entre 0°C y 50°C.

El tiempo de la reacción varía dependiendo de la temperatura de la reacción, el material inicial, el reactivo y el tipo de solvente empleado, y generalmente es desde 10 minutos hasta 12 horas, y preferiblemente desde 30 minutos hasta 5 horas.

Después de terminada la reacción, se puede obtener el compuesto deseado de esta reacción, por ejemplo, mediante concentración de la mezcla de la reacción, adición a la mezcla de un solvente orgánico inmiscible con agua tal como acetato de etilo, lavando la mezcla con agua, separación de la capa orgánica que contiene el compuesto deseado, secado de la capa orgánica sobre

sulfato de magnesio anhidro o similares, y luego evaporación del solvente orgánico para dar el producto deseado.

El producto obtenido, si es necesario, es purificado adicionalmente mediante tratamientos convencionales, por ejemplo, mediante recristalización, reprecipitación, cromatografía de columna en gel de sílice o similares.

Cuando R^{3b} es diferente de R^{3a}, puede ser posible introducir un sustituyente en un grupo amino, si es necesario. En este caso, después de eliminar un grupo protector para el grupo amino de una forma similar a la descrita en (A-7), la introducción del sustituyente se puede llevar a cabo según se describe más adelante.

El solvente empleado puede ser, por ejemplo, un hidrocarburo aromático tal como benceno, tolueno o xileno; un hidrocarburo halogenado tal como diclorometano, cloroformo, tetracloruro de carbono, dicloroetano, clorobenceno o diclorobenceno; un éster tal como formato de etilo, acetato de etilo, acetato de propilo, acetato de butilo o carbonato de dietilo; un éter tal como éter dietílico, éter diisopropílico, tetrahidrofurano, dioxano, dimetoxietano o éter dimetílico de di(etilen glicol); una cetona tal como acetona, metil etil cetona, metil isobutil cetona, isoforona o ciclohexanona; una amida tal como formamida, N,N-dimetilformamida, N,N-dimetilacetamida, N-metil-2-pirrolidinona o triamida hexametilfosfórica; o un sulfóxido tal como sulfóxido de dimetilo o sulfolano, y preferiblemente es un hidrocarburo halogenado o una amida, y más preferiblemente N,N-dimetilformamida, N,N-dimetilacetamida o diclorometano.

El reactivo empleado no está restringido particularmente siempre que pueda usarse en la reacción de desplazamiento por un grupo amino, y puede ser, por ejemplo, un reactivo en el cual un grupo suprimible tal como un átomo de halógeno o un grupo sulfonilo está unido a un grupo funcional deseado.

La base empleada puede ser, por ejemplo, una base

inorgánica, incluyendo un carbonato de metal alcalino tal como carbonato de sodio, carbonato de potasio o carbonato de litio; un carbonato hidrogenado de metal alcalino tal como carbonato hidrogenado de sodio, carbonato hidrogenado de potasio o carbonato hidrogenado de litio; un hidruro de metal alcalino tal como hidruro de litio, hidruro de sodio o hidruro de potasio; un hidróxido de metal alcalino tal como hidróxido de sodio, hidróxido de potasio o hidróxido de litio; y un fluoruro de metal alcalino tal como fluoruro de sodio o fluoruro de potasio; un alcóxido de metal alcalino tal como metóxido de sodio, etóxido de sodio, metóxido de potasio, etóxido de potasio, t-butóxido de potasio o metóxido de litio; un mercaptano de metal alcalino tal como mercaptano de sodio o etilmercaptano de sodio; o una base orgánica tal como N-metilmorfolina, trietilamina, tripropilamina, tributilamina, diisopropiletilamina, diciclohexilamina, N-metilpiperidina, piridina, 4-pirrolidinopiridina, picolina, 4-(N,N-dimetilamino)piridina, 2,6-di-(t-butil)-4-metilpiridina, quinolina, N,N-dimetilanilina, N,N-dietilanilina, 1,5-diazabiciclo[4.3.0]non-5-eno (DBN), 1,4-diazabiciclo[2.2.2]octano (DABCO) o 1,8-diazabiciclo[5.4.0]undec-7-eno (DBU), y preferiblemente es carbonato de potasio, hidruro de sodio o DBU.

La temperatura de la reacción varía dependiendo del material inicial y del reactivo, y está entre -30°C y 150°C, y preferiblemente entre 0°C y 100°C.

El tiempo de la reacción varía dependiendo de la temperatura de la reacción, el material inicial, el reactivo y el tipo de solvente empleado, y generalmente es desde 5 minutos hasta 48 horas, y preferiblemente desde 10 minutos hasta 15 horas.

Después de terminada la reacción, se puede obtener el compuesto deseado de esta reacción, por ejemplo, mediante concentración de la mezcla de la reacción, adición a la mezcla de un solvente orgánico inmiscible con agua tal como acetato de etilo,

lavando la mezcla con agua, separación de la capa orgánica que contiene el compuesto deseado, secado de la capa orgánica sobre sulfato de magnesio anhidro o similares, y luego evaporación del solvente orgánico para dar el producto deseado.

El producto obtenido, si es necesario, es purificado adicionalmente mediante tratamientos convencionales, por ejemplo, mediante recristalización, reprecipitación, cromatografía de columna en gel de sílice o similares.

(C-2b)

Este paso puede lograrse usando un R^{2a}-Lv o un aldehído o cetona que forma un grupo R^{2a} en un solvente inerte en la presencia de una base para dar un compuesto de la fórmula general (VII).

El solvente empleado puede ser, por ejemplo, un hidrocarburo alifático tal como hexano, ciclohexano, heptano, ligroina o éter de petróleo; un hidrocarburo aromático tal como benceno, tolueno o xileno; un hidrocarburo halogenado tal como diclorometano, cloroformo, tetracloruro de carbono, dicloroetano, clorobenceno o diclorobenceno; un éter tal como éter dietílico, éter diisopropílico, tetrahidrofurano, dioxano, dimetoxietano o éter dimetílico de di(etilen glicol); o un nitrilo tal como acetonitrilo o isobutironitrilo, y preferiblemente es tetrahidrofurano.

La base empleada puede ser, por ejemplo, diisopropilamida de litio, bencil(trimetilsilil)amida de litio, dimetilamida de litio, dietilamida de litio, bis(trimetilsilil)amida de litio o diciclohexilamida de litio, y preferiblemente es diisopropilamida de litio.

El reactivo empleado puede ser, por ejemplo, un haluro de alquilo de 1 a 6 átomos de carbono tal como yoduro de metilo, yoduro de etilo o yoduro de propilo; un alquil mesilato de 1 a 6 átomos de carbono; un alquil tosilato de 1 a 6 átomos de carbono; un haluro de aralquilo de 7 a 15 átomos de carbono tal como bromuro de bencilo, bromuro de 1-naftilmetilo, bromuro de 2-naftilmetilo o

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bromuro de fenetilo; un mesilato de aralquilo de 7 a 15 átomos de carbono; un tosilato de aralquilo de 7 a 15 átomos de carbono; un alquil aldehído de 1 a 6 átomos de carbono tal como formaldehido o acetaldehído; o una alquil cetona de 1 a 6 átomos de carbono tal como acetona.

La temperatura de la reacción varía dependiendo del material inicial y del reactivo, y está entre -100°C y 150°C, y preferiblemente entre -80°C y 50°C.

El tiempo de la reacción varía dependiendo de la temperatura de la reacción, el material inicial, el reactivo y el tipo de solvente empleado, y generalmente es desde 1 hora hasta 48 horas, y preferiblemente desde 1 hora hasta 10 horas.

Después de terminada la reacción, se puede obtener el compuesto deseado de esta reacción, por ejemplo, mediante concentración de la mezcla de la reacción, adición a la mezcla de un solvente orgánico inmiscible con agua tal como acetato de etilo, lavando la mezcla con agua, separación de la capa orgánica que contiene el compuesto deseado, secando la capa orgánica sobre sulfato de magnesio anhidro o similar, y luego evaporación del solvente orgánico para dar el producto deseado.

El producto obtenido, si es necesario, es purificado adicionalmente mediante tratamientos convencionales, por ejemplo, mediante recristalización, reprecipitación, cromatografía de columna en gel de sílice o similares.

(C-2c)

Este paso es un paso para la protección de un grupo hidroxilo, y se puede lograr fácilmente de acuerdo con procedimientos que son bien conocidos por una persona hábil en la técnica (por ejemplo, el procedimiento descrito en Protective Groups in Organic Synthesis, Tercera edición, T. W. Green, et al., John Wiley & Sons, Inc. (1999)), y preferiblemente es protección sililo (particularmente grupo t-

butildimetilsililo).

(C-2d)

Este paso se logra reduciendo el compuesto (VII) en un solvente inerte en la presencia de un agente reductor.

El solvente empleado puede ser, por ejemplo, un hidrocarburo alifático tal como hexano, ciclohexano, heptano, ligroina o éter de petróleo; un hidrocarburo aromático tal como benceno, tolueno o xileno; un hidrocarburo halogenado tal como diclorometano, cloroformo, tetracloruro de carbono, dicloroetano, clorobenceno o diclorobenceno; un éter tal como éter dietílico, éter diisopropílico, tetrahidrofurano, dioxano, dimetoxietano o éter dimetílico de di(etilen glicol); o un alcohol tal como metanol, etanol, propanol o isobutanol. Cuando el agente reductor es hidruro de aluminio y litio, hidruro de aluminio y diisobutilo o diborano, el solvente empleado puede ser un hidrocarburo alifático (particularmente hexano o ciclohexano), un hidrocarburo aromático (particularmente benceno o tolueno), un hidrocarburo halogenado (particularmente diclorometano) o un éter (particularmente éter dietílico o tetrahidrofurano). Cuando el agente reductor es borohidruro de sodio, el solvente empleado puede ser un alcohol (particularmente metanol o etanol).

El agente reductor empleado puede ser, por ejemplo, un compuesto de hidruro de aluminio tal como hidruro de aluminio y litio o hidruro de aluminio y diisobutilo; borohidruro de sodio; o diborano, y preferiblemente es hidruro de aluminio y diisobutilo.

La temperatura de la reacción varía dependiendo del material inicial y del reactivo, y está entre -100°C y 100°C, y preferiblemente entre -80°C y 50°C.

El tiempo de la reacción varía dependiendo de la temperatura de la reacción, el material inicial, el reactivo de la reacción y el tipo de solvente empleado, y generalmente es desde 10 minutos hasta 24 horas, y preferiblemente desde 30 minutos hasta 5 horas.

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Después de terminada la reacción, se puede obtener el compuesto deseado de esta reacción, por ejemplo, mediante concentración de la mezcla de la reacción, mediante adición a la mezcla de un solvente orgánico inmiscible con agua tal como acetato de etilo, lavando la mezcla con agua, mediante separación de la capa orgánica que contiene el compuesto deseado, secando la capa orgánica sobre sulfato de magnesio anhidro o similar, y luego evaporación del solvente orgánico para dar el producto deseado.

El producto obtenido, si es necesario, es purificado adicionalmente mediante tratamientos convencionales, por ejemplo, mediante recristalización, reprecipitación, cromatografía de columna en gel de sílice o similares.

(C-2e)

Este paso se lleva a cabo mediante la reacción Mitsunobu en un solvente inerte usando una amina o similares (C-2e1) o mediante una reacción de sustitución usando una amina o similares después de convertir un grupo hidroxilo en un grupo suprimible (C-2e2). El paso (C-2e1) se puede llevar a cabo de una forma similar a la indicada en (B-2a) excepto porque se emplea una amina o similares en lugar de Pro^{1}-SM. El paso (C-2e2) se puede llevar a cabo de una forma similar a la indicada en (B-2c) excepto porque se emplea una amina o similares en lugar de Pro^{1}-SM.

(C-2f)

Este paso es un paso para la desprotección de un grupo protector para un grupo hidroxilo, y se puede lograr fácilmente de acuerdo con procedimientos que son bien conocidos por una persona hábil en la técnica (por ejemplo, el procedimiento descrito en Protective Groups in Organic Synthesis, Tercera edición, T. W. Green, et al., John Wiley & Sons, Inc. (1999)).

(C-3)

Este paso se lleva a cabo de una forma similar a la indicada

en A-7, y se lleva a cabo mucho más preferiblemente usando ácido trifluoroacético o ácido acético.

(C-4)

Este paso se lleva a cabo de una forma similar a la indicada en B-2.

(C-5)

Este paso se lleva a cabo de una forma similar a la indicada en C-3.

El compuesto (I) de la presente invención, sales de él o profármacos de él aceptables farmacológicamente ejerce actividad inhibidora en la inhibición de agregación de plaquetas. Además, el compuesto (I) de la presente invención, sales de él o profármacos de él aceptables farmacológicamente muestra excelentes propiedades farmacocinéticas tales como absorción, distribución, permanencia en plasma, y similares, y bajas toxicidades en órganos tales como el riñón, el hígado y similares. Así, el compuesto (I) de la presente invención, sales de él o profármacos de él aceptables farmacológicamente son útiles, por ejemplo como fármacos, y particularmente útiles como agentes terapéuticos o profilácticos para diversas enfermedades trombóticas.

Cuando un compuesto de la presente invención se utiliza como un agente profiláctico o terapéutico para enfermedades como el descrito anteriormente, dicho compuesto que tiene la fórmula general (I), o sales de él o profármacos de él aceptables farmacológicamente, puede ser administrado solo o como una mezcla con excipientes aceptables farmacéuticamente, diluyentes y similares, en diversas formas de dosis tales como tabletas, cápsulas, gránulos, polvos, jarabes o similares para administración oral; e inyecciones, supositorios, parches, aplicación externa o similares para administración parenteral.

Cada una de las formulaciones anteriores se puede preparar

mediante métodos bien conocidos usando aditivos para la formulación tal como excipientes (por ejemplo, excipientes orgánicos, incluyendo derivados de azúcar tal como lactosa, sacarosa, glucosa, manitol o sorbitol; derivados de almidón tal como almidón de maíz, almidón de papa, α-almidón o dextrina; derivados de celulosa tal como celulosa cristalina; acacia; dextran; pululan; y excipientes inorgánicos incluyendo derivados de silicato tales como anhídrido de ácido silicílico ligero, silicato de aluminio sintético, silicato de calcio, o metasilicato de aluminio y magnesio; derivados de fosfato tales como fosfato de calcio hidrogenado; derivados de carbonato tales como carbonato de calcio; o derivados de sulfato tales como sulfato de calcio), lubricantes (por ejemplo, ácido esteárico; derivados de estearato metálico tal como estearato de calcio o estearato de magnesio; talco; sílice coloidal; ceras tal como cera de abejas o espermaceti; ácido bórico; ácido adípico; derivados de sulfato tal como sulfato de sodio; glicol; ácido fumárico; benzoato de sodio; DL-leucina; derivados laurilo de sulfato tal como lauril sulfato de sodio o lauril sulfato de magnesio; derivados de ácido silicílico tal como anhídrido silicílico o hidrato de ácido silicílico; o derivados de almidón descrito anteriormente), enlazantes (por ejemplo, hidroxipropilcelulosa, hidroxipropilmetilcelulosa, polivinilpirrolidona, macrogol o excipientes como los descritos anteriormente), desintegrantes (por ejemplo, derivados de celulosa tales como hidroxipropilcelulosa inferior sustituida, carboximetilcelulosa, carboximetilcelulosa de calcio o carboximetilcelulosa de sodio reticulada internamente; o almidón modificado químicamente o derivados de celulosa tal como carboximetilalmidón, carboximetilalmidón de sodio, o polivinilpirrolidona reticulada), emulsificantes (por ejemplo, arcilla coloidal tal como bentonita o veegum; hidróxidos metálicos tales como hidróxido de magnesio o hidróxido de aluminio; agentes

tensoactivos aniónicos tales como lauril sulfato de sodio o estearato de calcio; agentes tensoactivos catiónicos tales como cloruro de benzalconio; y agentes tensoactivos no iónicos tales como éteres alquílicos de polioxietileno, ésteres de ácido graso de polioxietilen sorbitán o ésteres de ácido graso de sacarosa), estabilizantes (por ejemplo, derivados de éster de ácido para-hidroxibenzoico tales como metilparaben o propilparaben; derivados de alcohol tales como clorobutanol, alcohol bencílico o alcohol feniletílico; cloruro de benzalconio; derivados de fenol tales como fenol o cresol; timerosal; ácido deshidroacético; o ácido sórbico), correctivos (por ejemplo, endulzantes, agentes acidificantes, saborizantes o similares que se utilizan convencionalmente) y diluyentes.

La dosis específica de un compuesto de la presente invención variará de acuerdo con la gravedad de los síntomas del paciente, edad y similares. Para administración oral a un adulto humano la cantidad de ingrediente activo en una unidad de dosis puede estar en el rango desde 0.016 mg/kg (preferiblemente 0.5 mg/kg) hasta 33.3 mg/kg (preferiblemente 25 mg/kg). Una unidad de dosis para administración intravenosa puede estar en el rango desde 0.008 mg/kg (preferiblemente 0.08 mg/kg) hasta 8.3 mg/kg (preferiblemente 4.2 mg/kg) de un compuesto de la presente invención. La unidad de dosis se puede administrar a un adulto humano desde 1 hasta 6 veces por día dependiendo de la gravedad de los síntomas del paciente.

Ejemplos

En lo sucesivo, la presente invención será descrita en mayor detalle por medio del Ejemplos, ejemplos de prueba y ejemplos de formulación.

Cuando se usa $CDCl_3$ como solvente para la medición de compuestos clorhidrato en los Ejemplos, se muestran los datos de RMN para las bases libres correspondientes. Las bases libres se

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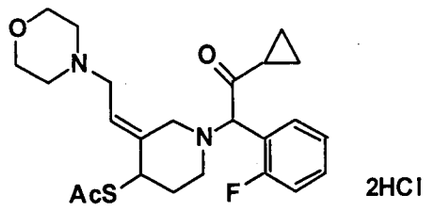
pueden obtener tratando una pequeña cantidad de un compuesto clorhidrato con una solución acuosa de carbonato de sodio hidrogenado y realizando la extracción con acetato de etilo o diclorometano.

(Ejemplo 1) diclorhidrato de (E)-4-(Acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-[2-(morfolin-4-il)etiliden]piperidina (Clorhidrato del compuesto del Compuesto No. 5-28)



(a) (E)-4-(t-Butildimetilsililoxi)-3-[(etoxicarbonil)metiliden]-1-(trifenilmetil)piperidina

A una solución de (E)-3-[(etoxicarbonil)metiliden]-1-(trifenilmetil)piperidin-4-ol (14.97 g) en N,N-dimetilformamida (130 ml) se le añadió cloruro de t-butildimetilsililo (6.86 g), imidazol (3.34 g) y 4-dimetilaminopiridina (0.43 g) bajo enfriamiento con hielo, y la mezcla resultante se agitó a temperatura ambiente durante la noche. La mezcla de la reacción se diluyó con acetato de etilo y se lavó con una solución acuosa saturada de cloruro de sodio, y se secó la capa orgánica sobre sulfato de sodio anhidro. Se eliminó el solvente in vacuo, y se purificó el residuo mediante cromatografía en una columna de gel de sílice (acetato de etilo / hexano = 1 / 19) para obtener el compuesto del título (16.38 g, rendimiento 86%) como un sólido amorfo incoloro.

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 0.01 (3H, s), 0.02 (3H, s), 0.90 (9H, s), 1.12 (3H, t, J=7.0), 1.59-1.74 (1H, m), 1.83-2.01 (3H, m), 3.00-3.12 (1H, m), 3.90 (1H, t, J=9.0), 3.96-4.15 (2H, m), 4.73 (1H, m), 6.06 (1H, s), 7.11-7.18 (3H, m), 7.20-7.28 (6H, m), 7.36-7.54 (6H, m).

(b) (E)-4-(t-Butildimetilsililoxi)-3-(2-hidroxietiliden)-1-

(trifenilmetil)piperidina

A una solución de (E)-4-(t-butildimetilsililoxi)-3-[(etoxicarbonil)metiliden]-1-(trifenilmetil)piperidina (15.14 g) obtenida en (a) anterior, en diclorometano (110 ml) se le añadió una solución de hidruro de diisobutilaluminio 1.01N en tolueno (66.40 ml) a -70°C, y la mezcla resultante se agitó a la misma temperatura durante 3 horas. La mezcla de la reacción se cargó con una solución acuosa de cloruro de amonio y luego se extrajo con acetato de etilo. Se lavó el extracto con una solución acuosa saturada de cloruro de sodio, y se secó la capa orgánica sobre sulfato de sodio anhidro. Se eliminó el solvente in vacuo, y se purificó el residuo mediante cromatografía en una columna de gel de sílice (acetato de etilo / hexano = 1 / 3) para obtener el compuesto del título (13.22 g, rendimiento 95%) como un sólido amorfo incoloro.

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 0.01 (6H, s), 0.88 (9H, s), 1.62-2.00 (4H, m), 2.88-3.05 (1H, m), 3.51-3.71 (1H, m), 3.86 (1H, m), 4.07-4.24 (2H, m), 5.79 (1H, t, J=7.0), 7.11-7.33 (9H, m), 7.36-7.58 (6H, m).

(c) (E)-4-(t-Butildimetilsililoxi)-3-[2-(tosiloxi)etiliden]-1-(trifenilmetil)piperidina

A una solución de (E)-4-(t-butildimetilsililoxi)-3-(2-hidroxietiliden)-1-(trifenilmetil)piperidina (1.11 g) obtenida en (b) anterior, y anhídrido p-toluenosulfónico (0.90 g) en diclorometano (25 ml), se le añadió trietilamina (0.37 ml) bajo enfriamiento con hielo, y la mezcla resultante se agitó a temperatura ambiente durante 2.5 horas. La mezcla de la reacción se cargó con una solución acuosa saturada de cloruro de sodio y luego se extrajo con acetato de etilo. Se lavó el extracto con una solución acuosa saturada de cloruro de sodio, y se secó la capa orgánica sobre sulfato de sodio anhidro. Se eliminó el solvente in vacuo para obtener el compuesto del título (1.64 g, rendimiento cuantitativo) como un aceite amarillo claro.

RMN con ^1H (400 MHz, $CDCl_3$) δ ppm : -0.04 (3H, s), -0.01 (3H, s), 0.86 (9H, s), 1.60-1.92 (4H, m), 2.47 (3H, s), 2.96 (1H, bs), 3.47 (1H, m), 3.79 (1H, m), 4.61 (2H, m), 5.65 (1H, t, J=7.5), 7.13-7.48 (17H, m), 7.73 (2H, d, J=9.0).

(d) (E)-4-(t-Butildimetilsililoxi)-3-[2-(morfolin-4-il)etiliden]-1-(trifenilmetil)piperidina

A una solución de (E)-4-(t-butildimetilsililoxi)-3-[2-(tosiloxi)etiliden]-1-(trifenilmetil)piperidina (1.64 g) obtenida en (c) anterior, y morfolina (0.29 ml) en un solvente mezclado de N,N-dimetilformamida (25 ml) y diclorometano (5 ml) se le añadió carbonato de potasio (0.34 g) bajo enfriamiento con hielo, y la mezcla resultante se agitó a temperatura ambiente durante la noche. La mezcla de la reacción se cargó con una solución acuosa saturada de cloruro de sodio y luego se extrajo con acetato de etilo. Se lavó el extracto con una solución acuosa saturada de cloruro de sodio, y se secó la capa orgánica sobre sulfato de sodio anhidro. Se eliminó el solvente in vacuo, y se purificó el residuo mediante cromatografía en una columna de gel de sílice (acetato de etilo / hexano = 2 / 3) para obtener el compuesto del título (1.01 g, rendimiento: 80%) como un aceite incoloro.

RMN con ^1H (400 MHz, $CDCl_3$) δ ppm : -0.03 (3H, s), -0.02 (3H, s), 0.84 (9H, s), 1.74-2.06 (4H, m), 2.42 (4H, bs), 2.77-2.93 (1H, m), 2.99 (1H, dd, J=13.5, 6.5), 3.07 (1H, dd, J=13.5, 6.5), 3.38-3.56 (1H, m), 3.71 (4H, t, J=4.5), 3.87 (1H, m), 5.62 (1H, t, J=6.5), 7.11-7.30 (9H, m), 7.38-7.55 (6H, m).

(e) (E)-4-Hidroxi-3-[2-(morfolin-4-il)etiliden]-1-(trifenilmetil)piperidina

A una solución de (E)-4-(t-butildimetilsililoxi)-3-[2-(morfolin-4-il)etiliden]-1-(trifenilmetil)piperidina (1.00 g) obtenida en (d) anterior en tetrahidrofurano (20 ml) se le añadió fluoruro de tetrabutilamonio(0.99 g) bajo enfriamiento con hielo, y la mezcla

resultante se agitó a temperatura ambiente durante 14 horas. La mezcla de la reacción se cargó con agua y luego se extrajo con acetato de etilo. Se lavó el extracto con una solución acuosa saturada de cloruro de sodio, y se secó la capa orgánica sobre sulfato de sodio anhidro. Se eliminó el solvente in vacuo, y se purificó el residuo mediante cromatografía en una columna de gel de sílice (metanol / diclorometano = 9 / 91) para obtener el compuesto del título (0.80 g, rendimiento cuantitativo) como un aceite incoloro.

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 1.74-1.86 (1H, m), 1.96-2.14 (2H, m), 2.45 (5H, bs), 2.59-2.69 (1H, m), 3.01 (2H, m), 3.10-3.34 (1H, m), 3.72 (4H, t, J=4.5), 3.98 (1H, m), 5.61 (1H, t, J=6.5), 7.11-7.32 (9H, m), 7.39-7.57 (6H, m).

(f) diclorhidrato de (E)-4-Hidroxi-3-[2-(morfolin-4-il)etiliden]piperidina

A una solución de (E)-4-hidroxi-3-[2-(morfolin-4-il)etiliden]-1-(trifenilmetil)piperidina (1.08 g) obtenido en (e) anterior en dioxano (9 ml) se le añadió una solución de cloruro de hidrógeno 4N en dioxano (3 ml) bajo enfriamiento con hielo, y la mezcla resultante se agitó a temperatura ambiente durante 15 minutos. La mezcla de la reacción se evaporó in vacuo, y se particionó el residuo con agua y acetato de etilo. Se eliminó la capa acuosa in vacuo para obtener el compuesto del título (0.69 g, rendimiento cuantitativo) como un sólido amorfo amarillo claro.

RMN con ^{1}H (400 MHz, DMSO-d_6) δ ppm : 1.66-1.77 (1H, m), 1.95-2.07 (1H, m), 3.10 (4H, m), 3.21-3.65 (3H, m), 3.73-4.02 (6H, m), 4.06 (1H, d, J=13.5), 4.19 (1H, m), 5.90 (1H, t, J=8.0).

(g) (E)-1-[2-Ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-hidroxi-3-[2-(morfolin-4-il)etiliden]piperidina

A una solución de diclorhidrato de (E)-4-hidroxi-3-[2-(morfolin-4-il)etiliden]piperidina (0.65 g) obtenido en (f) anterior y 2-bromo-2-(2-fluorofenil)-1-ciclopropiletanona (0.73 g) en N,N-dimetilformamida

(12 ml) se le añadió trietilamina (1.16 ml) bajo enfriamiento con hielo, y la mezcla resultante se agitó a temperatura ambiente durante la noche. La mezcla de la reacción se diluyó con acetato de etilo y se lavó con agua y una solución acuosa saturada de cloruro de sodio, y se secó la capa orgánica sobre sulfato de sodio anhidro. Se eliminó el solvente in vacuo, y se purificó el residuo mediante cromatografía en una columna de gel de sílice (metanol / diclorometano = 3 / 17) para obtener el compuesto del título (0.65 g, rendimiento 74%) como un sólido amorfo amarillo claro.

RMN con ^{1}H (500 MHz, $CDCl_3$) δ ppm : 0.78-0.90 (2H, m), 0.96-1.09 (2H, m), 1.66-1.78 (1H, m), 1.95-2.04 (1H, m), 2.15-2.25 (1H, m), 2.42 (4H, bs), 2.45-2.55 (1H, m), 2.78 y 3.00 (total 1H, cada d, J=12.5), 2.79-2.88 (1H, m), 2.95 (2H, d, J=6.5), 3.31 y 3.45 (total 1H, cada d, J=12.5), 3.70 (4H, t, J=4.5), 4.09 y 4.13 (total 1H, cada m), 4.69 y 4.71 (total 1H, cada s), 5.59 y 5.61 (total 1H, cada t, J=6.5), 7.11 (1H, m), 7.17 (1H, m), 7.29-7.36 (1H, m), 7.38-7.45 (1H, m).

(h) diclorhidrato de (E)-4-(Acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-[2-(morfolin-4-il)etiliden]piperidina

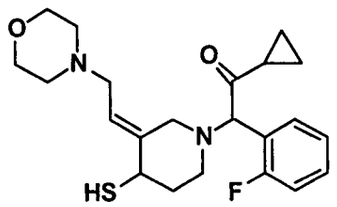
A una solución de (E)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-hidroxi-3-[2-(morfolin-4-il)etiliden]piperidina (890 mg) obtenido en (g) anterior en tolueno (15 ml) se le añadió ácido tioacético (0.33 ml) y dineopentil acetal de N,N-dimetilformamida (1.92 ml) bajo enfriamiento con hielo, y la mezcla resultante se agitó a temperatura ambiente durante 3 horas. La mezcla de la reacción se diluyó con acetato de etilo y se lavó con una solución acuosa saturada de cloruro de sodio, y se secó la capa orgánica sobre sulfato de sodio anhidro. Se eliminó el solvente in vacuo, y se purificó el residuo mediante cromatografía en una columna de gel de sílice (metanol / diclorometano = 1 / 19) para producir la forma libre (393 mg, rendimiento 38%) del compuesto del título como un sólido amorfo incoloro. A una solución de una parte de este compuesto (88

mg) en dioxano (4 ml) se le añadió una solución de cloruro de hidrógeno en dioxano 4N (0.25 ml) a temperatura ambiente, y se eliminó el solvente in vacuo para obtener el compuesto del título (111 mg, rendimiento cuantitativo) como un sólido amorfo incoloro.

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 0.76-0.90 (2H, m), 0.95-1.10 (2H, m), 1.74-1.85 (1H, m), 2.06-2.24 (2H, m), 2.28 y 2.29 (total 3H, cada s), 2.38 (4H, bs), 2.47-2.79 (2H, m), 2.80 y 3.06 (total 1H, cada d, J=12.5), 2.88 y 2.94 (total 2H, cada d, J=6.5), 3.29 y 3.37 (total 1H, cada d, J=12.5), 3.69 (4H, m), 4.30 y 4.33 (total 1H, cada t, J=4.5), 4.68 y 4.70 (total 1H, cada s), 5.64 (1H, t, J=6.5), 7.07-7.20 (2H, m), 7.29-7.43 (2H, m);

IR (KBr, cm^{-1}) : 1700, 1494.

(Ejemplo 2) diclorhidrato de (E)-1-[2-Ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-[2-(morfolin-4-il)etiliden]-4-sulfanilpiperidina (Clorhidrato del compuesto del Compuesto No. 5-27)



2HCl

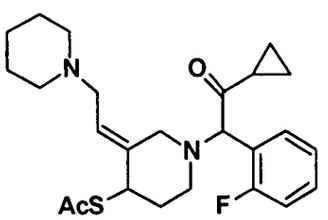
A una solución de (E)-4-(acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-[2-(morfolin-4-il)etiliden]piperidina (180 mg) obtenida en el ejemplo 1 (h) en metanol (4 ml) se le añadió carbonato de potasio (48 mg) bajo enfriamiento con hielo, y la mezcla resultante se agitó a temperatura ambiente durante 15 minutos. La mezcla de la reacción se diluyó con acetato de etilo y se lavó con una solución acuosa saturada de cloruro de sodio, y se secó la capa orgánica sobre sulfato de sodio anhidro. Se eliminó el solvente in vacuo, y se purificó el residuo usando una HPLC preparativa (YMC-Pack ODS-A; YMC, eluyente: acetonitrilo / 0.024N ácido clorhídrico = 15 / 85) para obtener el compuesto del título (83 mg, rendimiento 50%) como un sólido amorfo incoloro.

RMN con ^1H (400 MHz, $CDCl_3$) δ ppm : 0.77-0.91 (2H, m), 0.95-1.10 (2H, m), 1.67-1.77 (1H, m), 2.12-2.26 (2H, m), 2.39 (4H, bs), 2.46-2.95 (3H, m), 2.88 y 3.20 (total 2H, cada d, J=7.0), 3.13 y 3.37 (total 1H, cada d, J=12.5), 3.69 (4H, m), 3.80 (1H, m), 4.71 y 4.73 (total 1H, cada s), 5.59 y 5.62 (total 1H, cada t, J=7.0), 7.07-7.21 (2H, m), 7.28-7.37 (1H, m), 7.39-7.45 (1H, m);

IR (KBr, cm^{-1}) : 2556, 1712, 1494.

(Ejemplo 3)

(E)-4-(Acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-[2-(piperidin-1-il)etiliden]piperidina (Compuesto del compuesto No. 5-2)



(a) (E)-4-(t-Butildimetilsililoxi)-3-[2-(piperidin-1-il)etiliden]-1-(trifenilmetil)piperidina

Se sintetizó el compuesto del título en un rendimiento de 67% como un aceite incoloro usando piperidina en lugar de morfolina realizando una reacción similar a la mencionada en el Ejemplo 1 (d).

RMN con ^1H (400 MHz, $CDCl_3$) δ ppm : -0.01 (6H, s), 0.81 (9H, s), 1.37-1.61 (8H, m), 1.74-1.93 (2H, m), 2.31-2.39 (4H, m), 2.75-3.07 (4H, m), 3.86 (1H, m), 5.63 (1H, t, J=6.5), 7.11-7.18 (3H, m), 7.21-7.28 (6H, m), 7.41-7.51 (6H, m).

(b) (E)-4-Hidroxi-3-[2-(piperidin-1-il)etiliden]-1-(trifenilmetil) piperidina

Se sintetizó el compuesto del título en un rendimiento cuantitativo como un aceite incoloro usando (E)-4-(t-butildimetilsililoxi)-3-[2-(piperidin-1-il)etiliden]-1-(trifenilmetil) piperidina obtenida en (a) anterior realizando una reacción similar a la mencionada en el Ejemplo 1 (e).

RMN con ^1H (500 MHz, $CDCl_3$) δ ppm : 1.48-2.11 (14H, m), 2.69-3.46 (4H, m), 4.01 (1H, m), 5.89 (1H, t, J=5.0), 7.15-7.21 (3H, m), 7.24-7.31 (6H, m), 7.40-7.51 (6H, m).

(c) bis(trifluoroacetato hidrogenado) de (E)-4-Hidroxi-3-[2-(piperidin-1-il)etiliden]piperidina

A una solución de (E)-4-hidroxi-3-[2-(piperidin-1-il)etiliden]-1-(trifenilmetil)piperidina (412 mg) obtenido en (b) anterior en diclorometano (10 ml) se le añadió ácido trifluoroacético (0.21 ml) bajo enfriamiento con hielo, y la mezcla resultante se agitó a temperatura ambiente durante 3 horas. A la mezcla de la reacción se le añadió ácido trifluoroacético (0.21 ml), y la mezcla resultante se agitó a temperatura ambiente durante adicionalmente 1 hora. A la mezcla de la reacción se le añadió metanol (5 ml), y la mezcla resultante se evaporó in vacuo. Se particionó el residuo con agua y acetato de etilo, y se eliminó la capa acuosa in vacuo para obtener el compuesto del título (403 mg, rendimiento cuantitativo) como un sólido amorfo amarillo claro.

RMN con ^1H (400 MHz, $CDCl_3$) δ ppm : 1.35-1.49 (2H, m), 1.82-2.21 (6H, m), 2.73-2.82 (2H, m), 3.45-3.88 (7H, m), 4.12 (1H, d, J=13.0), 4.31-4.36 (1H, m), 6.01 (1H, t, J=8.0).

(d) (E)-1-[2-Ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-hidroxi-3-[2-(piperidin-1-il)etiliden]piperidina

Se sintetizó el compuesto del título en un rendimiento de 60% como un aceite amarillo claro usando bis(trifluoroacetato hidrogenado) de (E)-4-hidroxi-3-[2-(piperidin-1-il)etiliden]piperidina obtenido en (c) anterior realizando una reacción similar a la mencionada en el Ejemplo 1 (g).

RMN con ^1H (400 MHz, $CDCl_3$) δ ppm : 0.79-1.10 (4H, m), 1.38-1.84 (8H, m), 1.93-2.03 (1H, m), 2.21-2.55 (6H, m), 2.78-3.01 (3H, m), 3.32 y 3.41 (total 1H, cada d, J=12.5), 4.08-4.14 (1H, m), 4.67 y 4.69 (total 1H, cada s), 5.63 y 5.64 (total 1H, cada t, J=7.0), 7.07-

7.19 (2H, m), 7.28-7.46 (2H, m).

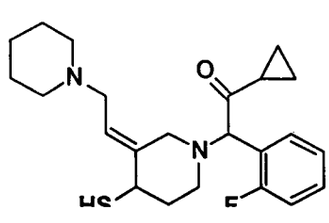
(e) (E)-4-(Acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-[2-(piperidin-1-il)etiliden]piperidina

A una solución de trifenilfosfina (290 mg) en tetrahidrofurano (4.5 ml) bajo una corriente de gas nitrógeno se le añadió una solución al 40% de diisopropil azodicarboxilato en tolueno (0.59 ml) a -10°C, y la mezcla resultante se agitó a la misma temperatura durante 1 hora. A continuación, a una mezcla de la reacción se le añadió por goteo una solución de (E)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-hidroxi-3-[2-(piperidin-1-il)etiliden]piperidina (211 mg) en tetrahidrofurano (1.5 ml) obtenido en (d) anterior y ácido tioacético (0.14 ml), y adicionalmente la mezcla resultante se agitó a temperatura ambiente durante 22 horas. La mezcla de la reacción se evaporó in vacuo, y se purificó el residuo mediante cromatografía en una columna de gel de sílice (metanol / diclorometano = 1 / 49) para obtener el compuesto del título (138 mg, rendimiento 57%) como un aceite amarillo claro.

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 0.78-0.90 (2H, m), 0.96-1.08 (2H, m), 1.41-1.50 (2H, m), 1.59-1.71 (4H, m), 1.75-1.84 (1H, m), 2.07-2.23 (2H, m), 2.28 y 2.29 (total 3H, cada s), 2.40-3.10 (9H, m), 3.16-3.39 (1H, m), 4.29 y 4.33 (total 1H, cada t, J=4.5), 4.68 y 4.72 (total 1H, cada s), 5.69 (1H, t, J=6.5), 7.08-7.21 (2H, m), 7.29-7.41 (2H, m);

IR (película líquida, cm^{-1}) : 1696, 1488.

(Ejemplo 4) bis(trifluoroacetato hidrogenado) de (E)-1-[2-Ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-[2-(piperidin-1-il)etiliden]-4-sulfanilpiperidina (Trifluoroacetato del compuesto del Compuesto No. 5-1)



2TFA

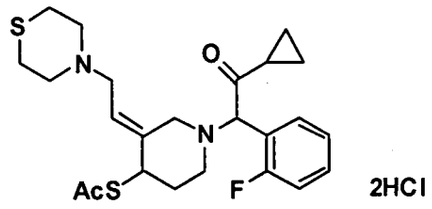
511

Se sintetizó el compuesto del título en un rendimiento de 11% como un aceite incoloro usando (E)-4-(acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-[2-(piperidin-1-il)etiliden]piperidina obtenida en el ejemplo 3 (e) realizando una reacción similar a la mencionada en el Ejemplo 2.

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 0.76-0.93 (2H, m), 0.99-1.10 (2H, m), 1.31-1.47 (2H, m), 1.63-2.07 (7H, m), 2.22-2.32 (1H, m), 2.56-3.87 (10H, m), 4.93 y 4.98 (total 1H, cada s), 5.74 (1H, t, J=6.5), 7.15-7.31 (3H, m), 7.36-7.46 (1H, m);

MS (FAB) m/z : 403 $(M+H)^+$.

(Ejemplo 5) diclorhidrato de (E)-4-(Acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-[2-(tiomorfolin-4-il)etiliden] piperidina (Clorhidrato del compuesto del Compuesto No. 5-30)



(a) (E)-4-(t-Butildimetilsililoxi)-3-[2-(tiomorfolin-4-il)etiliden]-1-(trifenilmetil)piperidina

Se sintetizó el compuesto del título en un rendimiento de 62% como un aceite incoloro usando tiomorfolina en lugar de morfolina realizando una reacción similar a la mencionada en el Ejemplo 1 (d).

RMN con ^{1}H (500 MHz, $CDCl_3$) δ ppm : -0.03 (3H, s), -0.02 (3H, s), 0.84 (9H, s), 1.76-1.95 (4H, m), 2.61-2.72 (7H, m), 2.77-2.91 (1H, m), 2.98-3.10 (2H, m), 3.31-3.66 (2H, m), 3.87 (1H, m), 5.56-5.63 (1H, m), 7.10-7.19 (3H, m), 7.21-7.35 (6H ,m), 7.38-7.53 (6H, m).

(b) (E)-4-Hidroxi-3-[2-(tiomorfolin-4-il)etiliden]-1-(trifenilmetil) piperidina

Se sintetizó el compuesto del título en un rendimiento de 99% como un sólido amorfo amarillo claro usando (E)-4-(t-butildimetilsililoxi)-3-[2-(tiomorfolin-4-il)etiliden]-1-(trifenilmetil) piperidina obtenido en (a) anterior realizando una reacción similar a la mencionada en el Ejemplo 1 (e).

RMN con ^1H (400 MHz, $CDCl_3$) δ ppm : 1.61-1.87 (2H, m), 1.98-2.14 (2H, m), 2.60-2.80 (8H, m), 2.98-3.06 (2H, m), 3.35-3.46 (2H, m), 3.93-4.02 (1H, m), 5.58 (1H, t, J=6.0), 7.12-7.20 (3H, m), 7.22-7.32 (6H, m), 7.38-7.56 (6H, m).

(c) bis(acetato hidrogenado) de (E)-4-Hidroxi-3-[2-(tiomorfolin-4-il)etiliden]piperidina

A una solución de (E)-4-hidroxi-3-[2-(tiomorfolin-4-il)etiliden]-1-(trifenilmetil)piperidina (4.91 g) obtenido en (b) anterior en diclorometano (100 ml) se le añadió ácido acético (44 ml) a temperatura ambiente, y la mezcla resultante se sometió a reflujo durante 1 hora. La mezcla de la reacción se evaporó in vacuo, y se purificó el residuo mediante cromatografía en una columna de gel de sílice en una columna de gel de sílice (metanol / diclorometano = 1 / 4) para obtener el compuesto del título (3.56 g, rendimiento 98%) como un cristal café claro.

RMN con ^1H (400 MHz, $CDCl_3$) δ ppm : 1.61-1.70 (1H, m), 1.97-2.02 (1H, m), 2.62-2.77 (8H, m), 2.82-2.90 (1H, m), 3.02-3.08 (2H, m), 3.17-3.23 (2H, m), 3.74-3.78 (1H, m), 4.15-4.20 (1H, m), 5.58 (1H, t, J=6.0).

(d) (E)-1-[2-Ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-hidroxi-3-[2-(tiomorfolin-4-il)etiliden]piperidina

Se sintetizó el compuesto del título en un rendimiento de 65% como un sólido amorfo café claro usando bis(acetato hidrogenado) de (E)-4-hidroxi-3-[2-(tiomorfolin-4-il)etiliden]piperidina obtenido en (c) anterior realizando una reacción similar a la mencionada en el Ejemplo 1 (g).

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RMN con ^{1}H (500 MHz, $CDCl_3$) δ ppm : 0.76-1.12 (4H, m), 1.61-1.82 (1H, m), 1.94-2.04 (1H, m), 2.14-2.24 (1H, m), 2.44-2.54 (1H, m), 2.59-2.73 (8H, m), 2.76 y 2.98 (total 1H, cada d, J=12.5), 2.77-2.89 (1H, m), 2.96 (2H, d, J=7.0), 3.30 y 3.45 (total 1H, cada d, J=12.5), 4.05-4.16 (1H, m), 4.69 y 4.70 (total 1H, cada s), 5.54-5.62 (1H, m), 7.06-7.22 (2H, m), 7.28-7.46 (2H, m).

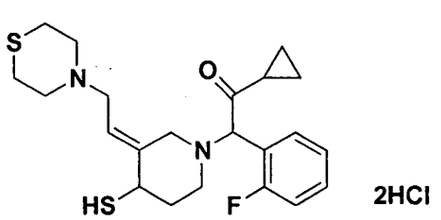
(e) diclorhidrato de (E)-4-(Acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-[2-(tiomorfolin-4-il)etiliden]piperidina

Se sintetizó el compuesto del título en un rendimiento de 26% como un cristal en polvo amarillo claro usando (E)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-hidroxi-3-[2-(tiomorfolin-4-il)etiliden] piperidina obtenido en (d) anterior realizando una reacción similar a la mencionada en el Ejemplo 1 (h).

RMN con ^{1}H (500 MHz, $CDCl_3$) δ ppm : 0.74-1.12 (4H, m), 1.50-1.62 (1H, m), 1.74-1.85 (1H, m), 2.06-2.27 (2H, m), 2.29 y 2.30 (total 3H, cada s), 2.44-2.72 (9H, m), 2.77 y 3.04 (total 1H, cada d, J=12.5), 2.84-2.98 (2H, m), 3.27 y 3.35 (total 1H, cada d, J=12.5), 4.26-4.36 (1H, m), 4.67 y 4.70 (total 1H, cada s), 5.57-5.64 (1H, m), 7.07-7.22 (2H, m), 7.28-2.45 (2H, m);

MS (FAB) m/z : 463 $(M+H)^+$.

(Ejemplo 6) diclorhidrato de (E)-1-[2-Ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-sulfanil-3-[2-(tiomorfolin-4-il)etiliden]piperidina (Clorhidrato del compuesto del Compuesto No. 5-29)



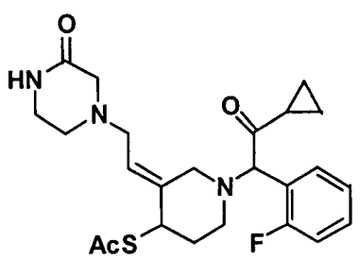
Se sintetizó el compuesto del título en un rendimiento de 94% como un cristal en polvo amarillo claro usando (E)-4-(acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-[2-(tiomorfolin-4-il)etiliden]piperidina obtenida en el ejemplo 5 (e) realizando una

reacción similar a la mencionada en el Ejemplo 2.

RMN con ^1H (500 MHz, $CDCl_3$) δ ppm : 0.77-1.12 (4H, m), 1.68-1.77 (1H, m), 2.11-2.27 (2H, m), 2.55-2.71 (9H, m), 2.72-2.85 (1H, m), 2.86-2.97 (2H, m), 3.13-3.24 (1H, m), 3.11 y 3.36 (total 1H, cada d, J=12.5), 3.70-3.82 (1H, m), 4.72 y 4.70 (total 1H, cada s), 5.51-5.63 (1H, m), 7.07-7.21 (2H, m), 7.29-7.45 (2H, m);

MS (FAB) m/z : 418 $(M+H)^+$.

(Ejemplo 7) (E)-4-(Acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-[2-(3-oxopiperazin-1-il)etiliden]piperidina (Compuesto del compuesto No. 5-88)



(a) (E)-4-(t-Butildimetilsililoxi)-3-[2-(3-oxopiperazin-1-il)etiliden]-1-(trifenilmetil)piperidina

Se sintetizó el compuesto del título en un rendimiento de 66% como un aceite café claro usando 2-oxopiperazina en lugar de morfolina realizando una reacción similar a la mencionada en el Ejemplo 1 (d).

RMN con ^1H (500 MHz, $CDCl_3$) δ ppm : 0.02 (6H, s), 0.85 (9H, s), 1.72-1.95 (4H, m), 2.60-2.66 (2H, m), 2.80-3.19 (5H, m), 3.25-3.47 (3H, m), 3.82-3.90 (1H, m), 5.57-5.64 (1H, m), 7.13-7.21 (3H, m), 7.22-7.32 (6H, m), 7.39-7.57 (6H, m).

(b) (E)-4-Hidroxi-3-[2-(3-oxopiperazin-1-il)etiliden]-1-(trifenilmetil) piperidina

Se sintetizó el compuesto del título en un rendimiento de 96% como un aceite amarillo claro usando (E)-4-(t-butildimetilsililoxi)-3-[2-(3-oxopiperazin-1-il)etiliden]-1-(trifenilmetil)piperidina obtenido en (a) anterior realizando una reacción similar a la mencionada en el Ejemplo 1 (e)

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RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 1.75-2.12 (4H, m), 2.62-2.69 (2H, m), 3.02-3.16 (2H, m), 3.32-3.42 (6H, m), 3.92-4.01 (1H, m), 5.57-5.62 (1H, m), 7.12-7.20 (3H, m), 7.22-7.31 (6H, m), 7.38-7.56 (6H, m).

(c) bis(acetato hidrogenado) de (E)-4-Hidroxi-3-[2-(3-oxopiperazin-1-il)etiliden]piperidina

Se sintetizó el compuesto del título en un rendimiento de 85% como un cristal café claro usando (E)-4-hidroxi-3-[2-(3-oxopiperazin-1-il)etiliden]-1-(trifenilmetil)piperidina obtenida en (b) anterior realizando una reacción similar a la mencionada en el Ejemplo 5 (c).

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 1.59-1.73 (2H, m), 2.57-2.61 (1H, m), 2.64-2.70 (2H, m), 3.08-3.25 (5H, m), 3.29-3.39 (3H, m), 3.73-3.78 (1H, m), 4.16-4.22 (1H, m), 5.56-5.63 (1H, m).

(d) (E)-1-[2-Ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-hidroxi-3-[2-(3-oxopiperazin-1-il)etiliden]piperidina

Se sintetizó el compuesto del título en un rendimiento de 63% como un sólido amorfo café claro usando (E)-4-hidroxi-3-[2-(3-oxopiperazin-1-il)etiliden]piperidina bis(acetato hidrogenado) obtenido en (c) anterior, realizando una reacción similar a la mencionada en el Ejemplo 1 (g).

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 0.76-1.10 (4H, m), 1.62-1.80 (2H, m), 1.94-2.05 (1H, m), 2.12-2.23 (1H, m), 2.43-2.53 (1H, m), 2.57-2.68 (2H, m), 2.73 y 2.98 (total 1H, cada d, J=12.5), 2.78-2.92 (1H, m), 2.94-3.08 (2H, m), 3.28-3.42 (3H, m), 3.45-3.52 (1H, m), 4.05-4.19 (1H, m), 4.67-4.74 (1H, m), 5.53-5.65 (1H, m), 7.06-7.23 (2H, m), 7.28-7.48 (2H, m).

(e) (E)-4-(Acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-[2-(3-oxopiperazin-1-il)etiliden]piperidina

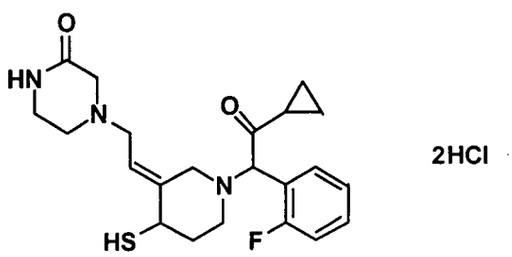
Se sintetizó el compuesto del título en un rendimiento de 22% como un sólido amorfo amarillo claro usando (E)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-hidroxi-3-[2-(3-oxopiperazin-1-il)etiliden]

piperidina obtenida en (d) anterior realizando una reacción similar a la mencionada en el Ejemplo 1 (h).

RMN con ^{1}H (500 MHz, $CDCl_3$) δ ppm : 0.69-1.10 (4H, m), 1.73-1.86 (1H, m), 2.06-2.26 (2H, m), 2.29 y 2.30 (total 3H, cada s), 2.44-2.72 (4H, m), 2.74-2.85 (1H, m), 2.95 y 3.01 (total 2H, cada d, J=7.0), 3.03-3.10 (2H, m), 3.28 y 3.38 (total 1H, cada d, J=12.5), 3.29-3.38 (2H, m), 4.26-4.36 (1H, m), 4.69 y 4.71 (total 1H, cada s), 5.62 (1H, t, J=7.0), 5.78 (1H, bs), 7.07-7.24 (2H, m), 7.28-7.48 (2H, m);

MS (FAB) m/z : 460 $(M+H)^+$.

(Ejemplo 8) diclorhidrato de (E)-1-[2-Ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-[2-(3-oxopiperazin-1-il)etiliden]-4-sulfanilpiperidina (Clorhidrato del compuesto del Compuesto No. 5-87)



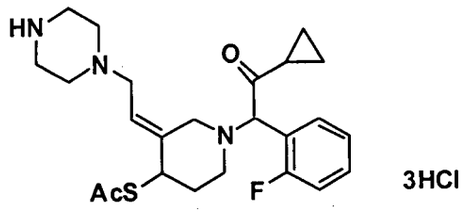
Se sintetizó el compuesto del título en un rendimiento de 91% como un cristal en polvo amarillo claro usando (E)-4-(acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-[2-(3-oxopiperazin-1-il)etiliden]piperidina obtenida en el ejemplo 7 (e) realizando una reacción similar a la mencionada en el Ejemplo 2.

RMN con ^{1}H (500 MHz, $CDCl_3$) δ ppm : 0.75-1.10 (4H, m), 1.69-1.78 (1H, m), 2.11-2.28 (2H, m), 2.53-2.70 (3H, m), 2.73-2.86 (1H, m), 2.92-3.22 (4H, m), 3.30-3.45 (3H, m), 3.66-3.82 (1H, m), 4.72 y 4.73 (total 1H, cada s), 5.52-5.64 (1H, m), 7.07-7.22 (2H, m), 7.29-7.44 (2H, m);

MS (FAB) m/z : 418 $(M+H)^+$.

(Ejemplo 9) triclorhidrato de (E)-4-(Acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-[2-(piperazin-1-il)etiliden]piperidina (Clorhidrato del compuesto del Compuesto

No. 5-32)



(a) (E)-3-{2-[4-(t-Butoxicarbonil)piperazin-1-il]etiliden}-4-(t-butildimetilsililoxi)-1-(trifenilmetil)piperidina

Se sintetizó el compuesto del título en un rendimiento de 61% como un sólido amorfo incoloro usando 1-(t-butoxicarbonil)piperazina en lugar de morfolina realizando una reacción similar a la mencionada en el Ejemplo 1 (d).

RMN con ^{1}H (500 MHz, $CDCl_3$) δ ppm : -0.03 (3H, s), -0.02 (3H, s), 0.84 (9H, s), 1.46 (9H, s), 1.73-1.96 (3H, m), 2.30-2.41 (4H, m), 2.74-3.12 (4H, m), 3.36-3.46 (4H, m), 3.47-3.52 (1H, m), 3.81-3.92 (1H, m), 5.66 (1H, t, J=6.0), 7.10-7.19 (3H, m), 7.20-7.32 (6H, m), 7.34-7.57 (6H, m).

(b) (E)-3-{2-[4-(t-Butoxicarbonil)piperazin-1-il]etiliden}-4-hidroxi-1-(trifenilmetil)piperidina

Se sintetizó el compuesto del título en un rendimiento de 99% como un sólido amorfo incoloro usando (E)-3-{2-[4-(t-butoxicarbonil)piperazin-1-il]etiliden}-4-(t-butildimetilsililoxi)-1-(trifenilmetil)piperidina obtenida en (a) anterior realizando una reacción similar a la mencionada en el Ejemplo 1 (e).

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 1.47 (9H, s), 1.57-1.84 (4H, m), 2.32-2.45 (4H, m), 2.92-3.08 (2H, m), 3.36-3.52 (6H, m), 3.93-4.03 (1H, m), 5.61 (1H, t, J=6.0), 7.11-7.20 (3H, m), 7.21-7.33 (6H, m), 7.40-7.55 (6H, m).

(c) bis(acetato hidrogenado) de (E)-3-{2-[4-(t-Butoxicarbonil)piperazin-1-il]etiliden}-4-hidroxipiperidina

Se sintetizó el compuesto del título en un rendimiento de 99% como un cristal café claro usando (E)-3-{2-[4-(t-

butoxicarbonil)piperazin-1-il]etiliden}-4-hidroxi-1-(trifenilmetil)piperidina obtenido en (b) anterior realizando una reacción similar a la mencionada en el Ejemplo 5 (c).

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 1.45 (9H, s), 1.56-1.73 (1H, m), 1.86-2.04 (1H, m), 2.32-2.46 (4H, m), 2.80-2.91 (1H, m), 2.94-3.07 (2H, m), 3.17-3.29 (2H, m), 3.35-3.46 (4H, m), 3.51 y 3.74 (total 1H, cada d, J=13.5), 4.03-4.11 (1H, m), 5.57-5.66 (1H, m).

(d) (E)-3-{2-[4-(t-Butoxicarbonil)piperazin-1-il]etiliden}-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-hidroxipiperidina

Se sintetizó el compuesto del título en un rendimiento de 64% como un sólido amorfo café claro usando bis(acetato hidrogenado) de (E)-3-{2-[4-(t-butoxicarbonil)piperazin-1-il]etiliden}-4-hidroxipiperidina obtenido en (c) anterior realizando una reacción similar a la mencionada en el Ejemplo 1 (g).

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 0.76-1.11 (4H, m), 1.46 (9H, s), 1.64-1.81 (2H, m), 1.93-2.04 (1H, m), 2.13-2.25 (1H, m), 2.28-2.40 (4H, m), 2.44-2.55 (1H, m), 2.76 y 2.99 (total 1H, cada d, J=13.0), 2.78-2.90 (1H, m), 2.90-2.98 (1H, m), 3.31 y 3.45 (total 1H, cada d, J=13.0), 3.37-3.45 (4H, m), 4.04-4.18 (1H, m), 4.69 y 4.70 (total 1H, cada s), 5.55-5.64 (1H, m), 7.06-7.21 (2H, m), 7.27-7.36 (1H, m), 7.37-7.45 (1H, m).

(e) (E)-4-(Acetilsulfanil)-3-{2-[4-(t-butoxicarbonil)piperazin-1-il]etiliden}-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]piperidina

Se sintetizó el compuesto del título en un rendimiento de 36% como un aceite café usando (E)-3-{2-[4-(t-butoxicarbonil)piperazin-1-il]etiliden}-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-hidroxipiperidina obtenido en (d) anterior realizando una reacción similar a la mencionada en el Ejemplo 1 (h).

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 0.76-1.10 (4H, m), 1.46 (9H, s), 1.75-1.84 (1H, m), 2.07-2.28 (2H, m), 2.22-2.37 (4H, m), 2.28 y 2.29 (total 3H, cada s), 2.47-2.62 (1H, m), 2.65-2.80 (1H, m), 2.79

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y 3.05 (total 1H, cada d, J=13.0), 2.84-2.90 (1H, m), 2.91-2.96 (1H, m), 3.29 y 3.36 (total 1H, cada d, J=13.0), 3.36-3.45 (4H, m), 4.27-4.36 (1H, m), 4.67 y 4.69 (total 1H, cada s), 5.63 (1H, t, J=6.5), 7.08-7.20 (2H, m), 7.28-7.36 (1H, m), 7.40 (1H, m).

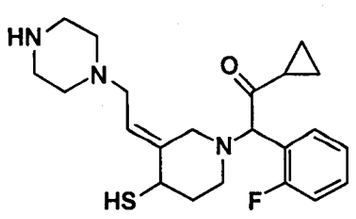
(f) triclorhidrato de (E)-4-(Acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-[2-(piperazin-1-il)etiliden]piperidina

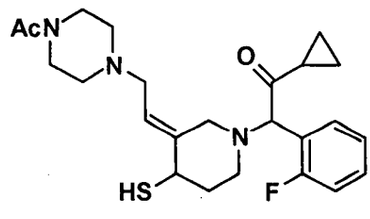
A una solución de (E)-4-(acetilsulfanil)-3-{2-[4-(t-butoxicarbonil)piperazin-1-il]etiliden}-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]piperidina (1.06 g) obtenida en (e) anterior en dioxano (21 ml) se le añadió una solución de cloruro de hidrógeno en dioxano 4N (24 ml) bajo enfriamiento con hielo, y la mezcla resultante se agitó a temperatura ambiente durante 3 horas. La mezcla de la reacción se evaporó in vacuo para obtener el compuesto del título (1.25 g, rendimiento cuantitativo) como un cristal amarillo claro.

RMN con ^{1}H (500 MHz, $CDCl_3$) δ ppm : 0.76-1.10 (4H, m), 1.62-1.85 (2H, m), 2.09-2.25 (2H, m), 2.28 (3H, s), 2.31-2.45 (4H, m), 2.47-2.62 (1H, m), 2.64-2.81 (1H, m), 2.80 y 3.05 (total 1H, cada d, J=12.5), 2.84-2.97 (4H, m), 3.29 y 3.35 (total 1H, cada d, J=12.5), 3.40-3.67 (1H, m), 4.26-4.36 (1H, m), 4.67 y 4.69 (total 1H, cada s), 5.64 (1H, t, J=7.0), 7.07-7.21 (2H, m), 7.28-7.45 (2H, m);

MS (FAB) m/z : 446 $(M+H)^+$.

(Ejemplo 10) (E)-1-[2-Ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-[2-(piperazin-1-il)etiliden]-4-sulfanilpiperidina (Compuesto del compuesto No. 5-31) y (E)-3-[2-(4-acetilpiperazin-1-il)etiliden]-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-sulfanilpiperidina (Compuesto del compuesto No. 5-33)





Ambos compuestos del título fueron sintetizados usando (E)-4-(acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-[2-(piperazin-1-il)etiliden]piperidina obtenida en el ejemplo 9 (f) realizando una reacción similar a la mencionada en el Ejemplo 2.

(E)-1-[2-Ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-[2-(piperazin-1-il)etiliden]-4-sulfanilpiperidina con un alto grado de polaridad: un aceite amarillo claro, rendimiento 12%.

RMN con ^{1}H (500 MHz, $CDCl_3$) δ ppm : 0.77-1.09 (4H, m), 1.67-1.76 (2H, m), 2.12-2.26 (2H, m), 2.29-2.43 (4H, m), 2.55-2.67 (1H, m), 2.70-2.82 (1H, m), 2.83-2.89 (4H, m), 2.90-2.95 (1H, m), 3.14 y 3.35 (total 1H, cada d, J=12.5), 3.43-3.68 (1H, m), 3.72-3.83 (1H, m), 4.70 y 4.71 (total 1H, cada s), 5.56-5.66 (1H, m), 7.06-7.21 (2H, m), 7.27-7.46 (2H, m);

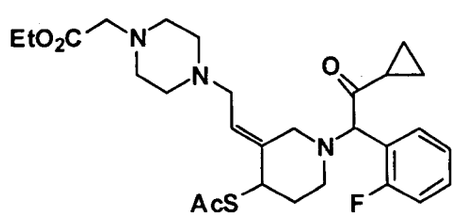
MS (FAB) m/z : 404 $(M+H)^+$.

(E)-3-[2-(4-Acetilpiperazin-1-il)etiliden]-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-sulfanilpiperidina con un bajo grado de polaridad: un aceite incoloro, rendimiento 46%.

RMN con ^{1}H (500 MHz, $CDCl_3$) δ ppm : 0.75-1.09 (4H, m), 1.69-1.77 (1H, m), 2.08 (3H, s), 2.12-2.26 (2H, m), 2.27-2.43 (4H, m), 2.54-2.69 (1H, m), 2.73-2.85 (1H, m), 2.87-2.97 (2H, m), 3.08 y 3.37 (total 1H, cada d, J=12.5), 3.13-3.24 (1H, m), 3.41-3.67 (4H, m), 3.69-3.82 (1H, m), 4.71 y 4.73 (total 1H, cada s), 5.53-5.64 (1H, m), 7.08-7.20 (2H, m), 7.28-7.44 (2H, m);

MS (FAB) m/z : 446 $(M+H)^+$.

(Ejemplo 11) (E)-4-(Acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[4-(etoxicarbonilmetil)piperazin-1-il]etiliden}piperidina (Compuesto del compuesto No. 5-46)



S21

(a) triclorhidrato de (E)-1-[2-Ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-hidroxi-3-[2-(piperazin-1-il)etiliden]piperidina

Se sintetizó el compuesto del título en un rendimiento de 99% como un cristal en polvo amarillo claro usando (E)-3-{2-[4-(t-butoxicarbonil)piperazin-1-il]etiliden}-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-hidroxipiperidina obtenida en el ejemplo 9 (d) realizando una reacción similar a la mencionada en el Ejemplo 9 (f).

RMN con ^{1}H (400 MHz, DMSO-d_6) δ ppm : 0.89-1.15 (4H, m), 1.74-1.96 (2H, m), 2.00-2.15 (1H, m), 2.82-4.25 (15H, m), 5.94-6.19 (2H, m), 7.40-7.54 (2H, m), 7.64-7.84 (2H, m).

(b) (E)-1-[2-Ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[4-(etoxicarbonilmetil)piperazin-1-il]etiliden}-4-hidroxipiperidina

A una suspensión de triclorhidrato de (E)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-hidroxi-3-[2-(piperazin-1-il)etiliden]piperidina (1.14 g) obtenido en (a) anterior en acetonitrilo (35 ml) se le añadió bromoacetato de etilo (0.31 ml) y trietilamina (1.92 ml) bajo enfriamiento con hielo, y la mezcla resultante se agitó a temperatura ambiente durante 1 hora. Después de que la mezcla de la reacción se evaporó in vacuo, se le vertió agua y se extrajo la mezcla con un solvente de diclorometano y isopropanol combinados. Se lavó la capa orgánica con una solución acuosa saturada de cloruro de sodio y se secó sobre sulfato de sodio anhidro. Se eliminó el solvente in vacuo, y se purificó el residuo mediante cromatografía en una columna de gel de sílice (metanol / diclorometano = 1 / 9) para obtener el compuesto del título (0.71 g, rendimiento 66%) como un aceite amarillo claro.

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 0.77-0.90 (2H, m), 0.95-1.08 (2H, m), 1.28 (3H, t, J=7.0), 1.65-1.80 (2H, m), 1.94-2.03 (1H, m), 2.16-2.25 (1H, m), 2.41-2.70 (8H, m), 2.75-2.88 (2H, m), 2.96-3.02 (2H, m), 3.20 (2H, s), 3.30 y 3.44 (total 1H, cada d, J=12.5), 4.06-4.15 (1H, m), 4.19 (2H, q, J=7.0), 4.68 y 4.70 (total 1H, cada s),

5.58-5.66 (1H, m), 7.07-7.21 (2H, m), 7.28-7.45 (2H, m).

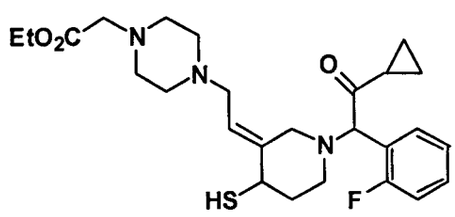
(c) (E)-4-(Acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[4-(etoxicarbonilmetil)piperazin-1-il]etiliden}piperidina

Se sintetizó el compuesto del título en un rendimiento de 23% como un aceite café claro usando (E)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[4-(etoxicarbonilmetil)piperazin-1-il]etiliden}-4-hidroxipiperidina obtenido en (b) anterior realizando una reacción similar a la mencionada en el Ejemplo 1 (h).

RMN con ^{1}H (500 MHz, $CDCl_3$) δ ppm : 0.77-1.09 (4H, m), 1.27 (3H, t, J=7.0), 1.75-1.83 (1H, m), 2.06-2.24 (2H, m), 2.28 (3H, s), 2.37-2.64 (8H, m), 2.65-2.81 (2H, m), 2.79 y 3.03 (total 1H, cada d, J=12.5), 2.85-2.90 (1H, m), 2.92-2.98 (1H, m), 3.19 (2H, s), 3.28 y 3.34 (total 1H, cada d, J=12.5), 4.19 (2H, q, J=7.0), 4.26-4.35 (1H, m), 4.66 y 4.68 (total 1H, cada s), 5.61-5.67 (1H, m), 7.06-7.20 (2H, m), 7.29-7.43 (2H, m);

MS (FAB) m/z : 532 $(M+H)^+$.

(Ejemplo 12) (E)-1-[2-Ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[4-(etoxicarbonilmetil)piperazin-1-il]etiliden}-4-sulfanilpiperidina (Compuesto del compuesto No. 5-45)



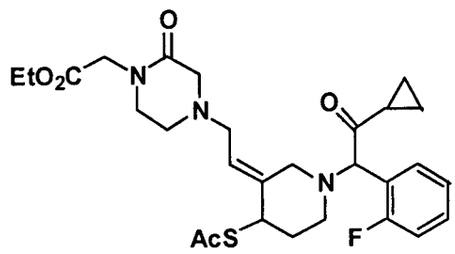
A una solución de (E)-4-(acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[4-(etoxicarbonilmetil)piperazin-1-il]etiliden}piperidina (111 mg) obtenida en el ejemplo 11 (c) en etanol (3 ml) se le añadió carbonato de potasio (289 mg) bajo enfriamiento con hielo, y la mezcla resultante se agitó a temperatura ambiente durante 2 horas. Después de que la mezcla de la reacción se vació en agua y se extrajo con diclorometano, se secó la capa orgánica

sobre sulfato de sodio anhidro. Se eliminó el solvente in vacuo para obtener el compuesto del título (77 mg, rendimiento 75%) como un aceite amarillo claro.

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 0.75-1.09 (4H, m), 1.27 (3H, t, J=7.0), 1.66-1.76 (1H, m), 2.09-2.26 (2H, m), 2.35-2.67 (8H, m), 2.69-2.84 (1H, m), 2.86-2.91 (1H, m), 2.91-2.98 (1H, m), 3.11 y 3.35 (total 1H, cada d, J=12.5), 3.18 (2H, s), 3.48 (2H, s), 3.68-3.81 (1H, m), 4.17 (2H, q, J=7.0), 4.68 y 4.69 (total 1H, cada s), 5.52-5.64 (1H, m), 7.02-7.19 (2H, m), 7.23-7.43 (2H, m);

MS (FAB) m/z : 490 $(M+H)^+$.

(Ejemplo 13) (E)-4-(Acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[4-(etoxicarbonilmetil)-3-oxopiperazin-1-il]etiliden}piperidina (Compuesto del compuesto No. 5-102)



(a) (E)-4-(t-Butildimetilsililoxi)-3-{2-[4-(etoxicarbonilmetil)-3-oxopiperazin-1-il]etiliden}-1-(trifenilmetil)piperidina

Se sintetizó el compuesto del título en un rendimiento de 13% como un sólido amorfo amarillo claro usando 1-(etoxicarbonilmetil)-2-oxo-piperazina clorhidrato en lugar de morfolina realizando una reacción similar a la mencionada en el Ejemplo 1 (d).

RMN con ^{1}H (500 MHz, $CDCl_3$) δ ppm : -0.01 (3H, s), -0.02 (3H, s), 0.85 (9H, s), 1.28 (3H, t, J=7.0), 1.69-2.08 (2H, m), 2.67-2.74 (2H, m), 3.00-3.20 (2H, m), 3.17 (2H, s), 3.34-3.42 (2H, m), 3.61-3.67 (2H, m), 3.73-3.81 (2H, m), 3.82-3.91 (1H, m), 4.11 (2H, s), 4.21 (2H, q, J=7.0), 5.56-5.65 (1H, m), 7.11-7.20 (3H, m), 7.21-7.32 (6H, m), 7.36-7.56 (6H, m).

(b) (E)-3-{2-[4-(Etoxicarbonilmetil)-3-oxopiperazin-1-il]etiliden}-4-hidroxi-1-(trifenilmetil)piperidina

Se sintetizó el compuesto del título en un rendimiento de 80% como un sólido amorfo amarillo claro usando (E)-4-(t-butildimetilsililoxi)-3-{2-[4-(etoxicarbonilmetil)-3-oxopiperazin-1-il]etiliden}-1-(trifenilmetil)piperidina obtenido en (a) anterior realizando una reacción similar a la mencionada en el Ejemplo 1 (e).

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 1.28 (3H, t, J=7.0), 1.76-1.86 (1H, m), 2.02-2.12 (1H, m), 2.70-2.78 (2H, m), 3.02-3.14 (2H, m), 3.20 (2H, s), 3.37-3.44 (2H, m), 3.60-3.68 (2H, m), 3.73-3.81 (2H, m), 3.93-4.02 (1H, m), 4.12 (2H, s), 4.21 (2H, q, J=7.0), 5.60 (1H, t, J=7.0), 7.11-7.20 (3H, m), 7.21-7.31 (6H, m), 7.38-7.53 (6H, m).

(c) (E)-3-{2-[4-(Etoxicarbonilmetil)-3-oxopiperazin-1-il]etiliden}-4-hidroxipiperidina bis(acetato hidrogenado)

Se sintetizó el compuesto del título en un rendimiento de 99% como un cristal café claro usando (E)-3-{2-[4-(etoxicarbonilmetil)-3-oxopiperazin-1-il]etiliden}-4-hidroxi-1-(trifenilmetil)piperidina obtenido en (b) anterior realizando una reacción similar a la mencionada en el Ejemplo 5 (c).

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 1.28 (3H, t, J=7.0), 1.56-1.69 (1H, m), 1.94-2.06 (2H, m), 2.70-2.88 (4H, m), 3.20 (2H, s), 3.37-3.49 (2H, m), 3.70-3.79 (2H, m), 4.10 (2H, s), 4.14-4.20 (2H, m), 4.20 (2H, q, J=7.0), 5.60 (1H, t, J=7.0).

(d) (E)-1-[2-Ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[4-(etoxicarbonilmetil)-3-oxopiperazin-1-il]etiliden}-4-hidroxipiperidina

Se sintetizó el compuesto del título en un rendimiento de 68% como un sólido amorfo café claro usando bis(acetato hidrogenado) de (E)-3-{2-[4-(etoxicarbonilmetil)-3-oxopiperazin-1-il]etiliden}-4-hidroxipiperidina obtenido en (c) anterior realizando una reacción similar a la mencionada en el Ejemplo 1 (g).

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 0.76-1.09 (4H, m), 1.28

525

(3H, t, J=7.0), 1.60-1.77 (2H, m), 1.94-2.04 (1H, m), 2.13-2.23 (1H, m), 2.43-2.53 (1H, m), 2.65-2.77 (2H, m), 2.79-2.90 (1H, m), 2.93-3.07 (2H, m), 3.16 (2H, s), 3.33 y 3.47 (total 1H, cada d, J=12.5), 3.35-3.42 (2H, m), 4.04-4.14 (1H, m), 4.11 (2H, s), 4.21 (2H, q, J=7.0), 4.70 y 4.71 (total 1H, cada s), 5.54-5.63 (1H, m), 7.05-7.21 (2H, m), 7.28-7.36 (1H, m), 7.37-7.45 (1H, m).

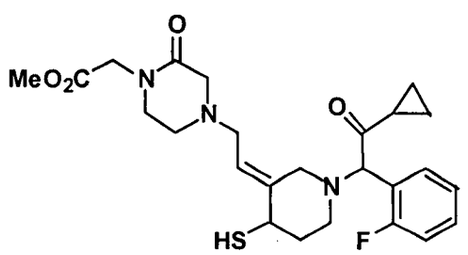
(e) (E)-4-(Acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[4-(etoxicarbonilmetil)-3-oxopiperazin-1-il]etiliden}piperidina

Se sintetizó el compuesto del título en un rendimiento de 34% como un aceite amarillo usando (E)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[4-(etoxicarbonilmetil)-3-oxopiperazin-1-il]etiliden}-4-hidroxipiperidina obtenida en (d) anterior realizando una reacción similar a la mencionada en el Ejemplo 1 (h).

RMN con ^{1}H (500 MHz, $CDCl_3$) δ ppm : 0.76-1.09 (4H, m), 1.28 (3H, t, J=7.0), 1.75-1.84 (1H, m), 2.09-2.25 (2H, m), 2.29 y 2.30 (total 3H, cada s), 2.48-2.59 (1H, m), 2.60-2.74 (2H, m), 2.75-2.83 (1H, m), 2.92-2.97 (1H, m), 2.99-3.03 (1H, m), 3.07 y 3.28 (total 1H, cada d, J=12.5), 3.09-3.17 (2H, m), 3.34-3.41 (2H, m), 3.46-3.52 (1H, m), 4.11 (2H, s), 4.21 (2H, q, J=7.0), 4.26-4.34 (1H, m), 4.69 y 4.70 (total 1H, cada s), 5.61 (1H, t, J=7.0), 7.07-7.21 (2H, m), 7.29-7.44 (2H, m);

MS (FAB) m/z : 546 $(M+H)^+$.

(Ejemplo 14) (E)-1-[2-Ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[4-(metoxicarbonilmetil)-3-oxopiperazin-1-il]etiliden}-4-sulfanilpiperidina (Compuesto del compuesto No. 5-99)



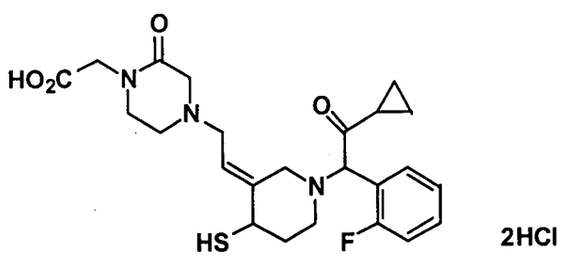
Se sintetizó el compuesto del título en un rendimiento de 93%

como un aceite amarillo usando (E)-4-(acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[4-(etoxicarbonilmetil)-3-oxopiperazin-1-il]etiliden}piperidina obtenida en el ejemplo 13 (e) realizando una reacción similar a la mencionada en el Ejemplo 2.

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 0.76-1.09 (4H, m), 1.69-1.77 (1H, m), 2.12-2.26 (2H, m), 2.53-2.73 (3H, m), 2.74-2.85 (1H, m), 2.93-3.04 (2H, m), 3.07 y 3.38 (total 1H, cada d, J=12.5), 3.12-3.22 (3H, m), 3.35-3.44 (2H, m), 3.68-3.81 (1H, m), 3.75 (3H, s), 4.13 (2H, s), 4.72 y 4.73 (total 1H, cada s), 5.57 y 5.61 (total 1H, cada t, J=7.0), 7.07-7.21 (2H, m), 7.29-7.44 (2H, m);

MS (FAB) m/z : 490 $(M+H)^+$.

(Ejemplo 15) diclorhidrato de (E)-3-{2-[4-(Carboximetil)-3-oxopiperazin-1-il]etiliden}-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-sulfanilpiperidina (Clorhidrato del compuesto del Compuesto No. 5-97)



A una solución de (E)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[4-(metoxicarbonilmetil)-3-oxopiperazin-1-il]etiliden}-4-sulfanilpiperidina (280 mg) obtenida en el ejemplo 14 en agua (1 ml) se le añadió 3N ácido clorhídrico (5 ml) a temperatura ambiente, y la mezcla resultante se agitó a 50°C durante 2.5 horas. La mezcla de la reacción se evaporó in vacuo, y se purificó el residuo usando una HPLC preparativa (YMC-Pack ODS-A; YMC, eluyente: acetonitrilo / 0.024N ácido clorhídrico = 15 / 85) para obtener el compuesto del título (203 mg, rendimiento 65%) como un cristal incoloro.

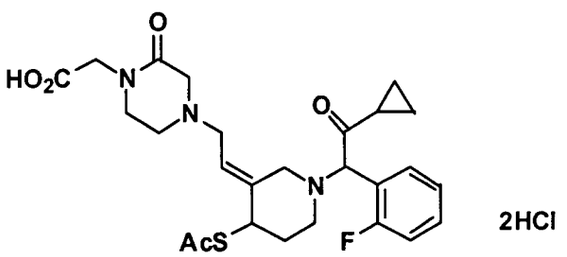
RMN con ^{1}H (400 MHz, piridina-d_5) δ ppm : 0.78-0.88 (2H, m), 0.94-1.18 (2H, m), 1.74-1.86 (1H, m), 2.14-2.28 (1H, m), 2.40-2.60 (1H, m), 2.60-2.80 (3H, m), 2.86-3.02 (1H, m), 3.02-3.15 (2H, m),

527

3.30-3.46 (3H, m), 3.50-3.66 (3H, m), 3.88 (1H, bs), 4.50 (2H, s), 4.94 (1H, s), 5.80 (1H, t, J=7.0), 7.18-7.36 (3H, m), 7.70-7.78 (1H, m);

MS (FAB) m/z : 476 $(M+H)^+$.

(Ejemplo 16) diclorhidrato de (E)-4-(Acetilsulfanil)-3-{2-[4-(carboximetil)-3-oxopiperazin-1-il]etiliden}-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]piperidina (Clorhidrato del compuesto del Compuesto No. 5-98)



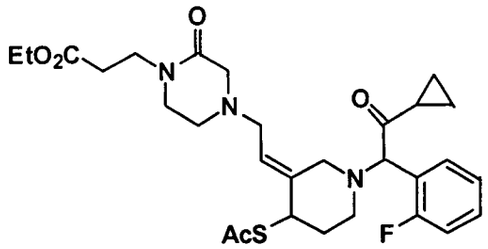
A una suspensión de diclorhidrato de (E)-3-{2-[4-(carboximetil)-3-oxopiperazin-1-il]etiliden}-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-sulfanilpiperidina (100 mg) obtenida en el ejemplo 15 en diclorometano (5 ml) se le añadió anhídrido acético (259 μl) y piridina (514 μl) bajo enfriamiento con hielo, y la mezcla resultante se agitó a temperatura ambiente durante 4 horas. La mezcla de la reacción se evaporó in vacuo, y se purificó el residuo mediante cromatografía en una columna de gel de sílice (metanol / diclorometano = 3 / 17) para producir la forma libre (85 mg, rendimiento 90%) del compuesto del título como un sólido café. A una solución de este compuesto en diclorometano (3 ml) se le añadió una solución de cloruro de hidrógeno en dioxano 4N (82 μl) a temperatura ambiente, y la mezcla de la reacción se evaporó in vacuo. Se cristalizó el residuo a partir de éter para obtener el compuesto del título (44 mg, rendimiento 45%) como un sólido amorfo amarillo claro.

RMN con ^1H (400 MHz, piridina-d_5) δ ppm : 0.72-0.85 (2H, m), 0.98-1.05 (1H, m), 1.06-1.16 (1H, m), 1.79-1.90 (1H, m), 2.15-2.26 (1H, m), 2.23 y 2.24 (total 3H, cada s), 2.35-2.49 (1H, m), 2.53-2.75

(3H, m), 2.75-2.91 (1H, m), 2.97-3.22 (3H, m), 3.30-3.38 (2H, m), 3.47-3.55 (2H, m), 3.56-3.65 (1H, m), 4.44-4.47 (2H, m), 4.51-4.55 (1H, m), 4.93 y 4.94 (total 1H, cada s), 5.81 y 5.83 (total 1H, cada t, J=7.0), 7.16-7.36 (3H, m), 7.64-7.72 (1H, m);

MS (FAB) m/z : 518 $(M+H)^+$.

(Ejemplo 17) (E)-4-(Acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-{4-[2-(etoxicarbonil)etil]-3-oxopiperazin-1-il}etiliden)piperidina (Compuesto del compuesto No. 5-108)



(a) (E)-4-(t-Butildimetilsililoxi)-3-(2-{4-[2-(etoxicarbonil)etil]-3-oxopiperazin-1-il}etiliden)-1-(trifenilmetil)piperidina

Se sintetizó el compuesto del título en un rendimiento de 44% como un aceite amarillo claro usando clorhidrato de 1-[2-(etoxicarbonil)-etil]-2-oxopiperazina en lugar de morfolina realizando una reacción similar a la mencionada en el Ejemplo 1 (d).

RMN con ^1H (500 MHz, $CDCl_3$) δ ppm : -0.01 (3H, s), -0.02 (3H, s), 0.86 (9H, s), 1.27 (3H, t, J=7.0), 1.70-1.95 (4H, m), 2.59-2.67 (2H, m), 2.63 (2H, t, J=7.0), 2.84-2.97 (2H, m), 2.99-3.17 (2H, m), 3.11 (2H, s), 3.34-3.42 (2H, m), 3.64 (2H, t, J=7.0), 3.83-3.92 (1H, m), 4.14 (2H, q, J=7.0), 5.57-5.64 (1H, m), 7.10-7.21 (3H, m), 7.22-7.33 (6H, m), 7.37-7.57 (6H, m).

(b) (E)-3-(2-{4-[2-(Etoxicarbonil)etil]-3-oxopiperazin-1-il}etiliden)-4-hidroxi-1-(trifenilmetil)piperidina

Se sintetizó el compuesto del título en un rendimiento de 96% como un sólido amorfo amarillo claro usando (E)-4-(t-butildimetilsililoxi)-3-(2-{4-[2-(etoxicarbonil)etil]-3-oxopiperazin-1-il}etiliden)-1-(trifenilmetil)piperidina obtenido en (a) anterior

realizando una reacción similar a la mencionada en el Ejemplo 1 (e).

RMN con ^{1}H (500 MHz, $CDCl_3$) δ ppm : 1.26 (3H, t, J=7.0), 1.64-1.87 (4H, m), 2.62 (2H, t, J=7.0), 2.64-2.71 (2H, m), 2.98-3.17 (2H, m), 3.12 (2H, s), 3.35-3.43 (4H, m), 3.63 (2H, t, J=7.0), 3.91-4.01 (1H, m), 4.14 (2H, q, J=7.0), 5.58 (1H, t, J=7.0), 7.10-7.20 (3H, m), 7.21-7.33 (6H, m), 7.37-7.57 (6H, m).

(c) bis(acetato hidrogenado) de (E)-3-(2-{4-[2-(Etoxicarbonil)etil]-3-oxopiperazin-1-il}etiliden)-4-hidroxipiperidina

Se sintetizó el compuesto del título en un rendimiento de 98% como un aceite café claro usando (E)-3-(2-{4-[2-(etoxicarbonil)etil]-3-oxopiperazin-1-il}etiliden)-4-hidroxi-1-(trifenilmetil)piperidina obtenido en (b) anterior realizando una reacción similar a la mencionada en el Ejemplo 5 (c).

RMN con ^{1}H (500 MHz, $CDCl_3$) δ ppm : 1.26 (3H, t, J=7.0), 1.63-1.73 (2H, m), 2.61 (2H, t, J=7.0), 2.65-2.72 (2H, m), 3.07-3.15 (4H, m), 3.17-3.41 (6H, m), 3.62 (2H, t, J=7.0), 4.13 (2H, q, J=7.0), 4.17-4.22 (1H, m), 5.61 (1H, t, J=7.0).

(d) (E)-1-[2-Ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-{4-[2-(etoxicarbonil)etil]-3-oxopiperazin-1-il}etiliden)-4-hidroxipiperidina

Se sintetizó el compuesto del título en un rendimiento de 77% como un aceite café claro usando bis(acetato hidrogenado) de (E)-3-(2-{4-[2-(etoxicarbonil)etil]-3-oxopiperazin-1-il}etiliden)-4-hidroxipiperidina obtenido en (c) anterior realizando una reacción similar a la mencionada en el Ejemplo 1 (g).

RMN con ^{1}H (500 MHz, $CDCl_3$) δ ppm : 0.78-0.90 (2H, m), 0.95-1.09 (2H, m), 1.26 (3H, t, J=7.0), 1.52-1.65 (2H, m), 1.67-1.78 (1H, m), 1.95-2.04 (1H, m), 2.13-2.22 (1H, m), 2.44-2.52 (1H, m), 2.56-2.68 (4H, m), 2.72 y 2.96 (total 1H, cada d, J=13.0), 2.79-2.90 (1H, m), 2.93-3.02 (2H, m), 3.32 y 3.47 (total 1H, cada d, J=13.0), 3.35-3.41 (2H, m), 3.63 (2H, t, J=7.0), 4.05-4.12 (1H, m), 4.14 (2H, q,

J=7.0), 4.70 y 4.71 (total 1H, cada s), 5.53-5.60 (1H, m), 7.08-7.21 (2H, m), 7.29-7.44 (2H, m).

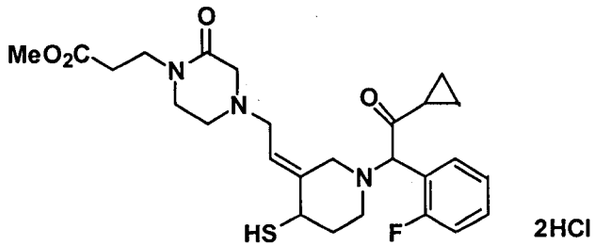
(e) (E)-4-(Acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-{4-[2-(etoxicarbonil)etil]-3-oxopiperazin-1-il}etiliden)piperidina

Se sintetizó el compuesto del título en un rendimiento de 22% como un aceite café claro usando (E)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-{4-[2-(etoxicarbonil)etil]-3-oxopiperazin-1-il}etiliden)-4-hidroxipiperidina obtenido en (d) anterior realizando una reacción similar a la mencionada en el Ejemplo 1 (h).

RMN con ^{1}H (500 MHz, $CDCl_3$) δ ppm : 0.77-1.08 (4H, m), 1.26 (3H, t, J=7.0), 1.76-1.84 (1H, m), 2.08-2.24 (2H, m), 2.29 y 2.30 (total 3H, cada s), 2.46-2.72 (6H, m), 2.74-2.82 (1H, m), 2.89-3.00 (2H, m), 3.01-3.09 (2H, m), 3.05 y 3.27 (total 1H, cada d, J=13.0), 3.33-3.40 (2H, m), 3.63 (2H, t, J=7.0), 4.14 (2H, q, J=7.0), 4.26-4.35 (1H, m), 4.68 y 4.70 (total 1H, cada s), 5.60 (1H, t, J=7.0), 7.08-7.20 (2H, m), 7.29-7.43 (2H, m);

MS (FAB) m/z : 560 $(M+H)^+$.

(Ejemplo 18) diclorhidrato de (E)-1-[2-Ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-{4-[2-(metoxicarbonil)etil]-3-oxopiperazin-1-il}etiliden)-4-sulfanilpiperidina (Clorhidrato del compuesto del Compuesto No. 5-105)



Se sintetizó el compuesto del título en un rendimiento de 71% como un cristal en polvo blanco usando (E)-4-(acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-{4-[2-(etoxicarbonil)etil]-3-oxopiperazin-1-il}etiliden)piperidina obtenida en el ejemplo 17 (e) realizando una reacción similar a la mencionada en el Ejemplo 2.

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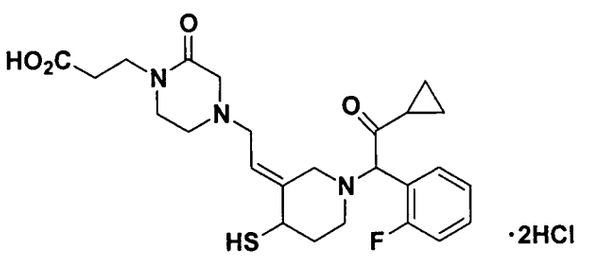
RMN con ^{1}H (500 MHz, $CDCl_3$) δ ppm : 0.78-0.90 (2H, m), 0.96-1.08 (2H, m), 1.68-1.78 (1H, m), 2.12-2.26 (2H, m), 2.53-2.68 (5H, m), 2.74-2.85 (1H, m), 2.90-3.01 (2H, m), 3.03-3.10 (3H, m), 3.19 (1H, s), 3.34-3.43 (2H, m), 3.63 (2H, t, J=7.0), 3.67-3.81 (1H, m), 3.69 (3H, s), 4.71 y 4.73 (total 1H, cada s), 5.55 y 5.59 (total 1H, cada t, J=7.0), 7.08-7.21 (2H, m), 7.30-7.36 (1H, m), 7.38-7.43 (1H, m);

MS (FAB) m/z : 504 $(M+H)^+$.

(Ejemplo 19) diclorhidrato de (E)-3-(2-{4-[2-(Carboxietil)]-3-oxopiperazin-1-il}etiliden)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-sulfanilpiperidina (Clorhidrato del compuesto del Compuesto No. 5-103)



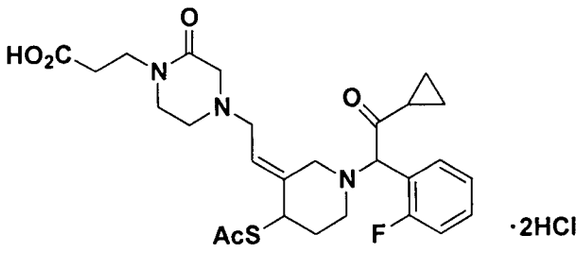
Se sintetizó el compuesto del título en un rendimiento de 48% como un cristal en polvo blanco usando (E)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-{4-[2-(metoxicarbonil)etil]-3-oxopiperazin-1-il}etiliden)-4-sulfanilpiperidina obtenida en el ejemplo 18 realizando una reacción similar a la mencionada en el Ejemplo 15.

RMN con ^{1}H (400 MHz, piridina-d_5) δ ppm : 0.77-1.11 (4H, m), 1.76-1.87 (1H, m), 2.14-2.27 (1H, m), 2.40-2.48 (1H, m), 2.64-2.73 (3H, m), 2.87-2.99 (3H, m), 3.04-3.13 (2H, m), 3.28-3.34 (3H, m), 3.44-3.47 (2H, m), 3.50 y 3.59 (total 1H, cada d, J=12.5), 3.85-3.93 (3H, m), 4.95 (1H, s), 5.77-5.82 (1H, m), 7.21-7.37 (3H, m), 7.69-7.75 (1H, m);

MS (FAB) m/z : 490 $(M+H)^+$.

(Ejemplo 20) (E)-4-(Acetilsulfanil)-3-(2-{4-[2-(carboxietil)]-3-oxopiperazin-1-il}etiliden)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]piperidina diclorhidrato (Clorhidrato del compuesto del

Compuesto No. 5-104)

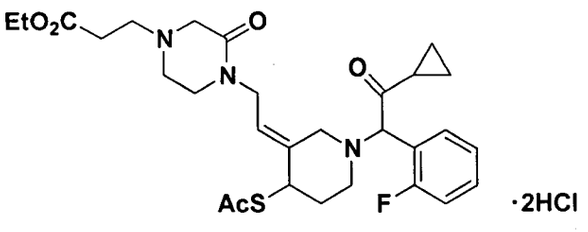


Se sintetizó el compuesto del título en un rendimiento de 35% como un cristal en polvo amarillo claro usando diclorhidrato de (E)-3-(2-{4-[2-(carboxietil)]-3-oxopiperazin-1-il}etiliden)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-sulfanilpiperidina obtenida en el ejemplo 19 realizando una reacción similar a la mencionada en el Ejemplo 16.

RMN con ^{1}H (500 MHz, $CDCl_3$) δ ppm : 0.78-1.17 (4H, m), 1.84-1.90 (1H, m), 2.21-2.29 (1H, m), 2.25 y 2.26 (total 3H, cada s), 2.39-2.46 (1H, m), 2.57-2.88 (3H, m), 2.90-2.94 (3H, m), 2.98-3.01 (2H, m), 3.19-3.28 (2H, m), 3.33-3.38 (2H, m), 3.41-3.44 (2H, m), 3.88-3.93 (2H, m), 4.54-4.55 (1H, m), 4.95 y 4.96 (total 1H, cada s), 5.82-5.86 (1H, m), 7.21-7.38 (3H, m), 7.66-7.73 (1H, m);

MS (FAB) m/z : 532 $(M+H)^+$.

(Ejemplo 21) diclorhidrato de (E)-4-(Acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-{4-[2-(etoxicarbonil)etil]-2-oxopiperazin-1-il}etiliden)piperidina (Clorhidrato del compuesto del Compuesto No. 5-80)



(a) (E)-4-(t-Butildimetilsililoxi)-3-(2-{4-[2-(etoxicarbonil)etil]-2-oxopiperazin-1-il}etiliden)-1-(trifenilmetil)piperidina

A una solución de hidruro de sodio (1.94 g) en N,N-dimetilformamida (430 ml) se le añadió una solución de (E)-4-(t-

butildimetilsililoxi)-3-[2-(tosiloxi)etiliden]-1-(trifenilmetil)piperidina (27.37 g) obtenida en el ejemplo 1 (c) y 1-[2-(etoxicarbonil)etilo]-3-oxopiperazina (9.70 g) en N,N-dimetilformamida (100 ml) bajo enfriamiento con hielo, y la mezcla resultante se agitó a temperatura ambiente durante 3 horas. La mezcla de la reacción se cargó con una solución acuosa saturada de cloruro de sodio y luego se extrajo con acetato de etilo. Se lavó el extracto con una solución acuosa saturada de cloruro de sodio, y se secó la capa orgánica sobre sulfato de sodio anhidro. Se eliminó el solvente in vacuo, y se purificó el residuo mediante cromatografía en una columna de gel de sílice (acetato de etilo / hexano = 2 / 3 - 1 / 1) para obtener el compuesto del título (14.79 g, rendimiento 54%) como un sólido amorfo amarillo claro.

RMN con ^{1}H (500 MHz, $CDCl_3$) δ ppm : -0.05 (3H, s), -0.02 (3H, s), 0.83 (9H, s), 1.26 (3H, t, J=7.5), 1.73-1.94 (2H, m), 2.48 (2H, t, J=7.5), 2.65-2.76 (4H, m), 2.84-2.93 (1H, m), 3.16 (2H, s), 3.20-3.27 (2H, m), 3.40-3.55 (1H, m), 3.81-4.18 (7H, m), 5.41-5.48 (1H, m), 7.11-7.29 (9H, m), 7.41-7.52 (6H, m).

(b) (E)-3-(2-{4-[2-(Etoxicarbonil)etil]-2-oxopiperazin-1-il}etiliden)-4-hidroxi-1-(trifenilmetil)piperidina

Se sintetizó el compuesto del título en un rendimiento de 99% como un sólido amorfo amarillo claro usando (E)-4-(t-butildimetilsililoxi)-3-(2-{4-[2-(etoxicarbonil)etil]-2-oxopiperazin-1-il}etiliden)-1-(trifenilmetil)piperidina obtenido en (a) anterior realizando una reacción similar a la mencionada en el Ejemplo 1 (e).

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 1.26 (3H, t, J=7.0), 1.60-1.86 (2H, m), 1.98-2.11 (1H, m), 2.49 (2H, t, J=7.0), 2.65-2.77 (4H, m), 3.16 (2H, s), 3.21-3.44 (3H, m), 3.88-4.20 (7H, m), 5.44 (1H, t, J=6.5), 7.10-7.31 (9H, m), 7.39-7.53 (6H, m).

(c) bis(acetato hidrogenado) de (E)-3-(2-{4-[2-(Etoxicarbonil)etil]-2-oxopiperazin-1-il}etiliden)-4-hidroxipiperidina

Se sintetizó el compuesto del título en un rendimiento de 99% como un aceite café claro usando (E)-3-(2-{4-[2-(etoxicarbonil)etil]-2-oxopiperazin-1-il}etiliden)-4-hidroxi-1-(trifenilmetil)piperidina obtenido en (b) anterior realizando una reacción similar a la mencionada en el Ejemplo 5 (c).

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 1.26 (3H, t, J=7.0), 1.62-1.83 (2H, m), 2.01-2.12 (1H, m), 2.49 (2H, t, J=7.0), 2.66-2.77 (4H, m), 2.90-3.01 (1H, m), 3.15 (2H, s), 3.23-3.45 (3H, m), 3.83-4.27 (6H, m), 5.57 (1H, t, J=7.5).

(d) (E)-1-[2-Ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-{4-[2-(etoxicarbonil)etil]-2-oxopiperazin-1-il}etiliden)-4-hidroxipiperidina

Se sintetizó el compuesto del título en un rendimiento de 93% como un aceite amarillo claro usando (E)-3-(2-{4-[2-(etoxicarbonil)etil]-2-oxopiperazin-1-il}etiliden)-4-hidroxipiperidina bis(acetato hidrogenado) obtenido en (c) anterior realizando una reacción similar a la mencionada en el Ejemplo 1 (g).

RMN con ^{1}H (500 MHz, $CDCl_3$) δ ppm : 0.78-0.91 (2H, m), 0.97-1.10 (2H, m), 1.26 (3H, t, J=7.5), 1.62-1.77 (2H, m), 1.95-2.03 (1H, m), 2.09-2.16 (1H, m), 2.43-2.54 (2H, m), 2.65-2.77 (4H, m), 2.78-2.89 (1H, m), 3.00 y 3.33 (total 1H, cada d, J=12.5), 3.15 (2H, s), 3.22-3.30 (2H, m), 3.47-3.55 (1H, m), 3.88-4.19 (5H, m), 4.73 y 4.75 (total 1H, cada s), 5.42-5.49 (1H, m), 7.08-7.20 (2H, m), 7.29-7.41 (2H, m).

(e) diclorhidrato de (E)-4-(Acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-{4-[2-(etoxicarbonil)etil]-2-oxopiperazin-1-il}etiliden)piperidina

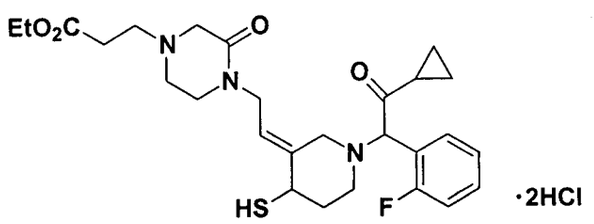
Se sintetizó el compuesto del título en un rendimiento de 4% como un cristal en polvo amarillo claro usando (E)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-{4-[2-(etoxicarbonil)etil]-2-oxopiperazin-1-il}etiliden)-4-hidroxipiperidina obtenido en (d) anterior realizando

una reacción similar a la mencionada en el Ejemplo 1 (h).

RMN con ^1H (400 MHz, $CDCl_3$) δ ppm : 0.75-1.09 (4H, m), 1.27 (3H, t, J=7.0), 1.72-1.84 (1H, m), 2.05-2.32 (6H, m), 2.43-2.83 (7H, m), 3.04-3.42 (6H, m), 3.77-4.35 (5H, m), 4.71 y 4.74 (total 1H, cada s), 5.43-5.52 (1H, m), 7.06-7.22 (2H, m), 7.29-7.41 (2H, m);

MS (FAB) m/z : 560 $(M+H)^+$.

(Ejemplo 22) diclorhidrato de (E)-1-[2-Ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-{4-[2-(etoxicarbonil)etil]-2-oxopiperazin-1-il}etiliden)-4-sulfanilpiperidina (Clorhidrato del compuesto del Compuesto No. 5-79)

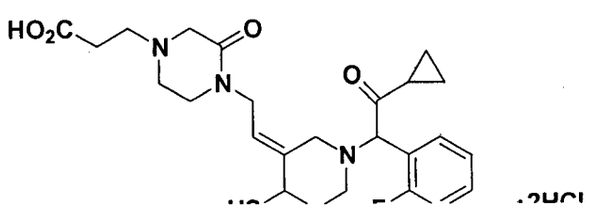


Se sintetizó el compuesto del título en un rendimiento de 80% como un cristal en polvo blanco usando (E)-4-(acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-{4-[2-(etoxicarbonil)etil]-2-oxopiperazin-1-il}etiliden)piperidina obtenida en el ejemplo 21 (e) realizando una reacción similar a la mencionada en el Ejemplo 12.

RMN con ^1H (400 MHz, piridina-d_5) δ ppm : 0.76-0.89 (2H, m), 0.99-1.08 (2H, m), 1.13 (3H, t, J=7.5), 1.72-1.85 (1H, m), 2.12-2.26 (1H, m), 2.38-3.00 (9H, m), 3.21-3.42 (5H, m), 3.51-3.68 (1H, m), 3.81 (1H, bs), 4.06-4.21 (4H, m), 4.96 (1H, s), 5.62-5.71 (1H, m), 7.19-7.40 (3H, m), 7.66-7.76 (1H, m);

MS (FAB) m/z : 518 $(M+H)^+$.

(Ejemplo 23) diclorhidrato (E)-3-(2-{4-[2-(Carboxietil)]-2-oxopiperazin-1-il}etiliden)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-sulfanilpiperidina (Clorhidrato del compuesto del Compuesto No. 5-75)

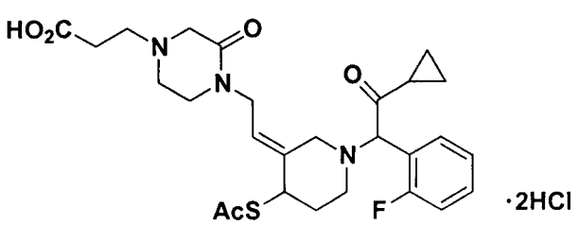


Se sintetizó el compuesto del título en un rendimiento de 88% como un cristal en polvo blanco usando (E)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-{4-[2-(etoxicarbonil)etil]-2-oxopiperazin-1-il}etiliden)-4-sulfanilpiperidina obtenida en el ejemplo 22 realizando una reacción similar a la mencionada en el Ejemplo 15.

RMN con ^{1}H (400 MHz, piridina-d_5) δ ppm : 0.77-0.89 (2H, m), 0.98-1.19 (2H, m), 1.71-1.84 (1H, m), 2.10-2.28 (1H, m), 2.38-3.01 (9H, m), 3.23-3.69 (6H, m), 3.81 (1H, bs), 4.05-4.29 (2H, m), 4.96 (1H, s), 5.63-5.72 (1H, m), 7.16-7.40 (3H, m), 7.67-7.78 (1H, m);

MS (FAB) m/z : 490 $(M+H)^+$.

(Ejemplo 24) (E)-4-(Acetilsulfanil)-3-(2-{4-[2-(carboxietil)]-2-oxopiperazin-1-il}etiliden)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]piperidina diclorhidrato (Clorhidrato del compuesto del Compuesto No. 5-76)

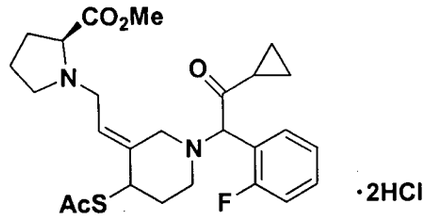


Se sintetizó el compuesto del título en un rendimiento de 44% como un cristal en polvo amarillo claro usando diclorhidrato de (E)-3-(2-{4-[2-(carboxietil)]-2-oxopiperazin-1-il}etiliden)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-sulfanilpiperidina obtenida en el ejemplo 23 realizando una reacción similar a la mencionada en el Ejemplo 16.

RMN con ^{1}H (400 MHz, piridina-d_5) δ ppm : 0.76-0.91 (2H, m), 1.01-1.20 (2H, m), 1.81-1.90 (1H, m), 2.14-2.29 (4H, m), 2.34-2.48 (1H, m), 2.53-2.92 (8H, m), 3.17-3.72 (6H, m), 4.00-4.31 (2H, m), 4.46-4.56 (1H, m), 4.95 y 4.97 (total 1H, cada s), 5.69-5.80 (1H, m), 7.18-7.40 (3H, m), 7.62-7.75 (1H, m);

MS (FAB) m/z : 532 $(M+H)^+$.

(Ejemplo 25) diclorhidrato de (E)-4-(Acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[(2S)-(metoxicarbonil)pirrolidin-1-il]etiliden}piperidina (Clorhidrato del compuesto del Compuesto No. 5-148)



(a) (E)-4-(t-Butildimetilsililoxi)-3-{2-[(2S)-(metoxicarbonil) pirrolidin-1-il]etiliden}-1-(trifenilmetil)piperidina

A una solución de (E)-4-(t-butildimetilsililoxi)-3-[2-(tosiloxi)etiliden]-1-(trifenilmetil)piperidina (4.50 g) obtenida en el ejemplo 1 (c) en N,N-dimetilformamida (60 ml) se le añadió clorhidrato de (2S)-(metoxicarbonil)pirrolidina (1.14 g) y trietilamina (2.11 ml) bajo enfriamiento con hielo, y la mezcla resultante se agitó a temperatura ambiente durante la noche. La mezcla de la reacción se cargó con una solución acuosa saturada de cloruro de sodio y luego se extrajo con acetato de etilo. Se lavó el extracto con una solución acuosa saturada de cloruro de sodio, y se secó la capa orgánica sobre sulfato de sodio anhidro. Se eliminó el solvente in vacuo, y se purificó el residuo mediante cromatografía en una columna de gel de sílice (acetato de etilo / hexano = 1 / 9) para obtener el compuesto del título (1.46 g, rendimiento 35%) como un sólido amorfo incoloro.

RMN con ^1H (500 MHz, $CDCl_3$) δ ppm : -0.04 (3H, s), -0.02 (3H, s), 0.84 (9H, s), 1.69-1.98 (7H, m), 2.03-2.13 (1H, m), 2.31-2.54 (1H, m), 2.71-2.98 (1H, m), 3.03-3.29 (3H, m), 3.37-3.48 (2H, m), 3.59 y 3.62 (total 3H, cada s), 3.80-3.93 (1H, m), 5.63-5.73 (1H, m), 7.08-7.19 (3H, m), 7.20-7.30 (6H, m), 7.36-7.56 (6H, m).

(b) (E)-4-Hidroxi-3-{2-[(2S)-(metoxicarbonil)pirrolidin-1-

il]etiliden}-1-(trifenilmetil)piperidina

Se sintetizó el compuesto del título en un rendimiento de 99% como un sólido amorfo amarillo claro usando (E)-4-(t-butildimetilsililoxi)-3-{2-[(2S)-(metoxicarbonil)pirrolidin-1-il]etiliden}-1-(trifenilmetil)piperidina obtenido en (a) anterior realizando una reacción similar a la mencionada en el Ejemplo 1 (e).

RMN con ^{1}H (500 MHz, $CDCl_3$) δ ppm : 1.73-1.85 (2H, m), 1.87-1.98 (2H, m), 2.01-2.18 (3H, m), 2.33-2.43 (2H, m), 2.53-2.75 (1H, m), 3.05-3.23 (4H, m), 3.26-3.37 (1H, m), 3.64 y 3.66 (total 3H, cada s), 3.92-4.04 (1H, m), 5.60-5.70 (1H, m), 7.10-7.20 (3H, m), 7.21-7.32 (6H, m), 7.37-7.57 (6H, m).

(c) bis(acetato hidrogenado) de (E)-4-Hidroxi-3-{2-[(2S)-(metoxicarbonil)pirrolidin-1-il]etiliden}piperidina

Se sintetizó el compuesto del título en un rendimiento cuantitativo como un aceite café claro usando (E)-4-hidroxi-3-{2-[(2S)-(metoxicarbonil)pirrolidin-1-il]etiliden}-1-(trifenilmetil)piperidina obtenido en (b) anterior realizando una reacción similar a la mencionada en el Ejemplo 5 (c).

RMN con ^{1}H (500 MHz, $CDCl_3$) δ ppm : 1.71-1.81 (2H, m), 1.87-2.05 (3H, m), 2.09-2.19 (2H, m), 2.34-2.43 (1H, m), 2.90-2.98 (1H, m), 3.09-3.33 (4H, m), 3.37-3.45 (1H, m), 3.73 y 3.74 (total 3H, cada s), 3.78 (1H, d, J=14.0), 4.18-4.25 (1H, m), 5.70 (1H, t, J=7.5).

(d) (E)-1-[2-Ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-hidroxi-3-{2-[(2S)-(metoxicarbonil)pirrolidin-1-il]etiliden}piperidina

Se sintetizó el compuesto del título en un rendimiento de 54% como un aceite café claro usando (E)-4-hidroxi-3-{2-[(2S)-(metoxicarbonil)pirrolidin-1-il]etiliden}piperidina bis(acetato hidrogenado) obtenido en (c) anterior realizando una reacción similar a la mencionada en el Ejemplo 1 (g).

RMN con ^{1}H (500 MHz, $CDCl_3$) δ ppm : 0.79-0.90 (2H, m), 0.96-1.09 (2H, m), 1.66-1.84 (2H, m), 1.87-2.02 (3H, m), 2.06-2.16 (1H,

m), 2.20-2.29 (1H, m), 2.31-2.39 (1H, m), 2.42-2.56 (1H, m), 2.74-2.86 (1H, m), 2.85 y 2.95 (total 1H, cada d, J=12.5), 2.98 y 3.06 (total 1H, cada d, J=12.5), 3.08-3.19 (2H, m), 3.21-3.45 (2H, m), 3.70 y 3.71 (total 3H, cada s), 4.06-4.16 (1H, m), 4.68 y 4.69 y 4.70 (total 1H, cada s), 5.61-5.70 (1H, m), 7.06-7.21 (2H, m), 7.28-7.35 (1H, m), 7.39-7.47 (1H, m).

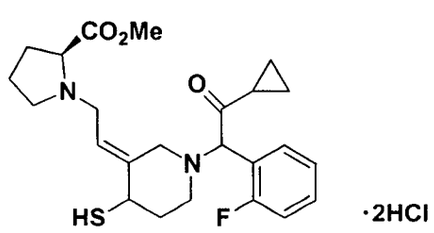
(e) diclorhidrato de (E)-4-(Acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[(2S)-(metoxicarbonil)pirrolidin-1-il]etiliden}piperidina

Se sintetizó el compuesto del título en un rendimiento de 22% como un cristal en polvo café claro usando (E)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-hidroxi-3-{2-[(2S)-(metoxicarbonil)pirrolidin-1-il]etiliden}piperidina obtenido en (d) anterior realizando una reacción similar a la mencionada en el Ejemplo 1 (h).

RMN con ^{1}H (500 MHz, $CDCl_3$) δ ppm : 0.78-0.90 (2H, m), 0.95-1.09 (2H, m), 1.72-1.82 (2H, m), 1.84-1.97 (2H, m), 2.04-2.40 (4H, m), 2.28 y 2.29 (total 3H, cada s), 2.43-2.63 (1H, m), 2.65-2.78 (1H, m), 2.81-3.35 (6H, m), 3.69 y 3.70 y 3.71 y 3.72 (total 3H, cada s), 4.26-4.32 (1H, m), 4.65 y 4.67 y 4.68 y 4.69 (total 1H, cada s), 5.67-5.73 (1H, m), 7.07-7.19 (2H, m), 7.29-7.35 (1H, m), 7.39-7.45 (1H, m);

MS (FAB) m/z : 489 $(M+H)^+$.

(Ejemplo 26) diclorhidrato de (E)-1-[2-Ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[(2S)-(metoxicarbonil)pirrolidin-1-il]etiliden}-4-sulfanilpiperidina (Clorhidrato del compuesto del Compuesto No. 5-147)



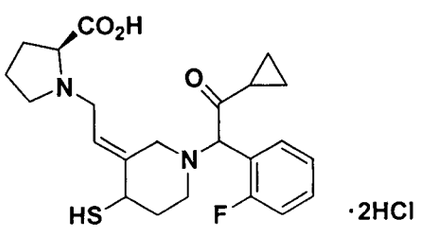
Se sintetizó el compuesto del título en un rendimiento de 46%

como un cristal en polvo rosa claro usando (E)-4-(acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[(2S)-(metoxicarbonil) pirrolidin-1-il]etiliden}piperidina obtenida en el ejemplo 25 (e) realizando una reacción similar a la mencionada en el Ejemplo 2.

RMN con ^{1}H (500 MHz, $CDCl_3$) δ ppm : 0.78-0.90 (2H, m), 0.95-1.08 (2H, m), 1.66-1.99 (4H, m), 2.05-2.38 (4H, m), 2.53-2.66 (1H, m), 2.67-2.86 (1H, m), 3.01-3.39 (6H, m), 3.65-3.79 (1H, m), 3.71 y 3.72 (total 3H, cada s), 4.69 y 4.71 (total 1H, cada s), 5.63-5.71 (1H, m), 7.07-7.19 (2H, m), 7.28-7.35 (1H, m), 7.40-7.46 (1H, m);

MS (FAB)m/z : 447 $(M+H)^+$.

(Ejemplo 27) diclorhidrato de (E)-3-{2-[(2S)-Carboxipirrolidin-1-il]etiliden}-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-sulfanilpiperidina (Clorhidrato del compuesto del Compuesto No. 5-145)



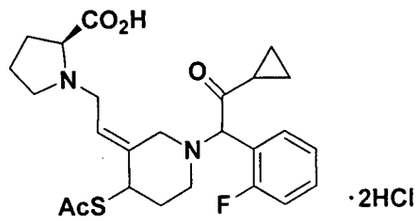
Se sintetizó el compuesto del título en un rendimiento de 76% como un cristal en polvo amarillo claro usando (E)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[(2S)-(metoxicarbonil)pirrolidin-1-il]etiliden}-4-sulfanilpiperidina obtenida en el ejemplo 26 realizando una reacción similar a la mencionada en el Ejemplo 15.

RMN con ^{1}H (400 MHz, piridina-d_5) δ ppm : 0.72-0.90 (2H, m), 0.95-1.20 (2H, m), 1.67-2.26 (4H, m), 2.28-2.53 (3H, m), 2.55-3.21 (3H, m), 3.37-4.38 (7H, m), 4.94-5.09 (1H, m), 6.10-6.31 (1H, m), 7.11-7.37 (3H, m), 7.62-7.83 (1H, m);

MS (FAB) m/z : 433 $(M+H)^+$.

(Ejemplo 28) diclorhidrato de (E)-4-(Acetilsulfanil)-3-{2-[(2S)-carboxipirrolidin-1-il]etiliden}-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]piperidina (Clorhidrato del compuesto del Compuesto No.

5-146)

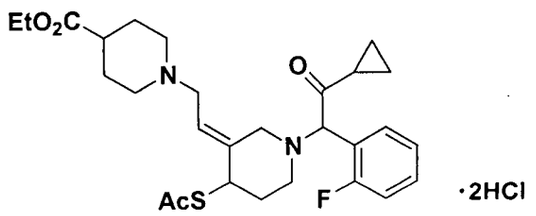


A una suspensión de diclorhidrato de (E)-3-{2-[(2S)-carboxipirrolidin-1-il]etiliden}-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-sulfanilpiperidina (100 mg) obtenida en el ejemplo 27 en diclorometano (5 ml) se le añadió anhídrido acético (28 μl) y trietilamina (97 μl) bajo enfriamiento con hielo, y la mezcla resultante se agitó a temperatura ambiente durante 2 horas. Se eliminó el solvente in vacuo, y se purificó el residuo usando una HPLC preparativa (YMC-Pack ODS-A; YMC, eluyente: acetonitrilo / agua que contiene trietilamina (0.2%) y ácido acético (0.2%) = 3 / 7) para producir la forma libre (57 mg, rendimiento 61%) del compuesto del título como un aceite café claro. A una solución de este compuesto en diclorometano (1 ml) se le añadió una solución de cloruro de hidrógeno en dioxano 4N (60 μl) a temperatura ambiente, y la mezcla de la reacción se evaporó in vacuo. Se cristalizó el residuo a partir de éter para obtener el compuesto del título (41 mg, rendimiento 62%) como un cristal en polvo café claro.

RMN con ^{1}H (400 MHz, piridina-d_5) δ ppm : 0.72-0.92 (2H, m), 0.99-1.21 (2H, m), 1.71-2.00 (3H, m), 2.12-2.35 (2H, m), 2.25 y 2.26 y 2.27 (total 3H, cada s), 2.38-2.89 (4H, m), 3.17-3.50 (3H, m), 3.55-4.06 (4H, m), 4.53 (1H, m), 4.94 y 4.97 y 4.99 (total 1H, cada s), 6.10-6.21 (1H, m), 7.16-7.39 (3H, m), 7.63-7.77 (1H, m);

MS (FAB) m/z : 475 $(M+H)^+$.

(Ejemplo 29) diclorhidrato de (E)-4-(Acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[4-(etoxicarbonil) piperidin-1-il]etiliden}piperidina (Clorhidrato del compuesto del Compuesto No. 5-8)



(a) (E)-4-(t-Butildimetilsililoxi)-3-{2-[4-(etoxicarbonil)piperidin-1-il]etiliden}-1-(trifenilmetil)piperidina

Se sintetizó el compuesto del título en un rendimiento de 37% como un sólido amorfo incoloro usando 4-(etoxicarbonil)piperidina en lugar de morfolina realizando una reacción similar a la mencionada en el Ejemplo 1 (d).

RMN con ^{1}H (500 MHz, $CDCl_3$) δ ppm : -0.04 (3H, s), -0.02 (3H, s), 0.83 (9H, s), 1.25 (3H, t, J=7.0), 1.68-2.07 (10H, m), 2.20-2.30 (1H, m), 2.77-2.91 (3H, m), 2.93-3.10 (2H, m), 3.27-3.65 (1H, m), 3.82-3.92 (1H, m), 4.13 (2H, q, J=7.0), 5.57-5.66 (1H, m), 7.06-7.19 (3H, m), 7.20-7.30 (6H, m), 7.36-7.58 (6H, m).

(b) (E)-3-{2-[4-(Etoxicarbonil)piperidin-1-il]etiliden}-4-hidroxi-1-(trifenilmetil)piperidina

Se sintetizó el compuesto del título en un rendimiento de 99% como un aceite incoloro usando (E)-4-(t-butildimetilsililoxi)-3-{2-[4-(etoxicarbonil)piperidin-1-il]etiliden}-1-(trifenilmetil)piperidina obtenido en (a) anterior realizando una reacción similar a la mencionada en el Ejemplo 1 (e).

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 1.25 (3H, t, J=7.0), 1.64-2.11 (10H, m), 2.24-2.35 (1H, m), 2.83-2.94 (2H, m), 2.94-3.07 (2H, m), 3.35-3.44 (2H, m), 3.95-4.01 (1H, m), 4.14 (2H, q, J=7.0), 5.62 (1H, t, J=6.0), 7.13-7.21 (3H, m), 7.23-7.33 (6H, m), 7.41-7.55 (6H, m).

(c) bis(acetato hidrogenado) de (E)-3-{2-[4-(Etoxicarbonil)piperidin-1-il]etiliden}-4-hidroxipiperidina

Se sintetizó el compuesto del título en un rendimiento de 99% como un cristal café usando (E)-3-{2-[4-(etoxicarbonil)piperidin-1-

il]etiliden}-4-hidroxi-1-(trifenilmetil)piperidina obtenido en (b) anterior realizando una reacción similar a la mencionada en el Ejemplo 5 (c).

RMN con ^{1}H (500 MHz, $CDCl_3$) δ ppm : 1.25 (3H, t, J=7.0), 1.41-1.50 (1H, m), 1.60-2.12 (6H, m), 2.23-2.34 (1H, m), 2.83-3.09 (5H, m), 3.30 (2H, q, J=7.0), 3.39-3.51 (1H, m), 3.75-3.82 (1H, m), 4.13 (2H, q, J=7.0), 4.19-4.25 (1H, m), 5.58-5.75 (1H, m).

(d) (E)-1-[2-Ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[4-(etoxicarbonil)piperidin-1-il]etiliden}-4-hidroxipiperidina

Se sintetizó el compuesto del título en un rendimiento de 63% como un aceite café claro usando (E)-3-{2-[4-(etoxicarbonil)piperidin-1-il]etiliden}-4-hidroxipiperidina bis(acetato hidrogenado) obtenido en (c) anterior realizando una reacción similar a la mencionada en el Ejemplo 1 (g).

RMN con ^{1}H (500 MHz, $CDCl_3$) δ ppm : 0.76-1.10 (4H, m), 1.25 (3H, t, J=7.0), 1.42-1.51 (1H, m), 1.65-2.04 (8H, m), 2.08-2.23 (2H, m), 2.27-2.37 (1H, m), 2.42-2.53 (1H, m), 2.76 y 2.96 (total 1H, cada d, J=12.5), 2.77-2.95 (1H, m), 3.00-3.07 (2H, m), 3.32 y 3.45 (total 1H, cada d, J=12.5), 4.06-4.11 (1H, m), 4.13 (2H, q, J=7.0), 4.69 y 4.72 (total 1H, cada s), 5.61-5.70 (1H, m), 7.07-7.21 (2H, m), 7.28-7.45 (2H, m).

(e) diclorhidrato de (E)-4-(Acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[4-(etoxicarbonil)piperidin-1-il]etiliden}piperidina

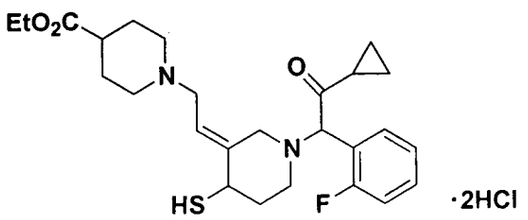
Se sintetizó el compuesto del título en un rendimiento de 17% como un cristal en polvo amarillo usando (E)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[4-(etoxicarbonil)piperidin-1-il]etiliden}-4-hidroxipiperidina obtenido en (d) anterior realizando una reacción similar a la mencionada en el Ejemplo 1 (h).

RMN con ^{1}H (500 MHz, $CDCl_3$) δ ppm : 0.77-1.11 (4H, m), 1.25 (3H, t, J=7.0), 1.67-1.98 (7H, m), 2.07-2.29 (3H, m), 2.28 y 2.29 (total 3H, cada s), 2.47-2.62 (1H, m), 2.65-2.96 (5H, m), 2.81 y 3.02

(total 1H, cada d, J=12.5), 3.26-3.39 (1H, m), 4.13 (2H, q, J=7.0), 4.27-4.36 (1H, m), 4.66 y 4.69 (total 1H, cada s), 5.64 (1H, t, J=7.0), 7.07-7.20 (2H, m), 7.28-7.45 (2H, m);

MS (FAB) m/z : 517 $(M+H)^+$.

(Ejemplo 30) diclorhidrato de (E)-1-[2-Ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[4-(etoxicarbonil)piperidin-1-il]etiliden}-4-sulfanilpiperidina (Clorhidrato del compuesto del Compuesto No. 5-7)

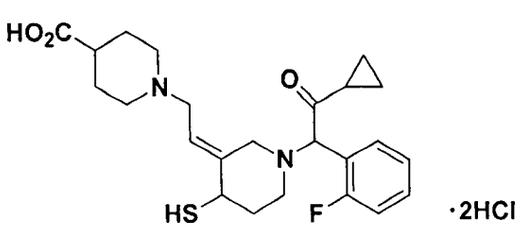


Se sintetizó el compuesto del título en un rendimiento de 97% como un cristal en polvo amarillo claro usando (E)-4-(acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[4-(etoxicarbonil) piperidin-1-il]etiliden}piperidina obtenida en el ejemplo 29 (e) realizando una reacción similar a la mencionada en el Ejemplo 12.

RMN con ^1H (500 MHz, $CDCl_3$) δ ppm : 0.75-1.10 (4H, m), 1.25 (3H, t, J=7.0), 1.67-1.80 (3H, m), 1.82-1.99 (4H, m), 2.10-2.31 (3H, m), 2.54-2.68 (1H, m), 2.69-2.97 (5H, m), 3.14 y 3.35 (total 1H, cada d, J=12.5), 3.16-3.23 (1H, m), 3.72-3.83 (1H, m), 4.13 (2H, q, J=7.0), 4.69 y 4.71 (total 1H, cada s), 5.61 (1H, m), 7.05-7.21 (2H, m), 7.23-7.46 (2H, m);

MS (FAB) m/z : 475 $(M+H)^+$.

(Ejemplo 31) diclorhidrato de (E)-3-{2-[4-(Carboxipiperidina)-1-il]etiliden}-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-sulfanilpiperidina (Clorhidrato del compuesto del Compuesto No. 5-3)



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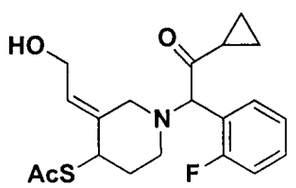
Se sintetizó el compuesto del título en un rendimiento de 90% como un cristal en polvo amarillo claro usando diclorhidrato de (E)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[4-(etoxicarbonil) piperidin-1-il]etiliden}-4-sulfanilpiperidina obtenida en el ejemplo 30 realizando una reacción similar a la mencionada en el Ejemplo 15.

RMN con ^{1}H (400 MHz, piridina-d_5) δ ppm : 0.73-0.83 (2H, m), 1.03-1.13 (2H, m), 1.73-1.81 (1H, m), 2.13-2.31 (2H, m), 2.47 (2H, br), 2.59-2.98 (7H, m), 3.04-3.27 (1H, m), 3.39 y 3.45 (total 1H, cada d, J=12.0), 3.51-3.68 (2H, m), 3.80-3.89 (3H, m), 5.00 y 5.01 (total 1H, cada s), 6.41 (1H, t, J=7.5), 7.22-7.25 (2H, m), 7.27-7.35 (1H, m), 7.58-7.60 (1H, m);

MS (FAB) m/z : 447 $(M+H)^+$.

(Ejemplo 32) (E)-4-(Acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-hidroxietiliden)piperidina (Compuesto del compuesto No. 3-2)



(a) (E)-4-(Acetilsulfanil)-3-[(etoxicarbonil)metiliden]-1-(trifenilmetil)piperidina

A una solución de (E)-3-[(etoxicarbonil)metiliden]-1-(trifenilmetil)piperidin-4-ol (23.06 g) en diclorometano (200 ml) se le añadió cloruro de metanosulfonilo (4.60 ml) y trietilamina (9.77 ml) bajo enfriamiento con hielo, y la mezcla resultante se agitó a temperatura ambiente durante 1 hora. Después se le vació una solución acuosa saturada de carbonato hidrogenado de sodio a la mezcla de la reacción y la mezcla resultante se extrajo con diclorometano, se secó la capa orgánica sobre sulfato de magnesio anhidro. Se eliminó el solvente in vacuo para obtener un producto

crudo de (E)-3-[(etoxicarbonil)metiliden]-4-mesiloxi-1-(trifenilmetil) piperidina como un sólido amorfo amarillo claro. A una solución de este compuesto en etanol (250 ml) se le añadió tioacetato de potasio (12.32 g) a temperatura ambiente, y la mezcla resultante se agitó a 70°C durante 1 hora. La mezcla de la reacción se evaporó in vacuo. Se diluyó el residuo con acetato de etilo y se lavó con agua y una solución acuosa saturada de cloruro de sodio, y se secó la capa orgánica sobre sulfato de magnesio anhidro. Se eliminó el solvente in vacuo, y se purificó el residuo mediante cromatografía en una columna de gel de sílice (acetato de etilo / hexano = 1 / 5) para obtener el compuesto del título (18.35 g, rendimiento 70%) como un sólido amorfo amarillo claro.

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 1.11(3H, t, J=7.0), 1.89-1.99 (1H, m), 2.10-2.24 (1H, m), 2.27 (3H, s), 2.30-2.40 (2H, m), 2.51-2.65 (1H, m), 3.83 (1H, m), 3.98-4.08 (2H, m), 4.30-4.37 (1H, m), 5.98 (1H, s), 7.12-7.51 (15H, m).

(b) (E)-3-(2-Hidroxietiliden)-4-sulfanil-1-(trifenilmetil)piperidina

A una solución de (E)-4-(acetilsulfanil)-3-[(etoxicarbonil)metiliden]-1-(trifenilmetil)piperidina (18.35 g) obtenida en (a) anterior en diclorometano (300 ml) se le añadió por goteo una solución 1.01N de hidruro de diisobutilaluminio en tolueno (151 ml) a -78°C, y la mezcla resultante se agitó a la misma temperatura durante 1 hora. A la mezcla de la reacción se le añadió una solución acuosa saturada tetrahidratada de tartrato de sodio y potasio, y la mezcla resultante se agitó a temperatura ambiente durante 3 horas. La mezcla de la reacción se extrajo con acetato de etilo y se lavó con agua y una solución acuosa saturada de cloruro de sodio, y se secó la capa orgánica sobre sulfato de sodio anhidro. Se eliminó el solvente in vacuo, y se purificó el residuo mediante cromatografía en una columna de gel de sílice (acetato de etilo / hexano / diclorometano = 1 / 2 / 1) para obtener el compuesto del título (10.00

g, rendimiento 66%) como un sólido amorfo amarillo claro.

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 1.75-1.92 (1H, m), 2.25-2.57 (3H, m), 2.74-3.13 (2H, m), 3.53-3.72 (1H, m), 4.03-4.22 (2H, m), 5.71-5.85 (1H, m), 7.10-7.60 (15H, m).

(c) (E)-3-[2-(t-Butildimetilsililoxi)etiliden]-4-sulfanil-1-(trifenilmetil)piperidina

A una solución de (E)-3-(2-hidroxietiliden)-4-sulfanil-1-(trifenilmetil)piperidina (10.00 g) obtenida en (b) anterior en diclorometano (100 ml) se le añadió cloruro de t-butildimetilsililo (5.63 g), trietilamina (5.23 ml) y 4-dimetilaminopiridina (0.15 g) bajo enfriamiento con hielo, y la mezcla resultante se agitó a temperatura ambiente durante 1 hora. La mezcla de la reacción se evaporó in vacuo. Se diluyó el residuo con diclorometano y se lavó con agua y una solución acuosa saturada de cloruro de sodio, y se secó la capa orgánica sobre sulfato de magnesio anhidro. Se eliminó el solvente in vacuo, y se purificó el residuo mediante cromatografía en una columna de gel de sílice (acetato de etilo / hexano = 1 / 10) para obtener el compuesto del título (10.66 g, rendimiento 83%) como un sólido amorfo incoloro.

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 0.01-0.05 (6H, m), 0.85-0.90 (9H, m), 1.73-1.85 (1H, m), 2.20-2.51 (3H, m), 2.86-3.20 (2H, m), 3.60-3.64 (1H, m), 4.11-4.19 (2H, m), 5.64-5.71 (1H, m), 7.12-7.53 (15H, m).

(d) (E)-4-(Acetilsulfanil)-3-[2-(t-butildimetilsililoxi)etiliden]-1-(trifenilmetil)piperidina

A una solución de (E)-3-[2-(t-butildimetilsililoxi)etiliden]-4-sulfanil-1-(trifenilmetil)piperidina (10.66 g) obtenido en (c) anterior en diclorometano (100 ml) se le añadió anhídrido acético (2.93 ml), piridina (5.00 ml) y 4-dimetilaminopiridina (0.13 g) bajo enfriamiento con hielo, y la mezcla resultante se agitó a temperatura ambiente durante 3 horas. La mezcla de la reacción se evaporó in vacuo. Se

diluyó el residuo con acetato de etilo y se lavó con agua y una solución acuosa saturada de cloruro de sodio, y se secó la capa orgánica sobre sulfato de magnesio anhidro. Se eliminó el solvente in vacuo, y se purificó el residuo mediante cromatografía en una columna de gel de sílice (acetato de etilo / hexano = 1 / 10) para obtener el compuesto del título (10.95 g, rendimiento 95%) como un sólido amorfo incoloro.

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 0.04-0.07 (6H, m), 0.83-0.92 (9H, m), 1.75-1.92 (1H, m), 2.19-2.34 (5H, m), 2.41-2.70 (1H, m), 2.90-3.13 (2H, m), 4.06-4.21 (2H, m), 4.21-4.34 (1H, m), 5.66 (1H, t, J=6.0), 7.11-7.54 (15H, m).

(e) trifluoroacetato hidrogenado de (E)-4-(Acetilsulfanil)-3-(2-hidroxietiliden)piperidina

A una solución de (E)-4-(acetilsulfanil)-3-[2-(t-butildimetilsililoxi)etiliden]-1-(trifenilmetil)piperidina (10.95 g) obtenida en (d) anterior en diclorometano (10 ml) se le añadió ácido trifluoroacético (15 ml) bajo enfriamiento con hielo, y la mezcla resultante se agitó a temperatura ambiente durante 1 hora. La mezcla de la reacción se evaporó in vacuo, y se purificó el residuo mediante cromatografía en una columna de gel de sílice (metanol / diclorometano = 1 / 10 – 1 / 1) para obtener el compuesto del título (6.90 g, rendimiento cuantitativo) como un aceite café.

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 1.96-2.10 (1H, m), 2.26-2.43 (4H, m), 3.13-3.28 (1H, m), 3.29-3.41 (1H, m), 3.57-3.67 (1H, m), 4.02-4.11 (1H, m), 4.14-4.28 (2H, m), 4.40-4.45 (1H, m), 6.04-6.11 (1H, m).

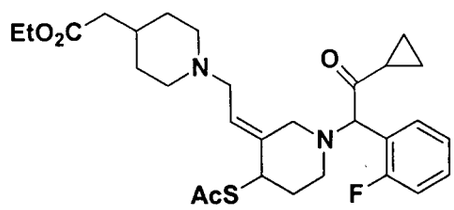
(f) (E)-4-(Acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-hidroxietiliden)piperidina

Se sintetizó el compuesto del título en un rendimiento de 74% como un aceite amarillo usando trifluoroacetato hidrogenado de (E)-4-(acetilsulfanil)-3-(2-hidroxietiliden)piperidina (6.90 g) obtenido en

(e) anterior realizando una reacción similar a la mencionada en el Ejemplo 1 (g).

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 0.75-0.92 (2H, m), 0.96-1.11 (2H, m), 1.59-1.87 (2H, m), 2.07-2.19 (1H, m), 2.19-2.34 (3H, m), 2.44-2.63 (1H, m), 2.64-2.79 (1H, m), 2.82 y 3.09 (total 1H, cada d, J=12.5), 3.26 y 3.41 (total 1H, cada d, J=12.5), 3.97-4.18 (2H, m), 4.23-4.37 (1H, m), 4.73 y 4.78 (total 1H, cada s), 5.75-5.87 (1H, m), 7.70-7.24 (2H, m), 7.29-7.41 (2H, m).

(Ejemplo 33) (E)-4-(Acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[4-(etoxicarbonilmetil)piperidin-1-il]etiliden}piperidina (Compuesto del compuesto No. 5-14)

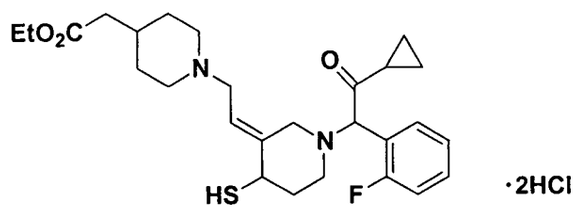


A una solución de (E)-4-(acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-hidroxietiliden)piperidina (500 mg) obtenida en el ejemplo 32 (f) y anhídrido p-toluenosulfónico (580 mg) en acetonitrilo (5 ml) se le añadió trietilamina (0.22 ml) bajo enfriamiento con hielo, la mezcla resultante se agitó a temperatura ambiente durante 5.5 horas. A la mezcla de la reacción se le añadió 4-(etoxicarbonilmetil)piperidina (450 mg) y trietilamina (0.37 ml), y la mezcla resultante se agitó a temperatura ambiente durante 3 horas y luego se dejó reposar durante 3 días. La mezcla de la reacción se diluyó con acetato de etilo y se lavó con agua, y se secó la capa orgánica sobre sulfato de magnesio anhidro. Se eliminó el solvente in vacuo, y se purificó aproximadamente el residuo mediante cromatografía en una columna de gel de sílice (metanol / diclorometano = 1 / 10) y luego se purificó usando una HPLC preparativa (YMC-Pack ODS-A; YMC, eluyente: acetonitrilo / agua con trietilamina (0.2%) y ácido acético (0.2%) = 13 / 7). La fracción

eluida se extrajo con acetato de etilo y se lavó con una solución acuosa saturada de cloruro de sodio, y se secó la capa orgánica sobre sulfato de magnesio anhidro. Se eliminó el solvente in vacuo para obtener el compuesto del título (204 mg, rendimiento 29%) como un aceite amarillo.

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 0.77-0.92 (2H, m), 0.94-1.10 (2H, m), 1.26 (3H, t, J=7.0), 1.55-1.89 (7H, m), 2.08-2.19 (2H, m), 2.21-2.26 (2H, m), 2.27-2.32 (3H, m), 2.48-2.61 (1H, m), 2.62-2.72 (1H, m), 2.72-3.40 (7H, m), 4.07-4.17 (2H, m), 4.24-4.36 (1H, m), 4.65-4.75 (1H, m), 5.69 (1H, bs), 7.08-7.22 (2H, m), 7.29-7.42 (2H, m).

(Ejemplo 34) diclorhidrato de (E)-1-[2-Ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[4-(etoxicarbonilmetil)piperidin-1-il]etiliden}-4-sulfanilpiperidina (Clorhidrato del compuesto del Compuesto No. 5-13)

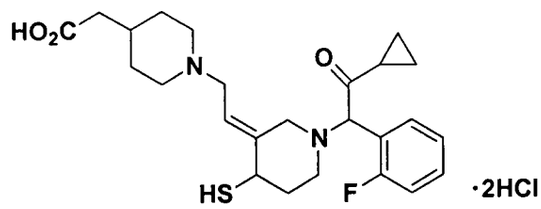


A una solución de (E)-4-(acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[4-(etoxicarbonilmetil)piperidin-1-il]etiliden}piperidina (204 mg) obtenida en el ejemplo 33 en etanol (10 ml) se hizo burbujear con cloruro de hidrógeno bajo enfriamiento con hielo, y la mezcla resultante se agitó a temperatura ambiente bajo condiciones herméticas durante la noche. La mezcla de la reacción se evaporó in vacuo para obtener el compuesto del título (201 mg, rendimiento 93%) como un sólido amorfo incoloro.

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 0.71-0.86 (2H, m), 1.03-1.12 (2H, m), 1.14 (3H, t, J=7.0), 1.71-1.82 (1H, m), 1.94-2.08 (2H, m), 2.09-2.49 (6H, m), 2.57-3.02 (4H, m), 3.33-3.48 (1H, m), 3.49-3.71 (4H, m), 3.76-3.83 (2H, m), 3.83-3.92 (1H, m), 4.11 (2H, q,

J=7.0), 5.03 y 5.04 (total 1H, cada s), 6.31-6.43 (1H, m), 7.13-7.31 (2H, m), 7.31-7.42 (1H, m), 7.54-7.65 (1H, m).

(Ejemplo 35) diclorhidrato de (E)-3-[2-(4-Carboximetilpiperidin-1-il)etiliden]-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-sulfanilpiperidina (Clorhidrato del compuesto del Compuesto No. 5-9)

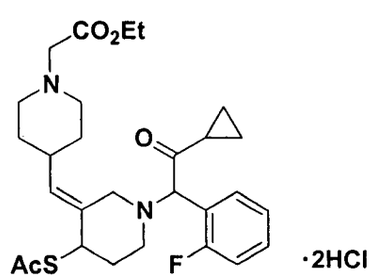


Se sintetizó el compuesto del título en un rendimiento de 57% como un sólido amorfo incoloro usando (E)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[4-(etoxicarbonilmetil)piperidin-1-il]etiliden}-4-sulfanilpiperidina diclorhidrato obtenida en el ejemplo 34 realizando una reacción similar a la mencionada en el Ejemplo 15.

RMN con ^{1}H (500 MHz, $CDCl_3$) δ ppm : 0.72-0.88 (2H, m), 1.04-1.17 (2H, m), 1.71-1.83 (1H, m), 1.94-2.11 (2H, m), 2.11-2.34 (5H, m), 2.46 (2H, bs), 2.65-2.76 (1H, m), 2.76-3.07 (4H, m), 3.46 (1H, d, J=12.5), 3.59 (1H, d, J=12.5), 3.62-3.75 (2H, m), 3.83-3.96 (2H, m), 5.08 (1H, s), 6.40 (1H, m), 7.22-7.31 (2H, m), 7.34-7.41 (1H, m), 7.61-7.67 (1H, m);

IR (KBr, cm^{-1}) :2556, 1714, 1493.

(Ejemplo 36) diclorhidrato de (E)-4-(Acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{[1-(etoxicarbonilmetil) piperidin-4-il]metiliden}piperidina (Clorhidrato del compuesto del Compuesto No. 3-32)



SS2

(a) 3-{[1-(Etoxicarbonilmetil)piperidin-4-il]hidroximetil}-1-(trifenilmetil)piperidin-4-ona

A una solución de 1-(trifenilmetil)piperidin-4-ona (22.99 g) en tetrahidrofurano (250 ml) se le añadió por goteo una solución 1.0N de bis(trimetilsilil)amida de sodio en tetrahidrofurano (68 ml) a -78°C, y la mezcla resultante se agitó a la misma temperatura durante 20 minutos. A la mezcla de la reacción se le añadió por goteo una solución de 1-(etoxicarbonilmetil)piperidin-4-carbaldehido (13.43 g) en tetrahidrofurano (35 ml) a -78°C, y la mezcla resultante se agitó a la misma temperatura durante 2 horas. La mezcla de la reacción se cargó con una solución acuosa saturada de cloruro de amonio y luego se extrajo con un solvente mezclado de acetato de etilo y éter dietílico. Se lavó el extracto con agua y una solución acuosa saturada de cloruro de sodio, y se secó la capa orgánica sobre sulfato de sodio anhidro. Se eliminó el solvente in vacuo, y se purificó el residuo mediante cromatografía en una columna de gel de sílice (acetato de etilo / hexano = 1 / 4 - 1 / 0) para obtener el compuesto del título (12.32 g, rendimiento 34%) como un sólido amorfo amarillo claro.

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 1.27 (3H, t, J=7.0), 1.41-2.18 (8H, m), 2.30-2.51 (1H, m), 2.67-3.25 (8H, m), 3.45-3.71 (2H, m), 4.18 (2H, q, J=7.0), 7.11-7.60 (15H, m).

(b) (E)-3-{[1-(Etoxicarbonilmetil)piperidin-4-il]metiliden}-1-(trifenilmetil)piperidin-4-ona

A una solución de 3-{[1-(etoxicarbonilmetil)piperidin-4-il]hidroximetil}-1-(trifenilmetil)-piperidin-4-ona (9.87 g) obtenida en (a) anterior en tetrahidrofurano (150 ml) se le añadió cloruro de metanosulfonilo (7.0 ml), 1,8-diazabiciclo[5.4.0]undec-7-eno (19 ml) y 4-dimetilaminopiridina (0.23 g) bajo enfriamiento con hielo, y la mezcla resultante se agitó a temperatura ambiente durante 17 horas. La mezcla de la reacción se diluyó con un solvente mezclado de

acetato de etilo y éter dietílico y se lavó con agua y una solución acuosa saturada de cloruro de sodio, y se secó la capa orgánica sobre sulfato de sodio anhidro. Se eliminó el solvente in vacuo, y se purificó el residuo mediante cromatografía en una columna de gel de sílice (acetato de etilo / hexano = 1 / 4 – 4 / 1) para obtener el compuesto del título (3.92 g, rendimiento 41%) como un sólido amorfo amarillo.

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 1.27 (3H, t, J=7.0), 1.50-1.66 (4H, m), 1.89-2.01 (1H, m), 2.10-2.21 (2H, m), 2.50-2.69 (4H, m), 2.83-2.93 (2H, m), 3.08-3.23 (4H, m), 4.18 (2H, q, J=7.0), 6.49 (1H, d, J=10.0), 7.14-7.33 (9H, m), 7.46-7.56 (6H, m).

(c) (E)-3-{[1-(Etoxicarbonilmetil)piperidin-4-il]metiliden}-1-(trifenilmetil)piperidin-4-ol

A una solución de (E)-3-{[1-(etoxicarbonilmetil)piperidin-4-il]metiliden}-1-(trifenilmetil)piperidin-4-ona (6.14 g) obtenida en (b) anterior en un solvente mezclado de etanol (40 ml) y diclorometano (40 ml) se le añadió borohidruro de sodio (0.55 g) bajo enfriamiento con hielo, y la mezcla resultante se agitó a temperatura ambiente durante 1 hora. La mezcla de la reacción se diluyó con acetato de etilo y se lavó con una solución acuosa saturada de carbonato de sodio hidrogenado y una solución acuosa saturada de cloruro de sodio, y se secó la capa orgánica sobre sulfato de sodio anhidro. Se eliminó el solvente in vacuo, y se purificó el residuo mediante cromatografía en una columna de gel de sílice (acetato de etilo / hexano = 2 / 3) para obtener el compuesto del título (4.17 g, rendimiento 68%) como un sólido amorfo incoloro.

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 1.29 (3H, t, J=7.5), 1.44-2.18 (7H, m), 2.77-3.22 (10H, m), 3.91-4.02 (1H, m), 4.20 (2H, q, J=7.5), 5.31 (1H, d, J=10.0), 7.09-7.30 (9H, m), 7.38-7.56 (6H, m).

(d) bis(trifluoroacetato hidrogenado) de (E)-4-(Acetilsulfanil)-3-{[1-(etoxicarbonilmetil)piperidin-4-il]metiliden}piperidina

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A una solución de (E)-3-{[1-(etoxicarbonilmetil)piperidin-4-il]metiliden}-1-(trifenilmetil)piperidin-4-ol (2.98 g) obtenido en (c) anterior en tolueno (50 ml) se le añadió ácido tioacético (1.20 ml) y dineopentil acetal de N,N-dimetilformamida (4.80 ml) bajo enfriamiento con hielo, y la mezcla resultante se agitó a temperatura ambiente durante 1.5 horas. La mezcla de la reacción se diluyó con acetato de etilo y se lavó con agua y una solución acuosa saturada de cloruro de sodio, y se secó la capa orgánica sobre sulfato de sodio anhidro. Se eliminó el solvente in vacuo, y se purificó el residuo mediante cromatografía en una columna de gel de sílice (acetato de etilo / hexano = 2 / 3) para obtener (E)-4-(acetilsulfanil)-3-{[1-(etoxicarbonilmetil)piperidin-4-il]metiliden}-1-(trifenilmetil)piperidina (1.97 g, con impurezas) como un sólido amorfo amarillo claro.

A una solución de la mezcla anterior (1.97 g) en diclorometano (30 ml) se le añadió ácido trifluoroacético (0.60 ml) bajo enfriamiento con hielo, y la mezcla resultante se agitó a temperatura ambiente durante 30 minutos. Se eliminó el solvente in vacuo, y se purificó el residuo mediante cromatografía en una columna de gel de sílice (etanol / diclorometano = 1 / 4 – 2 / 3) para obtener el compuesto del título (1.53 g, rendimiento 48%) como un sólido amorfo amarillo.

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 1.29 (3H, t, J=7.0), 1.67-2.61 (10H, m), 3.00-4.03 (10H, m), 4.25 (2H, q, J=7.0), 4.39 (1H, t, J=4.5), 5.71 (1H, d, J=10.0).

(e) diclorhidrato de (E)-4-(Acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{[1-(etoxicarbonilmetil)piperidin-4-il]metiliden}piperidina

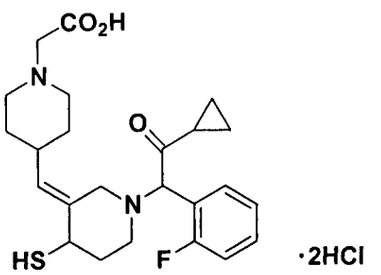
Se sintetizó el compuesto del título en un rendimiento de 81% como un sólido amorfo incoloro usando bis(trifluoroacetato hidrogenado) de (E)-4-(acetilsulfanil)-3-{[1-(etoxicarbonilmetil) piperidin-4-il]metiliden}piperidina obtenido en (d) anterior realizando

una reacción similar a la mencionada en el Ejemplo 1 (g).

RMN con ^1H (400 MHz, $CDCl_3$) δ ppm : 0.76-0.89 (2H, m), 0.90-1.12 (2H, m), 1.28 (3H, t, J=7.0), 1.39-2.34 (11H, m), 2.41-2.98 (7H, m), 3.18 y 3.19 (total 2H, cada s), 3.28-3.39 (1H, m), 4.13-4.33 (3H, m), 4.63 y 4.70 (total 1H, cada s), 5.38 (1H, d, J=9.0), 7.05-7.21 (2H, m), 7.27-7.37 (1H, m), 7.39-7.51 (1H, m);

IR (KBr, cm^{-1}) : 2614, 1697.

(Ejemplo 37) diclorhidrato de (E)-3-{[1-(Carboximetil)piperidin-4-il]metiliden}-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-sulfanilpiperidina (Clorhidrato del compuesto del Compuesto No. 3-27)



A una solución de (E)-4-(acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{[1-(etoxicarbonilmetil)piperidin-4-il]metiliden}piperidina (1.13 g) obtenida en el ejemplo 36 (e) en etanol (20 ml) se le hizo burbujear cloruro de hidrógeno bajo enfriamiento con hielo, y la mezcla resultante se agitó a temperatura ambiente bajo condición hermética durante 3 horas. Después de que la mezcla de la reacción se evaporó in vacuo, se disolvió el residuo obtenido en ácido clorhídrico 3N (20 ml) y la mezcla resultante se agitó a 50°C durante 12.5 horas. La mezcla de la reacción se removió in vacuo, y se purificó el residuo usando una HPLC preparativa (YMC-Pack ODS-A; YMC, eluyente: acetonitrilo / 0.024N ácido clorhídrico = 10 / 90) para obtener el compuesto del título (0.38 g, rendimiento 34%) como un sólido amorfo incoloro.

RMN con ^1H (400 MHz, piridina-d_5) δ ppm : 0.75-0.87 (2H, m), 0.96-1.19 (2H, m), 1.62-2.54 (8H, m), 2.62-3.19 (4H, m), 3.31-3.87

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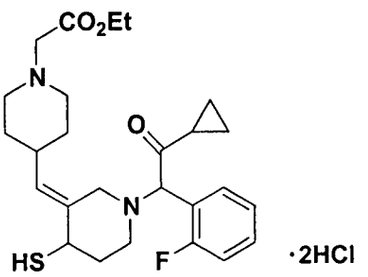
(5H, m), 4.10 y 4.11 (total 2H, cada s), 4.94 y 4.95 (total 1H, cada s), 5.49 y 5.50 (total 1H, cada d, J=9.0), 7.18-7.39 (3H, m), 7.70-7.78 (1H, m);

IR (KBr, cm^{-1}) : 2659, 1713, 1494.

(Ejemplo 38) diclorhidrato de (E)-1-[2-Ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{[1-(etoxicarbonilmetil)piperidin-4-il]metiliden}-4-sulfanilpiperidina (Clorhidrato del compuesto del Compuesto No. 3-31)



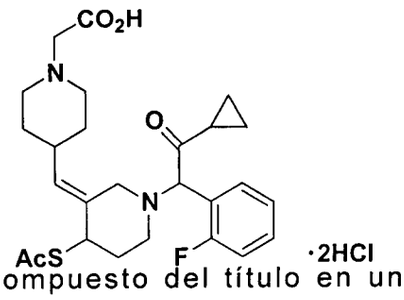
A una solución de diclorhidrato de (E)-3-{[1-(carboximetil)piperidin-4-il]metiliden}-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-sulfanilpiperidina (0.17 g) obtenida en el ejemplo 37 en etanol (4 ml) se le hizo burbujear cloruro de hidrógeno bajo enfriamiento con hielo, y la mezcla resultante se agitó a temperatura ambiente bajo condiciones herméticas durante 7 horas. La mezcla de la reacción se dejó reposar inmóvil a -20°C durante 3 días y luego se agitó a temperatura ambiente durante 7 horas más. La mezcla de la reacción se evaporó in vacuo, y se purificó el residuo mediante cromatografía en una columna de gel de sílice (etanol / diclorometano = 1 / 99 – 1 / 4) para obtener el compuesto del título (0.16 g, rendimiento 89%) como un sólido amorfo incoloro.

RMN con ^1H (400 MHz, $CDCl_3$) δ ppm : 0.77-1.12 (4H, m), 1.28 (3H, t, J=7.0), 1.41-2.36 (8H, m), 2.55-3.36 (10H, m), 3.68-3.81 (1H, m), 4.19 (2H, q, J=7.0), 4.66 y 4.72 (total 1H, cada s), 5.32 y 5.34 (total 1H, cada d, J=9.0), 7.03-7.55 (4H, m);

IR (KBr, cm^{-1}) : 2617, 1713, 1494.

(Ejemplo 39) diclorhidrato de (E)-4-(Acetilsulfanil)-3-{[(1-carboximetil)piperidin-4-il]metiliden}-1-[2-ciclopropil-1-(2-

fluorofenil)-2-oxoetil]piperidina (Clorhidrato del compuesto del Compuesto No. 3-28)

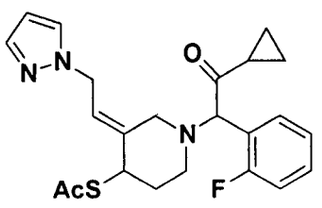


Se sintetizó el compuesto del título en un rendimiento de 52% como un sólido amorfo incoloro usando diclorhidrato de (E)-3-{[1-(carboximetil)piperidin-4-il]metiliden}-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-sulfanilpiperidina obtenida en el ejemplo 37 realizando una reacción similar a la mencionada en el Ejemplo 28.

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 0.73-0.89 (2H, m), 0.95-1.07 (2H, m), 1.67-2.34 (11H, m), 2.47-3.42 (10H, m), 4.21 y 4.27 (total 1H, cada t, J=4.5), 4.73 y 4.75 (total 1H, cada s), 5.37-5.45 (1H, m), 7.09-7.20 (2H, m), 7.31-7.39 (2H, m);

IR (KBr, cm^{-1}) : 2627, 1698.

(Ejemplo 40) (E)-4-(Acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-[2-(1H-pirazol-1-il)etiliden]piperidina (Compuesto del compuesto No. 1-2)



(a) (E)-4-(t-Butildimetilsililoxi)-3-[2-(1H-pirazol-1-il)etiliden]-1-(trifenilmetil)piperidina

A una solución de (E)-4-(t-butildimetilsililoxi)-3-(2-hidroxietiliden)-1-(trifenilmetil)piperidina (14.7 g) obtenida en el ejemplo 1 (b), 1H-pirazol (2.0 g) y 1,1'-(azodicarbonil)dipiperidina (8.9 g) en tolueno (150 ml) bajo una corriente de gas nitrógeno se le añadió tributilfosfina (8.8 ml) bajo enfriamiento con hielo, y la mezcla resultante se agitó a temperatura ambiente durante 1 hora. La

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mezcla de la reacción se evaporó in vacuo, y se purificó el residuo mediante cromatografía en una columna de gel de sílice (acetato de etilo / hexano = 1 / 6) para obtener el compuesto del título (9.78 g, rendimiento 57%) como un sólido amorfo incoloro.

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 0.04 (3H, s), 0.06 (3H, s), 0.89 (9H, s), 1.82 (1H, bs), 1.90-2.03 (3H, m), 3.04 (1H, bs), 3.74 (1H, bs), 3.97 (1H, m), 4.78-4.90 (2H, m), 5.86 (1H, t, J=7.0), 6.33-6.34 (1H, m), 7.22-7.23 (5H, m), 7.28-7.32 (4H, m), 7.48-7.68 (8H, m).

(b) (E)-4-Hidroxi-3-[2-(1H-pirazol-1-il)etiliden]-1-(trifenilmetil) piperidina

Se sintetizó el compuesto del título en un rendimiento de 77% como un cristal incoloro usando (E)-4-(t-butildimetilsililoxi)-3-[2-(1H-pirazol-1-il)etiliden]-1-(trifenilmetil)piperidina obtenido en (a) anterior realizando una reacción similar a la mencionada en el Ejemplo 1 (e).

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 1.44-1.50 (1H, m), 1.65-1.70 (1H, m), 1.82-1.89 (1H, m), 2.08-2.12 (1H, m), 2.85 (1H, bs), 3.38-3.41 (1H, m), 4.01 (1H, bs), 4.73-4.82 (2H, m), 5.79 (1H, t, J=6.5), 6.28 (1H, m), 7.15-7.17 (5H, m), 7.24-7.27 (4H, m), 7.42 (1H, m), 7.49 (6H, bs), 7.53 (1H, m).

(c) (E)-4-(Acetilsulfanil)-3-[2-(1H-pirazol-1-il)etiliden]-1-(trifenilmetil)piperidina

Se sintetizó el compuesto del título en un rendimiento de 56% como un sólido amorfo amarillo usando (E)-4-hidroxi-3-[2-(1H-pirazol-1-il)etiliden]-1-(trifenilmetil)piperidina obtenido en (b) anterior realizando una reacción similar a la mencionada en el Ejemplo 1 (h).

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 1.85-1.92 (1H, m), 2.24 (3H, s), 2.26-2.34 (1H, m), 2.64-2.67 (1H, m), 2.79-2.83 (1H, m), 4.21-4.36 (3H, m), 4.65-4.78 (2H, m), 5.79 (1H, t, J=7.0), 6.26 (1H, m), 7.11-7.15 (5H, m), 7.22-7.27 (4H, m), 7.42 (1H, m), 7.45 (6H, bs), 7.62 (1H, m).

(d) trifluoroacetato hidrogenado de (E)-4-(Acetilsulfanil)-3-[2-(1H-pirazol-1-il)etiliden]piperidina

Se sintetizó el compuesto del título en un rendimiento de 32% como un aceite café usando (E)-4-(acetilsulfanil)-3-[2-(1H-pirazol-1-il)etiliden]-1-(trifenilmetil)piperidina obtenido en (c) anterior realizando una reacción similar a la mencionada en el Ejemplo 3 (c).

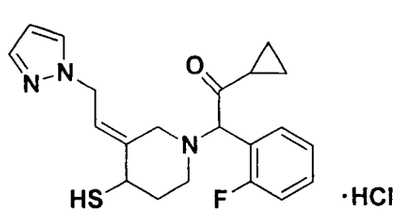
RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 2.03-2.07 (1H, m), 2.35 (3H, s), 2.38-2.45 (1H, m), 3.23-3.30 (1H, m), 3.38-3.43 (1H, m), 3.73 (1H, d, J=14.0), 4.12 (1H, d, J=14.0), 4.43-4.45 (1H, m), 4.68-4.84 (2H, m), 6.03 (1H, t, J=7.0), 6.23-6.24 (1H, m), 7.39-7.40 (1H, m), 7.46 (1H, bs).

(e) (E)-4-(Acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-[2-(1H-pirazol-1-il)etiliden]piperidina

Se sintetizó el compuesto del título en un rendimiento de 75% como un aceite amarillo usando trifluoroacetato hidrogenado de (E)-4-(acetilsulfanil)-3-[2-(1H-pirazol-1-il)etiliden]piperidina obtenido en (d) anterior realizando una reacción similar a la mencionada en el Ejemplo 1 (g).

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 0.75-0.88 (2H, m), 0.97-1.06 (2H, m), 1.79-1.86 (1H, m), 2.10-2.21 (1H, m), 2.22-2.31 (1H, m), 2.28 y 2.29 (total 3H, cada s), 2.49-2.62 (1H, m), 2.68-2.73 y 2.76-2.81 (total 1H, cada m), 2.89 y 3.16 (total 1H, cada d, J=12.5), 3.32 y 3.43 (total 1H, cada d, J=12.5), 4.28-4.35 (1H, m), 4.67-4.75 (3H, m), 5.80 (1H, t, J=7.0), 6.22-6.24 (1H, m), 7.08-7.17 (2H, m), 7.28-7.38 (3H, m), 7.47-7.48 (1H, m).

(Ejemplo 41) clorhidrato de (E)-1-[2-Ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-[2-(1H-pirazol-1-il)etiliden]-4-sulfanilpiperidina (Clorhidrato del compuesto del Compuesto No. 1-1)



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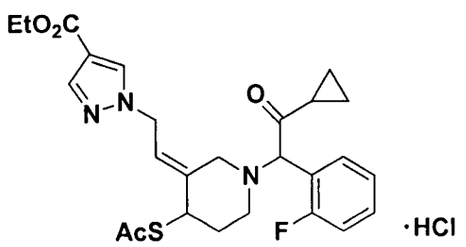
Se sintetizó el compuesto del título en un rendimiento de 27% como un sólido amorfo incoloro usando (E)-4-(acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-[2-(1H-pirazol-1-il)etiliden]piperidina obtenida en el ejemplo 40 (e) realizando una reacción similar a la mencionada en el Ejemplo 2.

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 0.77-0.80 (2H, m), 0.98-1.03 (1H, m), 1.06-1.13 (1H, m), 1.74-1.81 (1H, m), 2.13-2.24 (1H, m), 2.39-2.47 (1H, m), 2.51-2.54 (1H, m), 2.83-2.88 y 2.91-2.97 (total 1H, cada m), 3.33-3.38 (1H, m), 3.75-3.80 (1H, m), 4.90-4.96 (3H, m), 5.94-5.98 (1H, m), 6.33 (1H, t, J=2.0), 7.17-7.22 (1H, m), 7.26-7.32 (1H, m), 7.63-7.66 (3H, m), 7.70-7.71 (2H, m);

IR (KBr, cm^{-1}) : 1712, 1495.

(Ejemplo 42) clorhidrato de (E)-4-(Acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-[2-(4-etoxicarbonil-1H-pirazol-1-il)etiliden]piperidina (Clorhidrato del compuesto del Compuesto No. 1-26)



(a) (E)-4-(t-Butildimetilsililoxi)-3-[2-(4-etoxicarbonil-1H-pirazol-1-il)etiliden]-1-(trifenilmetil)piperidina

Se sintetizó el compuesto del título en un rendimiento de 83% como un sólido amorfo incoloro usando (E)-4-(t-butildimetilsililoxi)-3-(2-hidroxietiliden)-1-(trifenilmetil)piperidina obtenida en el ejemplo 1 (b) y 4-etoxicarbonil-1H-pirazol realizando una reacción similar a la mencionada en el Ejemplo 40 (a).

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 0.04 (6H, s), 0.88 (9H, s), 1.36-1.49 (2H, m), 1.40 (3H, t, J=7.0), 1.71-1.82 (1H, m), 1.90-2.00 (2H, m), 2.40 (1H, bs), 3.93-3.97 (1H, m), 4.34 (2H, q, J=7.0),

4.73-4.86 (2H, m), 5.84 (1H, t, J=7.0), 7.19-7.23 (5H, m), 7.27-7.32 (5H, m), 7.52 (5H, bs), 7.95 (1H, s), 7.97 (1H, s).

(b) (E)-3-[2-(4-Etoxicarbonil-1H-pirazol-1-il)etiliden]-4-hidroxi-1-(trifenilmetil)piperidina

Se sintetizó el compuesto del título en un rendimiento cuantitativo como un sólido amorfo incoloro usando (E)-4-(t-butildimetilsililoxi)-3-[2-(4-etoxicarbonil-1H-pirazol-1-il)etiliden]-1-(trifenilmetil)piperidina obtenida en (a) anterior realizando una reacción similar a la mencionada en el Ejemplo 1 (e).

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 1.34 (3H, t, J=7.0), 1.81-1.90 (1H, m), 2.07-2.12 (1H, m), 2.87 (2H, bs), 3.46 (2H, bs), 3.98 (1H, bs), 4.28 (2H, q, J=7.0), 4.68-4.79 (2H, m), 5.76 (1H, t, J=7.0), 7.12-7.15 (3H, m), 7.21-7.25 (6H, m), 7.45 (6H, bs), 7.89 (2H, s).

(c) (E)-4-(Acetilsulfanil)-3-[2-(4-etoxicarbonil-1H-pirazol-1-il) etiliden]-1-(trifenilmetil)piperidina

Se sintetizó el compuesto del título en un rendimiento de 88% como un sólido amorfo amarillo usando (E)-3-[2-(4-etoxicarbonil-1H-pirazol-1-il)etiliden]-4-hidroxi-1-(trifenilmetil)piperidina obtenido en (b) anterior realizando una reacción similar a la mencionada en el Ejemplo 1 (h).

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 1.26 (3H, t, J=7.0), 1.86-1.94 (1H, m), 2.21-2.24 (1H, m), 2.24 (3H, s), 3.80-3.83 (1H, m), 4.11 (2H, q, J=7.0), 4.19-4.27 (6H, m), 5.77 (1H, t, J=7.0), 7.12-7.17 (5H, m), 7.22-7.26 (5H, m), 7.43-7.45 (5H, m), 7.85 (1H, s), 7.91 (1H, s).

(d) trifluoroacetato hidrogenado de (E)-4-(Acetilsulfanil)-3-[2-(4-etoxicarbonil-1H-pirazol-1-il)etiliden]piperidina

Se sintetizó el compuesto del título en un rendimiento de 23% como un sólido café amorfo usando (E)-4-(acetilsulfanil)-3-[2-(4-etoxicarbonil-1H-pirazol-1-il)etiliden]-1-(trifenilmetil)piperidina

obtenida en (c) anterior realizando una reacción similar a la mencionada en el Ejemplo 3 (c).

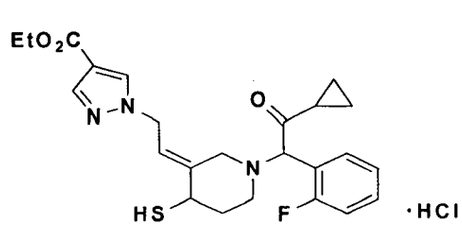
RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 1.33 (3H, t, J=7.0), 2.07-2.10 (1H, m), 2.36 (3H, s), 2.38-2.46 (1H, m), 3.22-3.28 (1H, m), 3.36-3.42 (1H, m), 3.73 (1H, d, J=14.0), 4.11 (1H, d, J=14.0), 4.27 (2H, q, J=7.0), 4.44-4.46 (1H, m), 4.72-4.84 (2H, m), 6.04-6.07 (1H, m), 7.85 (1H, s), 7.88 (1H, s).

(e) clorhidrato de (E)-4-(Acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-[2-(4-etoxicarbonil-1H-pirazol-1-il)etiliden]piperidina

Se sintetizó el compuesto del título en un rendimiento de 74% como un sólido amorfo amarillo usando trifluoroacetato hidrogenado de (E)-4-(acetilsulfanil)-3-[2-(4-etoxicarbonil-1H-pirazol-1-il)etiliden] piperidina obtenido en (d) anterior realizando una reacción similar a la mencionada en el Ejemplo 1 (g).

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 0.75-0.88 (2H, m), 1.00-1.07 (2H, m), 1.34 (3H, t, J=7.0), 1.80-1.87 (1H, m), 2.08-2.26 (2H, m), 2.28 y 2.30 (total 3H, cada s), 2.50-2.60 (1H, m), 2.67-2.72 y 2.78-2.82 (total 1H, cada m), 2.87 y 3.18 (total 1H, cada d, J=12.5), 3.29 y 3.44 (total 1H, cada d, J=12.5), 4.28 (2H, q, J=7.0), 4.33-4.35 (1H, m), 4.67-4.76 (3H, m), 5.79 (1H, t, J=7.0), 7.08-7.17 (2H, m), 7.29-7.37 (2H, m), 7.85-7.87 (2H, m).

(Ejemplo 43) clorhidrato de (E)-1-[2-Ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-[2-(4-etoxicarbonil-1H-pirazol-1-il)etiliden]-4-sulfanilpiperidina (Clorhidrato del compuesto del Compuesto No. 1-25)



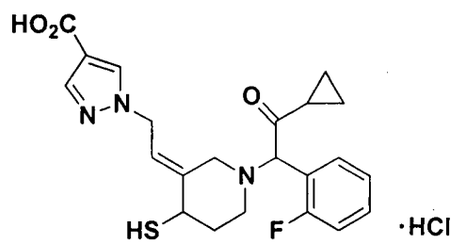
Se sintetizó el compuesto del título en un rendimiento de 46%

como un sólido amorfo amarillo usando (E)-4-(acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-[2-(4-etoxicarbonil-1H-pirazol-1-il)etiliden]piperidina obtenida en el ejemplo 42 (e) realizando una reacción similar a la mencionada en el Ejemplo 34.

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 0.76-0.88 (2H, m), 1.00-1.04 (2H, m), 1.35 (3H, t, J=7.0), 1.73-1.79 (1H, m), 2.09-2.12 (1H, m), 2.17-2.28 (1H, m), 2.54-2.60 y 2.61-2.67 (total 1H, cada m), 2.78-2.85 (1H, m), 3.04 y 3.24 (total 1H, cada d, J=12.5), 3.31 y 3.54 (total 1H, cada d, J=12.5), 3.65-3.70 y 3.73-3.77 (total 1H, cada m), 4.28 (2H, q, J=7.0), 4.69-4.77 (3H, m), 5.74-5.82 (1H, m), 7.09-7.17 (2H, m), 7.29-7.38 (2H, m), 7.87-7.90 (2H, m);

IR (KBr, cm^{-1}) : 2466, 1712, 1554.

(Ejemplo 44) clorhidrato de (E)-3-[2-(4-Carboxi-1H-pirazol-1-il)etiliden]-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-sulfanilpiperidina (Clorhidrato del compuesto del Compuesto No. 1-17)



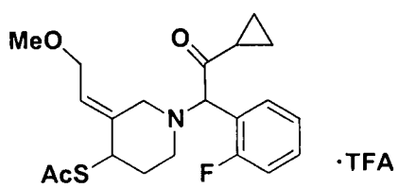
Se sintetizó el compuesto del título en un rendimiento de 14% como un sólido amorfo incoloro usando (E)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-[2-(4-etoxicarbonil-1H-pirazol-1-il)etiliden]-4-sulfanilpiperidina obtenida en el ejemplo 43 realizando una reacción similar a la mencionada en el Ejemplo 15.

RMN con ^{1}H (400 MHz, piridina-d_5) δ ppm : 0.79-0.82 (2H, m), 1.01-1.05 (1H, m), 1.09-1.13 (1H, m), 1.75-1.83 (1H, m), 2.16-2.25 (1H, m), 2.41-2.49 (1H, m), 2.62-2.68 (1H, m), 2.85-2.91 y 2.92-2.98 (total 1H, cada m), 3.35 y 3.38 (total 1H, cada d, J=13.0), 3.63 y 3.70 (total 1H, cada d, J=13.0), 3.79-3.82 (1H, m), 4.91-5.05 (3H, m),

5.99-6.03 (1H, m), 7.19-7.27 (2H, m), 7.29-7.35 (1H, m), 7.68-7.72 (1H, m), 8.43 (1H, s), 8.53 (1H, d, J=1.5);

IR (KBr, cm^{-1}) : 2546, 1709, 1555.

(Ejemplo 45) trifluoroacetato hidrogenado de (E)-4-(Acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-metoxietiliden)piperidina (Trifluoroacetato hidrogenado del compuesto del Compuesto No. 3-6)



(a) (E)-4-(t-Butildimetilsililoxi)-3-(2-metoxietiliden)-1-(trifenilmetil)piperidina

A una solución de (E)-4-(t-butildimetilsililoxi)-3-(2-hidroxietiliden)-1-(trifenilmetil)piperidina (1.85 g) obtenida en el ejemplo 1 (b) en N,N-dimetilformamida (20 ml) se le añadió hidruro de sodio (0.23 g) bajo enfriamiento con hielo, y la mezcla resultante se agitó a temperatura ambiente durante 15 minutos. A la mezcla de la reacción se le añadió yoduro de metilo (0.34 ml) a la misma temperatura, y la mezcla resultante se agitó a temperatura ambiente durante la noche. La mezcla de la reacción se diluyó con un solvente mezclado de acetato de etilo y éter y se lavó con una solución acuosa saturada de carbonato de sodio hidrogenado y una solución acuosa saturada de cloruro de sodio, y se secó la capa orgánica sobre sulfato de sodio anhidro. Se eliminó el solvente in vacuo, y se purificó el residuo mediante cromatografía en una columna de gel de sílice (acetato de etilo / hexano = 1 / 24) para obtener el compuesto del título (1.41 g, rendimiento 74%) como un aceite incoloro.

RMN con ^1H (400 MHz, $CDCl_3$) δ ppm : -0.02 (3H, s), -0.01 (3H, s), 0.86 (9H, s), 1.69-2.00 (4H, m), 2.87-2.96 (1H, m), 3.31 (3H, s),

3.49-3.61 (1H, m), 3.83-4.02 (3H, m), 5.72 (1H, t, J=8.0), 7.12-7.20 (3H, m), 7.22-7.28 (6H, m), 7.40-7.55 (6H, m).

(b) (E)-4-Hidroxi-3-(2-metoxietiliden)-1-(trifenilmetil)piperidina

Se sintetizó el compuesto del título en un rendimiento cuantitativo como un sólido amorfo incoloro usando (E)-4-(t-butildimetilsililoxi)-3-(2-metoxietiliden)-1-(trifenilmetil)piperidina obtenido en (a) anterior realizando una reacción similar a la mencionada en el Ejemplo 1 (e).

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 1.75-2.13 (4H, m), 2.66-2.81 (2H, m), 3.35 (3H, m), 3.88-4.02 (3H, m), 5.70 (1H, t, J=7.0), 7.13-7.20 (3H, m), 7.23-7.30 (6H, m), 7.43-7.53 (6H, m).

(c) bis(trifluoroacetato hidrogenado) de (E)-4-Hidroxi-3-(2-metoxietiliden)piperidina

Se sintetizó el compuesto del título en un rendimiento de 95% como un aceite incoloro usando (E)-4-hidroxi-3-(2-metoxietiliden)-1-(trifenilmetil)piperidina obtenido en (b) anterior realizando una reacción similar a la mencionada en el Ejemplo 3 (c).

RMN con ^{1}H (400 MHz, $CDCl_3$+DMSO-d_6) δ ppm : 1.88-2.13 (2H, m), 3.11-3.19 (1H, m), 3.32 (3H, s), 3.39-3.48 (1H, m), 3.75 (1H, d, J=13.5), 3.92 (1H, d, J=13.5), 4.01 (2H, d, J=6.0), 4.22-4.27 (1H, m), 5.87 (1H, t, J=6.0).

(d) (E)-1-[2-Ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-hidroxi-3-(2-metoxietiliden)piperidina

Se sintetizó el compuesto del título en un rendimiento de 78% como un aceite café usando (E)-4-hidroxi-3-(2-metoxietiliden)piperidina bis(trifluoroacetato hidrogenado) obtenido en (c) anterior realizando una reacción similar a la mencionada en el Ejemplo 1 (g).

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 0.78-1.09 (4H, m), 1.68-1.79 (1H, m), 1.96-2.05 (1H, m), 2.19-2.28 (1H, m), 2.42-2.54 (1H, m), 2.76-3.00 (2H, m), 3.30 (3H, s), 3.36 y 3.47 (total 1H, cada d,

J=12.0), 3.92 (2H, d, J=6.0), 4.07-4.15 (1H, m), 4.69 y 4.71 (total 1H, cada s), 5.68 y 5.69 (total 1H, cada t, J=6.0), 7.07-7.20 (2H, m), 7.28-7.46 (2H, m).

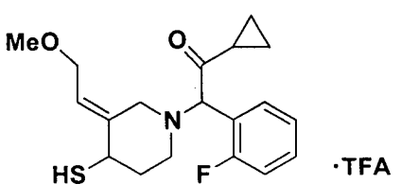
(e) trifluoroacetato hidrogenado de (E)-4-(Acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-metoxietiliden) piperidina

Se sintetizó el compuesto del título en un rendimiento de 30% como un aceite café claro usando (E)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-hidroxi-3-(2-metoxietiliden)piperidina obtenido en (d) anterior realizando una reacción similar a la mencionada en el Ejemplo 3 (e).

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 0.79-0.89 (2H, m), 0.95-1.08 (2H, m), 1.77-1.85 (1H, m), 2.11-2.28 (2H, m), 2.29 y 2.30 (total 3H, cada s), 2.46-3.08 (3H, m), 3.26 y 3.28 (total 3H, cada s), 3.30-3.56 (1H, m), 3.81-3.92 (2H, m), 4.28-4.36 (1H, m), 4.68 y 4.71 (total 1H, cada s), 5.72 (1H, t, J=6.5), 7.07-7.20 (2H, m), 7.29-7.35 (1H, m), 7.39-7.45 (1H, m);

IR (película líquida, cm^{-1}) : 1711, 1495.

(Ejemplo 46) trifluoroacetato hidrogenado de (E)-1-[2-Ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-metoxietiliden)-4-sulfanilpiperidina (Trifluoroacetato hidrogenado del compuesto del Compuesto No. 3-5)

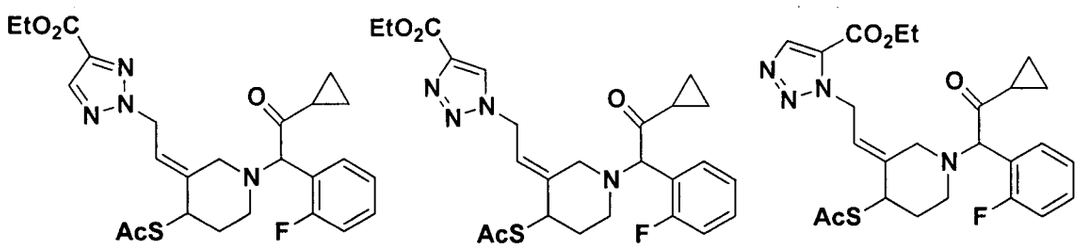


Se sintetizó el compuesto del título en un rendimiento de 60% como un aceite incoloro usando trifluoroacetato hidrogenado de (E)-4-(acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-metoxietiliden)piperidina obtenido en el ejemplo 45 (e) realizando una reacción similar a la mencionada en el Ejemplo 2.

RMN con ^1H (400 MHz, $CDCl_3$) δ ppm : 0.79-0.90 (2H, m), 0.95-1.09 (2H, m), 1.69-1.78 (1H, m), 2.13-2.32 (2H, m), 2.51-2.87 (2H, m), 3.03-3.57 (2H, m), 3.27 y 3.29 (total 3H, cada s), 3.70-3.92 (3H, m), 4.70 y 4.73 (total 1H, cada s), 5.68 y 5.71 (total 1H, cada t, J=6.5), 7.07-7.20 (2H, m), 7.28-7.46 (2H, m);

IR (película líquida, cm^{-1}) : 2564, 1714, 1495.

(Ejemplo 47) (E)-4-(Acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-[2-(4-etoxicarbonil-2H-1,2,3-triazol-2-il)etiliden]piperidina (Compuesto del compuesto No. 1-592), (E)-4-(acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-[2-(4-etoxicarbonil-1H-1,2,3-triazol-1-il)etiliden]piperidina (Compuesto del compuesto No. 1-492) y (E)-4-(acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-[2-(5-etoxicarbonil-1H-1,2,3-triazol-1-il)etiliden]piperidina (Compuesto del compuesto No. 1-498)



A una solución de (E)-4-(acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-hidroxietiliden)piperidina (1000 mg) obtenida en el ejemplo 32 (f) y 4-etoxicarbonil-1H-1,2,3-triazol (449 mg) en tolueno (10 ml) bajo una corriente de gas nitrógeno se le añadió 1,1'-(azodicarbonil)dipiperidina (802 mg) y tributilfosfina (0.79 ml) bajo enfriamiento con hielo, y la mezcla resultante se agitó a temperatura ambiente durante 18 horas. A la mezcla de la reacción se le añadió 4-etoxicarbonil-1H-1,2,3-triazol (224 mg), 1,1'-(azodicarbonil)dipiperidina (802 mg) y tributilfosfina (0.79 ml), y la mezcla resultante se agitó a temperatura ambiente durante 4.5 horas. A la mezcla de la reacción se le añadió 4-etoxicarbonil-1H-1,2,3-triazol (112 mg), 1,1'-(azodicarbonil)dipiperidina (200 mg) y

tributilfosfina (0.20 ml), y la mezcla resultante se agitó adicionalmente a temperatura ambiente durante 2 horas. La mezcla de la reacción se evaporó in vacuo, y se purificó aproximadamente el residuo mediante cromatografía en una columna de gel de sílice (acetato de etilo / hexano = 1 / 2 – 1 / 1) y luego se purificó usando una HPLC preparativa (YMC-Pack ODS-A; YMC, eluyente: acetonitrilo / 0.024N ácido clorhídrico = 15 / 85) para obtener los clorhidratos de los tres compuestos del título. Cada uno de los clorhidratos obtenidos se neutralizó con una solución acuosa saturada de carbonato de sodio hidrogenado y se extrajo con acetato de etilo. Se lavó el extracto con una solución acuosa saturada de cloruro de sodio, y se secó la capa orgánica sobre sulfato de magnesio anhidro. Se eliminó el solvente in vacuo para obtener los tres compuestos del título.

(E)-4-(Acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-[2-(4-etoxicarbonil-1H-1,2,3-triazol-1-il)etiliden]piperidina tuvo la mayor polaridad: un aceite incoloro, cantidad producida 120 mg, rendimiento 9%

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 0.76-0.90 (2H, m), 1.02-1.05 (2H, m), 1.42 (3H, t, J=7.0), 1.80-1.86 (1H, m), 1.98-2.04 (1H, m), 2.09-2.19 y 2.20-2.28 (total 1H, cada m), 2.29 y 2.31 (total 3H, cada s), 2.53-2.59 (1H, m), 2.66-2.71 y 2.78-2.84 (total 1H, cada m), 2.90 y 3.51 (total 1H, cada d, J=12.5), 3.28 (1H, bs), 4.25-4.27 y 4.32-4.34 (total 1H, cada m), 4.44 (2H, q, J=7.0), 4.80 y 4.81 (total 1H, cada s), 4.98-5.04 (2H, m), 5.80 (1H, t, J=7.5), 7.12-7.21 (2H, m), 7.31-7.39 (2H, m), 8.19 y 8.22 (total 1H, cada s).

(E)-4-(Acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-[2-(5-etoxicarbonil-1H-1,2,3-triazol-1-il)etiliden]piperidina la segunda polaridad más alta: un aceite amarillo, cantidad producida 219 mg, rendimiento 17%

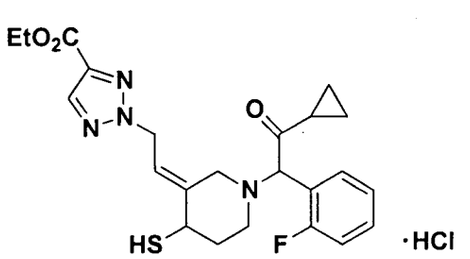
RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 0.81-0.91 (2H, m), 1.00-

1.11 (2H, m), 1.39 y 1.40 (total 3H, cada t, J=7.0), 1.77-1.84 (1H, m), 2.14-2.24 (2H, m), 2.25 (3H, s), 2.44-2.51 y 2.57-2.63 (total 1H, cada m), 2.68-2.77 (1H, m), 3.01 y 3.19 (total 1H, cada d, J=12.5), 3.48 y 3.53 (total 1H, cada d, J=12.5), 4.24-4.29 (1H, m), 4.37 y 4.38 (total 2H, cada q, J=7.0), 4.76 y 4.78 (total 1H, cada s), 5.27-5.35 (2H, m), 5.72-5.77 (1H, m), 7.09-7.20 (2H, m), 7.28-7.44 (2H, m), 8.07 (1H, s).

(E)-4-(Acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-[2-(4-etoxicarbonil-2H-1,2,3-triazol-2-il)etiliden]piperidina tuvo la menor polaridad: un aceite incoloro, cantidad producida 236 mg, rendimiento 18%

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 0.82-0.89 (2H, m), 1.00-1.08 (2H, m), 1.41 (3H, t, J=7.0), 1.79-1.86 (1H, m), 2.12-2.30 (2H, m), 2.27 y 2.28 (total 3H, cada s), 2.50-2.63 (1H, m), 2.68-2.80 (1H, m), 2.95 y 3.22 (total 1H, cada d, J=13.0), 3.34 y 3.68 (total 1H, cada d, J=13.0), 4.28-4.35 (1H, m), 4.43 (2H, q, J=7.0), 4.75 y 4.78 (total 1H, cada s), 5.05-5.13 (2H, m), 5.86 (1H, t, J=7.0), 7.11-7.22 (2H, m), 7.32-7.43 (2H, m), 8.03 (1H, s).

(Ejemplo 48) clorhidrato de (E)-1-[2-Ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-[2-(4-etoxicarbonil-2H-1,2,3-triazol-2-il)etiliden]-4-sulfanilpiperidina (Clorhidrato del compuesto del Compuesto No. 1-591)



Se sintetizó el compuesto del título en un rendimiento cuantitativo como un aceite amarillo claro usando (E)-4-(acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-[2-(4-etoxicarbonil-2H-1,2,3-triazol-2-il)etiliden]piperidina obtenida en el ejemplo 47 realizando una reacción similar a la mencionada en el

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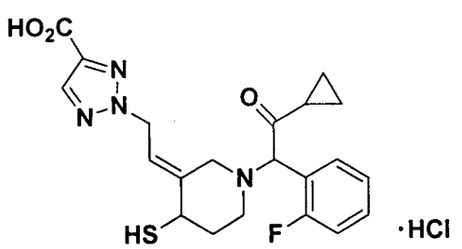
Ejemplo 34.

RMN con ^{1}H (400 MHz, piridina-d_5) δ ppm : 0.84-0.91 (2H, m), 1.01-1.07 (1H, m), 1.14-1.18 (1H, m), 1.23 (3H, t, J=7.0), 1.74-1.84 (1H, m), 2.14-2.24 (1H, m), 2.48-2.64 (2H, m), 2.84-2.98 (1H, m), 3.35-3.41 (1H, m), 3.69 y 3.75 (total 1H, cada d, J=12.5), 3.79-3.82 (1H, m), 4.35 (2H, q, J=7.0), 4.95 y 4.96 (total 1H, cada s), 5.30-5.35 (2H, m), 6.10-6.14 (1H, m), 7.23-7.35 (3H, m), 7.69-7.75 (1H, m), 8.37 (1H, s);

IR (KBr, cm^{-1}) : 2914, 1717.

(Ejemplo 49) clorhidrato de (E)-3-[2-(4-Carboxi-2H-1,2,3-triazol-2-il)etiliden]-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-sulfanilpiperidina (Clorhidrato del compuesto del Compuesto No. 1-587)



Se sintetizó el compuesto del título en un rendimiento de 74% como un sólido amorfo incoloro usando clorhidrato de (E)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-[2-(4-etoxicarbonil-2H-1,2,3-triazol-2-il)etiliden]-4-sulfanilpiperidina obtenido en el ejemplo 48 realizando una reacción similar a la mencionada en el Ejemplo 15.

RMN con ^{1}H (400 MHz, piridina-d_5) δ ppm : 0.80-0.94 (2H, m), 1.01-1.07 (1H, m), 1.14-1.19 (1H, m), 1.74-1.84 (1H, m), 2.14-2.25 (1H, m), 2.52-2.66 (2H, m), 2.84-2.98 (1H, m), 3.38-3.42 (1H, m), 3.70 y 3.76 (total 1H, cada d, J=13.0), 3.79-3.84 (1H, m), 4.95-4.97 (1H, m), 5.31-5.38 (2H, m), 6.12-6.17 (1H, m), 7.24-7.36 (3H, m), 7.71-7.78 (1H, m), 8.51 (1H, s);

IR (KBr, cm^{-1}) : 2927, 1712.

(Ejemplo 50) clorhidrato de (E)-1-[2-Ciclopropil-1-(2-fluorofenil)-

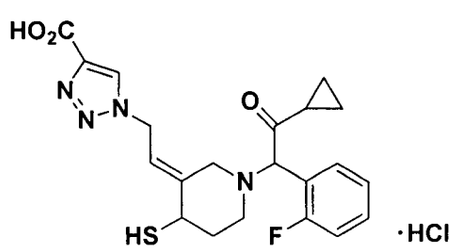
2-oxoetil]-3-[2-(4-etoxicarbonil-1H-1,2,3-triazol-1-il)etiliden]-4-sulfanilpiperidina (Clorhidrato del compuesto del Compuesto No. 1-491)

Se sintetizó el compuesto del título en un rendimiento cuantitativo como un aceite incoloro usando (E)-4-(acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-[2-(4-etoxicarbonil-1H-1,2,3-triazol-1-il)etiliden]piperidina obtenida en el ejemplo 47 realizando una reacción similar a la mencionada en el Ejemplo 34.

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 0.77-0.90 (2H, m), 1.02-1.05 (2H, m), 1.42 (3H, t, J=7.0), 1.54-1.58 (1H, m), 1.73-1.79 (1H, m), 1.99-2.03 (1H, m), 2.15-2.29 (1H, m), 2.53-2.58 y 2.62-2.67 (total 1H, cada m), 2.78-2.85 (1H, m), 3.27-3.35 (1H, m), 3.63-3.66 y 3.72-3.76 (total 1H, cada m), 4.44 (2H, q, J=7.0), 4.83 (1H, s), 5.01-5.06 (2H, m), 5.76-5.85 (1H, m), 7.12-7.26 (3H, m), 7.33-7.36 (1H, m), 8.23 y 8.24 (total 1H, cada s);

MS (FAB) m/z : 459 $(M+H)^+$

(Ejemplo 51) clorhidrato de (E)-3-[2-(4-Carboxi-1H-1,2,3-triazol-1-il)etiliden]-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-sulfanilpiperidina (Clorhidrato del compuesto del Compuesto No. 1-487)



Se sintetizó el compuesto del título en un rendimiento de 71% como un sólido amorfo incoloro usando clorhidrato de (E)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-[2-(4-etoxicarbonil-1H-1,2,3-

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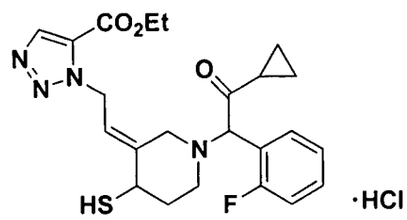
triazol-1-il)etiliden]-4-sulfanilpiperidina obtenido en el ejemplo 50 realizando una reacción similar a la mencionada en el Ejemplo 15.

RMN con ^{1}H (400 MHz, piridina-d_5) δ ppm : 0.77-0.81 (2H, m), 0.99-1.11 (2H, m), 1.73-1.81 (1H, m), 2.12-2.23 (1H, m), 2.29-2.36 (1H, m), 2.60-2.63 (1H, m), 2.82-2.96 (1H, m), 3.34 y 3.40 (total 1H, cada d, J=12.5), 3.65 y 3.73 (total 1H, cada d, J=12.5), 3.76-3.83 (1H, m), 4.96 y 4.97 (total 1H, cada s), 5.21-5.27 (2H, m), 5.96-6.01 (1H, m), 7.20-7.32 (3H, m), 7.64-7.68 (1H, m), 8.88 (1H, s);

IR (KBr, cm^{-1}) : 2927, 1711.

(Ejemplo 52) clorhidrato de (E)-1-[2-Ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-[2-(5-etoxicarbonil-1H-1,2,3-triazol-1-il)etiliden]-4-sulfanilpiperidina (Clorhidrato del compuesto del Compuesto No. 1-497)



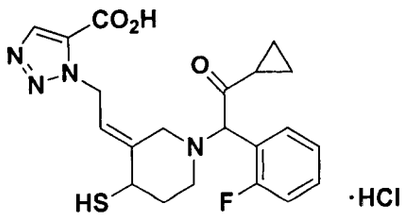
Se sintetizó el compuesto del título en un rendimiento de 90% como un sólido amorfo incoloro usando (E)-4-(acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-[2-(5-etoxicarbonil-1H-1,2,3-triazol-1-il)etiliden]piperidina obtenida en el ejemplo 47 realizando una reacción similar a la mencionada en el Ejemplo 34.

RMN con ^{1}H (400 MHz, piridina-d_5) δ ppm : 0.84-0.91 (2H, m), 1.03-1.09 (1H, m), 1.15-1.22 (1H, m), 1.21 (3H, t, J=7.0), 1.75-1.83 (1H, m), 2.15-2.25 (1H, m), 2.50-2.57 (1H, m), 2.60-2.68 (1H, m), 2.84-2.89 y 2.93-2.99 (total 1H, cada m), 3.46-3.54 (1H, m), 3.77-3.81 (2H, m), 4.28 (2H, q, J=7.0), 4.98 (1H, s), 5.52-5.56 (2H, m), 6.04-6.09 (1H, m), 7.21-7.35 (3H, m), 7.69-7.76 (1H, m), 8.39 (1H, s);

MS (FAB) m/z : 459 $(M+H)^+$.

(Ejemplo 53) clorhidrato de (E)-3-[2-(5-Carboxi-1H-1,2,3-triazol-1-il)etiliden]-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-

sulfanilpiperidina (Clorhidrato del compuesto del Compuesto No. 1-493)

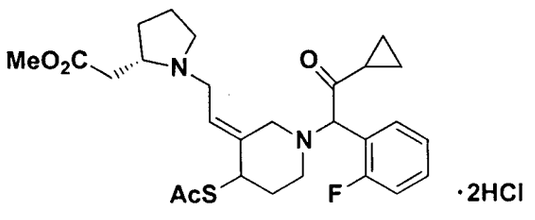


Se sintetizó el compuesto del título en un rendimiento de 68% como un sólido amorfo incoloro usando clorhidrato de (E)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-[2-(5-etoxicarbonil-1H-1,2,3-triazol-1-il)etiliden]-4-sulfanilpiperidina obtenido en el ejemplo 52 realizando una reacción similar a la mencionada en el Ejemplo 15.

RMN con ^{1}H (400 MHz, piridina-d_5) δ ppm : 0.77-0.91 (2H, m), 0.99-1.04 (1H, m), 1.13-1.19 (1H, m), 1.71-1.81 (1H, m), 2.10-2.21 (1H, m), 2.49-2.66 (2H, m), 2.78-2.96 (1H, m), 3.48-3.52 y 3.57-3.60 (total 1H, cada m), 3.77-3.83 (2H, m), 4.95 (1H, s), 5.68-5.72 (2H, m), 6.14-6.22 (1H, m), 7.21-7.33 (3H, m), 7.70-7.78 (1H, m), 8.55 (1H, s);

MS (FAB) m/z : 431 $(M+H)^+$.

(Ejemplo 54) diclorhidrato de (E)-4-(Acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[(2S)-(metoxicarbonilmetil)pirrolidin-1-il]etiliden}piperidina (Clorhidrato del compuesto del Compuesto No. 5-154)



Se sintetizó el compuesto del título en un rendimiento de 17% como un aceite amarillo usando (E)-4-(acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-hidroxietiliden)piperidina obtenida en el ejemplo 32 (f) y clorhidrato de (2S)-(metoxicarbonilmetil)pirrolidina realizando una reacción similar a la mencionada en el Ejemplo 33.

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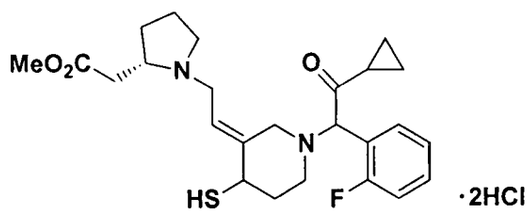
RMN con ^{1}H (500 MHz, piridina-d_5) δ ppm : 0.71-0.87 (2H, m), 1.02-1.15 (2H, m), 1.74-1.89 (2H, m), 1.89-2.04 (2H, m), 2.08-2.34 (5H, m), 2.54-2.81 (2H, m), 3.02-3.50 (5H, m), 3.53-3.69 (4H, m), 3.70-3.79 (1H, m), 3.79-3.99 (2H, m), 4.03-4.19 (1H, m), 4.42-4.51 (1H, m), 4.99-5.06 (1H, m), 6.29-6.41 (1H, m), 7.20-7.31 (2H, m), 7.32-7.41 (1H, m), 7.54-7.64 (1H, m);

IR (KBr, cm^{-1}) : 2547, 1700, 1494.

(Ejemplo 55) diclorhidrato de (E)-1-[2-Ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[(2S)-(metoxicarbonilmetil)pirrolidin-1-il]etiliden}-4-sulfanilpiperidina (Clorhidrato del compuesto del Compuesto No. 5-153)



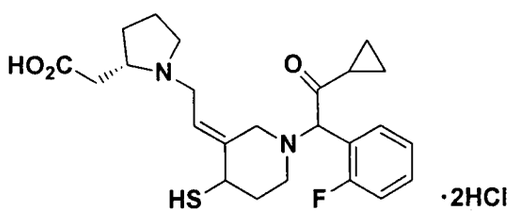
A una solución de diclorhidrato de (E)-4-(acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[(2S)-(metoxicarbonilmetil) pirrolidin-1-il]etiliden}piperidina (407 mg) obtenido en el ejemplo 54 en metanol (10 ml) se le hizo burbujear cloruro de hidrógeno bajo enfriamiento con hielo, y la mezcla resultante se agitó a temperatura ambiente bajo condiciones herméticas durante la noche. La mezcla de la reacción se removió in vacuo, y se purificó el residuo usando una HPLC preparativa (YMC-Pack ODS-A; YMC, eluyente: acetonitrilo / agua que contiene trietilamina (0.2%) y ácido acético (0.2%) = 1 / 1). La fracción eluida se extrajo con acetato de etilo y se lavó con una solución acuosa saturada de carbonato de sodio hidrogenado y una solución acuosa saturada de cloruro de sodio, y se secó la capa orgánica sobre sulfato de magnesio anhidro. Se eliminó el solvente in vacuo, y a una solución del residuo en diclorometano (10 ml) se le añadió una solución de cloruro de hidrógeno en dioxano 4N (0.26 ml) a temperatura ambiente. La

mezcla de la reacción se evaporó in vacuo para obtener el compuesto del título (192 mg, rendimiento 48%) como un sólido amorfo amarillo claro.

RMN con ^{1}H (500 MHz, piridina-d_5) δ ppm : 0.73-0.89 (2H, m), 1.02-1.14 (2H, m), 1.69-1.82 (1H, m), 1.82-2.11 (3H, m), 2.12-2.28 (2H, m), 2.29-2.43 (1H, m), 2.59-2.73 (1H, m), 2.74-2.98 (1H, m), 3.11-3.42 (3H ,m), 3.44-3.71 (5H, m), 3.76-4.02 (4H, m), 4.13-4.28 (1H, m), 5.00-5.07 (1H, m), 6.25-6.36 (1H, m), 7.22-7.32 (2H, m), 7.34-7.44 (1H, m), 7.58-7.67 (1H, m);

IR (KBr, cm^{-1}) : 2558, 1714, 1493.

(Ejemplo 56) diclorhidrato de (E)-3-{2-[(2S)-(Carboximetil)pirrolidin-1-il]etiliden}-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-sulfanilpiperidina (Clorhidrato del compuesto del Compuesto No. 5-151)



Se sintetizó el compuesto del título en un rendimiento de 46% como un sólido amorfo incoloro usando diclorhidrato de (E)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[(2S)-(metoxicarbonilmetil) pirrolidin-1-il]etiliden}-4-sulfanilpiperidina obtenida en el ejemplo 55 realizando una reacción similar a la mencionada en el Ejemplo 15.

RMN con ^{1}H (500 MHz, piridina-d_5) δ ppm : 0.71-0.86 (2H, m), 0.98-1.15 (2H, m), 1.71-1.90 (2H, m), 1.93-2.09 (2H, m), 2.11-2.24 (1H, m), 2.25-2.45 (2H, m), 2.56-2.75 (2H, m), 2.77-2.99 (1H, m), 3.26-4.05 (8H, m), 4.06-4.23 (1H, m), 4.95-5.02 (1H, m), 6.25-6.39 (1H, m), 7.19-7.29 (2H, m), 7.30-7.38 (1H ,m), 7.57-7.67 (1H, m);

IR (KBr, cm^{-1}) : 2562, 1713, 1493.

(Ejemplo 57) diclorhidrato de (E)-4-(Acetilsulfanil)-1-[2-

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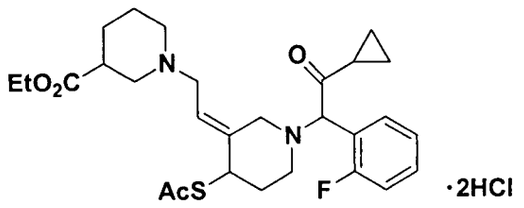
ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[3-(etoxicarbonil) piperidin-1-il]etiliden}piperidina (Clorhidrato del compuesto del Compuesto No. 5-342)

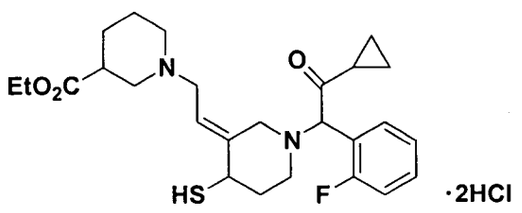


Se sintetizó el compuesto del título en un rendimiento de 61% como un sólido café amorfo usando (E)-4-(acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-hidroxietiliden)piperidina obtenida en el ejemplo 32 (f) y 3-(etoxicarbonil)piperidina realizando una reacción similar a la mencionada en el Ejemplo 33.

RMN con ^{1}H (400 MHz, piridina-d_5) δ ppm : 0.73-0.89 (2H, m), 1.02-1.14 (5H, m), 1.43-1.56 (1H, m), 1.65-1.76 (1H, m), 1.79-1.89 (1H, m), 1.98-2.09 (1H, m), 2.09-2.36 (6H, m), 2.54-2.84 (3H, m), 2.88-3.02 (1H, m), 3.17-3.66 (4H, m), 3.67-3.82 (3H, m), 4.02-4.11 (2H, m), 4.46-4.54 (1H, m), 4.99-5.05 (1H, m), 6.28-6.37 (1H, m), 7.18-7.42 (3H, m), 7.58-7.70 (1H, m);

IR (KBr, cm^{-1}) : 2526, 1710, 1493.

(Ejemplo 58) diclorhidrato de (E)-1-[2-Ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[3-(etoxicarbonil)piperidin}-1-il]etiliden}-4-sulfanilpiperidina (Clorhidrato del compuesto del Compuesto No. 5-341)



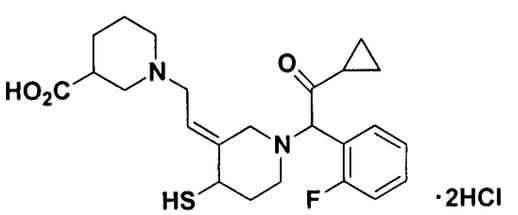
Se sintetizó el compuesto del título en un rendimiento de 49% como un sólido amorfo amarillo claro usando diclorhidrato de (E)-4-(acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[3-(etoxicarbonil)piperidin-1-il]etiliden}piperidina obtenida en el ejemplo

57 realizando una reacción similar a la mencionada en el Ejemplo 34.

RMN con ^{1}H (400 MHz, piridina-d_5) δ ppm : 0.74-0.86 (2H, m), 1.01-1.15 (5H, m), 1.45-1.56 (1H, m), 1.64-1.82 (2H, m), 1.98-2.38 (4H, m), 2.50-3.08 (5H, m), 3.27-3.92 (7H, m), 4.00-4.12 (2H, m), 4.97-5.03 (1H, m), 6.22-6.36 (1H, m), 7.20-7.38 (3H, m), 7.60-7.72 (1H, m);

IR (KBr, cm^{-1}) : 2533, 1726, 1493.

(Ejemplo 59) diclorhidrato de (E)-3-{2-[3-(Carboxipiperidin)-1-il]etiliden}-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-sulfanilpiperidina (Clorhidrato del compuesto del Compuesto No. 5-337)

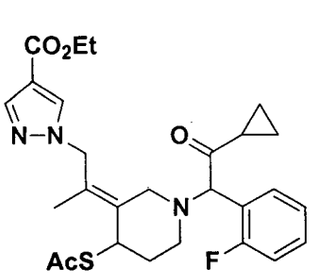


Se sintetizó el compuesto del título en un rendimiento de 72% como un sólido amorfo incoloro usando diclorhidrato de (E)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[3-(etoxicarbonil) piperidin}-1-il]etiliden}-4-sulfanilpiperidina obtenido en el ejemplo 58 realizando una reacción similar a la mencionada en el Ejemplo 15.

RMN con ^{1}H (500 MHz, piridina-d_5) δ ppm : 0.75-0.92 (2H, m), 1.02-1.17 (2H, m), 1.62-1.89 (3H, m), 2.11-2.38 (4H, m), 2.61-2.74 (1H, m), 2.74-3.00 (2H, m), 3.13-3.32 (1H, m), 3.37-3.54 (1H, m), 3.54-3.69 (3H, m), 3.85-4.10 (4H, m), 5.01-5.08 (1H, m), 6.27-6.37 (1H, m), 7.22-7.46 (3H, m), 7.65-7.79 (1H, m);

IR (KBr, cm^{-1}) : 2542, 1713, 1493.

(Ejemplo 60) (E)-4-(Acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{[2-(4-etoxicarbonil-1H-pirazol-1-il)-1-metil]etiliden}piperidina (Compuesto del compuesto No. 1-978)



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(a) (E)-3-[1-(Etoxicarbonil)etiliden]-4-hidroxi-1-(trifenilmetil) piperidina

A una solución de (E)-4-(t-butildimetilsililoxi)-3-[(etoxicarbonil)metiliden]-1-(trifenilmetil)piperidina (1.67 g) obtenida en el ejemplo 1 (a) en tetrahidrofurano (20 ml) se le añadió por goteo una solución 2.0 normal de diisopropilamida de litio en solución de heptano / tetrahidrofurano / etil benceno (2.30 ml) a -78°C, y la mezcla resultante se agitó a la misma temperatura durante 1 hora. A la mezcla de la reacción se le añadió por goteo yoduro de metilo (0.31 ml) a -78°C, y luego la mezcla resultante se agitó durante 2 horas mientras se calentaba gradualmente hasta temperatura ambiente. La mezcla de la reacción se cargó con una solución acuosa saturada de cloruro de amonio y luego se extrajo con acetato de etilo. Se lavó el extracto con agua y una solución acuosa saturada de cloruro de sodio, y se secó la capa orgánica sobre sulfato de sodio anhidro. Se eliminó el solvente in vacuo, y se purificó el residuo mediante cromatografía en una columna de gel de sílice (acetato de etilo / hexano = 3 / 97) para obtener una mezcla 1:2 (1.18 g, rendimiento 69%) de (E)-4-(t-butildimetilsililoxi)-3-[(1-etoxicarbonil)etiliden]-1-(trifenilmetil)piperidina y el isómero (Z) de él como un sólido amorfo amarillo claro. A una solución de esta mezcla (0.97 g) en tetrahidrofurano (15 ml) se le añadió una solución al 75% de fluoruro de tetrabutilamonio(1.40 g) en agua, y la mezcla resultante se agitó a 60°C durante 2 horas. La mezcla de la reacción se diluyó con acetato de etilo y se lavó con agua y una solución acuosa saturada de cloruro de sodio, y se secó la capa orgánica sobre sulfato de sodio anhidro. Se eliminó el solvente in vacuo, y se purificó el residuo mediante cromatografía en una columna de gel de sílice (acetato de etilo / hexano = 1 / 19 - 1 / 1) para obtener el

compuesto del título (292 mg, rendimiento 38%) como un aceite amarillo claro.

RMN con ^1H (400 MHz, $CDCl_3$) δ ppm : 1.03 (3H, t, J=7.0), 1.78-2.50 (6H, m), 2.74-2.83 (1H, m), 3.20-3.28 (1H, m), 3.84-4.03 (3H, m), 4.79 (1H, bs), 7.08-7.32 (9H, m), 7.37-7.50 (6H, m).

(b) (E)-4-(t-Butildimetilsililoxi)-3-[1-(etoxicarbonil)etiliden]-1-(trifenilmetil)piperidina

A una solución de (E)-3-[1-(etoxicarbonil)etiliden]-4-hidroxi-1-(trifenilmetil)piperidina (1.05 g) obtenida en (a) anterior en diclorometano (20 ml) se le añadió por goteo trifluorometanosulfonato de t-butildimetilsililo (0.60 ml) y 2,6-lutidina (0.83 ml) bajo enfriamiento con hielo, y la mezcla resultante se agitó a la misma temperatura durante 10 minutos. La mezcla de la reacción se cargó con una solución acuosa saturada de carbonato de sodio hidrogenado y luego se extrajo con acetato de etilo. Se lavó el extracto con una solución acuosa saturada de cloruro de sodio, y se secó la capa orgánica sobre sodio anhidro. Se eliminó el solvente in vacuo, y se purificó el residuo mediante cromatografía en una columna de gel de sílice (tolueno / hexano = 1 / 9 – 1 / 4, luego acetato de etilo / hexano = 1 / 9 – 1 / 4) para obtener el compuesto del título (1.05 g, rendimiento 79%) como un aceite amarillo claro.

RMN con ^1H (400 MHz, $CDCl_3$) δ ppm : -0.16 (3H, s), -0.06 (3H, s), 0.63 (9H, s), 0.99 (3H, t, J=7.5), 1.64-2.32 (7H, m), 2.75-2.83 (1H, m), 3.83-4.02 (3H, m), 4.68 (1H, bs), 7.07-7.34 (9H, m), 7.38-7.52 (6H, m).

(c) (E)-4-(t-Butildimetilsililoxi)-3-[(2-hidroxi-1-metil)etiliden]-1-(trifenilmetil)piperidina

A una suspensión de (E)-4-(t-butildimetilsililoxi)-3-[1-(etoxicarbonil)etiliden]-1-(trifenilmetil)piperidina (1.05 g) obtenido en (b) anterior en diclorometano (15 ml) se le añadió por goteo una solución 1.01N de hidruro de diisobutilaluminio en tolueno (5.7 ml) a

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-78°C, y la mezcla resultante se agitó a la misma temperatura durante 30 minutos. A la mezcla de la reacción se le añadió una solución acuosa de tartrato de sodio y potasio, y luego la mezcla resultante se agitó a temperatura ambiente durante 2 horas. La mezcla de la reacción se diluyó con acetato de etilo y se lavó con una solución acuosa saturada de cloruro de sodio, y se secó la capa orgánica sobre sulfato de sodio anhidro. Se eliminó el solvente in vacuo, y se purificó el residuo mediante cromatografía en una columna de gel de sílice (acetato de etilo / hexano = 1 / 19 - 1 / 4) para obtener el compuesto del título (0.72 g, rendimiento 74%) como un sólido amorfo incoloro.

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : -0.20 (3H, s), -0.07 (3H, s), 0.61 (9H, s), 1.62-2.20 (7H, m), 2.76-2.84 (1H, m), 3.57 (1H, d, J=12.0), 4.03-4.08 (2H, m), 4.70 (1H, bs), 7.08-7.28 (9H, m), 7.40-7.54 (6H, m).

(d) (E)-4-(t-Butildimetilsililoxi)-3-{[2-(4-etoxicarbonil-1H-pirazol-1-il)-1-metil]etiliden}-1-(trifenilmetil)piperidina

Se sintetizó el compuesto del título en un rendimiento de 94% como un sólido amorfo amarillo claro usando (E)-4-(t-butildimetilsililoxi)-3-[(2-hidroxi-1-metil)etiliden]-1-(trifenilmetil) piperidina obtenida en (c) anterior realizando una reacción similar a la mencionada en el Ejemplo 40 (a).

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : -0.20 (3H, s), -0.08 (3H, s), 0.62 (9H, s), 1.34 (3H, t, J=7.5), 1.62-2.08 (6H, m), 2.30-2.36 (1H, m), 2.83-2.90 (1H, m), 3.60-3.67 (1H, m), 4.22-4.35 (2H, m), 4.67-4.75 (3H, m), 7.07-7.33 (9H, m), 7.43-7.57 (6H, m), 7.77 (1H, s), 7.92 (1H, s).

(e) (E)-3-{[2-(4-Etoxicarbonil-1H-pirazol-1-il)-1-metil]etiliden}-4-hidroxi-1-(trifenilmetil)piperidina

Se sintetizó el compuesto del título en un rendimiento de 69% como un sólido amorfo amarillo usando (E)-4-(t-butildimetilsililoxi)-3-

{[2-(4-etoxicarbonil-1H-pirazol-1-il)-1-metil]etiliden}-1-(trifenilmetil) piperidina obtenido en (d) anterior realizando una reacción similar a la mencionada en el Ejemplo 1 (e).

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 1.36 (3H, t, J=7.5), 1.69 (3H, s), 1.86-2.35 (4H, m), 2.88-2.97 (1H, m), 3.75 (1H, d, J=13.5), 4.31 (2H, q, J=7.5), 4.62-4.73 (2H, m), 4.83 (1H, bs), 7.10-7.30 (9H, m), 7.40-7.56 (6H, m), 7.80 (1H, s), 7.92 (1H, s).

(f) trifluoroacetato hidrogenado de (E)-4-(Acetilsulfanil)-3-{[2-(4-etoxicarbonil-1H-pirazol-1-il)-1-metil]etiliden}piperidina

Se sintetizó el compuesto del título en un rendimiento de 67% como un aceite incoloro usando (E)-3-{[2-(4-etoxicarbonil-1H-pirazol-1-il)-1-metil]etiliden}-4-hidroxi-1-(trifenilmetil)piperidina obtenido en (e) anterior realizando una reacción similar a la mencionada en el Ejemplo 36 (d).

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 1.33 (3H, t, J=7.0), 1.80 (3H, s), 2.01-2.12 (1H, m), 2.37 (3H, s), 3.16-3.56 (4H, m), 4.28 (2H, q, J=7.0), 4.47 (1H, d, J=13.5), 4.72 (2H, s), 4.89 (1H, bs), 7.86 (1H, s), 7.88 (1H, s).

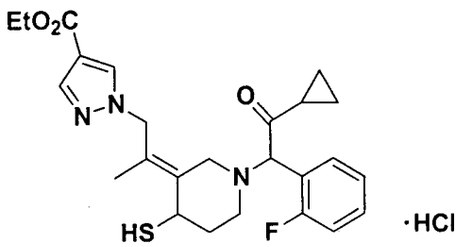
(g) (E)-4-(Acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{[2-(4-etoxicarbonil-1H-pirazol-1-il)-1-metil]etiliden}piperidina

Se sintetizó el compuesto del título en un rendimiento de 78% como un sólido amorfo incoloro usando trifluoroacetato hidrogenado de (E)-4-(acetilsulfanil)-3-{[2-(4-etoxicarbonil-1H-pirazol-1-il)-1-metil]etiliden}piperidina obtenido en (f) anterior realizando una reacción similar a la mencionada en el Ejemplo 1 (g).

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 0.65-1.08 (4H, m), 1.35 (3H, t, J=7.0), 1.70 y 1.73 (total 3H, cada s), 1.76-1.91 (1H, m), 2.02-2.99 (7H, m), 3.80-3.93 (1H, m), 4.24-4.34 (2H, m), 4.56-4.88 (5H, m), 7.08-7.23 (2H, m), 7.27-7.47 (2H, m), 7.77-7.91 (2H, m).

(Ejemplo 61) clorhidrato de (E)-1-[2-Ciclopropil-1-(2-fluorofenil)-

2-oxoetil]-3-{[2-(4-etoxicarbonil-1H-pirazol-1-il)-1-metil]etiliden}-4-sulfanilpiperidina (Clorhidrato del compuesto del Compuesto No. 1-977)

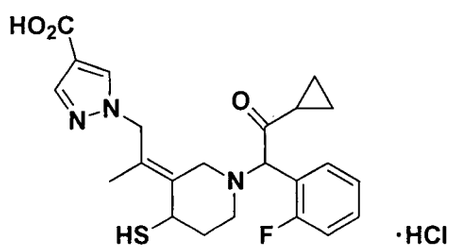


Se sintetizó el compuesto del título en un rendimiento de 64% como un sólido amorfo incoloro usando (E)-4-(acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{[2-(4-etoxicarbonil-1H-pirazol-1-il)-1-metil]etiliden}piperidina obtenida en el ejemplo 60 (g) anterior realizando una reacción similar a la mencionada en el Ejemplo 34.

RMN con ^{1}H (400 MHz, piridina-d_5) δ ppm : 0.69-0.87 (2H, m), 0.96-1.16 (2H, m), 1.22 (3H, t, J=7.0), 1.70-2.80 (7H, m), 2.89-3.00 (1H, m), 3.19 y 3.36 (total 1H, cada d, J=13.5), 4.01-4.48 (4H, m), 4.75-5.04 (3H, m), 7.14-7.37 (3H, m), 7.71-7.81 (1H, m), 8.25 (1H, s), 8.38 y 8.48 (total 1H, cada s);

IR (KBr, cm^{-1}) : 2611, 1713, 1494.

(Ejemplo 62) clorhidrato de (E)-3-{[2-(4-Carboxi-1H-pirazol-1-il)-1-metil]etiliden}-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-sulfanilpiperidina (Clorhidrato del compuesto del Compuesto No. 1-973)



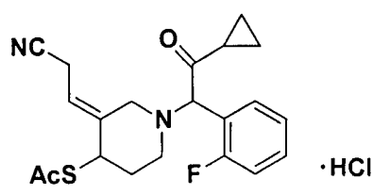
Se sintetizó el compuesto del título en un rendimiento de 75% como un sólido amorfo incoloro usando clorhidrato de (E)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{[2-(4-etoxicarbonil-1H-pirazol-1-il)-1-metil]etiliden}-4-sulfanilpiperidina obtenida en el

ejemplo 61 realizando una reacción similar a la mencionada en el Ejemplo 15.

RMN con ^{1}H (400 MHz, piridina-d_5) δ ppm : 0.72-0.88 (2H, m), 0.97-1.17 (2H, m), 1.57-3.03 (8H, m), 3.20 y 3.37 (total 1H, cada d, J=12.5), 4.06 y 4.18 (total 1H, cada d, J=12.5), 4.37-4.47 (1H, m), 4.77-5.04 (3H, m), 7.16-7.35 (3H, m), 7.74-7.84 (1H, m), 8.41 (1H, s), 8.47 y 8.57 (total 1H, cada s);

IR (KBr, cm^{-1}) : 2630, 1711, 1494.

(Ejemplo 63) clorhidrato de (E)-4-(Acetilsulfanil)-3-(2-cianoetiliden)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil] piperidina (Clorhidrato del compuesto del Compuesto No. 3-47)



(a) (E)-4-(t-Butildimetilsililoxi)-3-(2-cianoetiliden)-1-(trifenilmetil) piperidina

A una solución de cianuro de sodio (13.7 g) en un solvente mezclado de N,N-dimetilformamida (250 ml) y agua (25 ml) se le añadió (E)-4-(t-butildimetilsililoxi)-3-[2-(tosiloxi)etiliden]-1-(trifenilmetil)piperidina (34.4 g) obtenida en el ejemplo 1 (c) a temperatura ambiente, y la mezcla resultante se agitó durante 30 minutos. La mezcla de la reacción se cargó con agua y luego se extrajo con acetato de etilo. Se lavó el extracto con agua y una solución acuosa saturada de cloruro de sodio, y se secó la capa orgánica sobre sulfato de magnesio anhidro. Se eliminó el solvente in vacuo para obtener el compuesto del título (26.8 g, rendimiento cuantitativo) como un aceite café.

RMN con ^{1}H (500 MHz, $CDCl_3$) δ ppm : 0.01 (3H, s), 0.02 (3H, s), 0.88 (9H, s), 1.64-1.98 (4H, m), 2.94-3.16 (3H, m), 3.45-3.61 (1H, m), 3.82-3.89 (1H, m), 5.57 (1H, t, J=7.5), 7.12-7.36 (9H, m), 7.39-

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7.56 (6H, m).

(b) (E)-3-(2-Cianoetiliden)-1-(trifenilmetil)piperidin-4-ol

Se sintetizó el compuesto del título en un rendimiento de 65% como un sólido amorfo amarillo claro usando (E)-4-(t-butildimetilsililoxi)-3-(2-cianoetiliden)-1-(trifenilmetil)piperidina obtenida en (a) anterior realizando una reacción similar a la mencionada en el Ejemplo 1 (e).

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 1.75-2.28 (4H, m), 2.75-2.95 (1H, m), 3.07 (2H, m), 3.19-3.41 (1H, m), 3.91-4.02 (1H, m), 5.58 (1H, t, J=7.5), 7.14-7.35 (9H, m), 7.39-7.55 (6H, m).

(c) trifluoroacetato hidrogenado de (E)-4-(Acetilsulfanil)-3-(2-cianoetiliden)piperidina

Se sintetizó el compuesto del título en un rendimiento de 12% como un sólido incoloro usando (E)-3-(2-cianoetiliden)-1-(trifenilmetil)piperidin-4-ol obtenido en (b) anterior realizando una reacción similar a la mencionada en el Ejemplo 36 (d).

RMN con ^{1}H (400 MHz, DMSO-d_6) δ ppm : 1.82-1.93 (1H, m), 2.11-2.23 (1H, m), 2.37 (3H, s), 3.05-3.17 (1H, m), 3.25-3.43 (1H, m), 3.47 (2H, d, J=7.0), 3.60-3.68 (1H, m), 3.90-3.97 (1H, m), 4.40 (1H, m), 5.77 (1H, t, J=7.0).

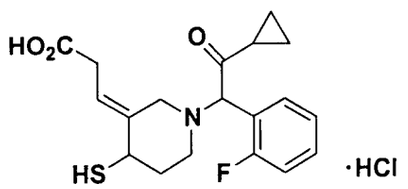
(d) clorhidrato de (E)-4-(Acetilsulfanil)-3-(2-cianoetiliden)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]piperidina

Se sintetizó el compuesto del título en un rendimiento de 58% como un aceite amarillo usando (E)-4-(acetilsulfanil)-3-(2-cianoetiliden)piperidina trifluoroacetato hidrogenado obtenido en (c) anterior realizando una reacción similar a la mencionada en el Ejemplo 1 (g).

RMN con ^{1}H (500 MHz, $CDCl_3$) δ ppm : 0.79-0.92 (2H, m), 0.99-1.09 (2H, m), 1.77-1.85 (1H, m), 2.05-2.27 (2H, m), 2.29 y 2.31 (total 3H, cada s), 2.46-2.58 (1H, m), 2.64-2.71 y 2.75-2.81 (total 1H, cada m), 2.76 y 3.08 (total 1H, cada d, J=12.5), 3.02-3.11 (2H, m), 3.15 y

3.33 (total 1H, cada d, J=12.5), 4.27 y 4.32 (total 1H, cada m), 4.74 y 4.77 (total 1H, cada s), 5.57 (1H, t, J=7.0), 7.11-7.23 (2H, m), 7.32-7.39 (2H, m).

(Ejemplo 64) clorhidrato de (E)-3-(2-Carboxietiliden)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-sulfanilpiperidina (Clorhidrato del compuesto del Compuesto No. 3-13)

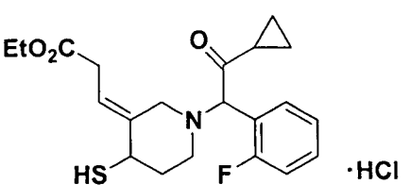


Se sintetizó el compuesto del título en un rendimiento de 39% como un sólido amorfo incoloro usando (E)-4-(acetilsulfanil)-3-(2-cianoetiliden)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]piperidina obtenida en el ejemplo 63 (d) realizando una reacción similar a la mencionada en el Ejemplo 37.

RMN con ^{1}H (500 MHz, piridina-d_5) δ ppm : 0.77-0.94 (2H, m), 0.97-1.04 (1H, m), 1.10-1.20 (1H, m), 1.75-1.85 (1H, m), 2.17-2.29 (1H, m), 2.51-2.60 (1H, m), 2.62-2.69 (1H, m), 2.87 y 2.97 (total 1H, cada m), 3.32-3.44 (3H, m), 3.59 (1H, m), 3.88-3.95 (1H, m), 4.91 y 4.93 (total 1H, cada s), 6.18-6.24 (1H, m), 7.17-7.26 (2H, m), 7.27-7.34 (1H, m), 7.70-7.75 (1H, m).

MS (FAB) m/z : 364 $(M+H)^+$.

(Ejemplo 65) clorhidrato de (E)-1-[2-Ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-[2-(etoxicarbonil)etiliden]-4-sulfanilpiperidina (Clorhidrato del compuesto del Compuesto No. 3-17)



Se sintetizó el compuesto del título en un rendimiento de 81% como un sólido amorfo incoloro usando clorhidrato de (E)-3-(2-carboxietiliden)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-

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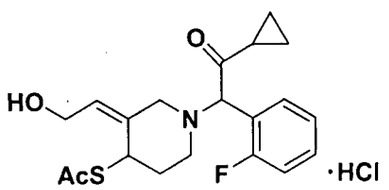
sulfanilpiperidina obtenida en el ejemplo 64 realizando una reacción similar a la mencionada en el Ejemplo 38.

RMN con ^{1}H (400 MHz, piridina-d_5) δ ppm : 0.76-0.88 (2H, m), 0.97-1.04 (1H, m), 1.11-1.17 (1H, m), 1.11 (3H, t, J=7.0), 1.73-1.84 (1H, m), 2.12-2.26 (1H, m), 2.44-2.53 (1H, m), 2.60-2.69 (1H, m), 2.80-2.99 (1H, m), 3.20-3.35(3H, m), 3.53 (1H, m), 3.87 (1H, m), 4.10 (2H, q, J=7.0), 4.91 y 4.92 (total 1H, cada s), 5.98-6.05 (1H, m), 7.17-7.26 (2H, m), 7.28-7.36 (1H, m), 7.66-7.72 (1H, m).

MS (FAB) m/z : 392 $(M+H)^+$.

(Ejemplo 66) clorhidrato de (Z)-4-(Acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-hidroxietiliden)piperidina (Clorhidrato del compuesto del Compuesto No. 4-2)



(a) (E)-3-(2-Hidroxietiliden)-1-(trifenilmetil)piperidin-4-ol

Se sintetizó el compuesto del título en un rendimiento de 86% como un sólido amorfo incoloro usando (E)-4-(t-butildimetilsililoxi)-3-(2-hidroxietiliden)-1-(trifenilmetil)piperidina obtenida en el ejemplo 1 (b) realizando una reacción similar a la mencionada en el Ejemplo 1 (e).

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 1.75-1.87 (2H, m), 2.02-2.04 (2H, m), 2.78 (1H, bs), 3.33 (1H, bs), 3.97 (1H, bs), 4.10-4.22 (2H, m), 5.74 (1H, t, J=7.0), 7.13-7.31 (15H, m).

(b) (E)-3-[2-(t-Butildifenilsililoxi)etiliden]-1-(trifenilmetil) piperidin-4-ol

A una solución de (E)-3-(2-hidroxietiliden)-1-(trifenilmetil)piperidin-4-ol (5.50 g) obtenido en (a) anterior en diclorometano (120 ml) se le añadió cloruro de t-butildifenilsililo (6.30 g), trietilamina (4.00 ml) y 4-dimetilaminopiridina (0.35 g) bajo enfriamiento con hielo, y la mezcla resultante se agitó a temperatura

ambiente durante 24 horas. La mezcla de la reacción se evaporó in vacuo y luego se diluyó con diclorometano. La mezcla resultante se lavó con agua y una solución acuosa saturada de cloruro de sodio, y se secó la capa orgánica sobre sulfato de magnesio anhidro. Se eliminó el solvente in vacuo, y se purificó el residuo mediante cromatografía en una columna de gel de sílice (acetato de etilo / hexano = 1 / 4) para obtener el compuesto del título (7.54 g, rendimiento 85%) como un sólido amorfo incoloro.

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 1.03 (9H, s), 1.68-1.81 (2H, m), 1.97-2.09 (2H, m), 2.64 (1H, bs), 3.03 (1H, bs), 3.89 (1H, bs), 4.22-4.35 (2H, m), 5.66 (1H, t, J=7.0), 7.04-7.50 (20H, m), 7.60-7.75 (5H, m).

(c) (E)-4-Acetoxi-3-[2-(t-butildifenilsililoxi)etiliden]-1-(trifenilmetil)piperidina

A una solución de (E)-3-[2-(t-butildifenilsililoxi)etiliden]-1-(trifenilmetil)piperidin-4-ol (512 mg) obtenido en (b) anterior en diclorometano (8 ml) se le añadió anhídrido acético (0.10 ml), trietilamina (0.17 ml) y 4-dimetilaminopiridina (10 mg) bajo enfriamiento con hielo, y la mezcla resultante se agitó a temperatura ambiente durante la noche. La mezcla de la reacción se diluyó con acetato de etilo y se lavó con una solución acuosa saturada de cloruro de sodio, y se secó la capa orgánica sobre sulfato de sodio anhidro. Se eliminó el solvente in vacuo, y se purificó el residuo mediante cromatografía en una columna de gel de sílice (acetato de etilo / hexano = 1 / 19 - 3 / 17) para obtener el compuesto del título (527 mg, rendimiento 96%) como un sólido amorfo incoloro.

RMN con ^{1}H (500 MHz, $CDCl_3$) δ ppm : 1.03 (9H, s), 1.76-1.89 (1H, m), 1.94-2.10 (4H, m), 2.40-2.76 (2H, m), 2.80-3.18 (1H, m), 3.39-3.64 (1H, m), 4.26 (2H, t, J=6.0), 4.99-5.11 (1H, m), 5.61 (1H, t, J=6.0), 7.03-7.48 (21H, m), 7.59-7.70 (4H, m).

(d) (Z)-4-(Acetilsulfanil)-3-(2-hidroxietiliden)-1-(trifenilmetil)

piperidina y (E)-4-(acetilsulfanil)-3-(2-hidroxietiliden)-1-(trifenilmetil)piperidina

Se disolvió cloruro de paladio (7 mg) y 1,1'-bis(difenilfosfino)ferroceno (44 mg) en 1,4-dioxano (4 ml) bajo una corriente de gas nitrógeno, y la mezcla resultante se agitó a temperatura ambiente durante 30 minutos. A la mezcla resultante se le añadió una solución de (E)-4-acetoxi-3-[2-(t-butildifenilsililoxi)etiliden]-1-(trifenilmetil)piperidina (527 mg) obtenida en (c) anterior en 1,4-dioxano (2 ml) y una solución de tioacetato de potasio (283 mg) en agua (1.5 ml), y la mezcla resultante se agitó a 100°C durante 6 horas. La mezcla de la reacción se diluyó con acetato de etilo y se lavó con una solución acuosa saturada de cloruro de sodio, y se secó la capa orgánica sobre sulfato de sodio anhidro. Se eliminó el solvente in vacuo, y se purificó el residuo mediante cromatografía en una columna de gel de sílice (acetato de etilo / hexano = 1 / 19 - 3 / 17) para obtener una mezcla 1:7 (479 mg, rendimiento 89%) de (Z)-4-(acetilsulfanil)-3-[2-(t-butildifenilsililoxi)etiliden]-1-(trifenilmetil)piperidina y su isómero (E) como un aceite incoloro.

A una solución de esta mezcla 1:7 (374 mg) en tetrahidrofurano (5 ml) se le añadió ácido acético (0.12 ml) y una solución al 75% de fluoruro de tetrabutilamonio(750 mg) en agua a temperatura ambiente, y la mezcla resultante se agitó a la misma temperatura durante 3 horas y at 50°C durante otras 2 horas. La mezcla de la reacción se diluyó con acetato de etilo y se lavó con una solución acuosa saturada de cloruro de sodio, y se secó la capa orgánica sobre sulfato de sodio anhidro. Se eliminó el solvente in vacuo, y se purificó el residuo mediante cromatografía en una columna de gel de sílice (acetato de etilo / hexano = 1 / 19 - 1 / 3) para obtener la forma (Z) del compuesto del título (25 mg, rendimiento 11%) como un sólido amorfo incoloro y la forma (E) (178 mg, rendimiento 74%)

como un cristal blanco.

(Z)-4-(Acetilsulfanil)-3-(2-hidroxietiliden)-1-(trifenilmetil) piperidina:

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 1.60 (1H, dd, J=12.0, 2.0), 1.77-1.83 (1H, m), 2.13 (1H, d, J=12.0), 2.20 (3H, s), 2.31-2.42 (1H, m), 3.03-3.10 (1H, m), 3.37 (1H, dd, J=12.0, 2.0), 4.19-4.28 (1H, m), 4.40-4.48 (1H, m), 4.86 (1H, d, J=4.0), 5.51 (1H, t, J=7.0), 7.11-7.54 (15H, m).

(E)-4-(Acetilsulfanil)-3-(2-hidroxietiliden)-1-(trifenilmetil) piperidina:

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 1.83-1.96 (1H, m), 2.21-2.42 (1H, m), 2.37 (3H, s), 2.95-3.16 (2H, m), 3.36-3.48 (1H, m), 3.60-3.79 (3H, m), 4.40 (1H, m), 5.98 (1H, t, J=6.0), 7.19-7.31 (9H, m), 7.36-7.40 (6H, m).

(e) clorhidrato de (Z)-4-(Acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-hidroxietiliden)piperidina

A una solución de (Z)-4-(acetilsulfanil)-3-(2-hidroxietiliden)-1-(trifenilmetil)piperidina (130 mg) obtenida en (d) anterior en diclorometano (5 ml) se le añadió ácido trifluoroacético (0.30 ml) bajo enfriamiento con hielo, y la mezcla resultante se agitó a temperatura ambiente durante 1 hora. Se eliminó el solvente in vacuo, y se purificó el residuo mediante cromatografía en una columna de gel de sílice (metanol / diclorometano = 1 / 5) para obtener trifluoroacetato hidrogenado de (Z)-4-(acetilsulfanil)-3-(2-hidroxietiliden)piperidina como un sólido amorfo incoloro.

A una solución del sólido amorfo anterior y 2-bromo-2-(2-fluorofenil)-1-ciclopropiletanona (150 mg) en acetonitrilo (2 ml) se le añadió trietilamina (0.10 ml) bajo enfriamiento con hielo, y la mezcla resultante se agitó a temperatura ambiente durante 15 minutos. La mezcla de la reacción se diluyó con acetato de etilo y se lavó con agua y una solución acuosa saturada de cloruro de sodio, y se secó

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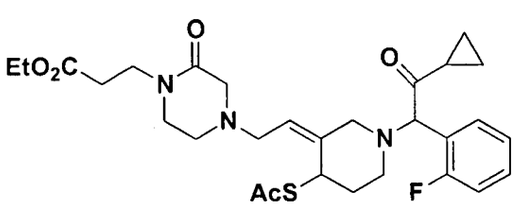
la capa orgánica sobre sulfato de sodio anhidro. Se eliminó el solvente in vacuo, y se purificó el residuo mediante cromatografía en una columna de gel de sílice (acetato de etilo / hexano = 1 / 1) para producir la forma libre (54 mg, rendimiento 49%) del compuesto del título como un sólido amorfo incoloro. A una solución de este compuesto en dioxano (3 ml) se le añadió una solución de cloruro de hidrógeno en dioxano 4N (0.11 ml) a temperatura ambiente, y se eliminó el solvente in vacuo para obtener el compuesto del título (61 mg, rendimiento cuantitativo) como un sólido amorfo incoloro.

RMN con ^{1}H (500 MHz, piridina-d_5) δ ppm : 0.70-0.84 (2H, m), 0.94-1.13 (2H, m), 1.75-1.89 (1H, m), 2.13-2.61 (3H, m), 2.19 (3H, s), 2.87-3.11 (1H, m), 2.91 y 3.07 (total 1H, cada d, J=12.0), 3.37 y 3.54 (total 1H, cada d, J=12.0), 4.54-4.64 (1H, m), 4.71-4.81 (1H, m), 4.83 y 4.88 (total 1H, cada s), 5.12 (1H, bs), 5.81 y 5.91 (total 1H, cada t, J=6.5), 7.17-7.24 (2H, m), 7.27-7.33 (1H, m), 7.61-7.68 (1H, m).

MS (FAB) m/z : 378 $(M+H)^+$.

(Ejemplo 67) (Z)-4-(Acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-{4-[2-(etoxicarbonil)etil]-3-oxopiperazin-1-il}etiliden)piperidina (Compuesto del compuesto No. 6-108)



Se sintetizó el compuesto del título en un rendimiento de 50% como un sólido amorfo incoloro usando (Z)-4-(acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-hidroxietiliden)piperidina obtenida en el ejemplo 66 (e) y 1-[2-(etoxicarbonil)etil]-2-oxopiperazina clorhidrato realizando una reacción similar a la mencionada en el Ejemplo 33.

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 0.79-0.90 (2H, m), 0.94-

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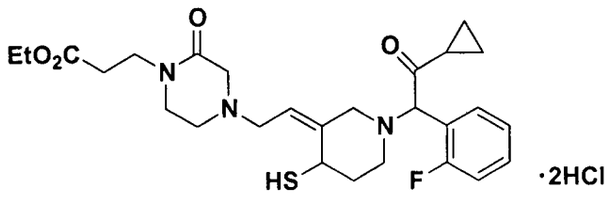
1.07 (2H, m), 1.26 y 1.27 (total 3H, cada t, J=7.0), 1.71-1.84 (1H, m), 2.06-2.50 (3H, m), 2.30 (3H, s), 2.57-2.72 (6H, m), 2.77-3.33 (5H, m), 3.34-3.42 (2H, m), 3.58-3.66 (2H, m), 4.13 y 4.15 (total 2H, cada q, J=7.0), 4.63 y 4.67 (total 1H, cada s), 4.78 (1H, bs), 5.27 y 5.36 (total 1H, cada t, J=7.0), 7.07-7.20 (2H, m), 7.28-7.44 (2H, m).

MS (FAB) m/z : 560 $(M+H)^+$.

(Ejemplo 68) diclorhidrato de (Z)-1-[2-Ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-{4-[2-(etoxicarbonil)etil]-3-oxopiperazin-1-il}etiliden)-4-sulfanilpiperidina (Clorhidrato del compuesto del Compuesto No. 6-107)

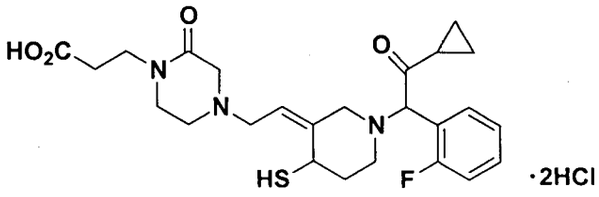


Se sintetizó el compuesto del título en un rendimiento de 66% como un sólido amorfo incoloro usando (Z)-4-(acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-{4-[2-(etoxicarbonil)etil]-3-oxopiperazin-1-il}etiliden)piperidina obtenida en el ejemplo 67 realizando una reacción similar a la mencionada en el Ejemplo 34.

RMN con ^1H (400 MHz, piridina-d_5) δ ppm : 0.71-0.83 (2H, m), 0.95-1.02 (1H, m), 1.05-1.11 (4H, m), 1.69-1.80 (1H, m), 2.15-2.30 (1H, m), 2.40-2.48 (1H, m), 2.64-3.00 (6H, m), 3.10-3.18 (2H, m), 3.19-3.51 (6H, m), 3.72-3.78 (2H, m), 4.07 y 4.08 (total 2H, cada q, J=7.0), 4.43 (1H, bs), 4.90 y 4.92 (total 1H, cada s), 5.35 y 5.43 (total 1H, cada t, J=7.0), 7.16-7.23 (2H, m), 7.27-7.33 (2H, m).

MS (FAB) m/z : 518 $(M+H)^+$.

(Ejemplo 69) diclorhidrato de (Z)-3-(2-{4-[2-(Carboxietil)]-3-oxopiperazin-1-il}etiliden)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-sulfanilpiperidina (Clorhidrato del compuesto del Compuesto No. 6-103)

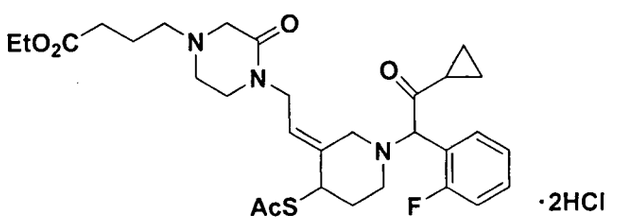


Se sintetizó el compuesto del título en un rendimiento de 95% como un sólido amorfo incoloro usando diclorhidrato de (Z)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-{4-[2-(etoxicarbonil)etil]-3-oxopiperazin-1-il}etiliden)-4-sulfanilpiperidina obtenido en el ejemplo 68 realizando una reacción similar a la mencionada en el Ejemplo 15.

RMN con ^{1}H (400 MHz, piridina-d_5) δ ppm : 0.69-0.85 (2H, m), 0.94-1.13 (2H, m), 1.66-1.82 (1H, m), 2.12-2.33 (1H, m), 2.39-2.50 (1H, m), 2.60-3.04 (6H, m), 3.08-3.43 (6H, m), 3.43-3.54 (2H, m), 3.83-3.94 (2H, m), 4.44 (1H, bs), 4.90 y 4.92 (total 1H, cada s), 5.33 y 5.44 (total 1H, cada t, J=7.0), 7.16-7.33 (3H, m), 7.64-7.72 (1H, m).

MS (FAB) m/z : 490 $(M+H)^+$.

(Ejemplo 70) diclorhidrato de (E)-4-(Acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-{4-[3-(etoxicarbonil) propil]-2-oxopiperazin-1-il}etiliden)piperidina (Clorhidrato del compuesto del Compuesto No. 5-86)



(a) (E)-4-(t-Butildimetilsililoxi)-3-(2-{4-[3-(etoxicarbonil)propil]-2-oxopiperazin-1-il}etiliden)-1-(trifenilmetil)piperidina

Se sintetizó el compuesto del título en un rendimiento de 62% como un aceite amarillo usando (E)-4-(t-butildimetilsililoxi)-3-[2-(tosiloxi)etiliden]-1-(trifenilmetil)piperidina obtenida en el ejemplo 1 (c) y 1-[3-(etoxicarbonil)propil]-3-oxopiperazina realizando una reacción similar a la mencionada en el Ejemplo 21 (a).

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : -0.05 (3H, s), -0.02 (3H, s), 0.83 (9H, s), 1.25 (3H, t, J=7.0), 1.75-1.94 (3H, m), 1.81 (2H, t,

J=7.0), 2.35 (2H, t, J=7.0), 2.41 (2H, t, J=7.0), 2.63 (2H, t, J=5.5), 2.80-2.95 (1H, m), 3.12 (2H, s), 3.18-3.27 (2H, m), 3.50 (1H, m), 3.81-3.89 (1H, m), 3.94-4.10 (3H, m), 4.12 (2H, q, J=7.0), 5.44 (1H, t, J=6.5), 7.10-7.19 (3H, m), 7.21-7.31 (6H, m), 7.37-7.56 (6H, m).

(b) (E)-3-(2-{4-[3-(Etoxicarbonil)propil]-2-oxopiperazin-1-il}etiliden)-4-hidroxi-1-(trifenilmetil)piperidina

Se sintetizó el compuesto del título en un rendimiento de 98% como un sólido amorfo amarillo usando (E)-4-(t-butildimetilsililoxi)-3-(2-{4-[3-(etoxicarbonil)propil]-2-oxopiperazin-1-il}etiliden)-1-(trifenilmetil)piperidina obtenido en (a) anterior realizando una reacción similar a la mencionada en el Ejemplo 1 (e).

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 1.24 (3H, t, J=7.0), 1.74-1.84 (1H, m), 1.80 (2H, t, J=7.0), 1.91-2.11 (3H, m), 2.34 (2H, t, J=7.0), 2.40 (2H, t, J=7.0), 2.65 (2H, t, J=6.0), 2.74 (1H, m), 3.12 (2H, s), 3.19-3.40 (1H, m), 3.25 (2H, t, J=5.5), 3.90-4.01 (2H, m), 4.02-4.09 (1H, m), 4.11 (2H, q, J=7.0), 5.43 (1H, t, J=6.5), 7.06-7.32 (9H, m), 7.35-7.58 (6H, m).

(c) (E)-4-(Acetilsulfanil)-3-(2-{4-[3-(etoxicarbonil)propil]-2-oxopiperazin-1-il}etiliden)-1-(trifenilmetil)piperidina

Se sintetizó el compuesto del título en un rendimiento de 10% como un sólido amorfo amarillo usando (E)-3-(2-{4-[3-(etoxicarbonil)propil]-2-oxopiperazin-1-il}etiliden)-4-hidroxi-1-(trifenilmetil)piperidina obtenida en (b) anterior realizando una reacción similar a la mencionada en el Ejemplo 1 (h).

RMN con ^{1}H (500 MHz, $CDCl_3$) δ ppm : 1.26 (3H, t, J=7.0), 1.74-1.88 (1H, m), 1.82 (2H, t, J=7.0), 2.15-2.39 (2H, m), 2.24 (3H, s), 2.36 (2H, t, J=7.5), 2.41 (2H, t, J=7.0), 2.49-2.70 (4H, m), 2.98-3.33 (1H, m), 3.13 (2H, s), 3.20 (2H, t, J=5.5), 3.92-4.07 (2H, m), 4.11 (2H, q, J=7.0), 4.25 (1H, bs), 5.44 (1H, t, J=6.5), 7.12-7.21 (3H, m), 7.23-7.32 (6H, m), 7.38-7.56 (6H, m).

(d) bis(trifluoroacetato hidrogenado) de (E)-4-(Acetilsulfanil)-3-

(2-{4-[3-(etoxicarbonil)propil]-2-oxopiperazin-1-il}etiliden) piperidina

Se sintetizó el compuesto del título en un rendimiento cuantitativo como un sólido amorfo anaranjado claro usando (E)-4-(acetilsulfanil)-3-(2-{4-[3-(etoxicarbonil)propil]-2-oxopiperazin-1-il}etiliden)-1-(trifenilmetil)piperidina obtenido en (c) anterior realizando una reacción similar a la mencionada en el Ejemplo 3 (c).

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 1.26 (3H, t, J=7.0), 1.93-2.05 (3H, m), 2.32-2.44 (1H, m), 2.35 (3H, s), 2.41 (2H, t, J=7.0), 2.99 (2H, t, J=7.5), 3.16-3.42 (4H, m), 3.50-3.82 (4H, m), 3.79 (2H, t, J=7.5), 4.13 (2H, q, J=7.0), 4.26-4.36 (2H, m), 4.42 (1H, m), 5.92 (1H, t, J=7.5).

(e) diclorhidrato de (E)-4-(Acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-{4-[3-(etoxicarbonil)propil]-2-oxopiperazin-1-il}etiliden)piperidina

Se sintetizó el compuesto del título en un rendimiento de 70% como un sólido amorfo café claro usando bis(trifluoroacetato hidrogenado) de (E)-4-(acetilsulfanil)-3-(2-{4-[3-(etoxicarbonil)propil]-2-oxopiperazin-1-il}etiliden)piperidina obtenido en (d) anterior realizando una reacción similar a la mencionada en el Ejemplo 1 (g).

RMN con ^{1}H (500 MHz, piridina-d_5) δ ppm : 0.76-0.88 (2H, m), 1.04-1.09 (1H, m), 1.10-1.18 (1H, m), 1.15 (3H, t, J=7.0), 1.77-1.91 (1H, m), 1.81 (2H, t, J=7.0), 2.15-2.35 (3H, m), 2.24 y 2.26 (total 3H, cada s), 2.38 (2H, t, J=7.0), 2.40-2.47 (1H, m), 2.48-2.75 (3H, m), 2.77-2.83 y 2.85-2.91 (total 1H, cada m), 3.06-3.32 (3H, m), 3.24 (2H, s), 3.64-3.70 (1H, m), 4.06-4.22 (1H, m), 4.13 (2H, q, J=7.0), 4.24-4.31 (1H, m), 4.52 (1H, m), 4.96 y 4.98 (total 1H, cada s), 5.73-5.81 (1H, m), 7.20-7.39 (3H, m), 7.65-7.73 (1H, m).

IR (KBr, cm^{-1}) : 1727, 1662, 1495.

(Ejemplo 71) diclorhidrato de (E)-1-[2-Ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-{4-[3-(etoxicarbonil)propil]-2-

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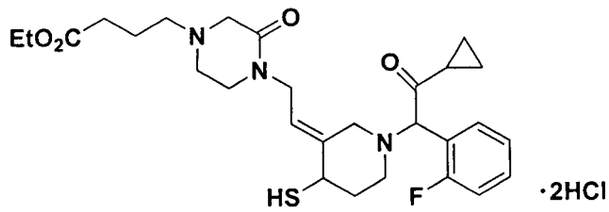
oxopiperazin-1-il}etiliden)-4-sulfanilpiperidina (Clorhidrato del compuesto del Compuesto No. 5-85)

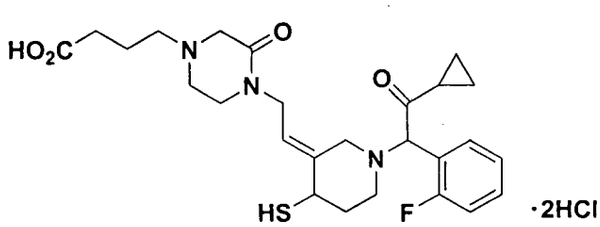


Se sintetizó el compuesto del título en un rendimiento de 35% como un sólido amorfo amarillo claro usando diclorhidrato de (E)-4-(acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-{4-[3-(etoxicarbonil)propil]-2-oxopiperazin-1-il}etiliden)piperidina obtenido en el ejemplo 70 (e) realizando una reacción similar a la mencionada en el Ejemplo 34.

RMN con ^{1}H (400 MHz, piridina-d_5) δ ppm : 0.79-0.88 (2H, m), 1.00-1.08 (1H, m), 1.10-1.19 (1H, m), 1.15 (3H, t, J=7.0), 1.74-1.88 (1H, m), 1.83 (2H, t, J=7.0), 2.14-2.27 (1H, m), 2.29-2.57 (3H, m), 2.33 (2H, t, J=7.0), 2.39 (2H, t, J=7.0), 2.61-2.74 (1H, m), 2.85-3.04 (1H, m), 3.24-3.32 (2H, m), 3.27 (2H, s), 3.39 (1H, dd, J=12.0, 3.5), 3.53-3.68 (1H, m), 3.80-3.86 (1H, m), 4.13 (2H, q, J=7.0), 4.17-4.29 (2H, m), 4.97 (1H, s), 5.68-5.75 (1H, m), 7.21-7.42 (3H, m), 7.68-7.75 (1H, m).

IR (KBr, cm^{-1}) : 2536, 1727, 1661, 1495.

(Ejemplo 72) diclorhidrato de (E)-3-(2-{4-[3-(Carboxipropil)]-2-oxopiperazin-1-il}etiliden)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-sulfanilpiperidina (Clorhidrato del compuesto del Compuesto No. 5-81)



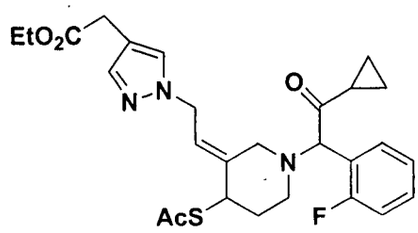
Se sintetizó el compuesto del título en un rendimiento de 57% como un sólido amorfo incoloro usando diclorhidrato de (E)-1-[2-

ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-{4-[3-(etoxicarbonil)propil]-2-oxopiperazin-1-il}etiliden)-4-sulfanilpiperidina obtenido en el ejemplo 71 realizando una reacción similar a la mencionada en el Ejemplo 15.

RMN con ^{1}H (500 MHz, piridina-d_5) δ ppm : 0.76-0.88 (2H, m), 1.01-1.08 (1H, m), 1.10-1.18 (1H, m), 1.74-1.84 (1H, m), 1.96 (2H, t, J=7.0), 2.13-2.28 (1H, m), 2.38-2.60 (5H, m), 2.42 (2H, t, J=7.0), 2.61-2.74 (1H, m), 2.84-3.00 (1H, m), 3.27 (2H, t, J=5.5), 3.30 (2H, s), 3.34-3.42 (1H, m), 3.55 y 3.64 (total 1H, cada d, J=12.5), 3.79-3.86 (1H, m), 4.10-4.28 (2H, m), 4.96 (1H, s), 5.67-5.74 (1H, m), 7.19-7.37 (3H, m), 7.68-7.76 (1H, m).

IR (KBr, cm^{-1}) : 2576, 1713, 1659, 1495.

(Ejemplo 73) (E)-4-(Acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[4-(etoxicarbonilmetil)-1H-pirazol-1-il]etiliden}piperidina (Compuesto del compuesto No. 1-62)



(a) (E)-4-(t-Butildimetilsililoxi)-3-{2-[4-(etoxicarbonilmetil)-1H-pirazol-1-il]etiliden}-1-(trifenilmetil)piperidina

Se sintetizó el compuesto del título en un rendimiento de 45% como un sólido amorfo incoloro usando (E)-4-(t-butildimetilsililoxi)-3-[2-(tosiloxi)etiliden]-1-(trifenilmetil)piperidina obtenida en el ejemplo 1 (c) y 4-(etoxicarbonilmetil)-1H-pirazol realizando una reacción similar a la mencionada en el Ejemplo 21 (a).

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 0.06 (6H, s), 0.88 (9H, s), 1.29 (3H, t, J=7.0), 1.89-2.04 (4H, m), 3.03 (1H, bs), 3.55 (2H, s), 3.69 (1H, bs), 3.93-3.98 (1H, m), 4.19 (2H, q, J=7.0), 4.73-4.84 (2H, m), 5.84 (1H, t, J=7.5), 7.17-7.37 (15H, m), 7.44 (1H, s), 7.49 (1H, s).

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(b) (E)-3-{2-[4-(Etoxicarbonilmetil)-1H-pirazol-1-il]etiliden}-4-hidroxi-1-(trifenilmetil)piperidina

Se sintetizó el compuesto del título en un rendimiento de 63% como un sólido amorfo incoloro usando (E)-4-(t-butildimetilsililoxi)-3-{2-[4-(etoxicarbonilmetil)-1H-pirazol-1-il]etiliden}-1-(trifenilmetil) piperidina obtenida en (a) anterior realizando una reacción similar a la mencionada en el Ejemplo 1 (e).

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 1.26 (3H, t, J=7.0), 1.58-1.61 (1H, m), 1.81-1.89 (1H, m), 2.00 (1H, bs), 2.08-2.14 (1H, m), 2.84 (1H, bs), 3.45 (1H, bs), 3.50 (2H, s), 4.00 (1H, bs), 4.16 (2H, q, J=7.0), 4.68-4.79 (2H, m), 5.77 (1H, t, J=7.0), 7.14-7.18 (3H, m), 7.24-7.28 (12H, m), 7.41 (1H, s), 7.44 (1H, s).

(c) (E)-4-(Acetilsulfanil)-3-{2-[4-(etoxicarbonilmetil)-1H-pirazol-1-il]etiliden}-1-(trifenilmetil)piperidina

Se sintetizó el compuesto del título en un rendimiento de 60% como un aceite amarillo usando (E)-3-{2-[4-(etoxicarbonilmetil)-1H-pirazol-1-il]etiliden}-4-hidroxi-1-(trifenilmetil)piperidina obtenida en (b) anterior realizando una reacción similar a la mencionada en el Ejemplo 1 (h).

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 1.25 (3H, t, J=7.0), 1.79-1.92 (1H, m), 2.24 (3H, s), 2.29-2.33 (2H, m), 3.10-3.14 (1H, m), 3.41 (2H, s), 3.98 (1H, bs), 4.13 (2H, q, J=7.0), 4.25-4.36 (2H, m), 4.61-4.73 (2H, m), 5.78 (1H, t, J=7.0), 7.12-7.20 (3H, m), 7.21-7.31 (6H, m), 7.40-7.56 (8H, m).

(d) trifluoroacetato hidrogenado de (E)-4-(Acetilsulfanil)-3-{2-[4-(etoxicarbonilmetil)-1H-pirazol-1-il]etiliden}piperidina

Se sintetizó el compuesto del título en un rendimiento de 20% como un aceite incoloro usando (E)-4-(acetilsulfanil)-3-{2-[4-(etoxicarbonilmetil)-1H-pirazol-1-il]etiliden}-1-(trifenilmetil)piperidina obtenida en (c) anterior realizando una reacción similar a la mencionada en el Ejemplo 3 (c).

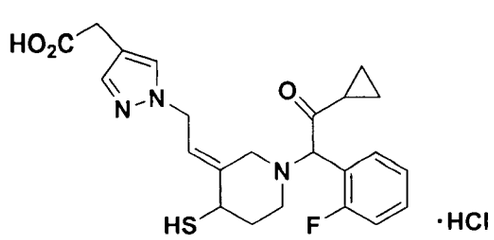
RMN con ^1H (400 MHz, $CDCl_3$) δ ppm : 1.28 (3H, t, J=7.0), 2.03-2.08 (1H, m), 2.36 (3H, s), 2.37-2.41 (1H, m), 3.24-3.31 (1H, m), 3.39-3.44 (1H, m), 3.47 (2H, s), 3.73 (1H, d, J=14.0), 4.10 (1H, d, J=14.0), 4.16 (2H, q, J=7.0), 4.44 (1H, t, J=4.0), 4.63-4.68 (1H, m), 4.73-4.80 (1H, m), 6.05 (1H, t, J=7.0), 7.41 (2H, s).

(e) (E)-4-(Acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[4-(etoxicarbonilmetil)-1H-pirazol-1-il]etiliden} piperidina

Se sintetizó el compuesto del título en un rendimiento de 57% como un aceite amarillo claro usando trifluoroacetato hidrogenado de (E)-4-(acetilsulfanil)-3-{2-[4-(etoxicarbonilmetil)-1H-pirazol-1-il]etiliden}piperidina obtenido en (d) anterior realizando una reacción similar a la mencionada en el Ejemplo 1 (g).

RMN con ^1H (400 MHz, $CDCl_3$) δ ppm : 0.75-0.88 (2H, m), 0.97-1.07 (2H, m), 1.27 (3H, t, J=7.0), 1.78-1.86 (1H, m), 2.12-2.22 (2H, m), 2.28 y 2.29 (total 3H, cada s), 2.49-2.62 (1H, m), 2.68-2.73 y 2.76-2.81 (total 1H, cada m), 2.88 y 3.15 (total 1H, cada d, J=12.5), 3.30 y 3.41 (total 1H, cada d, J=12.5), 3.46 (2H, s), 4.15 (2H, q, J=7.0), 4.28-4.34 (1H, m), 4.62-4.64 y 4.67-4.70 (total 2H, cada m), 4.71 y 4.74 (total 1H, cada s), 5.78 (1H, t, J=7.0), 7.07-7.17 (2H, m), 7.19-7.27 (1H, m), 7.28-7.37 (1H, m), 7.33 y 7.34 (total 1H, cada s), 7.39 (1H, s).

(Ejemplo 74) clorhidrato de (E)-3-{2-[4-(Carboximetil)-1H-pirazol-1-il]etiliden}-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-sulfanilpiperidina (Clorhidrato del compuesto del Compuesto No. 1-53)



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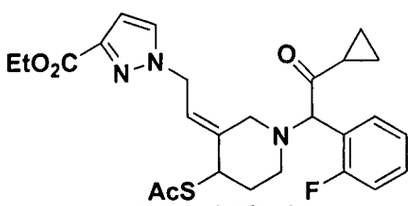
Se sintetizó el compuesto del título en un rendimiento de 28% como un sólido amorfo incoloro usando (E)-4-(acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[4-(etoxicarbonilmetil)-1H-pirazol-1-il]etiliden}piperidina obtenida en el ejemplo 73 (e) realizando una reacción similar a la mencionada en el Ejemplo 15.

RMN con ^{1}H (400 MHz, piridina-d_5) δ ppm : 0.78-0.83 (2H, m), 0.98-1.04 (1H, m), 1.09-1.15 (1H, m), 1.74-1.83 (1H, m), 2.14-2.24 (1H, m), 2.46-2.55 (1H, m), 2.61-2.67 (1H, m), 2.82-2.98 (1H, m), 3.36 y 3.67 (total 2H, cada d, J=12.5), 3.79 (3H, bs), 4.85-4.93 (3H, m), 5.98 (1H, t, J=7.0), 7.23-7.26 (2H, m), 7.29-7.35 (1H, m), 7.69-7.74 (1H, m), 7.81 (1H, s), 7.84 (1H, s).

MS (FAB) m/z : 444 $(M+H)^+$.

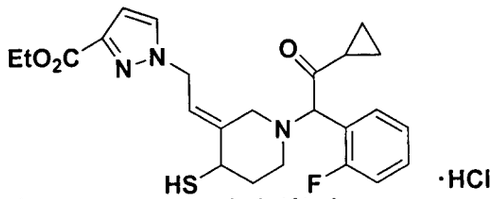
(Ejemplo 75) (E)-4-(Acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-[2-(3-etoxicarbonil-1H-pirazol-1-il)etiliden]piperidina (Compuesto del compuesto No. 1-14)



Se sintetizó el compuesto del título en un rendimiento de 12% como un aceite amarillo usando (E)-4-(acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-hidroxietiliden)piperidina obtenida en el ejemplo 32 (f) y 3-etoxicarbonil-1H-pirazol en lugar de 4-etoxicarbonil-1H-1,2,3-triazol realizando una reacción similar a la mencionada en el Ejemplo 47.

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 0.80-0.91 (2H, m), 0.99-1.11 (2H, m), 1.37 (3H, t, J=7.0), 1.76-1.84 (1H, m), 2.12-2.35 (2H, m), 2.26 (3H, s), 2.47 y 2.62 (total 1H, cada m), 2.73 (1H, m), 3.01 y 3.11 (total 1H, cada d, J=12.5), 3.48 y 3.51 (total 1H, cada d, J=12.5), 4.28-4.36 (3H, m), 4.75 y 4.77 (total 1H, cada s), 5.13-5.21 (2H, m), 5.70-5.74 (1H, m), 6.81-6.82 (1H, m), 7.09-7.21 (2H, m), 7.33 (1H, m), 7.43-7.49 (2H, m).

(Ejemplo 76) clorhidrato de (E)-1-[2-Ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-[2-(3-etoxicarbonil-1H-pirazol-1-il)etiliden]-4-sulfanilpiperidina (Clorhidrato del compuesto del Compuesto No. 1-13)

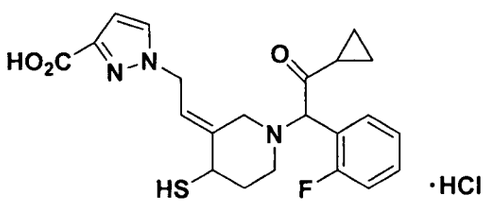


Se sintetizó el compuesto del título en un rendimiento de 39% como un sólido amorfo incoloro usando (E)-4-(acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-[2-(3-etoxicarbonil-1H-pirazol-1-il)etiliden]piperidina obtenida en el ejemplo 75 realizando una reacción similar a la mencionada en el Ejemplo 34.

RMN con ^{1}H (400 MHz, piridina-d_5) δ ppm : 0.84-0.92 (2H, m), 1.03-1.09 (1H, m), 1.16-1.24 (1H, m), 1.20 y 1.21 (total 3H, cada t, J=7.0), 1.74-1.82 (1H, m), 2.14-2.24 (1H, m), 2.55-2.68 (2H, m), 2.83-2.90 y 2.93-2.99 (total 1H, cada m), 3.46 y 3.54 (total 1H, cada t, d=12.0), 3.69-3.82 (2H, m), 4.26 (2H, q, J=7.0), 4.97 (1H, s), 5.43-5.46 (2H, m), 6.08 (1H, m), 6.99-7.00 (1H, m), 7.23-7.36 (3H, m), 7.68-7.69 (1H, m), 7.74-7.80 (1H, m).

MS (FAB) m/z : 458 $(M+H)^+$.

(Ejemplo 77) clorhidrato de (E)-3-[2-(3-Carboxi-1H-pirazol-1-il)etiliden]-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-sulfanilpiperidina (Clorhidrato del compuesto del Compuesto No. 1-5)



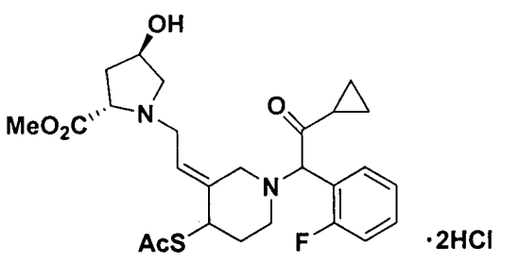
Se sintetizó el compuesto del título en un rendimiento de 34% como un sólido amorfo incoloro usando clorhidrato de (E)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-[2-(3-etoxicarbonil-1H-

pirazol-1-il)etiliden]-4-sulfanilpiperidina obtenido en el ejemplo 76 realizando una reacción similar a la mencionada en el Ejemplo 15.

RMN con ^{1}H (400 MHz, piridina-d_5) δ ppm : 0.81-0.95 (2H, m), 1.02-1.06 (1H, m), 1.16-1.21 (1H, m), 1.74-1.81 (1H, m), 2.14-2.22 (1H, m), 2.59-2.67 (2H, m), 2.85 y 2.95 (total 1H, cada m), 3.50 y 3.61 (total 1H, cada d, J=12.5), 3.77-3.84 (2H, m), 4.96 (1H, s), 5.59-5.63 (2H, m), 6.17-6.21 (1H, m), 7.19-7.34 (4H, m), 7.73 (1H, s), 7.75-7.81 (1H, m).

MS (FAB) m/z : 430 $(M+H)^+$.

(Ejemplo 78) diclorhidrato de (E)-4-(Acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[(2S,4R)-4-hidroxi-2-(metoxicarbonil)pirrolidin-1-il]etiliden}piperidina (Clorhidrato del compuesto del Compuesto No. 5-388)



Se sintetizó el compuesto del título en un rendimiento de 57% como un sólido amorfo amarillo usando (E)-4-(acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-hidroxietiliden)piperidina obtenida en el ejemplo 32 (f) y (2S,4R)-4-hidroxi-2-(metoxicarbonil)pirrolidina en lugar de 4-(etoxicarbonilmetil)piperidina realizando una reacción similar a la mencionada en el Ejemplo 33.

RMN con ^{1}H (400 MHz, piridina-d_5) δ ppm : 0.79-0.88 (2H, m), 1.00-1.07 (1H, m), 1.10-1.21 (1H, m), 1.82-1.93 (1H, m), 2.17-2.27 (1H, m), 2.25 y 2.26 (total 3H, cada s), 2.31-2.60 (4H, m), 2.67-2.92 (3H, m), 3.14-3.25 (1H, m), 3.36-3.53 (2H, m), 3.58-3.75 (1H, m), 3.69 y 3.71 (total 3H, cada s), 3.80-3.90 (1H, m), 4.53-4.58 (1H, m), 4.71-4.77 (1H, m), 4.92 y 4.95 (total 1H, cada s), 6.01-6.08 (1H, m), 7.20-7.34 (3H, m), 7.67-7.78 (1H, m).

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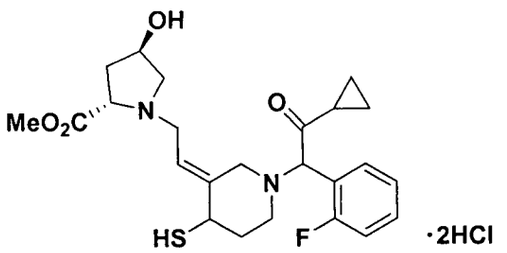
IR (KBr, cm^{-1}) : 1747, 1702, 1494.

(Ejemplo 79) diclorhidrato de (E)-1-[2-Ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[(2S,4R)-4-hidroxi-2-(metoxicarbonil) pirrolidin-1-il]etiliden}-4-sulfanilpiperidina (Clorhidrato del compuesto del Compuesto No. 5-387)

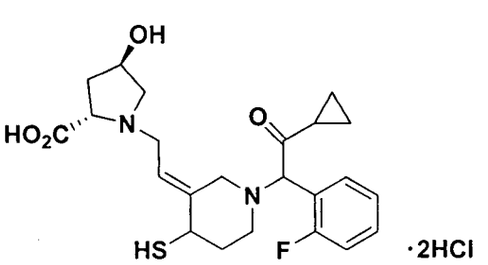


Se sintetizó el compuesto del título en un rendimiento de 58% como un sólido amorfo amarillo claro usando diclorhidrato de (E)-4-(acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[(2S,4R)-4-hidroxi-2-(metoxicarbonil)pirrolidin-1-il]etiliden}piperidina obtenida en el ejemplo 78 realizando una reacción similar a la mencionada en el Ejemplo 55.

RMN con ^1H (400 MHz, piridina-d_5) δ ppm : 0.77-0.97 (2H, m), 0.98-1.08 (1H, m), 1.09-1.21 (1H, m), 1.74-1.85 (1H, m), 2.13-2.29 (1H, m), 2.35-2.60 (4H, m), 2.61-2.71 (1H, m), 2.81-3.04 (2H, m), 3.34-3.61 (3H, m), 3.65-3.80 (1H, m), 3.72 y 3.73 y 3.74 (total 3H, cada s), 3.82-4.06 (2H, m), 4.72-4.80 (1H, m), 4.94 y 4.95 y 4.96 (total 1H, cada s), 5.95-6.06 (1H, m), 7.19-7.37 (3H, m), 7.71-7.81 (1H, m).

IR (KBr, cm^{-1}) : 2545, 1746, 1712, 1494.

(Ejemplo 80) diclorhidrato de (E)-3-{2-[(2S,4R)-2-Carboxi-4-hidroxipirrolidin-1-il]etiliden}-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-sulfanilpiperidina (Clorhidrato del compuesto del Compuesto No. 5-385)

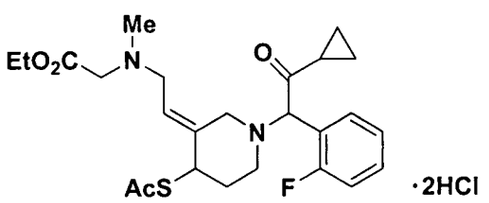


Se sintetizó el compuesto del título en un rendimiento de 75% como un sólido amorfo incoloro usando diclorhidrato de (E)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[(2S,4R)-4-hidroxi-2-(metoxicarbonil)pirrolidin-1-il]etiliden}-4-sulfanilpiperidina obtenida en el ejemplo 79 realizando una reacción similar a la mencionada en el Ejemplo 15.

RMN con ^{1}H (500 MHz, piridina-d_5) δ ppm : 0.76-0.95 (2H, m), 0.99-1.06 (1H, m), 1.11-1.20 (1H, m), 1.73-1.84 (1H, m), 2.15-2.26 (1H, m), 2.45-2.55 (1H, m), 2.56-2.86 (3H, m), 2.93-3.03 (1H, m), 3.34-4.03 (4H, m), 4.05-4.35 (3H, m), 4.53-4.66 (1H, m), 4.84-4.90 (1H, m), 4.97 y 4.99 y 5.00 y 5.02 (total 1H, cada s), 6.18-6.29 (1H, m), 7.16-7.34 (3H, m), 7.70-7.80 (1H, m).

IR (KBr, cm^{-1}) : 2559, 1738, 1711, 1494.

(Ejemplo 81) diclorhidrato de (E)-4-(Acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[N-(etoxicarbonilmetil)-N-metilamino]etiliden}piperidina (Clorhidrato del compuesto del Compuesto No. 3-55)



Se sintetizó el compuesto del título en un rendimiento de 56% como un sólido amorfo amarillo claro usando (E)-4-(acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-hidroxietiliden) piperidina obtenida en el ejemplo 32 (f) y clorhidrato de N-(etoxicarbonilmetil)-N-metilamina en lugar de 4-(etoxicarbonilmetil)piperidina realizando una reacción similar a la mencionada en el Ejemplo 33.

RMN con ^{1}H (500 MHz, piridina-d_5) δ ppm : 0.76-0.92 (2H, m), 0.99-1.06 (1H, m), 1.11-1.22 (1H, m), 1.13 y 1.14 (total 3H, cada t,

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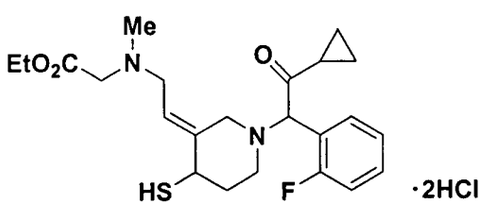
J=7.0), 1.81-1.93 (1H, m), 2.16-2.30 (1H, m), 2.25 y 2.26 (total 3H, cada s), 2.39-2.51 (1H, m), 2.45 y 2.47 (total 3H, cada s), 2.52-2.60 y 2.67-2.75 (total 1H, cada m), 2.77-2.90 (1H, m), 3.13 y 3.22 (total 1H, cada d, J=13.0), 3.27-3.51 (4H, m), 3.56-3.72 (1H, m), 4.13 (2H, q, J=7.0), 4.52-4.58 (1H, m), 4.94 y 4.96 (total 1H, cada s), 5.90-6.00 (1H, m), 7.20-7.30 (2H, m), 7.31-7.39 (1H, m), 7.66-7.74 (1H, m).

IR (KBr, cm^{-1}) : 1745, 1700, 1494.

(Ejemplo 82) diclorhidrato de (E)-1-[2-Ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[N-(etoxicarbonilmetil)-N-metilamino]etiliden}-4-sulfanilpiperidina (Clorhidrato del compuesto del Compuesto No. 3-54)



Se sintetizó el compuesto del título en un rendimiento de 63% como un sólido amorfo amarillo claro usando (E)-4-(acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[N-(etoxicarbonilmetil)-N-metilamino]etiliden}piperidina diclorhidrato obtenida en el ejemplo 81 realizando una reacción similar a la mencionada en el Ejemplo 34.

RMN con ^1H (500 MHz, piridina-d_5) δ ppm : 0.79-0.88 (2H, m), 1.01-1.07 (1H, m), 1.11-1.20 (1H, m), 1.14 y 1.15 (total 3H, cada t, J=7.0), 1.74-1.83 (1H, m), 2.16-2.27 (1H, m), 2.43-2.54 (1H, m), 2.47 y 2.49 (total 3H, cada s), 2.63-2.72 (1H, m),.2.81-2.90 y 2.93-3.00 (total 1H, cada m), 3.30-3.61 (6H, m), 3.84-3.89 (1H, m), 4.14 y 4.15 (total 2H, cada q, J=7.0), 4.94 y 4.95 (total 1H, cada s), 5.86-5.91 (1H, m), 7.21-7.28 (2H, m), 7.31-7.37 (1H, m), 7.70-7.75 (1H, m).

IR (KBr, cm^{-1}) : 2536, 1745, 1713, 1494.

(Ejemplo 83) diclorhidrato de (E)-3-{2-[N-(Carboximetil)-N-metilamino]etiliden}-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-sulfanilpiperidina (Clorhidrato del compuesto del Compuesto No.

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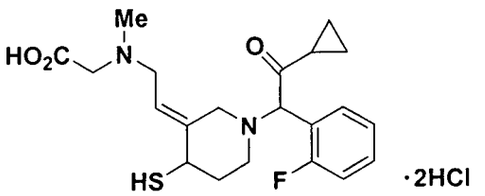
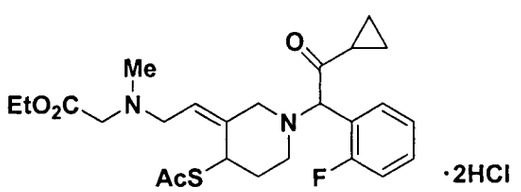


Se sintetizó el compuesto del título en un rendimiento de 17% como un sólido amorfo incoloro usando diclorhidrato de (E)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[N-(etoxicarbonilmetil)-N-metilamino]etiliden}-4-sulfanilpiperidina obtenida en el ejemplo 82 realizando una reacción similar a la mencionada en el Ejemplo 15.

RMN con ^{1}H (500 MHz, piridina-d_5) δ ppm : 0.79-0.92 (2H, m), 1.00-1.08 (1H, m), 1.12-1.21 (1H, m), 1.74-1.86 (1H, m), 2.15-2.28 (1H, m), 2.44-2.60 (1H, m), 2.63-2.75 (1H, m), 2.71 y 2.73 (total 3H, cada s), 2.80-2.89 y 2.93-3.02 (total 1H, cada m), 3.38-3.69 (4H, m), 3.72-3.93 (3H, m), 4.94 y 4.96 (total 1H, cada s), 5.99-6.06 (1H, m), 7.17-7.35 (3H, m), 7.69-7.76 (1H, m).

IR (KBr, cm^{-1}) : 2630, 1741, 1712, 1494.

(Ejemplo 84) diclorhidrato de (Z)-4-(Acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[N-(etoxicarbonilmetil)-N-metilamino]etiliden}piperidina (Clorhidrato del compuesto del Compuesto No. 4-55)



(a) (Z)-4-(Acetilsulfanil)-3-{2-[N-(etoxicarbonilmetil)-N-metilamino]etiliden}-1-(trifenilmetil)piperidina

Se sintetizó el compuesto del título en un rendimiento de 38% como un sólido amorfo incoloro usando (Z)-4-(acetilsulfanil)-3-(2-hidroxietiliden)-1-(trifenilmetil)piperidina obtenida en el ejemplo 66 (d) en lugar de (E)-4-(acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-

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2-oxoetil]-3-(2-hidroxietiliden)piperidina y clorhidrato de N-(etoxicarbonilmetil)-N-metilamina en lugar de 4-(etoxicarbonilmetil)piperidina realizando una reacción similar a la mencionada en el Ejemplo 33.

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 1.29 (3H, t, J=7.0), 1.73-1.85 (1H, m), 1.94-2.05 (1H, m), 2.15-2.52 (4H, m), 2.20 (3H, s), 2.41 (3H, s), 3.00-3.47 (4H, m), 4.21 (2H, q, J=7.0), 4.82 (1H, bs), 5.39 (1H, t, J=6.5), 7.03-7.75 (15H, m).

(b) bis(trifluoroacetato hidrogenado) de (Z)-4-(Acetilsulfanil)-3-{2-[N-(etoxicarbonilmetil)-N-metilamino]etiliden}piperidina

Se sintetizó el compuesto del título en un rendimiento de 90% como un sólido amorfo incoloro usando (Z)-4-(acetilsulfanil)-3-{2-[N-(etoxicarbonilmetil)-N-metilamino]etiliden}-1-(trifenilmetil)piperidina obtenida en (a) anterior realizando una reacción similar a la mencionada en el Ejemplo 3 (c).

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 1.30 (3H, t, J=7.0), 1.99-2.10 (1H, m), 2.35 (3H, s), 2.35-2.50 (1H, m), 2.88 (3H, s), 3.07-3.20 (1H, m), 3.36-3.49 (1H, m), 3.65-3.98 (5H, m), 4.25 (2H, q, J=7.0), 4.28-4.38 (1H, m), 4.78 (1H, bs), 5.78-5.86 (1H, m).

(c) diclorhidrato de (Z)-4-(Acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[N-(etoxicarbonilmetil)-N-metilamino]etiliden}piperidina

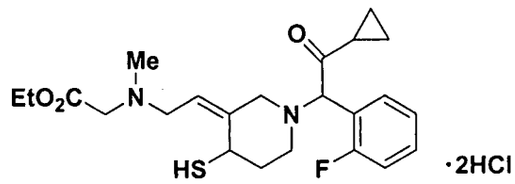
Se sintetizó el compuesto del título en un rendimiento de 50% como un sólido amorfo incoloro usando bis(trifluoroacetato hidrogenado) de (Z)-4-(acetilsulfanil)-3-{2-[N-(etoxicarbonilmetil)-N-metilamino]etiliden}piperidina obtenido en (b) anterior realizando una reacción similar a la mencionada en el Ejemplo 1 (g).

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 0.75-0.92 (2H, m), 0.93-1.09 (2H, m), 1.23-1.35 (3H, m), 1.70-1.87 (1H, m), 2.06-2.56 (2H, m), 2.29 (3H, s), 2.35 y 2.36 (total 3H, cada s), 2.65-3.00 (2H, m), 3.08-3.36 (6H, m), 4.14-4.25 (2H, m), 4.62 y 4.67 (total 1H, cada s),

4.79 (1H, bs), 5.35 y 5.45 (total 1H. cada t, J=6.5), 7.04-7.22 (2H, m), 7.26-7.48 (2H, m).

IR (KBr, cm^{-1}) : 1745, 1699, 1494.

(Ejemplo 85) diclorhidrato de (Z)-1-[2-Ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[N-(etoxicarbonilmetil)-N-metilamino]etiliden}-4-sulfanilpiperidina (Clorhidrato del compuesto del Compuesto No. 4-54)

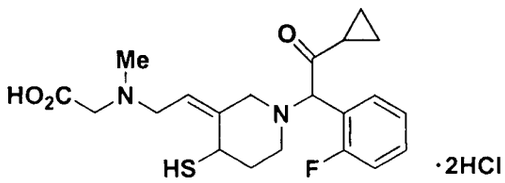


Se sintetizó el compuesto del título en un rendimiento de 90% como un sólido amorfo incoloro usando diclorhidrato de (Z)-4-(acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[N-(etoxicarbonilmetil)-N-metilamino]etiliden}piperidina obtenido en el ejemplo 84 realizando una reacción similar a la mencionada en el Ejemplo 34.

RMN con ^1H (400 MHz, $CDCl_3$) δ ppm : 0.75-0.91 (2H, m), 0.94-1.09 (2H, m), 1.22-1.33 (3H, m), 1.65-1.79 (1H, m), 2.07-2.28 (2H, m), 2.37 y 2.39 (total 3H, cada s), 2.44-3.35 (8H, m), 4.12-4.24 (2H, m), 4.30 (1H, bs), 4.68 y 4.73 (total 1H, cada s), 5.23 y 5.33 (total 1H, cada t, J=7.0), 7.05-7.21 (2H, m), 7.26-7.48 (2H, m).

IR (KBr, cm^{-1}) : 2626, 2560, 1745, 1712, 1494.

(Ejemplo 86) diclorhidrato de (Z)-3-{2-[N-(Carboximetil)-N-metilamino]etiliden}-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-sulfanilpiperidina (Clorhidrato del compuesto del Compuesto No. 4-50)



Se sintetizó el compuesto del título en un rendimiento de 50% como un sólido amorfo incoloro usando diclorhidrato de (Z)-1-[2-

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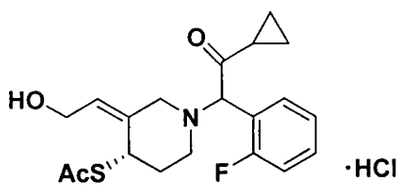
ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[N-(etoxicarbonilmetil)-N-metilamino] etiliden}-4-sulfanilpiperidina obtenido en el ejemplo 85 realizando una reacción similar a la mencionada en el Ejemplo 15.

RMN con ^{1}H (400 MHz, piridina-d_5) δ ppm : 0.71-0.94 (2H, m), 0.96-1.17 (2H, m), 1.71-1.87 (1H, m), 2.21-2.42 (1H, m), 2.43-2.56 (1H, m), 2.60-3.07 (2H, m), 2.98 y 3.02 (total 3H, cada s), 3.25-3.62 (2H, m), 4.00-4.26 (4H, m), 4.71 (1H, bs), 4.90 y 4.96 (total 1H, cada s), 5.76 y 5.87 (total 1H, cada t, J=7.0), 7.10-7.36 (3H, m), 7.62-7.72 (1H, m).

IR (KBr, cm^{-1}) : 2558, 1740, 1712, 1494.

(Ejemplo 87) clorhidrato de (4S)-(Z)-4-(Acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-hidroxietiliden) piperidina (Clorhidrato de la forma (4S) del compuesto del Compuesto No. 4-2)



(a) (4S)-(Z)-4-(Acetilsulfanil)-3-(2-hidroxietiliden)-1-(trifenilmetil) piperidina y (4R)-(Z)-4-(acetilsulfanil)-3-(2-hidroxietiliden)-1-(trifenilmetil)piperidina

Se separó (Z)-4-(Acetilsulfanil)-3-(2-hidroxietiliden)-1-(trifenilmetil)piperidina (102 mg) obtenida en el ejemplo 66 (d) usando una HPLC preparativa (Daicel, Chiralcel OD-H, eluyente: hexano / etanol / dietilamina = 90 / 10 / 0.1) para obtener (4S)-(Z)-4-(acetilsulfanil)-3-(2-hidroxietiliden)-1-(trifenilmetil)piperidina (41 mg) con un tiempo de retención menor y (4R)-(Z)-4-(acetilsulfanil)-3-(2-hidroxietiliden)-1-(trifenilmetil)piperidina (43 mg) con un tiempo de retención mayor, como sólidos amorfos incoloros, respectivamente.

La RMN con ^{1}H fue la misma que la de la (Z)-4-(acetilsulfanil)-3-(2-hidroxietiliden)-1-(trifenilmetil)piperidina del Ejemplo 66 (d).

[α]D de la forma (4S): -15.2° (c=1.00, MeOH)

[α]D de la forma (4R): +11.5° (c=0.50, MeOH)

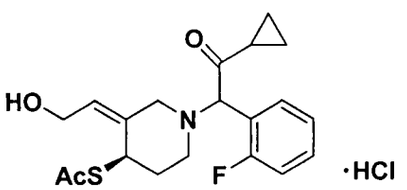
(b) clorhidrato de (4S)-(Z)-4-(Acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-hidroxietiliden)piperidina

Se sintetizó el compuesto del título en un rendimiento de 67% como un sólido amorfo incoloro usando (4S)-(Z)-4-(acetilsulfanil)-3-(2-hidroxietiliden)-1-(trifenilmetil)piperidina obtenido en (a) anterior realizando una reacción similar a la mencionada en el Ejemplo 66 (e).

La RMN con ^{1}H fue la misma que en el Ejemplo 66 (e).

IR(KBr, cm^{-1}): 3345, 1696, 1494.

(Ejemplo 88) clorhidrato de (4R)-(Z)-4-(Acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-hidroxietiliden) piperidina (Clorhidrato de la forma (4R) del compuesto del Compuesto No. 4-2)

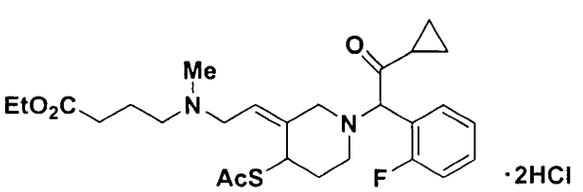


Se sintetizó el compuesto del título en un rendimiento de 70% como un sólido amorfo incoloro usando (4R)-(Z)-4-(acetilsulfanil)-3-(2-hidroxietiliden)-1-(trifenilmetil)piperidina obtenida en el ejemplo 87 (a) realizando una reacción similar a la mencionada en el Ejemplo 66 (e).

La RMN con ^{1}H fue la misma que en el Ejemplo 66 (e).

IR(KBr, cm^{-1}): 3350, 1696, 1494.

(Ejemplo 89) diclorhidrato de (Z)-4-(Acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-{N-[3-(etoxicarbonil) propil]-N-metilamino}etiliden)piperidina (Clorhidrato del compuesto del Compuesto No. 4-67)

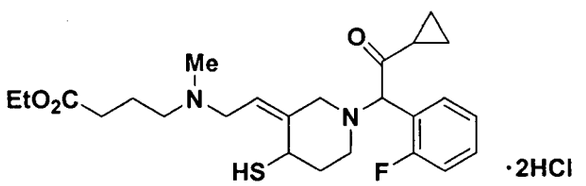


Se sintetizó el compuesto del título en un rendimiento de 43% como un sólido amorfo anaranjado claro usando (Z)-4-(acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-hidroxietiliden) piperidina obtenida en el ejemplo 66 (e) en lugar de (E)-4-(acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-hidroxietiliden)piperidina y clorhidrato de N-[3-(etoxicarbonil)propil]-N-metilamina en lugar de 4-(etoxicarbonilmetil)piperidina realizando una reacción similar a la mencionada en el Ejemplo 33.

RMN con ^{1}H (500 MHz, piridina-d_5) δ ppm : 0.76-0.85 (1H, m), 0.99-1.08 (2H, m), 1.09-1.18 (1H, m), 1.11 y 1.12 (total 3H, cada t, J=7.0), 1.81-1.89 (1H, m), 2.23-2.42 (3H, m), 2.25 y 2.26 (total 3H, cada s), 2.47-2.61 (1H, m), 2.51 (2H, t, J=7.0), 2.77 y 2.78 (total 3H, cada s), 2.96-3.13 (2H, m), 3.15-3.26 (2H, m), 3.35 y 3.55 (total 1H, cada d, J=12.0), 3.60-3.67 (1H, m), 3.98-4.12 (1H, m), 4.08 y 4.09 (total 2H, cada q, J=7.0), 4.13-4.23 (1H, m), 4.86 y 4.96 (total 1H, cada s), 4.89-4.94 (1H, m), 6.10 y 6.21 (total 1H, cada t, J=7.0), 7.19-7.38 (3H, m), 7.57-7.66 (1H, m).

IR (KBr, cm^{-1}) : 1725, 1712, 1495.

(Ejemplo 90) diclorhidrato de (Z)-1-[2-Ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-{N-[3-(etoxicarbonil)propil)]-N-metilamino}etiliden)-4-sulfanilpiperidina (Clorhidrato del compuesto del Compuesto No. 4-66)

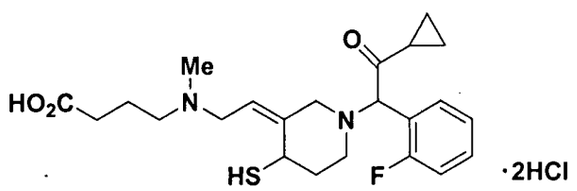


Se sintetizó el compuesto del título en un rendimiento de 76% como un sólido amorfo amarillo usando diclorhidrato de (Z)-4-(acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-{N-[3-(etoxicarbonil)propil]-N-metilamino}etiliden)piperidina obtenido en el ejemplo 89 realizando una reacción similar a la mencionada en el Ejemplo 34.

RMN con ^{1}H (500 MHz, piridina-d_5) δ ppm : 0.74-0.85 (1H, m), 0.87-0.96 (1H, m), 0.99-1.06 (1H, m), 1.07-1.15 (1H, m), 1.10 y 1.11 (total 3H, cada t, J=7.0), 1.74-1.85 (1H, m), 2.25-2.40 (3H, m), 2.43-2.54 (3H, m), 2.65-2.72 (1H, m), 2.81 y 2.83 (total 3H, cada s), 2.93-2.98 (1H, m), 3.19-3.64 (4H, m), 3.89-4.00 (2H, m), 4.07 y 4.09 (total 2H, cada q, J=7.0), 4.54-4.59 (1H, m), 4.89 y 4.95 (total 1H, cada s), 5.85 y 5.96 (total 1H, cada t, J=7.0), 7.17-7.25 (2H, m), 7.26-7.34 (1H, m), 7.57-7.68 (1H, m).

IR (KBr, cm^{-1}) : 2550, 1728, 1495.

(Ejemplo 91) diclorhidrato de (Z)-3-(2-{N-[3-(Carboxi)propil]-N-metilamino}etiliden)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-sulfanilpiperidina (Clorhidrato del compuesto del Compuesto No. 4-62)



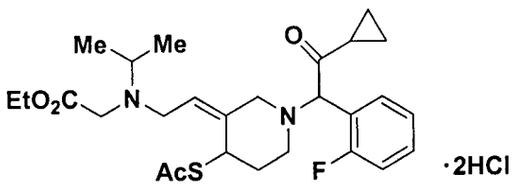
Se sintetizó el compuesto del título en un rendimiento de 50% como un sólido amorfo incoloro usando diclorhidrato de (Z)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-{N-[3-(etoxicarbonil) propil]-N-metilamino}etiliden)-4-sulfanilpiperidina obtenido en el ejemplo 90 realizando una reacción similar a la mencionada en el Ejemplo 15.

RMN con ^{1}H (500 MHz, piridina-d_5) δ ppm : 0.73-0.83 (1H, m), 0.86-0.97 (1H, m), 0.98-1.06 (1H, m), 1.07-1.17 (1H, m), 1.71-1.85 (1H, m), 2.25-2.54 (4H, m), 2.58-2.89 (3H, m), 2.81 y 2.83 (total 3H, cada s), 2.90-3.01 (1H, m), 3.21-3.37 (2H, m), 3.39-3.48 (1H, m), 3.50-3.56 (1H, m), 3.86-4.00 (2H, m), 4.53-4.60 (1H, m), 4.89 y 4.97 (total 1H, cada s), 5.86 y 5.97 (total 1H, cada t, J=7.0), 7.16-7.24 (2H, m), 7.25-7.34 (1H, m), 7.62-7.68 (1H, m).

IR (KBr, cm^{-1}) : 2553, 1713, 1494.

(Ejemplo 92) diclorhidrato de (Z)-4-(Acetilsulfanil)-1-[2-

ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[N-(etoxicarbonilmetil)-N-isopropilamino]etiliden}piperidina (Clorhidrato del compuesto del Compuesto No. 4-79)

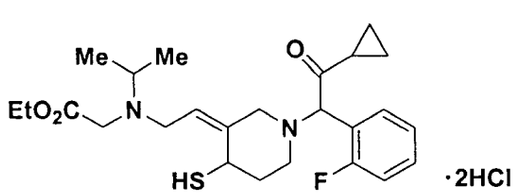


Se sintetizó el compuesto del título en un rendimiento de 33% como un sólido café amorfo usando (Z)-4-(acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-hidroxietiliden)piperidina obtenida en el ejemplo 66 (e) en lugar de (E)-4-(acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-hidroxietiliden)piperidina y N-(etoxicarbonilmetil)-N-isopropilamina en lugar de 4-(etoxicarbonilmetil)piperidina realizando una reacción similar a la mencionada en el Ejemplo 33.

RMN con ^{1}H (400 MHz, piridina-d_5) δ ppm : 0.74-0.86 (2H, m), 0.98-1.13 (2H, m), 1.04 y 1.06 (total 3H, cada d, J=6.5), 1.07 y 1.09 (total 3H, cada d ,J=6.5), 1.17 y 1.19 (total 3H, cada t, J=7.0), 1.85-1.96 (1H, m), 2.28 (3H, s), 2.30-2.41 (1H, m), 2.42-2.52 (1H, m), 2.59-2.68 (1H, m), 2.90-3.01 (1H, m), 3.03-3.12 (1H, m), 3.13-3.22 (1H, m), 3.36-3.70 (5H, m), 4.18 y 4.20 (total 2H, cada q, J=7.0), 4.87 y 4.92 (total 1H, cada s), 5.14 (1H, bs), 5.63 y 5.72 (total 1H, cada t, J=7.0), 7.19-7.27 (2H, m), 7.29-7.36 (1H, m), 7.64-7.70 (1H, m).

IR (KBr, cm^{-1}) : 1745, 1696, 1495.

(Ejemplo 93) diclorhidrato de (Z)-1-[2-Ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[N-(etoxicarbonilmetil)-N-isopropilamino]etiliden}-4-sulfanilpiperidina (Clorhidrato del compuesto del Compuesto No. 4-78)

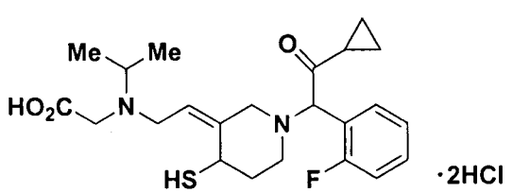


Se sintetizó el compuesto del título en un rendimiento de 41% como un sólido amorfo incoloro usando diclorhidrato de (Z)-4-(acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[N-(etoxicarbonilmetil)-N-isopropilamino]etiliden}piperidina obtenido en el ejemplo 92 realizando una reacción similar a la mencionada en el Ejemplo 34.

RMN con ^{1}H (400 MHz, piridina-d_5) δ ppm : 0.75-0.83 (2H, m), 0.97-1.13 (2H, m), 1.03 (3H, d, J=6.5), 1.06 (3H, d, J=6.5), 1.16 y 1.18 (total 3H, cada t, J=7.0), 1.73-1.85 (1H, m), 2.22-2.37 (1H, m), 2.45-2.54 (1H, m), 2.66-2.75 (1H, m), 2.81-3.27 (3H, m), 3.36-3.55 (5H, m), 4.17 y 4.18 (total 2H, cada q, J=7.0), 4.61 (1H, bs), 4.89 y 4.93 (total 1H, cada s), 5.44 y 5.55 (total 1H, cada t, J=7.0), 7.18-7.24 (2H, m), 7.27-7.34 (1H, m), 7.67-7.74 (1H, m).

IR (KBr, cm^{-1}) : 2545, 1745, 1712, 1494.

(Ejemplo 94) diclorhidrato de (Z)-3-{2-[N-(Carboximetil)-N-isopropilamino]etiliden}-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-sulfanilpiperidina (Clorhidrato del compuesto del Compuesto No. 4-74)



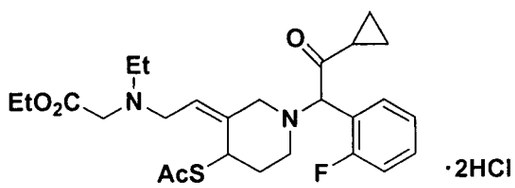
Se sintetizó el compuesto del título en un rendimiento de 40% como un sólido amorfo incoloro usando diclorhidrato de (Z)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[N-(etoxicarbonilmetil)-N-isopropilamino]etiliden}-4-sulfanilpiperidina obtenido en el ejemplo 93 realizando una reacción similar a la mencionada en el Ejemplo 15.

RMN con ^{1}H (400 MHz, piridina-d_5) δ ppm : 0.70-0.87 (2H, m), 0.94-1.04 (1H, m), 1.05-1.19 (1H, m), 1.13 y 1.14 (total 3H, cada d, J=6.5), 1.15 y 1.16 (total 3H, cada d, J=6.5), 1.71-1.84 (1H, m), 2.22-2.41 (1H, m), 2.48-2.57 (1H, m), 2.64-3.02 (2H, m), 3.21-3.44 (2H, m), 3.49-3.69 (5H, m), 4.67 (1H, bs), 4.87 y 4.92 (total 1H, cada s),

5.55 y 5.67 (total 1H, cada t, J=7.0), 7.16-7.23 (2H, m), 7.25-7.32 (1H, m), 7.66-7.73 (1H, m).

IR (KBr, cm^{-1}) : 2554, 1740, 1712, 1494.

(Ejemplo 95) diclorhidrato de (Z)-4-(Acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[N-(etoxicarbonilmetil)-N-etilamino]etiliden}piperidina (Clorhidrato del compuesto del Compuesto No. 4-73)

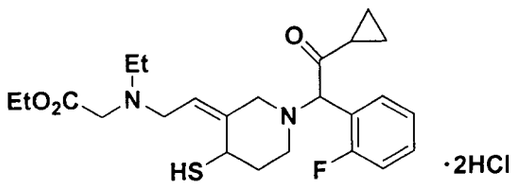


Se sintetizó el compuesto del título en un rendimiento de 38% como un sólido café amorfo usando (Z)-4-(acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-hidroxietiliden)piperidina obtenida en el ejemplo 66 (e) en lugar de (E)-4-(acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-hidroxietiliden)piperidina y N-(etoxicarbonilmetil)-N-etilamina en lugar de 4-(etoxicarbonilmetil)piperidina realizando una reacción similar a la mencionada en el Ejemplo 33.

RMN con ^1H (500 MHz, piridina-d_5) δ ppm : 0.74-0.88 (2H, m), 0.99-1.05 (1H, m), 1.07-1.15 (1H, m), 1.10 y 1.12 (total 3H, cada t, J=7.5), 1.17 y 1.18 (total 3H, cada t, J=7.0), 1.84-1.94 (1H, m), 2.27 (3H, s), 2.30-2.68 (3H, m), 2.83 y 2.86 (total 2H, cada d, J=7.5), 2.92-3.01 (1H, m), 3.05-3.12 (1H, m), 3.40 y 3.55 (total 1H, cada d, J =13.0), 3.52-3.67 (3H, m), 3.72-3.81 (1H, m), 4.15-4.22 (2H, m), 4.89 y 4.94 (total 1H, cada s), 5.12 (1H, bs), 5.63 y 5.73 (total 1H, cada t, J=7.0), 7.20-7.26 (2H, m), 7.30-7.36 (1H, m), 7.64-7.69 (1H, m).

IR (KBr, cm^{-1}) : 1745, 1697, 1494.

(Ejemplo 96) diclorhidrato de (Z)-1-[2-Ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[N-(etoxicarbonilmetil)-N-etilamino]etiliden}-4-sulfanilpiperidina (Clorhidrato del compuesto del Compuesto No. 4-72)

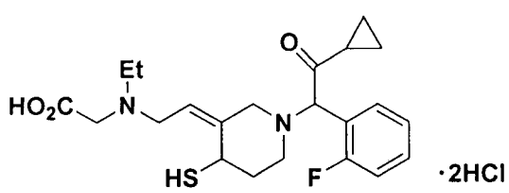


Se sintetizó el compuesto del título en un rendimiento de 64% como un sólido amorfo incoloro usando diclorhidrato de (Z)-4-(acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[N-(etoxicarbonilmetil)-N-etilamino]etiliden}piperidina obtenida en el ejemplo 95 realizando una reacción similar a la mencionada en el Ejemplo 34.

RMN con ^{1}H (400 MHz, piridina-d_5) δ ppm : 0.71-0.86 (2H, m), 0.96-1.04 (1H, m), 1.06-1.20 (1H, m), 1.09 (3H, t, J=7.0), 1.15 y 1.16 (total 3H, cada t, J=7.0), 1.70-1.85 (1H, m), 2.17-2.36 (1H, m), 2.44-2.54 (1H, m), 2.64-3.04 (4H, m), 3.25 y 3.40 (total 1H, cada d, J=12.5), 3.37-3.62 (5H, m), 4.16 y 4.17 (total 2H, cada q, J=7.0), 4.57 (1H, bs), 4.90 y 4.94 (total 1H, cada s), 5.46 y 5.57 (total 1H, cada t, J=7.0), 7.16-7.26 (2H, m), 7.27-7.36 (1H, m), 7.64-7.76 (1H, m).

IR (KBr, cm^{-1}) : 2558, 1744, 1712, 1494.

(Ejemplo 97) diclorhidrato de (Z)-3-{2-[N-(Carboximetil)-N-etilamino]etiliden}-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-sulfanilpiperidina (Clorhidrato del compuesto del Compuesto No. 4-68)



Se sintetizó el compuesto del título en un rendimiento de 53% como un sólido amorfo incoloro usando diclorhidrato de (Z)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[N-(etoxicarbonilmetil)-N-etilamino]etiliden}-4-sulfanilpiperidina obtenida en el ejemplo 96 realizando una reacción similar a la mencionada en el Ejemplo 15.

RMN con ^{1}H (400 MHz, piridina-d_5) δ ppm : 0.72-0.92 (2H, m),

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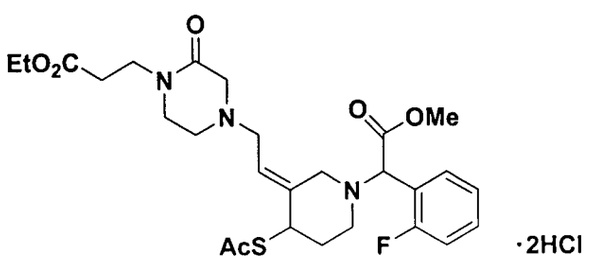
0.97-1.05 (1H, m), 1.06-1.15 (1H, m), 1.33 y 1.35 (total 3H, cada t, J=7.0), 1.72-1.84 (1H, m), 2.23-2.41 (1H, m), 2.46-2.56 (1H, m), 2.62-2.98 (2H, m), 3.22-3.58 (4H, m), 3.71-4.12 (4H, m), 4.68 (1H, bs), 4.89 y 4.95 (total 1H, cada s), 5.17 y 5.89 (total 1H, cada t, J=7.0), 7.16-7.24 (2H, m), 7.25-7.34 (1H, m), 7.64-7.72 (1H, m).

IR (KBr, cm^{-1}) : 2556, 1740, 1713, 1494.

(Ejemplo 98) diclorhidrato de (E)-4-(Acetilsulfanil)-3-(2-{4-[2-(etoxicarbonil)etil]-3-oxopiperazin-1-il}etiliden)-1-[1-(2-fluorofenil)-2-metoxi-2-oxoetil]piperidina (Clorhidrato del compuesto del Compuesto No. 11-108)



(a) (E)-4-(Acetilsulfanil)-3-(2-{4-[2-(etoxicarbonil)etil]-3-oxopiperazin-1-il}etiliden)-1-(trifenilmetil)piperidina

Se sintetizó el compuesto del título en un rendimiento de 40% como un cristal en polvo amarillo usando (E)-3-(2-{4-[2-(etoxicarbonil)etil]-3-oxopiperazin-1-il}etiliden)-4-hidroxi-1-(trifenilmetil)piperidina obtenida en el ejemplo 17 (b) realizando una reacción similar a la mencionada en el Ejemplo 1 (h).

RMN con ^1H (400 MHz, $CDCl_3$) δ ppm : 1.27 (3H, t, J=7.0), 1.79-1.91 (1H, m), 2.14-2.32 (2H, m), 2.24 (3H, s), 2.51-2.66 (6H, m), 2.93-3.06 (3H, m), 3.09 (2H, s), 3.38 (2H, t, J=5.0), 3.63 (2H, t, J=7.0), 4.15 (2H, q, J=7.0), 4.25 (1H, m), 5.59 (1H, t, J=7.0), 7.13-7.22 (3H, m), 7.23-7.34 (6H, m), 7.40-7.54 (6H, m).

(b) bis(trifluoroacetato hidrogenado) de (E)-4-(Acetilsulfanil)-3-(2-{4-[2-(etoxicarbonil)etil]-3-oxopiperazin-1-il}etiliden)piperidina

Se sintetizó el compuesto del título en un rendimiento de 81% como un aceite café usando (E)-4-(acetilsulfanil)-3-(2-{4-[2-(etoxicarbonil)etil]-3-oxopiperazin-1-il}etiliden)-1-(trifenilmetil)

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piperidina obtenida en (a) anterior realizando una reacción similar a la mencionada en el Ejemplo 3 (c).

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 1.26 (3H, t, J=7.0), 2.00-2.09 (1H, m), 2.36 (3H, s), 2.38-2.45 (1H, m), 2.62 (2H, t, J=6.5), 2.86-2.95 (1H, m), 2.97-3.06 (1H, m), 3.17-3.26 (1H, m), 3.28-3.45 (5H, m), 3.50-3.54 (2H, m), 3.63 (2H, t, J=7.0), 3.67 (1H, d, J=13.0), 4.13 (2H, q, J=7.0), 4.16 (1H, d, J=13.0), 4.43-4.47 (1H, m), 5.59 (1H, t, J=7.0).

(c) diclorhidrato de (E)-4-(Acetilsulfanil)-3-(2-{4-[2-(etoxicarbonil)etil]-3-oxopiperazin-1-il}etiliden)-1-[1-(2-fluorofenil)-2-metoxi-2-oxoetil]piperidina

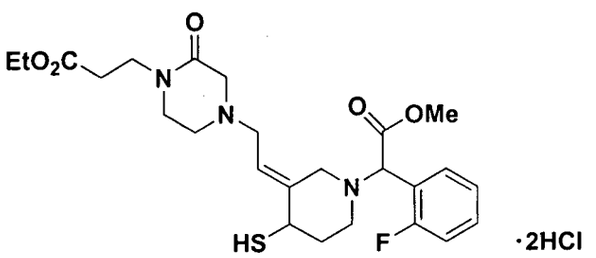
A una solución de bis(trifluoroacetato hidrogenado) de (E)-4-(acetilsulfanil)-3-(2-{4-[2-(etoxicarbonil)etil]-3-oxopiperazin-1-il}etiliden)piperidina (0.76 g) obtenido en (b) anterior y bromo(2-fluorofenil)acetato de metilo (0.45 g) en acetonitrilo (10 ml) se le añadió trietilamina (0.51 ml) bajo enfriamiento con hielo, y la mezcla resultante se agitó a temperatura ambiente durante 30 minutos. La mezcla de la reacción se diluyó con acetato de etilo y se lavó con agua y una solución acuosa saturada de cloruro de sodio, y se secó la capa orgánica sobre sulfato de magnesio anhidro. Se eliminó el solvente in vacuo, y se purificó el residuo mediante cromatografía en una columna de gel de sílice (metanol / diclorometano = 1 / 20) para producir la forma libre (0.50 g, rendimiento 74%) del compuesto del título como un aceite amarillo claro. A una solución de este compuesto en diclorometano (8 ml) se le añadió una solución de cloruro de hidrógeno en dioxano 4N (0.69 ml) a temperatura ambiente, y la mezcla de la reacción se evaporó in vacuo para obtener el compuesto del título (0.66 g, rendimiento cuantitativo) como un sólido amorfo café claro.

RMN con ^{1}H (400 MHz, piridina-d_5) δ ppm : 1.12 (3H, t, J=7.0), 1.80-1.89 (1H, m), 2.14-2.24 (1H, m), 2.25 y 2.27 (total 3H, cada s),

2.45-2.65 (2H, m), 2.73 (2H, t, J=7.0), 2.77-3.02 (5H, m), 3.19 y 3.37 (total 1H, cada d, J=12.5), 3.23 y 3.25 (total 2H, cada s), 3.29-3.36 (2H, m), 3.68 (3H, s), 3.76 (2H, t, J=7.0), 4.10 (2H, q, J=7.0), 4.50-4.57 (1H, m), 4.95 y 4.97 (total 1H, cada s), 5.81 (1H, t, J=7.0), 7.20-7.28 (2H, m), 7.31-7.38 (1H, m), 7.73-7.80 (1H, m).

IR (KBr, cm^{-1}) : 1752, 1730, 1697, 1664, 1497.

(Ejemplo 99) diclorhidrato de (E)-3-(2-{4-[2-(Etoxicarbonil)etil]-3-oxopiperazin-1-il}etiliden)-1-[1-(2-fluorofenil)-2-metoxi-2-oxoetil]-4-sulfanilpiperidina (Clorhidrato del compuesto del Compuesto No. 11-107)



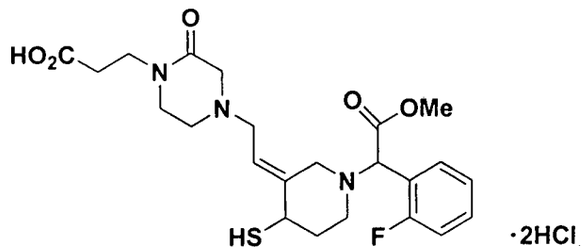
Se sintetizó el compuesto del título en un rendimiento de 65% como un sólido amorfo incoloro usando diclorhidrato de (E)-4-(acetilsulfanil)-3-(2-{4-[2-(etoxicarbonil)etil]-3-oxopiperazin-1-il}etiliden)-1-[1-(2-fluorofenil)-2-metoxi-2-oxoetil]piperidina obtenido en el ejemplo 98 realizando una reacción similar a la mencionada en el Ejemplo 34.

RMN con ^1H (400 MHz, piridina-d_5) δ ppm : 1.12 (3H, t, J=7.0), 1.71-1.83 (1H, m), 2.11-2.24 (1H, m), 2.54-2.65 (2H, m), 2.67-2.82 (1H, m), 2.74 (2H, t, J=7.0), 2.96-3.09 (1H, m), 3.01 (2H, t, J=6.5), 3.26 (2H, s), 3.34 (2H, t, J=5.0), 3.37 y 3.48 (total 1H, cada d, J=12.5), 3.60 y 3.73 (total 1H, cada d, J=12.5), 3.67 (3H, s), 3.77 (2H, t, J=7.0), 3.80-3.89 (1H, m), 4.10 (2H, q, J=7.0), 4.94 y 4.95 (total 1H, cada s), 5.69-5.78 (1H, m), 7.18-7.28 (2H, m), 7.30-7.38 (1H, m), 7.75-7.83 (1H, m).

IR (KBr, cm^{-1}) : 2522, 1752, 1730, 1661, 1496.

(Ejemplo 100) diclorhidrato de (E)-3-(2-{4-[2-(Carboxietil)]-3-

oxopiperazin-1-il}etiliden)-1-[1-(2-fluorofenil)-2-metoxi-2-oxoetil]-4-sulfanilpiperidina (Clorhidrato del compuesto del Compuesto No. 11-103)

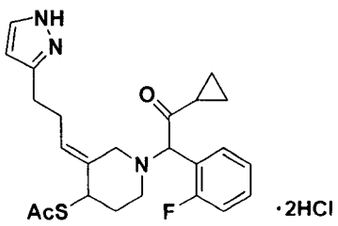


Se sintetizó el compuesto del título en un rendimiento cuantitativo como un sólido amorfo incoloro usando diclorhidrato de (E)-3-(2-{4-[2-(etoxicarbonil)etil]-3-oxopiperazin-1-il}etiliden)-1-[1-(2-fluorofenil)-2-metoxi-2-oxoetil]-4-sulfanilpiperidina obtenido en el ejemplo 99 realizando una reacción similar a la mencionada en el Ejemplo 15.

RMN con ^{1}H (400 MHz, piridina-d_5) δ ppm : 1.71-1.83 (1H, m), 2.12-2.24 (1H, m), 2.53-2.64 (2H, m), 2.67-2.84 (1H, m), 2.92 (2H, t, J=7.0), 2.95-3.09 (1H, m), 2.99 (2H, t, J=6.5), 3.26 y 3.27 (total 2H, cada s), 3.34-3.46 (2H, m), 3.37 y 3.47 (total 1H, cada d, J=12.5), 3.60 y 3.72 (total 1H, cada d, J=12.5), 3.67 (3H, s), 3.80-3.88 (1H, m), 3.91 (2H, t, J=7.0), 4.94 y 4.95 (total 1H, cada s), 5.69-5.78 (1H, m), 7.18-7.26 (2H, m), 7.29-7.36 (1H, m), 7.75-7.82 (1H, m).

IR (KBr, cm^{-1}) : 2570, 1750, 1659, 1496.

(Ejemplo 101) diclorhidrato de (E)-4-(Acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{3-[1H-pirazol-3(5)-il]propiliden}piperidina (Clorhidrato del compuesto del Compuesto No. 1-264)



(a) (E)-3-{3-[1-(t-Butoxicarbonil)-1H-pirazol-3-il]-1-hidroxipropil}-

1-(trifenilmetil)piperidin-4-ona

Se sintetizó el compuesto del título en un rendimiento de 45% como un sólido amorfo incoloro usando 3-[1-(t-butoxicarbonil)-1H-pirazol-3-il]propanal en lugar de 1-(etoxicarbonilmetil)piperidin-4-carbaldehido realizando una reacción similar a la mencionada en el Ejemplo 36 (a).

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 1.63 (9H, s), 1.66-1.80 (2H, m), 1.84-2.01 (1H, m), 2.37-2.45 (1H, m), 2.68-2.95 (4H, m), 3.11-3.32 (2H, m), 3.73-3.84 (2H, m), 6.16 (1H, d, J=2.5), 7.14-7.21 (3H, m), 7.23-7.34 (6H, m), 7.41-7.59 (6H, m), 7.94 (1H, d, J=2.5).

(b) (E)-3-{3-[1-(t-Butoxicarbonil)-1H-pirazol-3-il]propiliden}-1-(trifenilmetil)piperidin-4-ona

A una solución de (E)-3-{3-[1-(t-butoxicarbonil)-1H-pirazol-3-il]-1-hidroxipropil}-1-(trifenilmetil)piperidin-4-ona (1.92 g) obtenido en (a) anterior en diclorometano (45 ml) se le añadió cloruro de metanosulfonilo (0.29 ml) y trietilamina (0.61 ml) bajo enfriamiento con hielo, y la mezcla resultante se agitó a la misma temperatura durante 2.5 horas. La mezcla de la reacción se diluyó con acetato de etilo y se lavó con una solución acuosa saturada de cloruro de sodio, y se secó la capa orgánica sobre sulfato de sodio anhidro. Se eliminó el solvente in vacuo para obtener un compuesto mesilo (2.14 g) como un sólido amorfo incoloro. A una solución de este compuesto en tetrahidrofurano (50 ml) se le añadió 1,8-diazabiciclo[5.4.0]undeca-7-eno (0.98 ml), la mezcla resultante se sometió a reflujo durante 2 horas. La mezcla de la reacción se diluyó con acetato de etilo y se lavó con una solución acuosa saturada de amoniaco y una solución acuosa saturada de cloruro de sodio, y se secó la capa orgánica sobre sulfato de sodio anhidro. Se eliminó el solvente in vacuo, y se purificó el residuo mediante cromatografía en una columna de gel de sílice (acetato de etilo / hexano = 7 / 13) para obtener el compuesto del título (1.20 g,

rendimiento 65%) como un sólido amorfo incoloro.

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 1.64 (9H, s), 2.28-2.35 (2H, m), 2.58 (2H, bs), 2.66 (2H, t, J=6.0), 2.79 (2H, t, J=7.5), 3.12 (2H, bs), 6.12 (1H, d, J=2.5), 6.68 (1H, t, J=7.5), 7.12-7.21 (3H, m), 7.22-7.32 (6H, m), 7.41-7.56 (6H, m), 7.94 (1H, d, J=2.5).

(c) (E)-3-{3-[1-(t-Butoxicarbonil)-1H-pirazol-3-il]propiliden}-4-hidroxi-1-(trifenilmetil)piperidina

Se sintetizó el compuesto del título en un rendimiento de 68% como un sólido incoloro usando (E)-3-{3-[1-(t-butoxicarbonil)-1H-pirazol-3-il]propiliden}-1-(trifenilmetil)piperidin-4-ona obtenido en (b) anterior realizando una reacción similar a la mencionada en el Ejemplo 36 (c).

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 1.63 (9H, s), 1.72-1.83 (1H, m), 2.01-2.25 (2H, m), 2.31-2.42 (2H, m), 2.59 (2H, bs), 2.78 (2H, t, J=7.5), 3.06 (1H, bs), 3.98 (1H, bs), 5.52 (1H, t, J=7.5), 6.15 (1H, d, J=2.5), 7.09-7.19 (3H, m), 7.20-7.31 (6H, m), 7.36-7.56 (6H, m), 7.97 (1H, d, J=2.5).

(d) trifluoroacetato hidrogenado de (E)-3-{3-[1-(t-Butoxicarbonil)-1H-pirazol-3-il]propiliden}-4-hidroxipiperidina

Se sintetizó el compuesto del título en un rendimiento de 65% como un aceite incoloro usando (E)-3-{3-[1-(t-butoxicarbonil)-1H-pirazol-3-il]propiliden}-4-hidroxi-1-(trifenilmetil)piperidina obtenido en (c) anterior realizando una reacción similar a la mencionada en el Ejemplo 3 (c).

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 1.60 (9H, s), 1.91-2.05 (2H, m), 2.39-2.50 (1H, m), 2.53-2.65 (1H, m), 2.75-2.92 (2H, m), 3.27-3.38 (1H, m), 3.58-3.70 (1H, m), 3.88-3.96 (1H, m), 3.97-4.06 (1H, m), 4.37 (1H, m), 5.73 (1H, t, J=8.0), 6.18 (1H, d, J=2.5), 7.85 (1H, d, J=2.5).

(e) (E)-3-{3-[1-(t-Butoxicarbonil)-1H-pirazol-3-il]propiliden}-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-hidroxipiperidina

Se sintetizó el compuesto del título en un rendimiento de 93% como un sólido amorfo incoloro usando trifluoroacetato hidrogenado de (E)-3-{3-[1-(t-butoxicarbonil)-1H-pirazol-3-il]propiliden}-4-hidroxipiperidina obtenido en (d) anterior realizando una reacción similar a la mencionada en el Ejemplo 1 (g).

RMN con ^{1}H (400 MHz, $CDCl_3$ + D_2O) δ ppm : 0.77-0.89 (2H, m), 0.92-1.08 (2H, m), 1.64 (9H, s), 1.66-1.77 (1H, m), 1.89-2.10 (1H, m), 2.17-2.27 (1H, m), 2.29-2.39 (2H, m), 2.41-2.55 (1H, m), 2.69-2.82 (3H, m), 2.84 y 2.93 (total 1H, cada d, J=12.5), 3.16 y 3.26 (total 1H, cada d, J=12.5), 4.08 (1H, m), 4.67 y 4.68 (total 1H, cada s), 5.52 (1H, m), 6.18 y 6.19 (total 1H, cada d, J=2.5), 7.06-7.22 (2H, m), 7.25-7.34 (1H, m), 7.38-7.46 (1H, m), 7.95 y 7.96 (total 1H, cada d, J=2.5).

(f) (E)-4-(Acetilsulfanil)-3-{3-[1-(t-butoxicarbonil)-1H-pirazol-3-il]propiliden}-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil] piperidina

Se sintetizó el compuesto del título en un rendimiento de 17% como un aceite incoloro usando (E)-3-{3-[1-(t-butoxicarbonil)-1H-pirazol-3-il]propiliden}-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-hidroxipiperidina obtenida en (e) anterior realizando una reacción similar a la mencionada en el Ejemplo 1 (h).

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 0.77-0.91 (2H, m), 0.92-1.09 (2H, m), 1.65 (9H, s), 1.71-1.84 (1H, m), 2.06-2.62 (5H, m), 2.28 y 2.29 (total 3H, cada s), 2.65-2.92 (4H, m), 3.28-3.39 (1H, m), 4.32 (1H, m), 4.63 y 4.69 (total 1H, cada s), 5.59 (1H, m), 6.15 y 6.19 (total 1H, cada d, J=2.5), 7.06-7.22 (2H, m), 7.25-7.47 (2H, m), 7.95 y 7.96 (total 1H, cada d, J=2.5).

(g) diclorhidrato de (E)-4-(Acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{3-[1H-pirazol-3(5)-il]propiliden} piperidina

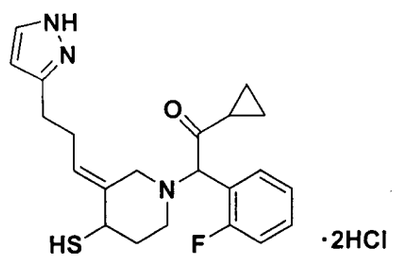
Se sintetizó el compuesto del título en un rendimiento

cuantitativo como un sólido amorfo incoloro usando (E)-4-(acetilsulfanil)-3-{3-[1-(t-butoxicarbonil)-1H-pirazol-3-il]propiliden}-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]piperidina obtenido en (f) anterior realizando una reacción similar a la mencionada en el Ejemplo 9 (f).

RMN con ^{1}H (400 MHz, piridina-d_5) δ ppm : 0.75-0.90 (2H, m), 0.95-1.05 (1H, m), 1.08-1.17 (1H, m), 1.81-1.92 (1H, m), 2.17-2.32 (1H, m), 2.25 y 2.27 (total 3H, cada s), 2.42-2.74 (4H, m), 2.76-2.95 (3H, m), 3.00 y 3.07 (total 1H, cada d, J=12.5), 3.58 y 3.67 (total 1H, cada d, J=12.5), 4.56 (1H, m), 4.87 y 4.92 (total 1H, cada s), 5.85 (1H, m), 6.30 y 6.31 (total 1H, cada d, J=2.0), 7.18-7.36 (3H, m), 7.64-7.74 (1H, m), 7.81 y 7.82 (total 1H, cada d, J=2.0).

MS (FAB) m/z : 442 $(M+H)^+$.

(Ejemplo 102) diclorhidrato de (E)-1-[2-Ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{3-[1H-pirazol-3(5)-il]propiliden}-4-sulfanilpiperidina (Clorhidrato del compuesto del Compuesto No. 1-263)



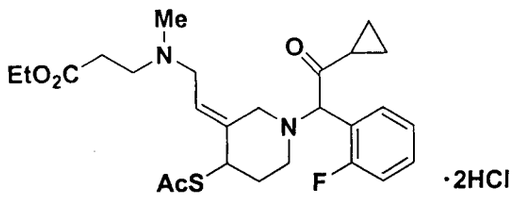
Se sintetizó el compuesto del título en un rendimiento de 82% como un sólido amorfo incoloro usando diclorhidrato de (E)-4-(acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{3-[1H-pirazol-3(5)-il]propiliden}piperidina obtenida en el ejemplo 101 (g) realizando una reacción similar a la mencionada en el Ejemplo 34.

RMN con ^{1}H (400 MHz, piridina-d_5) δ ppm : 0.73-0.89 (2H, m), 0.94-1.04 (1H, m), 1.06-1.17 (1H, m), 1.71-1.82 (1H, m), 2.13-2.28 (1H, m), 2.44-2.61 (3H, m), 2.62-2.72 (1H, m), 2.79-3.01 (1H, m), 2.91 y 2.92 (total 2H, cada t, J=7.5), 3.32 y 3.41 (total 1H, cada d, J=12.5), 3.48 y 3.49 (total 1H, cada d, J=12.5), 3.85 (1H, m), 4.90 y

4.92 (total 1H, cada s), 5.75 y 5.76 (total 1H, cada t, J=7.5), 6.31 y 6.32 (total 1H, cada d, J=2.0), 7.16-7.35 (3H, m), 7.69-7.76 (1H, m), 7.82 y 7.83 (total 1H, cada d, J=2.0).

MS (FAB) m/z : 400 $(M+H)^+$.

(Ejemplo 103) diclorhidrato de (E)-4-(Acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-{N-[2-(etoxicarbonil)etil]-N-metilamino}etiliden)piperidina (Clorhidrato del compuesto del Compuesto No. 3-61)



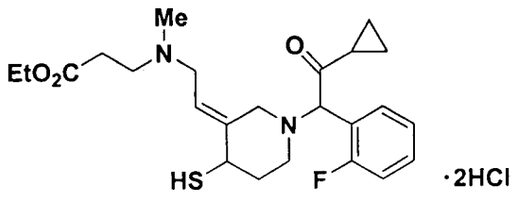
Se sintetizó el compuesto del título en un rendimiento de 35% como un sólido amorfo incoloro usando (E)-4-(acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-hidroxietiliden)piperidina obtenida en el ejemplo 32 (f) y N-[2-(etoxicarbonil)etil]-N-metilamina en lugar de 4-(etoxicarbonilmetil)piperidina realizando una reacción similar a la mencionada en el Ejemplo 33.

RMN con ^1H (500 MHz, piridina-d_5 + D_2O) δ ppm : 0.79-0.96 (2H, m), 1.06-1.16 (2H, m), 1.16 (3H, t, J=7.0), 1.81-1.90 (1H, m), 2.17-2.37 (2H, m), 2.31 y 2.34 (total 3H, cada s), 2.50-2.57 y 2.67-2.74 (total 1H, cada m), 2.73 y 2.75 (total 3H, cada s), 2.79-2.89 (1H, m), 2.94-3.02 (2H, m), 3.11 y 3.24 (total 1H, cada d, J=12.5), 3.26-3.41 (2H, m), 3.62-3.68 (2H, m), 3.70-3.75 (1H, m), 4.14 (2H, q, J=7.0), 4.46-4.51 (1H, m), 5.03 y 5.04 (total 1H, cada s), 6.07 y 6.09 (total 1H, cada t, J=7.5), 7.28-7.40 (2H, m), 7.45-7.52 (1H, m), 7.67-7.73 (1H, m).

IR (KBr, cm^{-1}) : 1730, 1709, 1495.

(Ejemplo 104) diclorhidrato de (E)-1-[2-Ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-{N-[2-(etoxicarbonil)etil]-N-metilamino}etiliden)-4-sulfanilpiperidina (Clorhidrato del

compuesto del Compuesto No. 3-60)

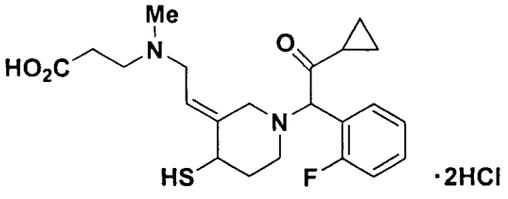


Se sintetizó el compuesto del título en un rendimiento de 31% como un sólido amorfo incoloro usando diclorhidrato de (E)-4-(acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-{N-[2-(etoxicarbonil)etil)-N-metilamino}etiliden)piperidina obtenida en el ejemplo 103 realizando una reacción similar a la mencionada en el Ejemplo 34.

RMN con ^{1}H (400 MHz, piridina-d_5 + D_2O) δ ppm : 0.79-0.98 (2H, m), 1.05-1.17 (2H, m), 1.17 (3H, t, J=7.0), 1.75-1.86 (1H, m), 2.19-2.34 (2H, m), 2.63-2.73 (1H, m), 2.80 y 2.83 (total 3H, cada s), 2.76-2.84 y 2.89-2.97 (total 1H, cada m), 3.01 y 3.03 (total 2H, cada t, J=7.0), 3.35-3.47 (3H, m), 3.52 y 3.60 (total 1H, cada d, J=12.5), 3.66-3.80 (2H, m), 3.89-3.95 (1H, m), 4.15 (2H, q, J=7.0), 5.01 y 5.03 (total 1H, cada s), 6.05-6.12 (1H, m), 7.29-7.39 (2H, m), 7.45-7.53 (1H, m), 7.67-7.73 (1H, m).

IR (KBr, cm^{-1}) : 2463, 1730, 1495.

(Ejemplo 105) diclorhidrato de (E)-3-(2-{N-[2-(Carboxi)etil]-N-metilamino}etiliden)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-sulfanilpiperidina (Clorhidrato del compuesto del Compuesto No. 3-56)



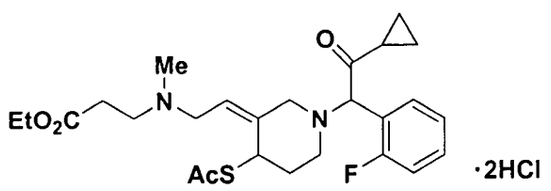
Se trató (E)-4-(Acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-{N-[2-(etoxicarbonil)etil)-N-metilamino}etiliden) piperidina (365 mg) obtenida en el ejemplo 103 con ácido clorhídrico

3N (10 ml) y luego la mezcla resultante se agitó a 60°C durante 3 horas. La mezcla de la reacción se evaporó in vacuo, y se purificó el residuo usando una HPLC preparativa (YMC-Pack ODS-A; YMC, eluyente: acetonitrilo / 0.012N ácido clorhídrico = 15 / 85) para obtener el compuesto del título (271 mg, rendimiento 74%) como un sólido amorfo incoloro.

RMN con ^{1}H (500 MHz, piridina-d_5 + D_2O) δ ppm : 0.77-0.86 (1H, m), 0.87-0.94 (1H, m), 1.07-1.15 (2H, m), 1.75-1.84 (1H, m), 2.20-2.31 (2H, m), 2.64-2.71 (1H, m), 2.76-2.83 y 2.89-2.96 (total 1H, cada m), 2.98 y 2.99 (total 3H, cada s), 3.21 y 3.22 (total 2H, cada t, J=7.0), 3.44 y 3.45 (total 1H, cada d, J=12.0), 3.55 y 3.62 (total 1H, cada d, J=12.0), 3.59-3.68 (2H, m), 3.88-3.94 (2H, m), 3.93-4.02 (1H, m), 5.03 y 5.05 (total 1H, cada s), 6.15 (1H, t, J=7.5), 7.27-7.38 (2H, m), 7.43-7.50 (1H, m), 7.66-7.72 (1H, m).

IR (KBr, cm^{-1}) : 2553, 1713, 1494.

(Ejemplo 106) diclorhidrato de (Z)-4-(Acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-{N-[2-(etoxicarbonil) etil]-N-metilamino}etiliden)piperidina (Clorhidrato del compuesto del Compuesto No. 4-61)

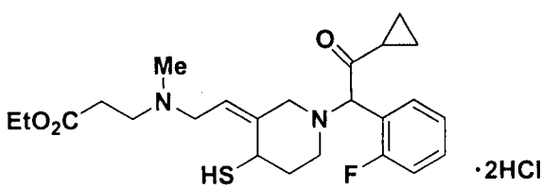


Se sintetizó el compuesto del título en un rendimiento de 36% como un sólido amorfo incoloro usando (Z)-4-(acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-hidroxietiliden)piperidina obtenida en el ejemplo 66 (e) en lugar de (E)-4-(acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-hidroxietiliden)piperidina y N-[2-(etoxicarbonil)etil)-N-metilamina en lugar de 4-(etoxicarbonilmetil)piperidina realizando una reacción similar a la mencionada en el Ejemplo 33.

RMN con ^{1}H (400 MHz, piridina-d_5) δ ppm : 0.76-0.84 (1H, m), 0.96-1.18 (3H, m), 1.07 y 1.08 (total 3H, cada t, J=7.0), 1.80-1.91 (1H, m), 2.23-2.42 (1H, m), 2.26 y 2.27 (total 3H, cada s), 2.46-2.65 (2H, m), 2.77 y 2.79 (total 3H, cada s), 2.95-3.13 (2H, m), 3.22-3.32 (2H, m), 3.40-3.57 (3H, m), 3.93-4.20 (2H, m), 4.07 y 4.08 (total 2H, cada q, J=7.0), 4.87 y 4.95 (total 1H, cada s), 4.93-4.99 (1H, m), 6.02 y 6.13 (total 1H, cada t, J=7.0), 7.20-7.39 (3H, m), 7.58-7.67 (1H, m).

IR (KBr, cm^{-1}) : 1731, 1711, 1494.

(Ejemplo 107) diclorhidrato de (Z)-1-[2-Ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-{N-[2-(etoxicarbonil)etil]-N-metilamino}etiliden)-4-sulfanilpiperidina (Clorhidrato del compuesto del Compuesto No. 4-60)



Se sintetizó el compuesto del título en un rendimiento de 60% como un sólido amorfo incoloro usando diclorhidrato de (Z)-4-(acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-{N-[2-(etoxicarbonil)etil]-N-metilamino}etiliden)piperidina obtenida en el ejemplo 106 realizando una reacción similar a la mencionada en el Ejemplo 34.

RMN con ^{1}H (400 MHz, piridina-d_5 + D_2O) δ ppm : 0.77-0.89 (1H, m), 0.90-0.98 (1H, m), 0.99-1.06 (1H, m), 1.07-1.15 (1H, m), 1.12 y 1.13 (total 3H, cada t, J=7.0), 1.75-1.88 (1H, m), 2.25-2.50 (2H, m), 2.58-3.01 (2H, m), 2.86 y 2.90 (total 3H, cada s), 3.08-3.18 (2H, m), 3.31 y 3.37 (total 1H, cada d, J=12.5), 3.42-3.57 (3H, m), 3.86-4.02 (2H, m), 4.10 y 4.12 (total 2H, cada q, J=7.0), 4.61-4.66 (1H, m), 4.87 y 4.94 (total 1H, cada s), 5.71 y 5.84 (total 1H, cada t, J=7.5), 7.22-7.30 (2H, m), 7.34-7.43 (1H, m), 7.63-7.70 (1H, m).

IR (KBr, cm^{-1}) : 2550, 1730, 1714, 1494.

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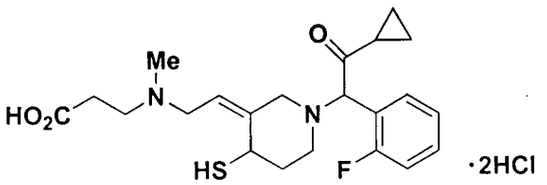
(Ejemplo 108) diclorhidrato de (Z)-3-(2-{N-[2-(Carboxi)etil)-N-metilamino}etiliden)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-sulfanilpiperidina (Clorhidrato del compuesto del Compuesto No. 4-56)

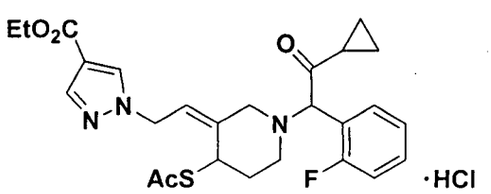


Se sintetizó el compuesto del título en un rendimiento de 42% como un sólido amorfo incoloro usando diclorhidrato de (Z)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-{N-[2-(etoxicarbonil)etil]-N-metilamino}etiliden)-4-sulfanilpiperidina obtenida en el ejemplo 107 realizando una reacción similar a la mencionada en el Ejemplo 15.

RMN con ^{1}H (500 MHz, piridina-d_5 + D_2O) δ ppm : 0.79-0.96 (2H, m), 0.99-1.05 (1H, m), 1.06-1.13 (1H, m), 1.76-1.87 (1H, m), 2.28-2.48 (2H, m), 2.60-2.99 (2H, m), 2.83 y 2.87 (total 3H, cada s), 3.13 y 3.16 (total 2H, cada t, J=7.0), 3.30 y 3.36 (total 1H, cada d, J=12.0), 3.42-3.56 (3H, m), 3.80-3.97 (2H, m), 4.60-4.64 (1H, m), 4.87 y 4.93 (total 1H, cada s), 5.65 y 5.78 (total 1H, cada t, J=7.0), 7.23-7.30 (2H, m), 7.36-7.44 (1H, m), 7.64-7.70 (1H, m).

MS (FAB) m/z : 421 $(M+H)^+$.

(Ejemplo 109) clorhidrato de (Z)-4-(Acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-[2-(4-etoxicarbonil-1H-pirazol-1-il)etiliden]piperidina (Clorhidrato del compuesto del Compuesto No. 2-26)



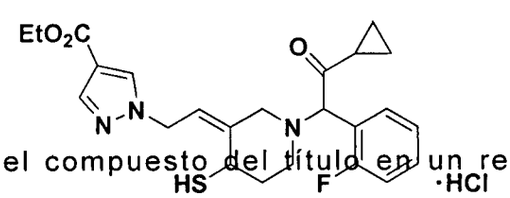
Se sintetizó el compuesto del título en un rendimiento de 11% como un sólido amorfo amarillo claro usando (Z)-4-(acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-hidroxietiliden) piperidina obtenida en el ejemplo 66 (e) y 4-etoxicarbonil-1H-pirazol

realizando una reacción similar a la mencionada en el Ejemplo 40 (a).

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 0.77-0.89 (2H, m), 0.96-1.06 (2H, m), 1.33 y 1.34 (total 3H, cada t, J=7.0), 1.81-1.89 (1H, m), 2.10-2.21 (2H, m), 2.30-2.38 (1H, m), 2.32 (3H, s), 2.79 y 2.97 (total 1H, cada d, J=12.0), 2.83-2.85 y 2.98-3.00 (total 1H, cada m), 3.15 y 3.30 (total 1H, cada d, J=12.0), 4.28 y 4.29 (total 2H, cada q, J=7.0), 4.67 y 4.71 (total 1H, cada s), 4.83 (1H, bs), 4.90-5.05 (2H, m), 5.47 y 5.56 (total 1H, cada t, J=7.0), 7.09-7.18 (2H, m), 7.30-7.39 (2H, m), 7.86 y 7.87 (total 1H, cada s), 7.88 y 7.90 (total 1H, cada s).

IR (KBr, cm^{-1}) : 1713, 1495.

(Ejemplo 110) (Z)-1-[2-Ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-[2-(4-etoxicarbonil-1H-pirazol-1-il)etiliden]-4-sulfanilpiperidina clorhidrato (Clorhidrato del compuesto del Compuesto No. 2-25)



Se sintetizó el compuesto del título en un rendimiento de 88% como un sólido amorfo incoloro usando clorhidrato de (Z)-4-(acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-[2-(4-etoxicarbonil-1H-pirazol-1-il)etiliden]piperidina obtenido en el ejemplo 109 realizando una reacción similar a la mencionada en el Ejemplo 34.

RMN con ^{1}H (400 MHz, piridina-d_5) δ ppm : 0.73-0.83 (2H, m), 0.97-1.04 (1H, m), 1.06-1.13 (1H, m), 1.18-1.25 (3H, m), 1.75-1.84 (1H, m), 2.20-2.36 (1H, m), 2.65-2.71 y 2.97-3.01 (total 1H, cada m), 2.82-2.93 (2H, m), 3.23 y 3.40 (total 1H, cada d, J=12.0), 3.37 y 3.53 (total 1H, cada d, J=12.0), 4.25-4.34 (2H, m), 4.68 (1H, bs), 4.91 y 4.93 (total 1H, cada s), 5.02 y 5.05 (total 2H, cada d, J=7.0), 5.52 y 5.63 (total 1H, cada t, J=7.0), 7.17-7.25 (2H, m), 7.29-7.34 (1H, m), 7.64-7.68 (1H, m), 8.28 y 8.29 (total 1H, cada s), 8.41 y 8.44 (total 1H, cada s).

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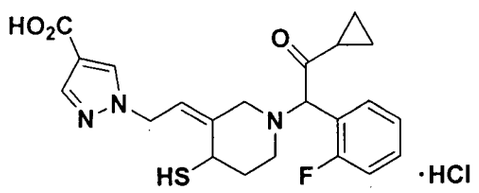
IR (KBr, cm^{-1}) : 2541, 1713, 1494.

(Ejemplo 111) clorhidrato de (Z)-3-[2-(4-Carboxi-1H-pirazol-1-il)etiliden]-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-sulfanilpiperidina (Clorhidrato del compuesto del Compuesto No. 2-17)

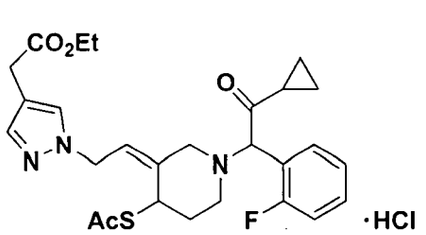


Se sintetizó el compuesto del título en un rendimiento de 49% como un sólido amorfo incoloro usando (Z)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-[2-(4-etoxicarbonil-1H-pirazol-1-il)etiliden]-4-sulfanilpiperidina clorhidrato obtenida en el ejemplo 110 realizando una reacción similar a la mencionada en el Ejemplo 15.

RMN con ^1H (400 MHz, piridina-d_5) δ ppm : 0.71-0.84 (2H, m), 0.96-1.04 (1H, m), 1.06-1.15 (1H, m), 1.72-1.89 (1H, m), 2.17-2.36 (1H, m), 2.62-3.02 (3H, m), 3.22 y 3.39 (total 1H, cada d, J=12.0), 3.37 y 3.53 (total 1H, cada d, J=12.5), 4.68 (1H, bs), 4.90 y 4.92 (total 1H, cada s), 4.98-5.09 (2H, m), 5.52 y 5.63 (total 1H, cada t, J=7.0), 7.16-7.35 (3H, m), 7.66 (1H, m), 8.43 y 8.45 (total 1H, cada s), 8.52 y 8.55 (total 1H, cada s).

IR (KBr, cm^{-1}) : 3399, 2547, 1710, 1494.

(Ejemplo 112) clorhidrato de (Z)-4-(Acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[4-(etoxicarbonilmetil)-1H-pirazol-1-il]etiliden}piperidina (Clorhidrato del compuesto del Compuesto No. 2-62)



(a) (Z)-4-Acetoxi-3-[2-(t-butildifenilsililoxi)etiliden]-1-(trifenilmetil)piperidina

A una solución de (E)-4-acetoxi-3-[2-(t-butildifenilsililoxi)etiliden]-1-(trifenilmetil)piperidina (200 mg) obtenida en el ejemplo 66 (c) y 1,1'-bis(difenilfosfino)ferroceno (33 mg) en tolueno (2 ml) se le añadió una solución de acetato de potasio (147 mg) en agua (1 ml) a temperatura ambiente y luego acetato de paladio (7 mg) a 50°C, y la mezcla resultante se agitó a la misma temperatura durante 1.5 horas. La mezcla de la reacción se diluyó con acetato de etilo y se lavó con agua y una solución acuosa saturada de cloruro de sodio, y se secó la capa orgánica sobre sulfato de sodio anhidro. Se eliminó el solvente in vacuo, y se purificó el residuo mediante cromatografía en una columna de gel de sílice (acetato de etilo / hexano = 1 / 19 - 1 / 9) para obtener a 1:11 mixture (143 mg) del compuesto del título y su isómero (E) como un sólido amorfo incoloro. Esta mezcla se purificó adicionalmente usando una HPLC preparativa (YMC-Pack ODS-A; YMC, eluyente: acetonitrilo / agua = 19 / 1) para obtener el compuesto del título (3 mg, rendimiento 2%) y la forma (E) (73 mg, rendimiento 37%) de él como un sólido amorfo incoloro, respectivamente.

RMN con 1H (400 MHz, CDCl3) δ ppm : 1.10 (9H, s), 1.67-1.80 (1H, m), 1.77 (3H, s), 1.84-1.96 (2H, m), 2.25-2.37 (1H, m), 2.69-2.81 (1H, m), 3.07-3.16 (1H, m), 4.38 (1H, dd, J=14.0, 4.5), 4.54 (1H, dd, J=14.0, 7.0), 5.42 (1H, bs), 5.55 (1H, dd, J=7.0, 4.5), 7.14-7.20 (3H, m), 7.23-7.30 (6H, m), 7.37-7.50 (12H, m), 7.71-7.77 (4H, m).

(b) (Z)-3-[2-(t-Butildifenilsililoxi)etiliden]-1-(trifenilmetil) piperidin-4-ol

A una solución de (Z)-4-acetoxi-3-[2-(t-butildifenilsililoxi)etiliden]-1-(trifenilmetil)piperidina (3.00 g) obtenida en (a) anterior en metanol (60 ml) se le añadió carbonato de potasio (2.00 g) bajo enfriamiento con hielo, y la mezcla resultante se agitó a temperatura ambiente durante 4 horas. Se eliminaron las partículas insolubles en la mezcla de la reacción mediante filtración, y el

solvente se evaporó in vacuo. El residuo obtenido se diluyó con acetato de etilo y se lavó con una solución acuosa saturada de cloruro de sodio, y se secó la capa orgánica sobre sulfato de sodio anhidro. Se eliminó el solvente in vacuo, y se purificó el residuo mediante cromatografía en una columna de gel de sílice (acetato de etilo / hexano = 1 / 10) para obtener el compuesto del título (2.02 g, rendimiento 72%) como un sólido amorfo incoloro.

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 1.06 (9H, s), 1.72-1.83 (1H, m), 1.89-2.01 (1H, m), 2.06-2.27 (1H, m), 2.40-2.65 (2H, m), 2.77-2.95 (1H, m), 4.30-4.41 (3H, m), 5.50 (1H, t, J=6.5), 7.12-7.20 (3H, m), 7.22-7.31 (6H, m), 7.34-7.53 (12H, m), 7.64-7.77 (4H, m).

(c) (Z)-3-(2-Hidroxietiliden)-1-(trifenilmetil)piperidin-4-ol

Se sintetizó el compuesto del título en un rendimiento de 96% como un sólido amorfo incoloro usando (Z)-3-[2-(t-butildifenilsililoxi)etiliden]-1-(trifenilmetil)piperidin-4-ol obtenido en (b) anterior realizando una reacción similar a la mencionada en el Ejemplo 1 (e).

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 1.78-1.89 (1H, m), 1.97-2.09 (1H, m), 2.11-2.67 (3H, m), 2.79-2.95 (1H, m), 4.21 (1H, dd, J=12.5, 6.5), 4.31 (1H, dd, J=12.5, 7.5), 4.55 (1H, bs), 5.52 (1H, dd, J=7.5, 6.5), 7.11-7.18 (3H, m), 7.21-7.30 (6H, m), 7.41-7.55 (6H, m).

(d) (Z)-3-(2-Acetoxietiliden)-1-(trifenilmetil)piperidin-4-ol

A una suspensión de (Z)-3-(2-hidroxietiliden)-1-(trifenilmetil)piperidin-4-ol (33.0 g) obtenido en (c) anterior en diclorometano (500 ml) se le añadió una solución de anhídrido acético (8.0 ml) en diclorometano (60 ml) y trietilamina (24.0 ml) bajo enfriamiento con hielo, y la mezcla resultante se agitó a temperatura ambiente durante 20 horas. La mezcla de la reacción se diluyó con diclorometano y se lavó con agua y una solución acuosa saturada de cloruro de sodio, y se secó la capa orgánica sobre sulfato de sodio anhidro. Se eliminó el solvente in vacuo, y se purificó el residuo

mediante cromatografía en una columna de gel de sílice (acetato de etilo / hexano = 1 / 2) para obtener el compuesto del título (30.9 g, rendimiento 84%) como un sólido amorfo incoloro.

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 1.85-2.17 (5H, m), 2.36-2.45 (1H, m), 2.50-2.59 (1H, m), 2.62-2.74 (1H, m), 2.97-3.09 (1H, m), 4.53 (1H, dd, J=12.0, 6.0), 4.74 (1H, bs), 5.05 (1H, dd, J=12.0, 9.0), 5.35 (1H, dd, J=9.0, 6.0), 7.11-7.19 (3H, m), 7.21-7.29 (6H, m), 7.40-7.52 (6H, m).

(e) (Z)-4-(t-Butildimetilsililoxi)-3-(2-acetoxietiliden)-1-(trifenilmetil)piperidina

Se sintetizó el compuesto del título en un rendimiento de 68% como un sólido amorfo incoloro usando (Z)-3-(2-acetoxietiliden)-1-(trifenilmetil)piperidin-4-ol obtenido en (d) anterior realizando una reacción similar a la mencionada en el Ejemplo 1 (a).

RMN con ^{1}H (500 MHz, $CDCl_3$) δ ppm : -0.13 (3H, s), -0.05 (3H, s), 0.67 (9H, s), 1.69-1.78 (1H, m), 1.84-1.93 (1H, m), 2.08 (3H, s), 2.12-2.30 (1H, m), 2.43-2.68 (2H, m), 2.79-2.98 (1H, m), 4.40 (1H, bs), 4.66-4.85 (2H, m), 5.35 (1H, t, J=7.5), 7.08-7.18 (3H, m), 7.20-7.29 (6H, m), 7.39-7.54 (6H, m).

(f) (Z)-4-(t-Butildimetilsililoxi)-3-(2-hidroxietiliden)-1-(trifenilmetil)piperidina

Se sintetizó el compuesto del título en un rendimiento de 94% como un sólido amorfo incoloro usando (Z)-4-(t-butildimetilsililoxi)-3-(2-acetoxietiliden)-1-(trifenilmetil)piperidina obtenido en (e) anterior realizando una reacción similar a la mencionada en el Ejemplo 112 (b).

RMN con ^{1}H (500 MHz, $CDCl_3$) δ ppm : -0.09 (3H, s), -0.03 (3H, s), 0.72 (9H, s), 1.71-1.94 (2H, m), 2.21-2.85 (4H, m), 4.16-4.36 (2H, m), 4.46 (1H, bs), 5.50 (1H, t, J=7.0), 7.09-7.18 (3H, m), 7.20-7.29 (6H, m), 7.39-7.56 (6H, m).

(g) (Z)-4-(t-Butildimetilsililoxi)-3-{2-[4-(etoxicarbonilmetil)-1H-

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pirazol-1-il]etiliden}-1-(trifenilmetil)piperidina

A una solución de (Z)-4-(t-butildimetilsililoxi)-3-(2-hidroxietiliden)-1-(trifenilmetil)piperidina (5.80 g) obtenido en (f) anterior y anhídrido p-toluenosulfónico (3.80 g) en acetonitrilo (60 ml) se le añadió trietilamina (1.94 ml) a temperatura ambiente, y la mezcla resultante se agitó a la misma temperatura durante 2.5 horas. La mezcla de la reacción se diluyó con acetato de etilo y se lavó con agua y una solución acuosa saturada de cloruro de sodio, y se secó la capa orgánica sobre sulfato de sodio anhidro. Se eliminó el solvente in vacuo para obtener (Z)-4-(t-butildimetilsililoxi)-3-[2-(tosiloxi)etiliden]-1-(trifenilmetil)piperidina (9.08 g, rendimiento cuantitativo) como un aceite café.

A una solución de 4-(etoxicarbonilmetil)-1H-pirazol (1.80 g) en N,N-dimetilformamida (40 ml) se le añadió hidruro de sodio (0.56 g) bajo enfriamiento con hielo, y la mezcla resultante se agitó a la misma temperatura durante 20 minutos. A la mezcla de la reacción se le añadió una solución de (Z)-4-(t-butildimetilsililoxi)-3-[2-(tosiloxi)etiliden]-1-(trifenilmetil)piperidina obtenida anteriormente en N,N-dimetilformamida (10 ml), y luego la mezcla resultante se agitó a temperatura ambiente durante 1.5 horas y at 60°C durante adicionalmente 30 minutos. La mezcla de la reacción se diluyó con acetato de etilo y se lavó con agua y una solución acuosa saturada de cloruro de sodio, y se secó la capa orgánica sobre sulfato de sodio anhidro. Se eliminó el solvente in vacuo, y se purificó el residuo mediante cromatografía en una columna de gel de sílice (acetato de etilo / hexano = 1 / 5 - 1 / 4) para obtener el compuesto del título (3.83 g, rendimiento 52%) como un aceite amarillo.

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : -0.11 (3H, s), -0.04 (3H, s), 0.70 (9H, s), 1.22-1.31 (3H, m), 1.72-1.99 (4H, m), 2.15-2.40 (1H, m), 2.53-2.79 (1H, m), 3.51 (2H, s), 4.16 (2H, q, J=7.5), 4.51-4.57 (1H, m), 4.88-4.98 (2H, m), 5.46 (1H, t, J=7.0), 7.09-7.28 (15H, m),

7.42 (1H, s), 7.45 (1H, s).

(h) (Z)-3-{2-[4-(Etoxicarbonilmetil)-1H-pirazol-1-il]etiliden}-4-hidroxi-1-(trifenilmetil)piperidina

Se sintetizó el compuesto del título en un rendimiento de 67% como un sólido amorfo incoloro usando (Z)-4-(t-butildimetilsililoxi)-3-{2-[4-(etoxicarbonilmetil)-1H-pirazol-1-il]etiliden}-1-(trifenilmetil) piperidina obtenida en (g) anterior realizando una reacción similar a la mencionada en el Ejemplo 1 (e).

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 1.26 (3H, t, J=7.0), 1.92-2.00 (1H, m), 2.08-2.23 (2H, m), 2.57-2.69 (2H, m), 2.91-3.03 (1H, m), 3.44 (2H, s), 4.14 (2H, q, J=7.0), 4.59-4.68 (1H, m), 4.75 (1H, m), 4.97-5.06 (1H, m), 5.48 (1H, t, J=8.0), 7.10-7.29 (15H, m), 7.36 (1H, s), 7.37 (1H, s).

(i) (Z)-4-(Acetilsulfanil)-3-{2-[4-(etoxicarbonilmetil)-1H-pirazol-1-il]etiliden}-1-(trifenilmetil)piperidina

Se sintetizó el compuesto del título en un rendimiento de 88% como un sólido café amorfo usando (Z)-3-{2-[4-(etoxicarbonilmetil)-1H-pirazol-1-il]etiliden}-4-hidroxi-1-(trifenilmetil)piperidina obtenida en (h) anterior realizando una reacción similar a la mencionada en el Ejemplo 1 (h).

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 1.26 (3H, t, J=7.0), 1.62-1.69 (1H, m), 1.80-1.87 (1H, m), 2.06-2.12 (1H, m), 2.23 (3H, s), 2.36-2.49 (1H, m), 3.06-3.14 (1H, m), 3.38-3.44 (1H, m), 3.47 (2H, s), 4.15 (2H, q, J=7.0), 4.85-4.89 (1H, m), 4.95 (2H, d, J=6.5), 5.50 (1H, t, J=6.5), 7.12-7.30 (15H, m), 7.37 (1H, s), 7.42 (1H, s).

(j) trifluoroacetato hidrogenado de (Z)-4-(Acetilsulfanil)-3-{2-[4-(etoxicarbonilmetil)-1H-pirazol-1-il]etiliden}piperidina

Se sintetizó el compuesto del título en un rendimiento de 87% como un aceite café usando (Z)-4-(acetilsulfanil)-3-{2-[4-(etoxicarbonilmetil)-1H-pirazol-1-il]etiliden}-1-(trifenilmetil)piperidina obtenido en (i) anterior realizando una reacción similar a la

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mencionada en el Ejemplo 3 (c).

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 1.26 (3H, t, J=7.0), 2.06-2.10 (1H, m), 2.39 (3H, s), 2.39-2.51 (1H, m), 3.10-3.21 (1H, m), 3.38-3.46 (1H, m), 3.47 (2H, s), 3.62-3.77 (2H, m), 4.12 (2H, q, J=7.0), 4.86 (1H, m), 4.89-5.04 (2H, m), 5.80 (1H, t, J=6.5), 7.42 (1H, s), 7.43 (1H, s).

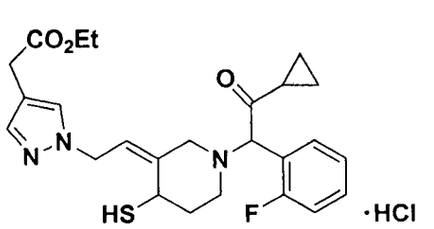
(k) clorhidrato de (Z)-4-(Acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[4-(etoxicarbonilmetil)-1H-pirazol-1-il]etiliden}piperidina

Se sintetizó el compuesto del título en un rendimiento de 80% como un sólido amorfo amarillo claro usando trifluoroacetato hidrogenado de (Z)-4-(acetilsulfanil)-3-{2-[4-(etoxicarbonilmetil)-1H-pirazol-1-il]etiliden}piperidina obtenido en (j) anterior realizando una reacción similar a la mencionada en el Ejemplo 1 (g).

RMN con ^{1}H (400 MHz, piridina-d_5) δ ppm : 0.70-0.83 (2H, m), 0.96-1.12 (2H, m), 1.11 y 1.12 (total 3H, cada t, J=7.0), 1.81-1.93 (1H, m), 2.04-2.15 (1H, m), 2.26-2.44 (2H, m), 2.26 (3H, s), 2.48-2.59 (1H, m), 2.90-2.98 y 3.04-3.12 (total 1H, cada m), 3.31 y 3.46 (total 1H, cada d, J=12.0), 3.61 (2H, s), 4.11 y 4.12 (total 2H, cada q, J=7.0), 4.87 y 4.90 (total 1H, cada s), 5.05-5.23 (3H, m), 5.65 y 5.74 (total 1H, cada t, J=6.5), 7.16-7.27 (2H, m), 7.28-7.36 (1H, m), 7.57-7.65 (1H, m), 7.69 y 7.72 (total 1H, cada s), 7.73 y 7.75 (total 1H, cada s).

MS (FAB) m/z : 514 $(M+H)^+$.

(Ejemplo 113) clorhidrato de (Z)-1-[2-Ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[4-(etoxicarbonilmetil)-1H-pirazol-1-il]etiliden}-4-sulfanilpiperidina (Clorhidrato del compuesto del Compuesto No. 2-61)

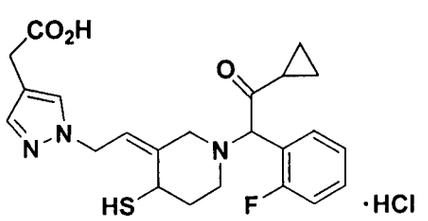


Se sintetizó el compuesto del título en un rendimiento de 45% como un sólido amorfo incoloro usando clorhidrato de (Z)-4-(acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[4-(etoxicarbonilmetil)-1H-pirazol-1-il]etiliden}piperidina obtenida en el ejemplo 112 (k) realizando una reacción similar a la mencionada en el Ejemplo 34.

RMN con ^{1}H (400 MHz, piridina-d_5) δ ppm : 0.71-0.81 (2H, m), 0.95-1.13 (2H, m), 1.11 y 1.12 (total 3H, cada t, J=7.0), 1.71-1.83 (1H, m), 2.16-2.36 (1H, m), 2.38-2.47 (1H, m), 2.61-3.02 (3H, m), 3.18 y 3.36 (total 1H, cada d, J=12.5), 3.51 y 3.61 (total 1H, cada d, J=12.5), 3.64 (2H, s), 4.11 y 4.12 (total 2H, cada q, J=7.0), 4.63 (1H, m), 4.87-4.97 (2H, m), 5.46 y 5.58 (total 1H, cada t, J=6.5), 7.15-7.35 (3H, m), 7.56-7.78 (3H, m).

MS (FAB) m/z : 472 $(M+H)^+$.

(Ejemplo 114) clorhidrato de (Z)-3-{2-[4-(Carboximetil)-1H-pirazol-1-il]etiliden}-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-sulfanilpiperidina (Clorhidrato del compuesto del Compuesto No. 2-53)



Se sintetizó el compuesto del título en un rendimiento de 23% como un sólido amorfo incoloro usando clorhidrato de (Z)-4-(acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-{2-[4-(etoxicarbonilmetil)-1H-pirazol-1-il]etiliden}piperidina obtenida en el ejemplo 112 (k) realizando una reacción similar a la mencionada en el Ejemplo 105.

RMN con ^{1}H (400 MHz, piridina-d_5) δ ppm : 0.71-0.83 (2H, m), 0.96-1.12 (2H, m), 1.73-1.82 (1H, m), 2.19-2.35 (1H, m), 2.40-2.48 (1H, m), 2.80-3.00 (2H, m), 3.18 y 3.35 (total 1H, cada d, J=11.5),

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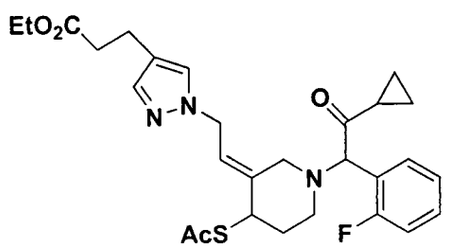
3.35 y 3.51 (total 1H, cada d, J=11.5), 3.79 y 3.80 (total 2H, cada s), 4.64 (1H, bs), 4.86-5.01 (2H, m), 4.88 y 4.91 (total 1H, cada s), 5.47 y 5.59 (total 1H, cada t, J=7.0), 7.16-7.33 (3H, m), 7.65 (1H, m), 7.78 y 7.81 (total 1H, cada s), 7.83 y 7.85 (total 1H, cada s).

MS (FAB) m/z : 444 $(M+H)^+$.

(Ejemplo 115) (E)-4-(Acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-{4-[2-(etoxicarbonil)etil)-1H-pirazol-1-il}etiliden)piperidina (Compuesto del compuesto No. 1-88)



(a) (E)-4-(t-Butildimetilsililoxi)-3-(2-{4-[2-(etoxicarbonil)etil]-1H-pirazol-1-il}etiliden)-1-(trifenilmetil)piperidina

Se sintetizó el compuesto del título en un rendimiento de 64% como un aceite incoloro usando (E)-4-(t-butildimetilsililoxi)-3-[2-(tosiloxi)etiliden]-1-(trifenilmetil)piperidina obtenida en el ejemplo 1 (c) y 4-[2-(etoxicarbonil)etil]-1H-pirazol realizando una reacción similar a la mencionada en el Ejemplo 21 (a).

RMN con ^1H (400 MHz, $CDCl_3$) δ ppm : 0.06 (6H, s), 0.88 (9H, s), 1.27 (3H, t, J=7.0), 1.82 (1H, m), 1.90-2.03 (3H, m), 2.60 (2H, t, J=7.0), 2.86 (2H, t, J=7.0), 3.03 (1H, bs), 3.70 (1H, bs), 3.91-3.98 (1H, m), 4.16 (2H, q, J=7.0), 4.71-4.81 (2H, m), 5.81-5.84 (1H, m), 7.21 (3H, m), 7.28-7.33 (9H, m), 7.40 (1H, s), 7.53 (4H, m).

(b) (E)-3-(2-{4-[2-(Etoxicarbonil)etil]-1H-pirazol-1-il}etiliden)-4-hidroxi-1-(trifenilmetil)piperidina

Se sintetizó el compuesto del título en un rendimiento de 58% en un sólido amorfo incoloro usando (E)-4-(t-butildimetilsililoxi)-3-(2-{4-[2-(etoxicarbonil)etil]-1H-pirazol-1-il}etiliden)-1-(trifenilmetil) piperidina obtenida en (a) anterior realizando una reacción similar a la mencionada en el Ejemplo 1 (e).

RMN con ^1H (400 MHz, $CDCl_3$) δ ppm : 1.23 (3H, t, J=7.0), 1.57-1.63 (1H, m), 1.81-1.90 (1H, m), 2.10-2.14 (1H, m), 2.34 (1H, bs), 2.56 (2H, t, J=7.0), 2.80 (2H, t, J=7.0), 2.84 (1H, bs), 3.42 (1H, bs), 4.01 (1H, m), 4.12 (2H, q, J=7.0), 4.65-4.76 (2H, m), 5.75 (1H, t, J=7.0), 7.14-7.27 (10H, m), 7.35 (1H, s), 7.48 (6H, m).

(c) (E)-4-(Acetilsulfanil)-3-(2-{4-[2-(etoxicarbonil)etil]-1H-pirazol-1-il}etiliden)-1-(trifenilmetil)piperidina

Se sintetizó el compuesto del título en un rendimiento de 65% como un aceite incoloro usando (E)-3-(2-{4-[2-(etoxicarbonil)etil]-1H-pirazol-1-il}etiliden)-4-hidroxi-1-(trifenilmetil)piperidina obtenida en (b) anterior realizando una reacción similar a la mencionada en el Ejemplo 1 (h).

RMN con ^1H (400 MHz, $CDCl_3$) δ ppm : 1.24 (3H, t, J=7.0), 1.86-1.94 (1H, m), 2.25 (3H, s), 2.31 (2H, m), 2.56 (2H, t, J=7.0), 2.81 (2H, t, J=7.0), 2.86 (1H, m), 4.12 (2H, q, J=7.0), 4.16-4.34 (3H, m), 4.58-4.71 (2H, m), 5.77 (1H, t, J=7.0), 7.15-7.29 (10H, m), 7.36 (1H, s), 7.60 (6H, m).

(d) trifluoroacetato hidrogenado de (E)-4-(Acetilsulfanil)-3-(2-{4-[2-(etoxicarbonil)etil]-1H-pirazol-1-il}etiliden)piperidina

Se sintetizó el compuesto del título en un rendimiento de 23% como un aceite incoloro usando (E)-4-(acetilsulfanil)-3-(2-{4-[2-(etoxicarbonil)etil]-1H-pirazol-1-il}etiliden)-1-(trifenilmetil)piperidina obtenida en (c) anterior realizando una reacción similar a la mencionada en el Ejemplo 3 (c).

RMN con ^1H (400 MHz, $CDCl_3$) δ ppm : 1.25 (3H, t, J=7.0), 2.03-2.09 (1H, m), 2.36 (3H, s), 2.39-2.47 (1H, m), 2.55 (2H, t, J=7.0), 2.79 (2H, t, J=7.0), 3.24-3.31 (1H, m), 3.41-3.49 (1H, m), 3.75 (1H, d, J=14.0), 4.11-4.17 (3H, m), 4.44 (1H, m), 4.63 (1H, dd, J=15.5, 5.5), 4.83 (1H, dd, J=15.5, 9.0), 5.93-5.96 (1H, m), 7.31 (1H, s), 7.39 (1H, s).

(e) (E)-4-(Acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-

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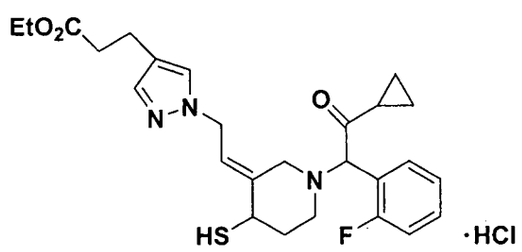
oxoetil]-3-(2-{4-[2-(etoxicarbonil)etil]-1H-pirazol-1-il}etiliden) piperidina

Se sintetizó el compuesto del título en un rendimiento de 67% como un aceite incoloro usando trifluoroacetato hidrogenado de (E)-4-(acetilsulfanil)-3-(2-{4-[2-(etoxicarbonil)etil]-1H-pirazol-1-il}etiliden)piperidina obtenido en (d) anterior realizando una reacción similar a la mencionada en el Ejemplo 1 (g).

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 0.77-0.89 (2H, m), 0.99-1.07 (2H, m), 1.25 (3H, t, J=7.0), 1.83 (1H, m), 2.15 (2H, m), 2.29 y 2.30 (total 3H, cada s), 2.54 (2H, t, J=7.0), 2.55-2.64 (1H, m), 2.68-2.76 (1H, m), 2.78 (2H, t, J=7.0), 2.84-2.92 y 3.12-3.18 (total 1H, cada m), 3.26-3.35 y 3.39-3.46 (total 1H, cada m), 4.14 (2H, q, J=7.0), 4.28-4.35 (1H, m), 4.60-4.76 (3H, m), 5.77 (1H, m), 7.09-7.22 (2H, m), 7.27-7.42 (4H, m).

(Ejemplo 116) clorhidrato de (E)-1-[2-Ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-{4-[2-(etoxicarbonil)etil]-1H-pirazol-1-il}etiliden)-4-sulfanilpiperidina (Clorhidrato del compuesto del Compuesto No. 1-87)



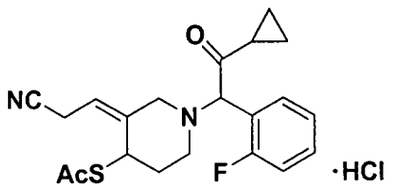
Se sintetizó el compuesto del título en un rendimiento de 74% como un sólido amorfo incoloro usando (E)-4-(acetilsulfanil)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-3-(2-{4-[2-(etoxicarbonil)etil]-1H-pirazol-1-il}etiliden)piperidina obtenida en el ejemplo 115 (e) realizando una reacción similar a la mencionada en el Ejemplo 34.

RMN con ^{1}H (400 MHz, piridina-d_5) δ ppm : 0.77-0.83 (2H, m), 0.99-1.06 (1H, m), 1.09-1.16 (1H, m), 1.12 (3H, t, J=7.0), 1.74-1.83 (1H, m), 2.14-2.24 (1H, m), 2.47-2.52 (1H, m), 2.62 (2H, t, J=7.0), 2.65 (1H, m), 2.86 (2H, t, J=7.0), 2.83-2.99 (1H, m), 3.34 y 3.36

(total 1H, cada d, J=12.5), 3.77-3.81 (1H, m), 4.12 (2H, q, J=7.0), 4.84-4.92 (3H, m), 4.93 y 4.95 (total 1H, cada s), 5.95-5.99 (1H, m), 7.19-7.27 (2H, m), 7.28-7.36 (1H, m), 7.58 (1H, s), 7.62 (1H, s), 7.66-7.73 (1H, m).

MS (FAB) m/z : 486 $(M+H)^+$.

(Ejemplo 117) clorhidrato de (Z)-4-(Acetilsulfanil)-3-(2-cianoetiliden)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil] piperidina (Clorhidrato del compuesto del Compuesto No. 4-47)



(a) (Z)-4-(t-Butildimetilsililoxi)-3-(2-cianoetiliden)-1-(trifenilmetil) piperidina

A una solución de (Z)-4-(t-butildimetilsililoxi)-3-(2-hidroxietiliden)-1-(trifenilmetil)piperidina (10.00 g) obtenida en el ejemplo 112 (f) en benceno (500 ml) se le añadió tributilfosfina (6.10 g), cianhidrina de acetona (3.60 g) y 1,1'-azobis(N,N-dimetilformamida) (5.20 g), y la mezcla resultante se agitó a temperatura ambiente durante 2 horas. La mezcla de la reacción se diluyó con acetato de etilo y se lavó con una solución acuosa saturada de cloruro de sodio, y se secó la capa orgánica sobre sulfato de magnesio anhidro. Se eliminó el solvente in vacuo, y se purificó el residuo mediante cromatografía en una columna de gel de sílice (acetato de etilo / hexano = 1 / 6) para obtener el compuesto del título (9.27 g, rendimiento 91%) como un sólido amorfo incoloro.

RMN con ^1H (400 MHz, $CDCl_3$) δ ppm : 0.00-0.10 (6H, m), 0.81 (9H, s), 1.82-2.01 (2H, m), 2.15-3.02 (4H, m), 3.35-3.60 (2H, m), 4.40 (1H, bs), 5.29 (1H, t, J=7.5), 7.18-7.25 (3H, m), 7.28-7.36 (5H, m), 7.46-7.59 (7H, m).

(b) (Z)-3-(2-Cianoetiliden)-1-(trifenilmetil)piperidin-4-ol

Se sintetizó el compuesto del título en un rendimiento

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cuantitativo como un sólido amorfo incoloro usando (Z)-4-(t-butildimetilsililoxi)-3-(2-cianoetiliden)-1-(trifenilmetil)piperidina obtenido en (a) anterior realizando una reacción similar a la mencionada en el Ejemplo 1 (e).

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 1.86-1.97 (1H, m), 1.99-2.10 (1H, m), 2.23-2.54 (2H, m), 2.64-2.88 (2H, m), 3.37 (2H, d, J=7.5), 4.50 (1H, bs), 5.30 (1H, t, J=7.5), 7.13-7.20 (1H, m), 7.23-7.31 (7H, m), 7.42-7.52 (7H, m).

(c) (Z)-4-(Acetilsulfanil)-3-(2-cianoetiliden)-1-(trifenilmetil) piperidina

Se sintetizó el compuesto del título en un rendimiento de 83% como un sólido amorfo incoloro usando (Z)-3-(2-cianoetiliden)-1-(trifenilmetil)piperidin-4-ol obtenido en (b) anterior realizando una reacción similar a la mencionada en el Ejemplo 1 (h).

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 1.54-1.64 (1H, m), 1.78-1.85 (1H, m), 2.08 (1H, d, J=13.0), 2.22 (3H, s), 2.34-2.45 (1H, m), 3.06-3.13 (1H, m), 3.28 (1H, dd, J=18.0, 7.0), 3.41 (1H, d, J=13.0), 3.47 (1H, dd, J=18.0, 7.0), 4.68 (1H, m), 5.24 (1H, t, J=7.0), 7.13-7.32 (7H, m), 7.39-7.53 (8H, m).

(d) trifluoroacetato hidrogenado de (Z)-4-(Acetilsulfanil)-3-(2-cianoetiliden)piperidina

Se sintetizó el compuesto del título en un rendimiento de 54% como un sólido amorfo incoloro usando (Z)-4-(acetilsulfanil)-3-(2-cianoetiliden)-1-(trifenilmetil)piperidina obtenido en (c) anterior realizando una reacción similar a la mencionada en el Ejemplo 3 (c).

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 2.02-2.12 (1H, m), 2.36-2.47 (1H, m), 2.39 (3H, s), 3.04-3.17 (1H, m), 3.33-3.77 (5H, m), 4.70 (1H, bs), 5.59 (1H, t, J=7.0).

(e) clorhidrato de (Z)-4-(Acetilsulfanil)-3-(2-cianoetiliden)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]piperidina

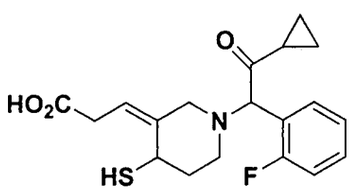
Se sintetizó el compuesto del título en un rendimiento de 80%

como un sólido amorfo incoloro usando trifluoroacetato hidrogenado de (Z)-4-(acetilsulfanil)-3-(2-cianoetiliden)piperidina obtenido en (d) anterior realizando una reacción similar a la mencionada en el Ejemplo 1 (g).

RMN con ^{1}H (400 MHz, $CDCl_3$) δ ppm : 0.75-0.88 (2H, m), 0.97-1.07 (2H, m), 1.27 (3H, t, J=7.0), 1.78-1.86 (1H, m), 2.12-2.22 (2H, m), 2.28 y 2.29 (total 3H, cada s), 2.49-2.62 (1H, m), 2.68-2.73 y 2.76-2.81 (total 1H, cada m), 2.88 y 3.15 (total 1H, cada d, J=12.5), 3.30 y 3.41 (total 1H, cada d, J=12.5), 3.46 (2H, s), 4.15 (2H, q, J=7.0), 4.28-4.34 (1H, m), 4.62-4.64 y 4.67-4.70 (total 2H, cada m), 4.71 y 4.74 (total 1H, cada s), 5.78 (1H, t, J=7.0), 7.07-7.17 (2H, m), 7.19-7.27 (1H, m), 7.28-7.37 (1H, m), 7.33 y 7.34 (total 1H, cada s), 7.39 (1H, s).

MS (FAB) m/z : 387 $(M+H)^+$.

(Ejemplo 118) (Z)-3-(2-Carboxietiliden)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]-4-sulfanilpiperidina (Compuesto del compuesto No. 4-13)



Se trató clorhidrato de (Z)-4-(Acetilsulfanil)-3-(2-cianoetiliden)-1-[2-ciclopropil-1-(2-fluorofenil)-2-oxoetil]piperidina (48 mg) obtenido en el ejemplo 117 (e) con ácido clorhídrico 6N (6 ml) a temperatura ambiente y luego la mezcla resultante se agitó a 60°C durante 3 horas. La mezcla de la reacción se evaporó in vacuo, y se purificó el residuo usando una HPLC preparativa (YMC-Pack ODS-A; YMC, eluyente: acetonitrilo / agua / ácido acético / trietilamina = 1 / 1 / 0.05 / 0.05) para obtener el compuesto del título (22 mg, rendimiento 56%) como un aceite incoloro.

RMN con ^{1}H (400 MHz, piridina-d_5) δ ppm : 0.72-0.86 (2H, m),

0.96-1.04 (1H, m), 1.07-1.15 (1H, m), 1.70-1.84 (1H, m), 2.19-2.38 (1H, m), 2.46-2.54 (1H, m), 2.61-3.09 (2H, m), 3.30 y 3.39 (total 1H, cada d, J=14.0), 3.41-3.58 (3H, m), 4.55 (1H, bs), 4.89 y 4.93 (total 1H, cada s), 5.72 y 5.83 (total 1H, cada t, J=7.5), 7.15-7.25 (2H, m), 7.26-7.34 (1H, m), 7.67-7.73 (1H, m).

MS (FAB) m/z : 364 $(M+H)^+$.

(Ejemplo de prueba 1) Prueba para confirmar el efecto inhibidor de agregación de plaquetas in vitro

Ratas macho Sprague-Dawley (8 semanas de edad, Japan SLC, Inc.), 3 a 4 animales por grupo, se usaron para la prueba. Se midió la agregación de plaquetas con un agregómetro de plaquetas automático (MCM Hema Tracer 313M, MC Medical, Inc.) mediante un método parcialmente modificado de Born et al., The Journal of Physiology, Vol. 168, Sección 178 (1963). Se tomó una muestra de 6.3 ml de sangre de la aorta ventral de una rata anestesiada con pentobarbital (40 mg/kg) usando solución de citrato de sodio al 3.8% (p/v) (0.7 ml) como anticoagulante. La sangre obtenida que contiene citrato fue centrifugada (230 g, 15 minutos, temperatura ambiente) para separar un plasma rico en plaquetas (abreviado en lo sucesivo como PRP). La sangre después de la separación de PRP se centrifugó adicionalmente (2,000 g, 10 minutos, temperatura ambiente) para separar un plasma bajo en plaquetas (abreviado en lo sucesivo como PPP). Después de que se midió la cantidad de plaquetas en sangre en PRP con un contador de corpúsculos de sangre automático de múltiples elementos (KX-21N, Sysmex Corporation), Se le añadió PPP para ajustar el conteo de plaquetas en sangre a 5×10^8/ml. Después de que se pipeteó el PRP (239 μl) en cubetas, se le añadió compuestos de prueba (1 μl) disueltos en sulfóxido de dimetilo (DMSO) al PRP y las cubetas se colocaron en el agregómetro de plaquetas automático. Se le añadió DMSO (1 μl) en lugar de los compuestos de prueba para el grupo de control.

Después de calentamiento preliminar (37°C) durante 1.5 minutos, se le añadió 10 μl de solución de 5'-difosfato de adenosina (ADP) (concentración final a 10 μM) para producir la agregación de plaquetas. Se midió la agregación de plaquetas durante 5 minutos y se determinó la velocidad de agregación de plaquetas máxima. Los resultados se muestran en la Tabla 7.

(Tabla 7)

Compuesto de prueba	Ejemplo de prueba 1 (% inhibición) 10 μg/ml
Compuesto del ejemplo 15	90
Compuesto del ejemplo 18	73
Compuesto del ejemplo 19	77
Compuesto del ejemplo 22	67
Compuesto del ejemplo 23	77
Compuesto del ejemplo 44	81
Compuesto del ejemplo 50	79
Compuesto del ejemplo 51	81
Compuesto del ejemplo 74	80
Compuesto del ejemplo 83	68
Compuesto del ejemplo 86	82
Compuesto del ejemplo 91	74
Compuesto del ejemplo 111	82

Los compuestos de la presente invención mostraron un considerable efecto inhibidor de agregación de plaquetas. Los compuestos de la presente invención son útiles como fármaco antitrombótico.

(Ejemplo de prueba 2) Prueba para confirmar el efecto inhibidor

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de agregación de plaquetas ex vivo

Se usaron ratas macho Sprague-Dawley (8 semanas de edad, Japan SLC, Inc.), 3 a 4 animales por grupo, para la prueba. Se midió la agregación de plaquetas con un agregómetro de plaquetas automático (MCM Hema Tracer 313M, MC Medical, Inc.) mediante un método parcialmente modificado de Born et al., The Journal of Physiology, Vol. 168, Sección 178 (1963). Se administraron oralmente los compuestos de prueba suspendidos en solución de goma arábiga al 5% o en dimetilacetamida al 10% / polietilen glicol 400 al 64%/ solución de Tween 80 al 16% en una proporción de dosis de 1 mL/kg 4 horas antes de tomar la muestra de sangre. Se administró vehículo 4 horas en una proporción de dosis de 1 mL/kg antes de tomar la muestra de la sangre para el grupo de control. SE tomó una muestra de 6.3 ml de sangre de la aorta ventral de una rata anestesiada con pentobarbital (40 mg/kg) usando solución de citrato de sodio al 3.8% (p/v) (0.7 ml) como anticoagulante. La sangre con citrato obtenida fue centrifugada (230 g, 15 minutos, temperatura ambiente) para separar el PRP. La sangre después de la separación de PRP se centrifugó adicionalmente (2,000 g, 10 minutos, temperatura ambiente) para separar el PPP. Después de que se midió la cantidad de plaquetas en sangre en el PRP con un contador de corpúsculos de sangre automático de múltiples elementos (KX-21N, Sysmex Corporation), se le añadió PPP para ajustar las plaquetas en sangre a 5×10^8/ml. Después de que se pipeteó el PRP (240 μl) en cubetas, las cubetas se colocaron en el agregómetro de plaquetas automático. Después de calentamiento preliminar (37°C) durante 1.5 minutos, se le añadió 10 μl de solución de ADP (concentración final 3 μM) para producir la agregación de plaquetas. Se midió la agregación de plaquetas durante 5 minutos y se determinó la velocidad de agregación de plaquetas máxima. Los

resultados se muestran en la Tabla 8.

(Tabla 8)

Compuesto de prueba	Ejemplo de prueba 1 (% inhibición)	
	3 mg/kg	10 mg/kg
Compuesto del ejemplo 13	-	63
Compuesto del ejemplo 17	-	92
Compuesto del ejemplo 18	-	74
Compuesto del ejemplo 19	-	60
Compuesto del ejemplo 21	-	90
Compuesto del ejemplo 22	-	79
Compuesto del ejemplo 23	-	72
Compuesto del ejemplo 24	-	85
Compuesto del ejemplo 25	-	92
Compuesto del ejemplo 26	-	92
Compuesto del ejemplo 29	-	89
Compuesto del ejemplo 30	-	93
Compuesto del ejemplo 31	-	82
Compuesto del ejemplo 32	-	86
Compuesto del ejemplo 36	-	80
Compuesto del ejemplo 38	-	66
Compuesto del ejemplo 44	61	-
Compuesto del ejemplo 62	-	94
Compuesto del ejemplo 64	-	94
Compuesto del ejemplo 66	-	87
Compuesto del ejemplo 72	-	76
Compuesto del ejemplo 74	-	100
Compuesto del ejemplo 78	-	75
Compuesto del ejemplo 81	-	83

Compuesto del ejemplo 82	-	81
Compuesto del ejemplo 84	-	82
Compuesto del ejemplo 85	-	82
Compuesto del ejemplo 89	-	83
Compuesto del ejemplo 111	-	82

Los compuestos de la presente invención mostraron un considerable efecto inhibidor de agregación de plaquetas. Los compuestos de la presente invención son útiles como fármaco antitrombótico.

(Ejemplo de preparación 1) cápsulas duras

Cada cápsula estándar de gelatina dura de dos partes se rellena con 100 mg de compuesto pulverizado del Ejemplo 1, 150 mg de lactosa, 50 mg de celulosa y 6 mg de estearato de magnesio para preparar cápsulas en unidad simple, las cuales se lavan y luego se secan.

(Ejemplo de preparación 2) cápsulas blandas

Se prepara una mezcla del compuesto del Ejemplo 2 en aceite digerible, tal como aceite de soya, aceite de algodón y aceite de oliva y se inyecta en gelatina con una bomba de intercambio directo para obtener cápsulas suaves cápsulas que contienen 100 mg de una sustancia activa, las cuales se lavan y luego se secan.

(Ejemplo de preparación 3) Tabletas

Se preparan tabletas de acuerdo con un método común usando 100 mg del compuesto del Ejemplo 3, 0.2 mg de dióxido de silicio coloidal, 5 mg de estearato de magnesio, 275 mg de microcelulosa cristalina, 11 mg de almidón y 98.8 mg de lactosa.

Si se desea, se le aplica un recubrimiento a la tableta.

(Ejemplo de preparación 4) Suspensión

Se prepara una suspensión de tal forma que 5 ml de la

suspensión contengan 100 mg de compuesto del Ejemplo 4 pulverizado finamente, 100 mg de carboximetil celulosa de sodio, 5 mg de benzoato de sodio, 1.0 g de solución de sorbitol (Farmacopea japonesa) y 0.025 ml de vanillina.

(Ejemplo de preparación 5) Crema

Se prepara una crema mezclando 100 mg de compuesto del Ejemplo 5 pulverizado finamente en 5 g de una crema que contiene 40% de petrolato blanco, 3% de cera microcristalina, 10% de lanolina, 5% de Span 20, 0.3% de Tween 20 y 41.7% de agua.

(Ejemplo de preparación 6) Agente de inyección

1.5 % por peso del compuesto del Ejemplo 6 fue la mezcla resultante, se agitó en 10 % por peso de propilen glicol y después se ajustó el volumen hasta un volumen predeterminado con agua para inyección, se esterilizó la mezcla para preparar una preparación inyectable.

Aplicabilidad industrial

Los compuestos de acuerdo con la presente invención son estables químicamente y tienen excelente actividad inhibidora de activación de plaquetas y actividad inhibidora de trombosis, y también sus respuestas son rápidas y sus toxicidades son bajas. Por lo tanto, los compuestos son útiles como fármacos para profilaxis, para evitar recurrencia o para terapia (en particular, para terapia) de tromboembolismo o enfermedades inducidas por activación de plaquetas, tales como agregación de plaquetas o reacción de liberación de plaquetas, por ejemplo, restenosis después de intervención coronaria percutánea (PCI), angioplastia, endarterectomía, o colocación de endoprótesis; síndromes coronarios agudos; angina estable o inestable; infarto al miocardio; fibrilación atrial; ataque isquémico cerebral; infarto cerebral; ateroesclerosis; enfermedades cardiovasculares y cerebrovasculares asociadas con diabetes mellitus, tales como tromboembolismo;

enfermedades arteriales periféricas; trombocitopenia inducida por heparina (HIT); púrpura trombocitopénica trombótica (TTP); síndromes de anticuerpo antifosfolípido; trombosis venosa; y septicemia.

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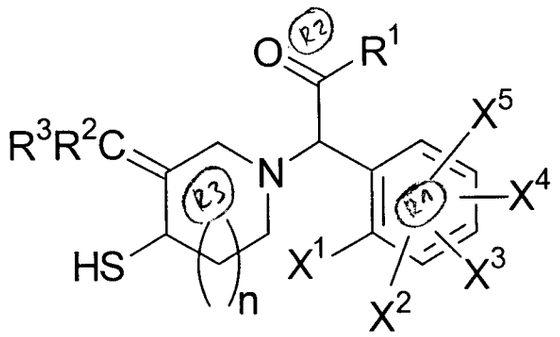
REIVINDICACIONES

1.Un compuesto que tiene la fórmula general (I) que se muestra a continuación,



(I)

[En donde R^1 representa un átomo de hidrógeno, un grupo alquilo de 1 a 6 átomos de carbono que puede estar sustituido (dicho grupo sustituyente representa un átomo de halógeno o un grupo alcoxi de 1 a 6 átomos de carbono), un grupo cicloalquilo de 3 a 6 átomos de carbono que puede estar sustituido (dicho grupo sustituyente representa un átomo de halógeno o un grupo alcoxi de 1 a 6 átomos de carbono), un grupo alcoxi de 1 a 6 átomos de carbono que puede estar sustituido (dicho grupo sustituyente representa un átomo de halógeno o un grupo alcoxi de 1 a 6 átomos de carbono), o un grupo arilo de 6 a 10 átomos de carbono que puede estar sustituido (dicho grupo sustituyente representa un átomo de halógeno, un grupo alquilo de 1 a 6 átomos de carbono, un grupo alcoxi de 1 a 6 átomos de carbono, un grupo ciano, o un grupo nitro);

R^2 representa un átomo de hidrógeno, un átomo de halógeno, un grupo carboxi, un grupo alcoxicarbonilo de 2 a 7 átomos de carbono, un grupo carbamoilo, un grupo ciano, un grupo alquilo de 1 a 6 átomos de carbono, un grupo alquilo halogenado de 1 a 6 átomos de carbono, un grupo alquilo de 1 a 6 átomos de carbono sustituido por un grupo heteroarilo, un grupo alcoxi de 1 a 6 átomos de carbono, un grupo alcoxi halogenado de 1 a 6 átomos de carbono, un grupo hidroxi alquilo de 1 a 6 átomos de carbono, un grupo

alcoxialquilo de 2 a 12 átomos de carbono, un grupo formilo, un grupo alcanoilo de 2 a 7 átomos de carbono, un grupo cicloalquilcarbonilo de 4 a 7 átomos de carbono, un grupo alquilcarbamoilo de 2 a 7 átomos de carbono, un grupo di(alquilo de 1 a 6 átomos de carbono)carbamoilo, un grupo de la fórmula R^4-CO-CR^5R^6-$(CH_2)_m$ {en donde R^4 representa un grupo hidroxilo, un grupo amino, un grupo alquilo de 1 a 6 átomos de carbono, un grupo alquilamino de 1 a 6 átomos de carbono, un grupo di(alquil de 1 a 6 átomos de carbono)amino, un grupo hidroxiamino, un grupo alcoxiamino de 1 a 6 átomos de carbono o un grupo alcoxi de 1 a 6 átomos de carbono; R^5 y R^6 son iguales o diferentes y representan cada uno un átomo de hidrógeno o un grupo alquilo de 1 a 6 átomos de carbono; y m representa un entero desde 0 hasta 5}, un grupo de la fórmula R^7-CO-$(CH_2)_l$-N(R^8) {en donde R^7 representa un grupo hidroxilo, un grupo amino, un grupo alquilo de 1 a 6 átomos de carbono, un grupo alquilamino de 1 a 6 átomos de carbono, un grupo di(alquil de 1 a 6 átomos de carbono)amino, un grupo hidroxiamino, un grupo alcoxiamino de 1 a 6 átomos de carbono o un grupo alcoxi de 1 a 6 átomos de carbono; R^8 representa un átomo de hidrógeno o un grupo alquilo de 1 a 6 átomos de carbono; y l representa un entero desde 0 hasta 5} o un grupo sulfamoil alquilo de 1 a 6 átomos de carbono;

R^3 representa un grupo alquilo sustituido de 1 a 6 átomos de carbono {dicho grupo sustituyente representa un grupo arilo de 6 a 10 átomos de carbono o un grupo arilo de 6 a 10 átomos de carbono sustituido con desde 1 hasta 5 sustituyentes seleccionados del <Grupo sustituyente α>; un grupo heterociclilo o un grupo heterociclilo sustituido con desde 1 hasta 5 sustituyentes seleccionados del <Grupo sustituyente α> (dichos grupos heterociclilo pueden estar sustituidos con desde 1 hasta 4 grupos oxo); un grupo heteroarilo o un grupo heteroarilo sustituido con

desde 1 hasta 5 sustituyentes seleccionados del <Grupo sustituyente α>; o un sustituyente seleccionado del <Grupo sustituyente β>}, o un grupo heterociclilo o un grupo heterociclilo sustituido con desde 1 hasta 5 sustituyentes seleccionados del <Grupo sustituyente α> (dichos grupos heterociclilo pueden estar sustituidos con desde 1 hasta 4 grupos oxo);

X^1, X^2, X^3, X^4 y X^5 representan cada uno independientemente un átomo de hidrógeno, un átomo de halógeno, un grupo amino, un grupo carboxi, un grupo carbamoilo, un grupo ciano, un grupo nitro, un grupo alquilo de 1 a 6 átomos de carbono, un grupo alquilo halogenado de 1 a 6 átomos de carbono, un grupo alcoxi de 1 a 6 átomos de carbono o un grupo alcoxi halogenado de 1 a 6 átomos de carbono;

n representa un entero desde 0 hasta 2,

El <Grupo sustituyente α> está definido por un átomo de halógeno, un grupo amino, un grupo carboxi, un grupo alcoxicarbonilo de 2 a 7 átomos de carbono, un grupo carbamoilo, un grupo ciano, un grupo hidroxilo, un grupo nitro, un grupo alquilo de 1 a 6 átomos de carbono, un grupo alquilo halogenado de 1 a 6 átomos de carbono, un grupo alquilo de 1 a 6 átomos de carbono sustituido con grupo(s) heteroarilo, un grupo alcoxi de 1 a 6 átomos de carbono, un grupo alcoxi halogenado de 1 a 6 átomos de carbono, un grupo hidroxi alquilo de 1 a 6 átomos de carbono, un grupo alcoxialquilo de 2 a 12 átomos de carbono, un grupo formilo, un grupo alcanoilo de 2 a 7 átomos de carbono, un grupo cicloalquilcarbonilo de 4 a 7 átomos de carbono, un grupo alquilamino de 1 a 6 átomos de carbono, un grupo di(alquil de 1 a 6 átomos de carbono)amino, un grupo alquilcarbamoilo de 2 a 7 átomos de carbono, un grupo di(alquil de 1 a 6 átomos de carbono)carbamoilo, un grupo de la fórmula R^4-CO-CR^5R^6-$(CH_2)_m$- {en donde R^4 representa un grupo hidroxilo, un grupo amino, un

grupo alquilo de 1 a 6 átomos de carbono, un grupo alquilamino de 1 a 6 átomos de carbono, un grupo di(alquil de 1 a 6 átomos de carbono)amino, un grupo hidroxiamino, un grupo alcoxiamino de 1 a 6 átomos de carbono o un grupo alcoxi de 1 a 6 átomos de carbono; R^5 y R^6 son iguales o diferentes y representan cada uno un átomo de hidrógeno o un grupo alquilo de 1 a 6 átomos de carbono; y m representa un entero desde 0 hasta 5} y un grupo sulfamoil alquilo de 1 a 6 átomos de carbono; y

El <Grupo sustituyente β> está definido por un átomo de halógeno, un grupo amino, un grupo carboxi, un grupo alcoxicarbonilo de 2 a 7 átomos de carbono, un grupo carbamoilo, un grupo ciano, un grupo hidroxilo, un grupo nitro, un grupo alcoxi de 1 a 6 átomos de carbono, un grupo alcoxi halogenado de 1 a 6 átomos de carbono, un grupo formilo, un grupo alcanoilo de 2 a 7 átomos de carbono, un grupo cicloalquilcarbonilo de 4 a 7 átomos de carbono, un grupo alquilamino de 1 a 6 átomos de carbono, un grupo di(alquil de 1 a 6 átomos de carbono)amino, un grupo alquilcarbamoilo de 2 a 7 átomos de carbono, un grupo di(alquilo de 1 a 6 átomos de carbono)carbamoilo, un grupo hidroxiaminocarbonilo, un grupo (alcoxi de 1 a 6 átomos de carbono)aminocarbonilo, un grupo de la fórmula R^9-CO-$(CH_2)_k$-N(R^{10})- {en donde R^9 representa un grupo hidroxilo, un grupo amino, un grupo alquilo de 1 a 6 átomos de carbono, un grupo alquilamino de 1 a 6 átomos de carbono, un grupo di(alquil de 1 a 6 átomos de carbono)amino, un grupo hidroxiamino, un grupo alcoxiamino de 1 a 6 átomos de carbono o un grupo alcoxi de 1 a 6 átomos de carbono; R^{10} representa un átomo de hidrógeno o un grupo alquilo de 1 a 6 átomos de carbono; y k representa un entero desde 0 hasta 5} y un grupo sulfamoil alquilo de 1 a 6 átomos de carbono], sales de él o profármacos de él aceptables farmacológicamente.

2. Un compuesto de acuerdo con la reivindicación 1, en

donde R^1 representa un grupo alquilo de 1 a 6 átomos de carbono, un grupo alquilo halogenado de 1 a 6 átomos de carbono, un grupo cicloalquilo de 3 a 6 átomos de carbono, un grupo cicloalquilo halogenado de 3 a 6 átomos de carbono o un grupo alcoxi de 1 a 6 átomos de carbono, sales de él o profármacos de él aceptables farmacológicamente.

3. Un compuesto de acuerdo con la reivindicación 1, en donde R^1 representa un grupo cicloalquilo de 3 a 6 átomos de carbono, un grupo cicloalquilo halogenado de 3 a 6 átomos de carbono o un grupo alcoxi de 1 a 6 átomos de carbono, sales de él o profármacos de él aceptables farmacológicamente.

4. Un compuesto de acuerdo con la reivindicación 1 en donde R^1 representa un grupo cicloalquilo de 3 a 6 átomos de carbono o un grupo alcoxi de 1 a 6 átomos de carbono, sales de él o profármacos de él aceptables farmacológicamente.

5. Un compuesto de acuerdo con la reivindicación 1, en donde R^1 representa un grupo ciclopropilo o un grupo metoxi, sales de él o profármacos de él aceptables farmacológicamente.

6. Un compuesto de acuerdo con la reivindicación 1, en donde R^1 es un grupo ciclopropilo, sales de él o profármacos de él aceptables farmacológicamente.

7. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 hasta 6, en donde R^2 representa un átomo de hidrógeno o un grupo alquilo de 1 a 6 átomos de carbono, sales de él o profármacos de él aceptables farmacológicamente.

8. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 hasta 6, en donde R^2 representa un átomo de hidrógeno o un grupo metilo, sales de él o profármacos de él aceptables farmacológicamente.

9. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 hasta 6, en donde R^2 representa un átomo de

hidrógeno, sales de él o profármacos de él aceptables farmacológicamente.

10. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 hasta 9, en donde R^3 representa un grupo alquilo sustituido de 1 a 6 átomos de carbono {dicho grupo sustituyente representa un grupo heterociclilo o un grupo heterociclilo sustituido con 1 o 2 sustituyentes seleccionados del <Grupo sustituyente α> (dichos grupos heterociclilo pueden estar sustituidos por 1 o 2 grupos oxo), un grupo heteroarilo o un grupo heteroarilo sustituido con 1 o 2 sustituyentes seleccionados del <Grupo sustituyente α> o un sustituyente seleccionado del <Grupo sustituyente β>}, o un grupo heterociclilo o un grupo heterociclilo sustituido con 1 o 2 sustituyentes seleccionados del <Grupo sustituyente α> (dichos grupos heterociclilo pueden estar sustituidos por 1 o 2 grupos oxo), sales de él o profármacos de él aceptables farmacológicamente.

11. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 hasta 9, en donde R^3 representa un grupo alquilo sustituido de 1 a 6 átomos de carbono {dicho grupo sustituyente representa un grupo heterociclilo de 4 a 7 miembros que contiene al menos un átomo de nitrógeno que puede estar sustituido con 1 o 2 sustituyentes seleccionados del <Grupo sustituyente α1> (dicho grupo heterociclilo puede estar sustituido por un grupo oxo), un grupo heteroarilo que contiene al menos un átomo de nitrógeno que puede estar sustituido con 1 o 2 sustituyentes seleccionados del <Grupo sustituyente α1>, un grupo carboxi, un grupo alcoxicarbonilo de 2 a 7 átomos de carbono, un grupo ciano, un grupo hidroxilo, un grupo alcoxi de 1 a 6 átomos de carbono o un grupo de la fórmula R^9-CO-$(CH_2)_k$-N(R^{10})- (en donde R^9 representa un grupo hidroxilo o un grupo alcoxi de 1 a 6 átomos de carbono; R^{10} representa un grupo alquilo de 1 a 6 átomos de carbono; y k representa un entero desde 1

hasta 5)}, o un grupo heterociclilo de 4 a 7 miembros que contiene al menos un átomo de nitrógeno que puede estar sustituido con un sustituyente seleccionado del <Grupo sustituyente α1> (dicho grupo heterociclilo puede estar sustituido por un grupo oxo), y

El <Grupo sustituyente α1> es un grupo que consiste en un grupo carboxi, un grupo alcoxicarbonilo de 2 a 7 átomos de carbono y un grupo de la fórmula R^4-CO-CR^5R^6-$(CH_2)_m$- (en donde R^4 representa un grupo hidroxilo, un grupo amino, un grupo alquilamino de 1 a 6 átomos de carbono, un grupo di(alquil de 1 a 6 átomos de carbono)amino, un grupo hidroxiamino, un grupo alcoxiamino de 1 a 6 átomos de carbono o un grupo alcoxi de 1 a 6 átomos de carbono; R^5 y R^6 representan cada uno un átomo de hidrógeno; y m representa un entero desde 0 hasta 5), sales de él o profármacos de él aceptables farmacológicamente.

12. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 hasta 9, en donde R^3 representa un grupo alquilo sustituido de 1 a 3 átomos de carbono {dicho grupo sustituyente representa un grupo pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo, piperazinilo, pirazolilo, triazolilo o tetrazolilo que puede estar sustituido con 1 o 2 sustituyentes seleccionados del <Grupo sustituyente α2> (dicho grupo pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo o piperazinilo puede estar sustituido por un grupo oxo), un grupo carboxi, un grupo alcoxicarbonilo de 2 a 4 átomos de carbono, un grupo hidroxilo o un grupo de la fórmula R^9-CO-$(CH_2)_k$-N(R^{10})- (en donde R^9 representa un grupo hidroxilo o un grupo alcoxi de 1 a 3 átomos de carbono; R^{10} representa un grupo alquilo de 1 a 3 átomos de carbono y k representa un entero desde 1 hasta 3)}, o un grupo pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo o piperazinilo que puede estar sustituido por un sustituyente seleccionado del <Grupo sustituyente α2> (dicho grupo pirrolidinilo, piperidinilo, morfolinilo, tiomorfolinilo o piperazinilo

puede estar sustituido por un grupo oxo), y

El <Grupo sustituyente α2> es un grupo que consiste en un grupo carboxi, un grupo alcoxicarbonilo de 2 a 4 átomos de carbono y un grupo de la fórmula R^4-CO-CR^5R^6-$(CH_2)_m$- (en donde R^4 representa un grupo hidroxilo o un grupo alcoxi de 1 a 3 átomos de carbono, R^5 y R^6 representan cada uno un átomo de hidrógeno, y m representa un entero desde 0 hasta 2), sales de él o profármacos de él aceptables farmacológicamente.

13. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 hasta 9, en donde R^3 representa un grupo metilo o etilo sustituido {dicho grupo sustituyente representa un grupo pirrolidinilo, piperidinilo, piperazinilo o pirazolilo que puede estar sustituido con 1 o 2 sustituyentes seleccionados del <Grupo sustituyente α3> (dicho grupo pirrolidinilo, piperidinilo o piperazinilo puede estar sustituido por un grupo oxo), un grupo carboxi o un grupo de la fórmula R^9-CO-$(CH_2)_k$-N(R^{10})- (en donde R^9 representa un grupo hidroxilo, un grupo metoxi o un grupo etoxi; R^{10} representa un grupo metilo, un grupo etilo o un grupo isopropilo; y k representa un entero desde 1 hasta 3), y

El <Grupo sustituyente α3> es un grupo que consiste en un grupo carboxi, un grupo metoxicarbonilo, un grupo etoxicarbonilo, un grupo carboximetilo, un grupo metoxicarbonilmetilo, un grupo etoxicarbonilmetilo, un grupo 2-(carboxi)etilo, un grupo 2-(metoxicarbonil)etilo y un grupo 2-(etoxicarbonil)etilo, sales de él o profármacos de él aceptables farmacológicamente.

14. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 hasta 13 en donde X^1, X^2, X^3, X^4 y X^5 representan independientemente un átomo de hidrógeno o un átomo de halógeno, sales de él o profármacos de él aceptables farmacológicamente.

15. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 hasta 13 en donde X^1 y X^2 representan

independientemente un átomo de hidrógeno o un átomo de halógeno; y X^3, X^4 y X^5 representan un átomo de hidrógeno, sales de él o profármacos de él aceptables farmacológicamente.

16. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 hasta 13 en donde X^1 representa un átomo de halógeno; y X^2, X^3, X^4 y X^5 representan un átomo de hidrógeno, sales de él o profármacos de él aceptables farmacológicamente.

17. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 hasta 13 en donde X^1 representa un átomo de flúor; y X^2, X^3, X^4 y X^5 representan un átomo de hidrógeno, sales de él o profármacos de él aceptables farmacológicamente.

18. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 hasta 17 en donde n representa 0 o 1, sales de él o profármacos de él aceptables farmacológicamente.

19. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 hasta 17 en donde n representa 1, sales de él o profármacos de él aceptables farmacológicamente.

20. Un compuesto de acuerdo con cualquiera de las reivindicaciones 1 hasta 19 en donde un profármaco que es un éster aceptable farmacológicamente se forma en la porción sulfanilo, sales de él o profármacos de él aceptables farmacológicamente.

21. El compuesto de acuerdo con la reivindicación 20 en donde un grupo funcional que forma el éster aceptable farmacológicamente con un grupo sulfanilo es un grupo alcanoilo de 1 a 6 átomos de carbono o un grupo arilcarbonilo, sales de él o profármacos de él aceptables farmacológicamente.

22. El compuesto de acuerdo con la reivindicación 20 en donde un grupo funcional que forma el éster aceptable farmacológicamente con un grupo sulfanilo es un grupo alcanoilo de 1 a 3 átomos de carbono o un grupo benzoilo, sales de él o profármacos de él aceptables farmacológicamente.

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23. El compuesto de acuerdo con la reivindicación 20, en donde un grupo funcional que forma el éster aceptable farmacológicamente con un grupo sulfanilo es un éster formado con un grupo acetilo, sales de él o profármacos de él aceptables farmacológicamente.

24. Una composición farmacéutica que contiene un compuesto de acuerdo con cualquiera de las reivindicaciones 1 hasta 23, sales de él o profármacos de él aceptables farmacológicamente como ingrediente activo.

25. Una composición farmacéutica de acuerdo con la reivindicación 24, en donde la composición farmacéutica es una composición para agentes profilácticos o terapéuticos para enfermedades relacionadas con formación de trombos o émbolos. USO

26. Uso de un compuesto de acuerdo con cualquiera de las reivindicaciones 1 hasta 23, sales de él o profármacos de él aceptables farmacológicamente para fabricar una composición farmacéutica. USO

27. Uso de acuerdo con la reivindicación 26, en donde la composición farmacéutica es una composición para agentes profilácticos o terapéuticos para enfermedades relacionadas con formación de trombos o émbolos. USO

28. Uso de un compuesto de acuerdo con cualquiera de las reivindicaciones 1 hasta 23, sales de él o profármacos de él aceptables farmacológicamente para agentes profilácticos o terapéuticos para enfermedades relacionadas con formación de trombos o émbolos. USO

29. Un método profiláctico o terapéutico para enfermedades mediante la administración de un compuesto de acuerdo con cualquiera de las reivindicaciones 1 hasta 23, sales de él o profármacos de él aceptables farmacológicamente a animales de sangre caliente en dosis efectivas farmacológicamente. MO

30. Un método de acuerdo con la reivindicación 29 en donde las enfermedades son enfermedades relacionadas con formación de trombos o émbolos.

31. Un método de acuerdo con la reivindicación 29 o 30 en donde los animales de sangre caliente son humanos.

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RESUMEN

Se describe un compuesto representado por la fórmula general (I) siguiente, una sal de él aceptable farmacológicamente, o un profármaco de él. (I) (En la fórmula, R^1 representa un átomo de hidrógeno, un grupo alquilo de 1 a 6 átomos de carbono sustituido opcionalmente, un grupo cicloalquilo de 3 a 6 átomos de carbono sustituido opcionalmente o similar; R^2 representa un átomo de hidrógeno, un átomo de halógeno, un grupo carboxi, un grupo alcoxicarbonilo de 2 a 7 átomos de carbono, un grupo carbamoilo, un grupo ciano, un grupo alquilo de 1 a 6 átomos de carbono, un grupo alquilo halogenado de 1 a 6 átomos de carbono; un grupo alquilo de 1 a 6 átomos de carbono sustituido con un grupo heteroarilo o similar; R^3 representa un grupo alquilo sustituido de 1 a 6 átomos de carbono, un grupo heterociclilo, o un grupo heterociclilo mono- hasta penta- sustituido; X^1, X^2, X^3, X^4 y X^5 representan independientemente un átomo de hidrógeno, un átomo de halógeno, un grupo amino, un grupo carboxi, un grupo carbamoilo, un grupo ciano, un grupo nitro, un grupo alquilo de 1 a 6 átomos de carbono o similar; y n representa un entero de 0-2.)

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2006/310556

A. CLASSIFICATION OF SUBJECT MATTER
C07D211/72(2006.01)i, *A61K31/445*(2006.01)i, *A61K31/454*(2006.01)i, *A61K31/4545*(2006.01)i, *A61K31/496*(2006.01)i, *A61K31/5377*(2006.01)i, *A61K31/541*(2006.01)i, *A61P7/02*(2006.01)i, *C07D401/06*(2006.01)i
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)
C07D211/72(2006.01), *A61K31/445*(2006.01), *A61K31/454*(2006.01), *A61K31/4545*(2006.01), *A61K31/496*(2006.01), *A61K31/5377*(2006.01), *A61K31/541*(2006.01), *A61P7/02*(2006.01), *C07D401/06*(2006.01)

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

Jitsuyo Shinan Koho	1922-1996	Jitsuyo Shinan Toroku Koho	1996-2006
Kokai Jitsuyo Shinan Koho	1971-2006	Toroku Jitsuyo Shinan Koho	1994-2006

Electronic data base consulted during the international search (name of data base and, where practicable, search terms used)
CAOLD(STN), CAplus(STN), REGISTRY(STN)

C. DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	JP 11-315020 A (Sankyo Co., Ltd.), 16 November, 1999 (16.11.99), (Family: none)	1-27
P,A	WO 2005/051913 A1 (Sankyo Co., Ltd.), 09 June, 2005 (09.06.05), & JP 2005-179350 A	1-27
A	JP 10-120649 A (Sankyo Co., Ltd.), 12 May, 1998 (12.05.98), & WO 98/08811 A1 & NZ 334389 A & CA 2263983 A & AU 9740312 A1 & EP 934928 A1 & CN 1235596 A & IL 128690 A1 & KR 2000035839 A & US 6087379 A & NO 9900951 A	1-27

☒ Further documents are listed in the continuation of Box C. ☐ See patent family annex.

* Special categories of cited documents:
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"X" document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone
"Y" document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art
"&" document member of the same patent family

Date of the actual completion of the international search 19 July, 2006 (19.07.06)	Date of mailing of the international search report 25 July, 2006 (25.07.06)
Name and mailing address of the ISA/ Japanese Patent Office Facsimile No.	Authorized officer Telephone No.

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2006/310556

C (Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
A	JP 11-310570 A (Sankyo Co., Ltd.), 09 November, 1999 (09.11.99), & WO 99/43648 A1 & CA 2322171 A & AU 9926413 A1 & BR 9908319 A & EP 1063230 A1 & NZ 506574 A & US 6610708 B1 & NO 2000004279 A	1-27

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INTERNATIONAL SEARCH REPORT

International application No.
PCT/JP2006/310556

Box No. II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

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

1. [X] Claims Nos.: 28-31
because they relate to subject matter not required to be searched by this Authority, namely:
The inventions as set forth in claims 28 to 31 pertain to methods for treatment of the human body by therapy.

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

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

Box No. III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

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

1. [ ] As all required additional search fees were timely paid by the applicant, this international search report covers all searchable claims.
2. [ ] As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. [ ] As only some of the required additional search fees were timely paid by the applicant, this international search report covers only those claims for which fees were paid, specifically claims Nos.:
4. [ ] No required additional search fees were timely paid by the applicant. Consequently, this international search report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

the

[ ] The additional search fees were accompanied by the applicant's protest and, where applicable, payment of a protest fee..

[ ] The additional search fees were accompanied by the applicant's protest but the applicable protest fee was not paid within the time limit specified in the invitation.

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

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PATENT COOPERATION TREATY

PCT/JP2006/310556

From the INTERNATIONAL BUREAU

PCT

NOTIFICATION OF THE RECORDING OF A CHANGE

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

To:

YAGUCHI, Toshiaki
c/o DAIICHI SANKYO COMPANY, LIMITED
1-16-13, Kitakasai
Edogawa-ku, Tokyo 134-8630
JAPON

Date of mailing *(day/month/year)* 14 May 2007 (14.05.2007)	
Applicant's or agent's file reference SANKYOFP0607	IMPORTANT NOTIFICATION
International application No. PCT/JP2006/310556	International filing date *(day/month/year)* 26 May 2006 (26.05.2006)

1. The following indications appeared on record concerning:

☒ the applicant ☐ the inventor ☐ the agent ☐ the common representative

Name and Address	State of Nationality	State of Residence
SANKYO COMPANY, LIMITED 5-1, Nihonbashi-Honcho 3-chome, Chuo-ku Tokyo 1038426 Japan	JP	JP
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

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

☒ the person ☐ the name ☐ the address ☐ the nationality ☐ the residence

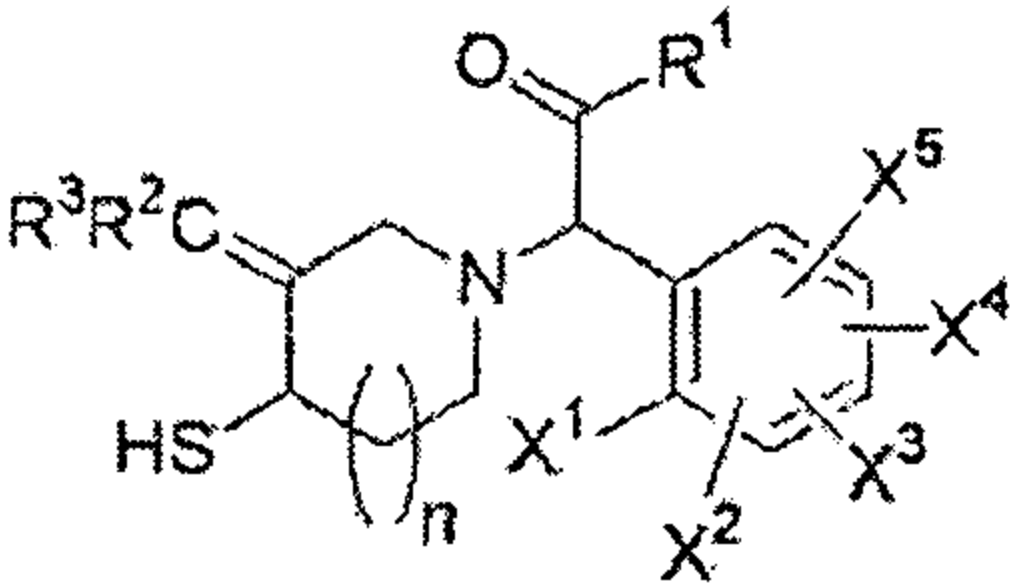
Name and Address	State of Nationality	State of Residence
DAIICHI SANKYO COMPANY, LIMITED 3-5-1, Nihombashi-honcho Chuo-ku, Tokyo 103-8426 Japan	JP	JP
	Telephone No.	
	Facsimile No.	
	Teleprinter No.	

3. Further observations, if necessary:

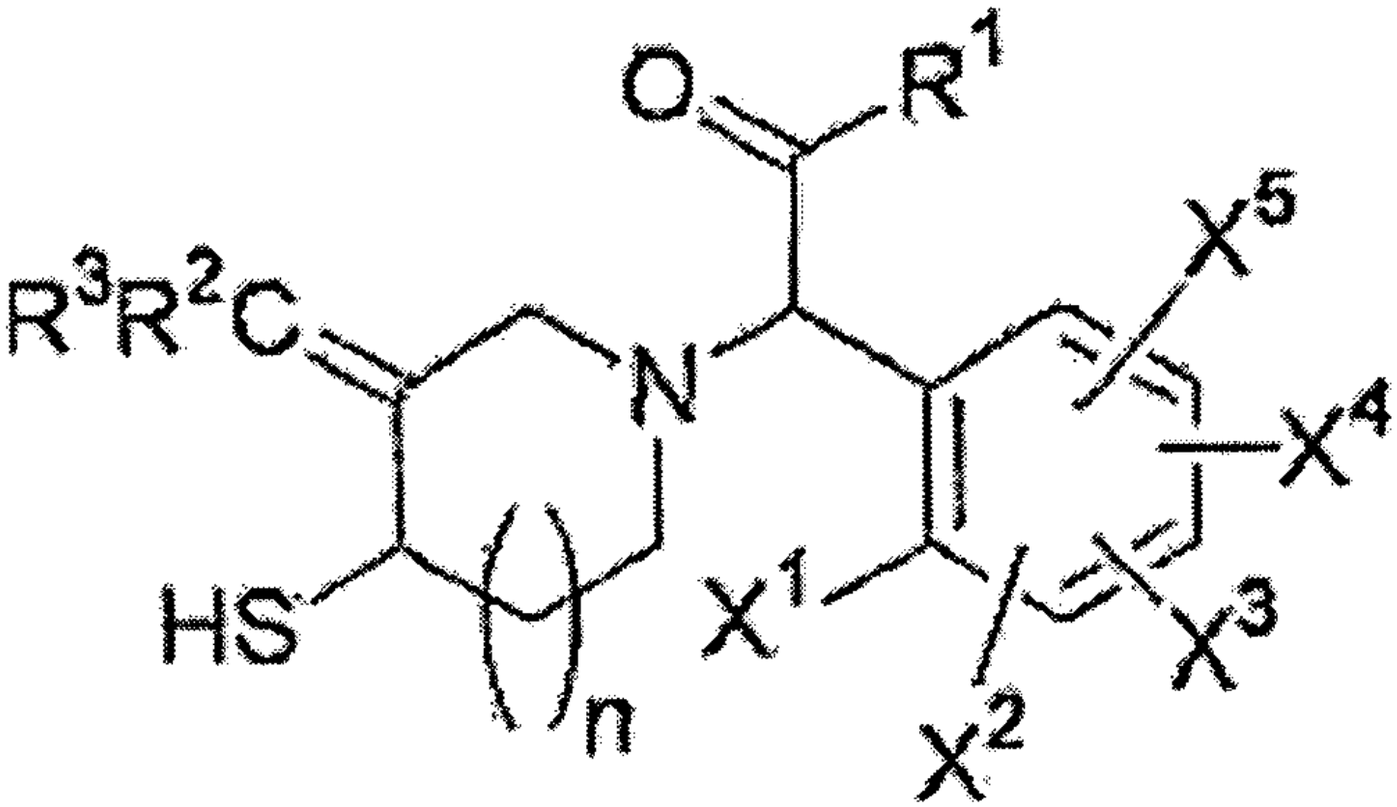
4. A copy of this notification has been sent to:

☒ the receiving Office
☐ the International Searching Authority
☐ the International Preliminary Examining Authority
☒ the designated Offices concerned
☐ the elected Offices concerned
☐ other:

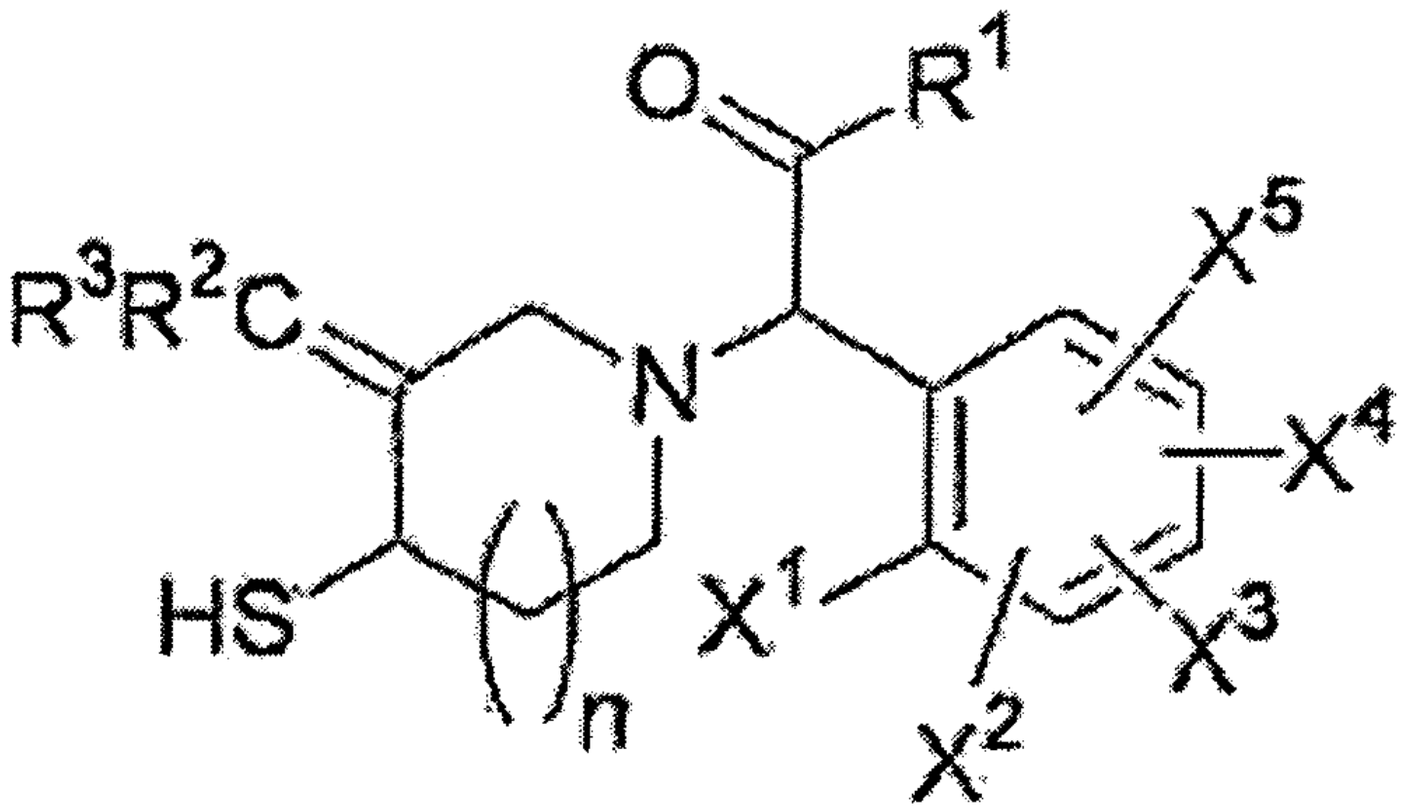
The International Bureau of WIPO 34, chemin des Colombettes 1211 Geneva 20, Switzerland Facsimile No. +41 22 338 82 70	Authorized officer Sunder Jutaporn Facsimile No. +41 22 338 70 10 Telephone No. +41 22 338 74 08



(I)



(I)



(I)

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SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

NIT : 800176089-2

RECIBO OFICIAL DE CAJA : 07 - 104,466
FECHA : DICIEMBRE 26 DE 2007

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO
No. 07-136830- -00000-0000
Fecha: 2007-12-27 18:02:02 Dep. 2020 NUECREACIONE
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 674

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

DEPOSITANTE	TIPO PAGO	BANCO	CUENTA	No. PAGO	FECHA PGO	Vr. PAGO
CAVELIER ABOGADOS	CONSIGNACION	BANCO POPULAR	050-00110-6	63768292	26/12/2007	33,356,000.00

***** C O N C E P T O *****

CANT.	RENTISTICO	CONCEPTO	TOTAL CONCEPTO
1	50005-01-01 SOLICITUDES	1 TRAMITES DE SOL. DE PATENTE DE IN	482,000.00
		TOTAL : $	482,000.00

SON: CUATROCIENTOS OCHENTA Y DOS MIL PESOS

RESPONSABLE : _____

RECIBO DE CAJA APLICADO AL EXPEDIENTE No._____

Colo 15869-841-008-7

SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

No. 07-136830- -00000-0000

Fecha: 2007-12-27 18:02:02 Dep. 2020 NUECREACIONI
Tra. 11 PATENTEIYII Eve: 378 FASENACIONALI
Act. 411 PRESENTACION Folios: 674

Industria y Comercio
SUPERINTENDENCIA

REQUISITOS MINIMOS PARA ADMISION A TRAMITE PCT

PATENTE DE INVENCION [ ] MODELO DE UTILIDAD [ ]

- Indicación de que se solicita la concesión de una patente [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Descripción de la invención [ ]
- Dibujos de ser estos pertinentes [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

DISEÑO INDUSTRIAL [ ]

- Indicación de que se solicita el registro de Diseño Industrial [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica y fotográfica del Diseño Industrial o muestra del material que incorpora el diseño [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

ESQUEMA DE TRAZADO [ ]

- Indicación de que se solicita el registro de un Esquema de Trazado [ ]
- Datos de identificación del solicitante o de la persona que presenta la solicitud [ ]
- Representación gráfica del esquema trazado [ ]
- Comprobante de pago de las tasas establecidas [ ]

COMPLETA [ ] INCOMPLETA [ ]

Edgar Navarro

Firma Responsable

Fecha 27-12-07

Carrera 13 No. 27-00 Piso 5, 7 y 10
Conmutador: 3 82 08 40
Fax: 350 52 20
E-mail: info@sic.gov.co
www.sic.gov.co
Bogotá, D.C., Colombia

REPUBLICA DE COLOMBIA
SUPERINTENDENCIA DE INDUSTRIA Y COMERCIO

Folio 676

2020
Bogotá D.C.,

Doctor(a)
FERRERO EMILIO
Apoderado(a) y/o Representante de
DAIICHI SANKYO COMPANY, LIMITED

REFERENCIA	Radicación No.	7 136830
	Solicitud internacional	PCT/JP2006/310556
	Fecha inicio fase nacional	27/12/2007
	Trámite	11
	Evento	378
	Actuación	416
	Oficio No.	5426
	Folios	1

Teniendo en cuenta que la solicitud de privilegio de patente que se tramita bajo el expediente indicado en la referencia, reúne los requisitos de forma establecidos en la Decisión 486 de la Comisión de la Comunidad Andina, el Tratado de Cooperación en Materia de Patentes (PCT), el Reglamento y la Circular Única de la Superintendencia de Industria y Comercio, se envía el extracto de la solicitud a la Oficina de Comunicaciones para efecto de su publicación en la Gaceta de Propiedad Industrial.

Cúmplase
Dado en Bogotá DC,

ALIX CARMENZA CESPEDES DE VERGEL
Jefe de la división de Nuevas Creaciones

adpa11